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IABS Conference on Globalisation of specifications, Tokyo, 23-25 June 2025

Global landscape of specifications: a European Pharmacopoeia perspective

Dr. Emmanuelle Charton, Head of Division B,
European Pharmacopeia Department
EDQM

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Structure of my talk

- ★The EDQM and European Pharmacopoeia
- ★Flexibility of standards
- ★Participation of Ph. Eur. in global harmonisation efforts
- ★Pyrogenicity case study

EDQM and the European Pharmacopoeia

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European Directorate for the Quality of Medicines & HealthCare, EDQM

- ★ Part of the Council of Europe
- ★ Founded in **1964**
- ★ Partial agreement: European Pharmacopoeia: official in 39 members states & the EU (there are 33 observers to the work of the Ph. Eur.)
- ★ Contributes to **public health and access to good quality medicines and healthcare in Europe**

* EU: European Union; TFDA: Taiwan Food and Drug Administration; WHO: World Health Organization

Harmonisation of specifications is our daily job!

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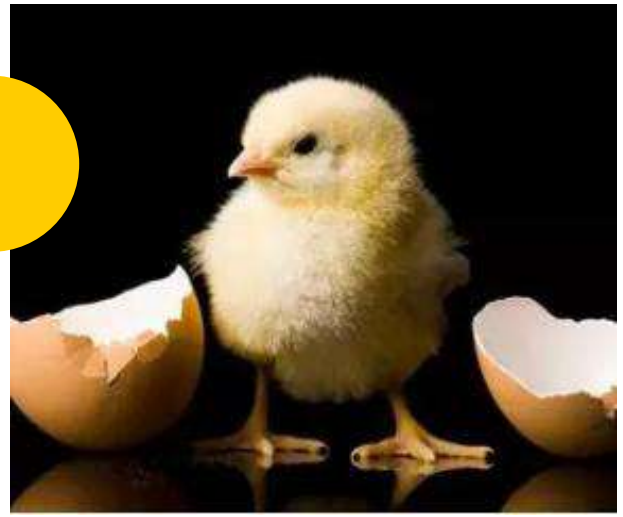
European Pharmacopoeia: how specifications are set

- Monographs elaborated based on approved products (analytical procedures and acceptance criteria)
- If several products approved: monographs are written so as to not exclude already approved products from the market
- When needed and justified, Ph. Eur. provides additional specifications based on data obtained from marketed products
  - Examples: (see back-up slides)
    - protamine sulfate
    - antibiotics

Manufacturer: « My product is safe but does not comply with Ph. Eur. »

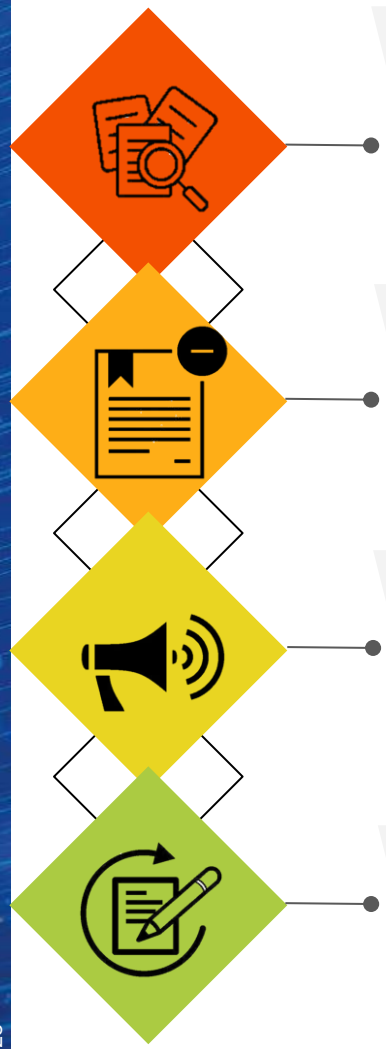
Authority: « First, the text has to be modified »



Ph. Eur. « First, this has to be authorised »

Manufacturer: « I would like to propose a modification of the text »

Demonstration of suitability of monographs



Manufacturer to evaluate the **suitability of the monograph** for QC of their article. Their choice of analytical procedures may be influenced by:

- the manufacturing process and/or
- the composition of the medicinal product.

When a competent authority considers a specification described in a monograph **insufficient** to ensure quality of the article, it may **request more-appropriate specifications** from the **manufacturer** in line with national or regional regulations.

In such cases, the competent authority informs the Ph. Eur. Commission through either

- the national pharmacopoeia authority or
- the Secretariat of the Ph. Eur. Commission

Details of the alleged insufficiency and the additional specifications : provided by the **manufacturer** to the national pharmacopoeia authority or the EDQM (Helpdesk)

➔ the decision to revise the monograph will be taken by the Ph. Eur. Commission.

Flexibility of the Ph. Eur.

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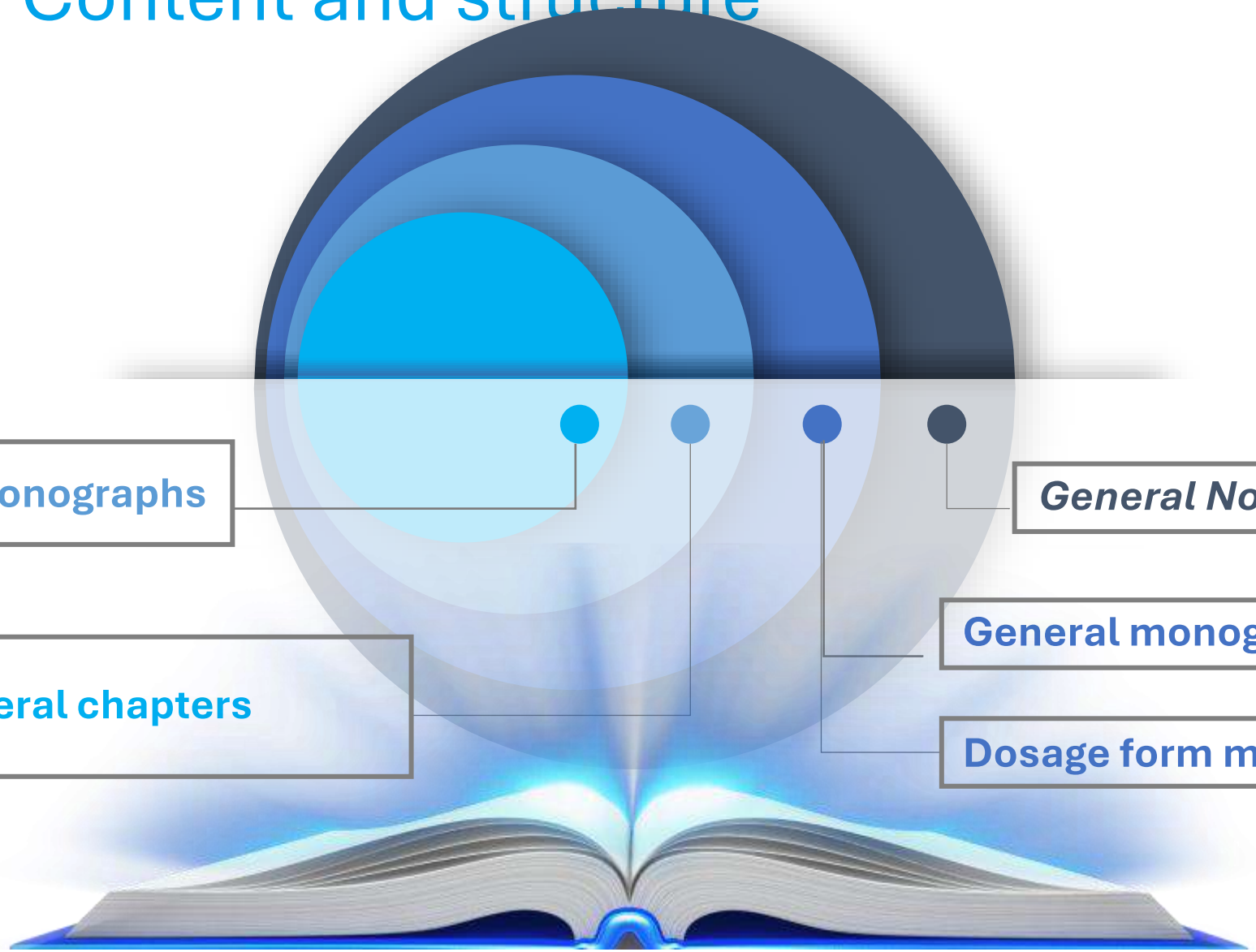
Ph. Eur.: Content and structure



Individual monographs

General chapters

General Notices

General monographs

Dosage form monographs

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General Notices – answers to a lot of questions!

- Such as:
  - What does compliance mean?
  - What is mandatory, what is not?
  - What to do when implementing a pharmacopoeial procedure?
  - What about alternative analytical procedures?
  - What about waiving of tests?
  - What does “suitable” mean?
- And many more…

An on-demand webinar is available if you want to learn more about the recent changes
https://www.edqm.eu/en/-/getting-the-big-picture-what-has-changed-in-the-ph.-eur.-general-notices

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."

- ✓ 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 remains the reference procedure

CHAPTER 5.27
COMPARABILITY OF ALTERNATIVE ANALYTICAL PROCEDURES

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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

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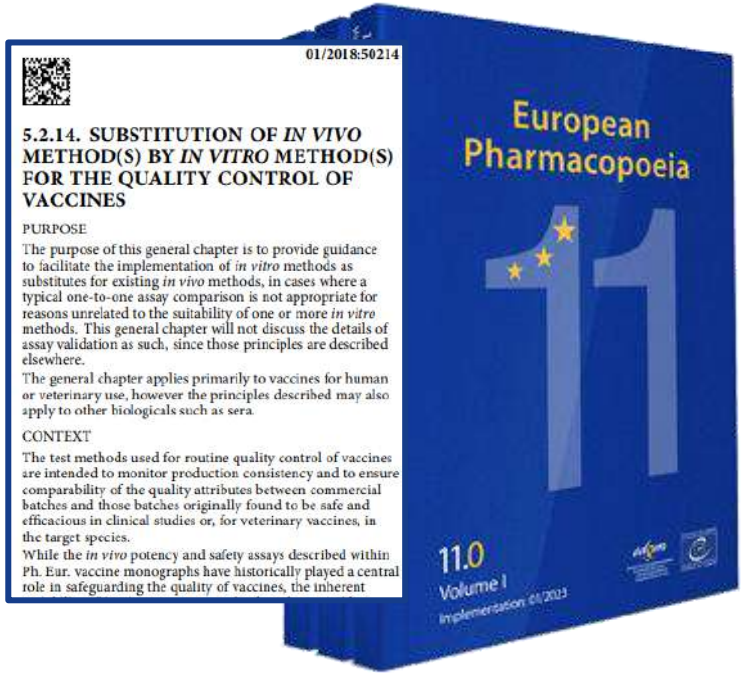
5.2.14 Substitution of in vivo methods for the QC of vaccines

- The introduction of *in vitro* methods to replace *in vivo* methods often prevented due to the characteristics of *in vivo* methods (e.g. variability, validation status of *in vivo* methods, product attributes assessed differently)

- Demonstration of equivalence may not only be but also of limited relevance

→ General chapter 5.2.14

→ Chapter elaborated to facilitate the transition to *in vitro* methods



5.2.14 Substitution of in vivo methods for the QC of vaccines

- Chapter 5.2.14 provides guidance on how to introduce alternative *in vitro* methods, where a head-to-head comparison is not possible

- Envisages the possibility that the relevance and performance of the *in vitro* method be demonstrated without such head-to-head comparison: concept of "substitution" as an alternative approach for replacement

- Focus on the scientific rationale behind the *in vitro* methods and the validation package

Biotherapeutic product monographs

Production section (Ph. Eur. General Notices)

- Requirements related to process-dependent heterogeneity **set in a flexible way** (*e.g.* glycan profile, charged variants)

Test procedures

- Generic methods of analysis (*e.g.* developed according to general chapters) – **suitable** procedures
- Specific analytical procedures – '**example**' procedure

Acceptance criteria for quality attributes

- Numeric limits/ ranges (specific activity; primary structure; related proteins; HMW species)
- 'As authorised by the competent authority' (process-dependent quality attributes)

Reference preparations

- Ph. Eur. reference standards for SST
- *In-house reference preparation* – for comparative purpose (*e.g.* matching LC profiles)

Monograph flexibility

Individual monographs can address complexity of biotherapeutics

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Participation of Ph. Eur. in Global Harmonisation Efforts

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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/minimises 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 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*2
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 2024-2025
*3 : Under revision

All general 31 chapters have now been harmonised!

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
E-41 Starch, Potato
E-42 Starch, Rice
E-43 Starch, Wheat
E-44 Stearic Acid
E-45 Sucrose*3
E-46 Talc *3
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 harmonisation
*3 : Under revision

48 of the 62 excipient monographs have now been harmonized

International Meeting of World Pharmacopoeias (IMWP)

- **Goals for IMWP**

Establish a common framework for pharmacopoeial standard-setting

Harmonize approaches and policies

Create a guiding set of principles for appropriate, design, development, maintenance, publishing and distribution of pharmacopoeial standards

Strengthen collaboration and exchange among pharmacopoeias

Reduce duplication of work and increase level of prospective convergence

- **Started in 2012**, meetings organised by WHO together with host
- **for all interested world pharmacopoeias**
- **Yearly face-to-face meetings** to exchange on on-going topics (meetings in 2021-2022 as videoconference); usually **15-30 representatives**
- Elaboration of **Good Pharmacopoeial Practices (GPhP)**
- "**pharmacopoeial alert system**" – nitrosamines and work on Favipiravir IMWP monograph
- **Last meeting** 6-7 February 2025, New Delhi, India - report
- **Next meeting May-June 2026,** organised by Brazilian Pharmacopoeia

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IMWP as a venue

- discussion forum to
  - get to know sister pharmacopoeias
  - build trust among pharmacopoeias
  - exchange information, knowledge and expertise,
    e.g. to inform each other of recent challenges and share solutions found

- PDG committed to support pharmacopoeial harmonisation of quality standards by liaising with other world pharmacopoeias (e.g. via IMWP) and by sharing PDG texts with all IMWP pharmacopoeias
  - for comments at public consultation stage and
  - after sign-off for optional implementation following GPhP

Pyrogenicity case study

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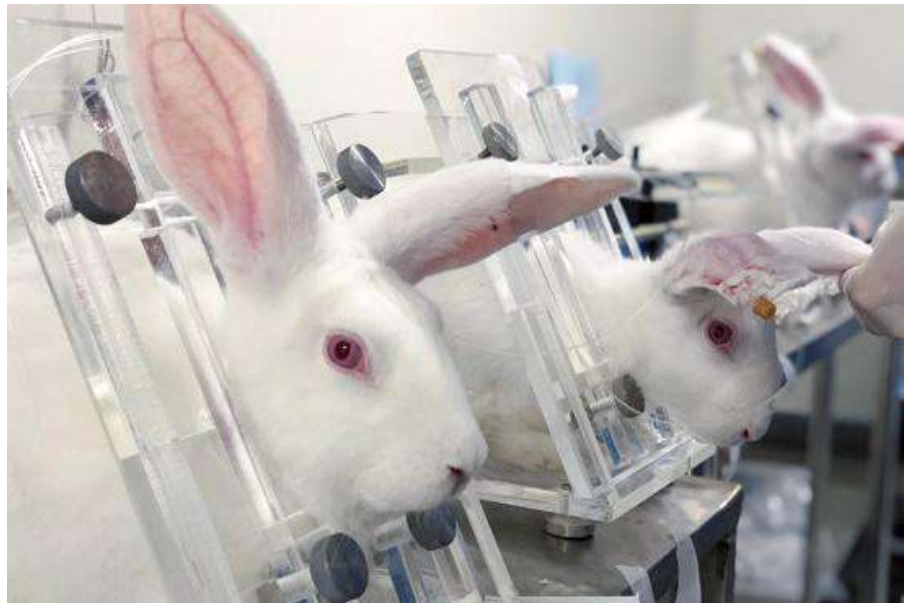
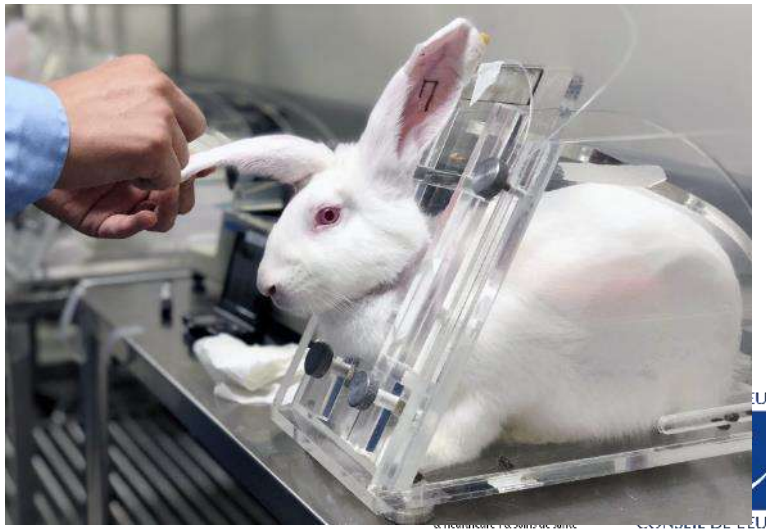
The Rabbit Pyrogen Test (RPT)



- ★ Principle: rectal measurement of the rise in body temperature in rabbits following IV injection of the substance to be examined
- ★ Historical test, can detect endotoxin and non-endotoxin pyrogens
- ★ But: not quantitative, low sensitivity, no controls, animal-based (method variability, animal welfare…), method not harmonised across regions



The test still consumes a large number of animals **(400,000/year globally)**

Background to the new Ph. Eur. Pyrogenicity strategy

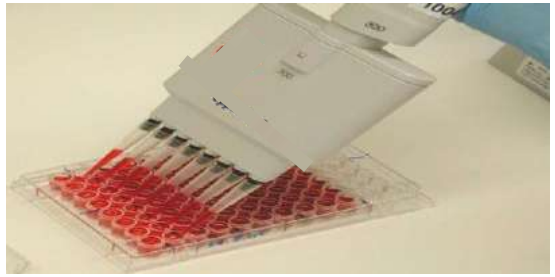
1971

Pyrogens (2.6.8)

1987

BET (2.6.14)

2010



MAT (2.6.30)

2020

BET using rFC (2.6.32)

The RPT continues to be widely performed

- **New chapter *5.1.13* 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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Phasing out the RPT- Communication to stakeholders

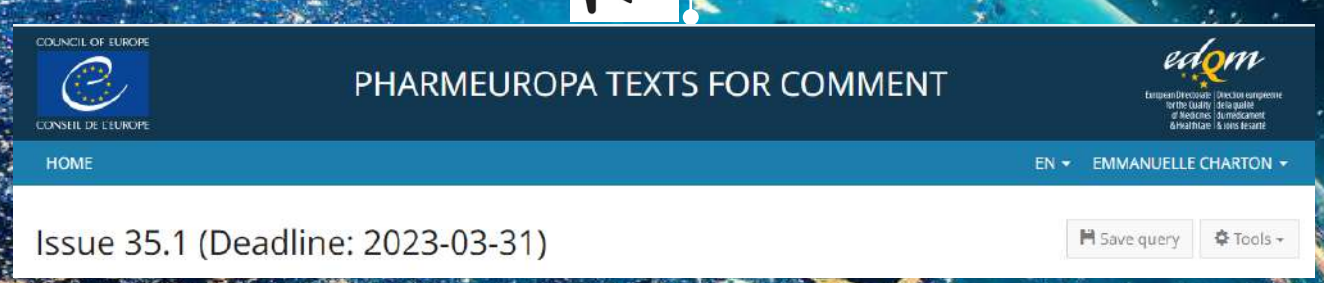
Project started, with announcement of the timelines

Strategy paper

EDQM 11th edition Conference
EDQM, Strasbourg
(19-21/09)

EPAA/EDQM Conference
EU Commission, Brussels
(14-16/02/23)

2021 | June | September | October | November | 2022 | March | May | June | Sep | 2023 | Jan | Feb | September | November | 2024



Suppression of Rabbit Pyrogen Test: Major Milestone Achieved!

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

This concerns 57 texts

Non animal pyrogenicity approaches instead (BET, MAT)

- ★ As a result, the use of the RPT will **no longer** be required in any text of the Ph. Eur.
- ★ Implementation date : **1 July 2025**
- ★ The chapter itself will be removed from the Ph. Eur. on 1 January 2026
- ★ A major achievement for animal welfare and the advancement of modern in vitro ap[illegible]es

Deletion of the Rabbit Pyrogen test: aftermath of June 2024

An achievement applauded by stakeholders!

"Finally we are there ! European Pharmacopoeia is the first regulatory body to take this courageous decision."

"So happy to hear that advances are being made in this area. Hoping to see other regions and nations follow suit."

"Finally- so good to hear"

"Great achievement!"

"Fantastic news"

"More than good news! Time has come to replace RPT with the MAT!"

"Congratulations, finally after a more than 40 years journey!"

"Sincere gratitude to the scientists and regulators who made this possible!"

"Hoping that this change will spread globally"

*"Good ! and what about **Horseshoe crabs**?"*

"we have to save them next"

*"Looking forward to see also for **horseshoe crabs**"*

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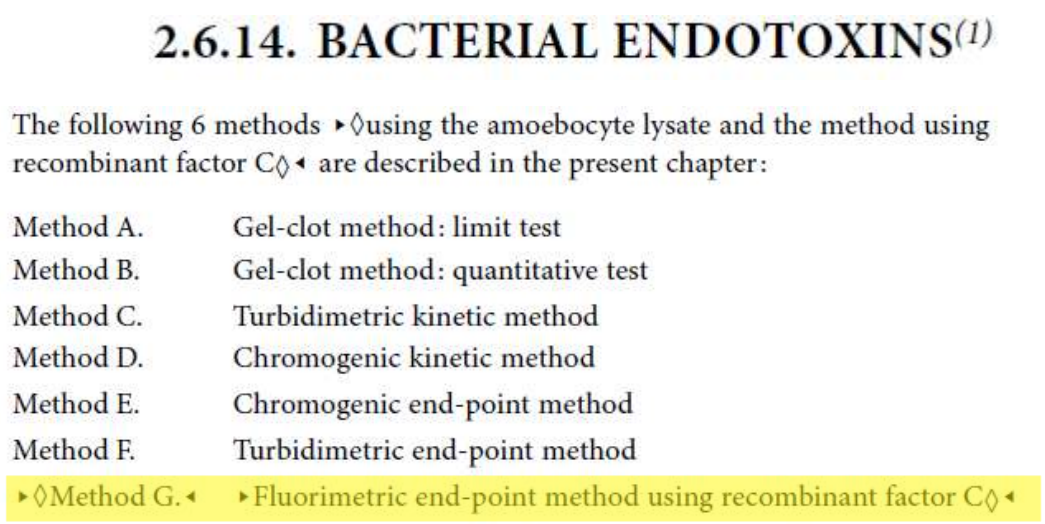
Bacterial endotoxin test: inclusion of rFC as new method G in general chapter 2.6.14

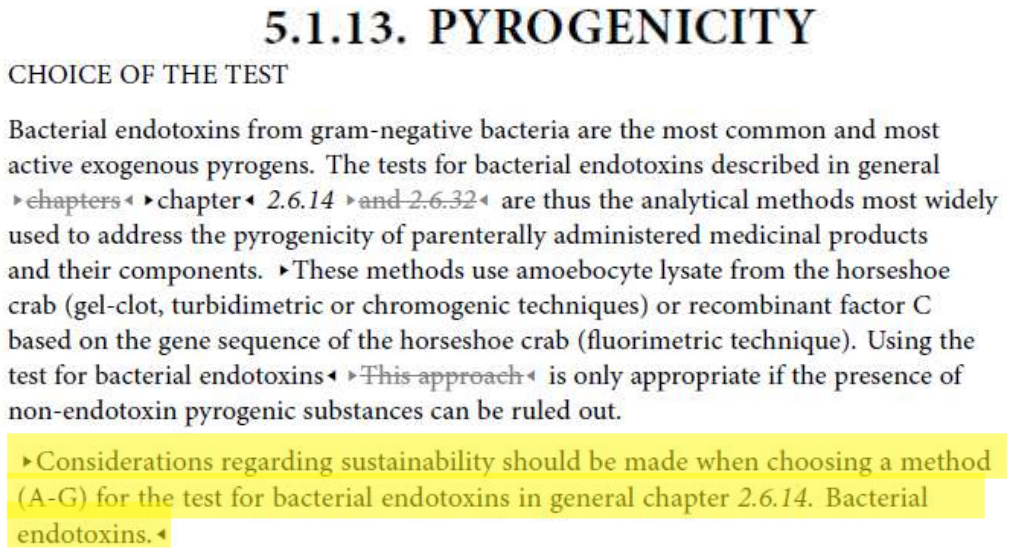
- At its March 2025 Session, the Ph. Eur. Commission decided to **revise chapter 2.614** *Bacterial Endotoxins* **to include** the test using recombinant factor C (**rFC**) as the 7th BET method (i.e. as new method G)
- This revision will give the possibility to use rFC in all Ph. Eur. texts referring to chapter 2.6.14 (~500 texts) and will give full recognition of the **equivalence of rFC with** all the **LAL** methods
- In addition, chapter 5.1.13 will be revised to reflect the changes to chapter 2.6.14 and highlight that considerations regarding **sustainability** should be made when choosing a BET method
- The revised chapters 2.6.14 & 5.1.13 have been released for **public consultation in Pharmeuropa 37.2** (commenting period from 1st April to end of June 2025)



2.6.14. BACTERIAL ENDOTOXINS(1)

The following 6 methods ▸◊using the amoebocyte lysate and the method using recombinant factor C◊◂ are described in the present chapter:

Method A.	Gel-clot method: limit test
Method B.	Gel-clot method: quantitative test
Method C.	Turbidimetric kinetic method
Method D.	Chromogenic kinetic method
Method E.	Chromogenic end-point method
Method F.	Turbidimetric end-point method
▸◊Method G.◂	▸Fluorimetric end-point method using recombinant factor C◊◂



5.1.13. PYROGENICITY

CHOICE OF THE TEST

Bacterial endotoxins from gram-negative bacteria are the most common and most active exogenous pyrogens. The tests for bacterial endotoxins described in general ▸~~chapters~~◂ ▸chapter◂ *2.6.14* ▸~~and 2.6.32~~◂ are thus the analytical methods most widely used to address the pyrogenicity of parenterally administered medicinal products and their components. ▸These methods use amoebocyte lysate from the horseshoe crab (gel-clot, turbidimetric or chromogenic techniques) or recombinant factor C based on the gene sequence of the horseshoe crab (fluorimetric technique). Using the test for bacterial endotoxins◂ ▸~~This approach~~◂ is only appropriate if the presence of non-endotoxin pyrogenic substances can be ruled out.

▸Considerations regarding sustainability should be made when choosing a method (A-G) for the test for bacterial endotoxins in general chapter *2.6.14.* Bacterial endotoxins.◂

Impact on the Pharmacopoeia Discussion Group (PDG)

- Ph. Eur. informed PDG of this initiative
- PDG committed to follow the same direction at a later stage – see Press release from March 2025 meeting, published on the EDQM website on 19 May 2025
- https://www.edqm.eu/en/-/pharmacopoeial-discussion-group-achievements-14

The PDG held productive discussions on aligning innovative approaches to the test for Bacterial Endotoxins using recombinant reagents. Through continuous and open dialogue, the PDG reached a major achievement by approving a unified position among the four member pharmacopoeias regarding the goal to include methods using recombinant reagents in the harmonised chapter. Details on this important topic are shown in the Appendix, below.

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PDG progress: recombinant reagents for BET

★ **Bacterial Endotoxin Test (Q-06):**
common position published :
- PDG committed to make efforts to decrease the use of animals and animal derived reagents.
- PDG pharmacopoeias and respective regulatory framework are at different stages of acceptance regarding recombinant reagents (rFC, rCR).
- PDG‘s (long-term) goal is to include new methods using recombinant reagents in the harmonised chapter.

Save the date! Follow-up EPAA/EDQM event

25-27 February 2026 Brussels

Phasing out the RPT

Recombinant reagents for BET

The European Partnership for Alternative Approaches to Animal Testing

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Take away message: The Ph. Eur. is…

- … providing **flexibility** in the use of its standards
- …participating in the establishment of **innovative approaches to QC** of medicines in Europe
- …facilitating the **regulatory framework** in Europe **and beyond** by the establishement of standardised approaches
- …. promoting **globalisation** of these approaches

Thank you for your attention!

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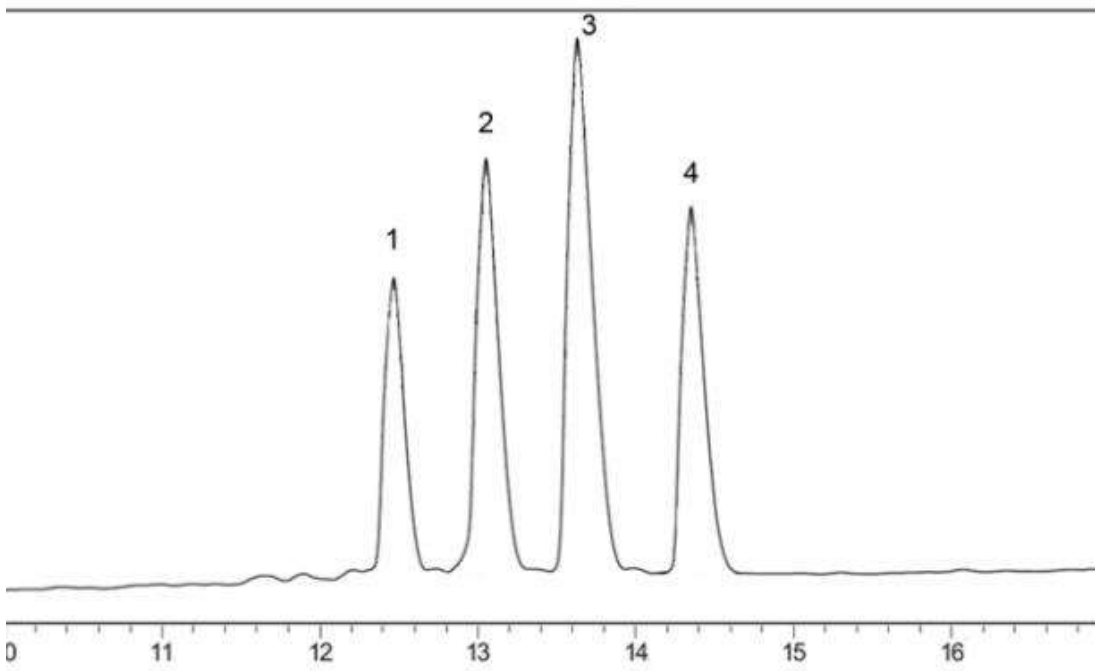
Back up slides

Case study, protamine sulfate

- ★Important stabiliser for insulin preparations
- ★Extracted from sperm of salmon
- ★Peptide composition of the extract varies according to species and geographical areas
- ★Japan is the principal source of wild salmon used for extraction
- ★2011 earthquake and tsunami disrupted the supply chain
- ★Purity test developed, together with acceptance criteria, based on batch data from commercial lots



omatogram for the test for related substances of protamin
reference solution (a)

Recombinant cascade reagent (rCR)

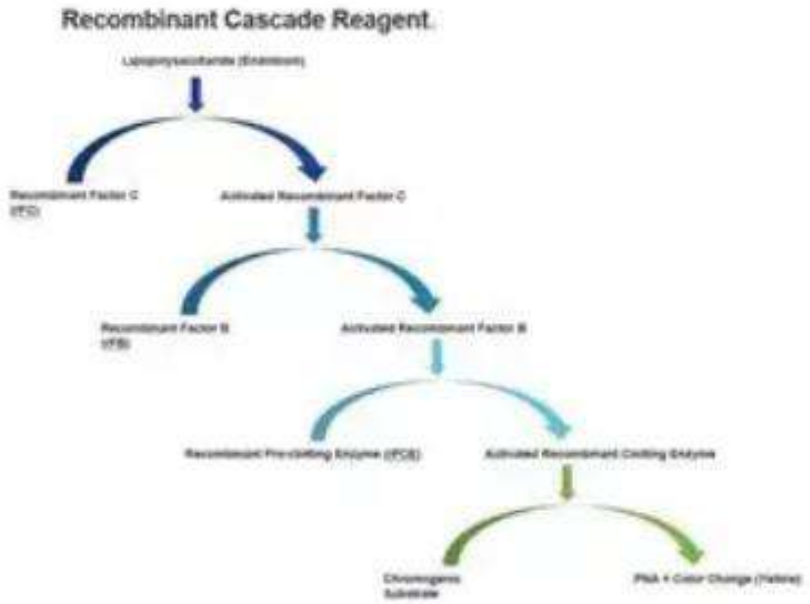
★ Kits still recent

★ Few peer-reviewed litterature

★ Few user's data

★ No medicinal product approved using this reagent in Europe

→ Alternative method



➢ When mature…

➢ Addition of new METHOD H in *2.6.14*