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

edqm

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

COUNCIL OF EUROPE

CONSEIL DE L'EUROPE

European Pharmacopoeia Commission (EPC)

Cathie VIELLE

Head of the European Pharmacopoeia Department

EDQM / CoE

First … something about me

- Pharmacist
- Joined EDQM in May 2009, as Head of the European Pharmacopoeia Department and Secretary to the EPC
- Before:
  - several positions in Quality - from QA compliance to Head of Quality (QA, QC, Regulatory affairs) - in a manufacturing site for worldwide markets
  - supply chain department in headquarter

Ph. Eur. Process

Ph. Eur. monograph elaboration/revision: main steps

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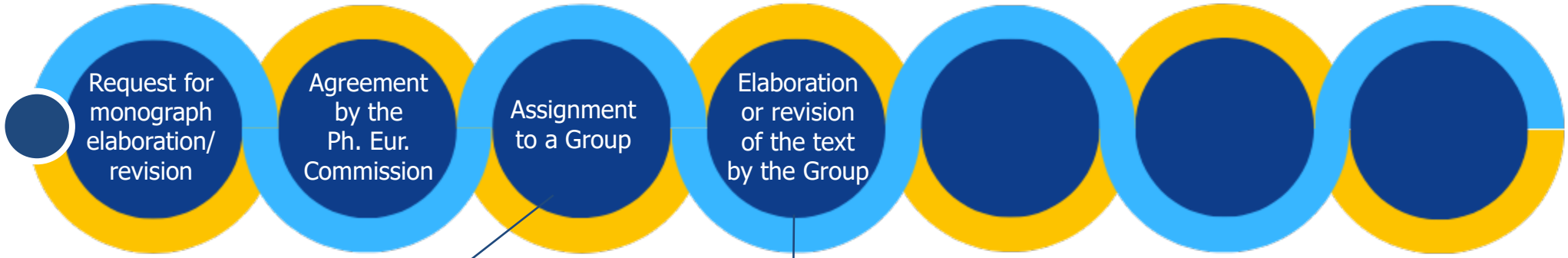
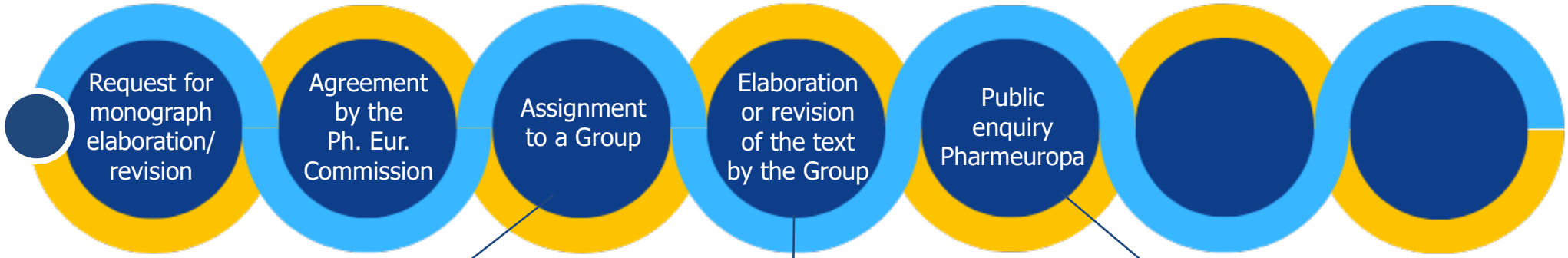


- **Data package** (current specifications, analytical procedures; validation data; batch and stability data)
- **Material** for testing
- *Candidate material for RS establishment*

- **Review** of data package
- **Laboratory study/collaborative testing**
- **Draft** new or revised monograph

Ph. Eur. monograph elaboration/revision: main steps



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- **Draft published for comments** (3 months commenting period)
- **Evaluation of stakeholder feedback** (technical comments, data)

Ph. Eur. monograph elaboration/revision: main steps

Once published, texts need to be regularly renewed

Request for monograph elaboration/ revision

Agreement by the Ph. Eur. Commission

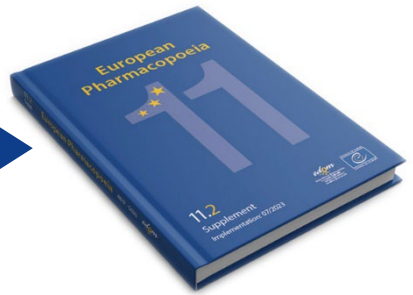
Assignment to a Group

Elaboration or revision of the text by the Group

Public enquiry Pharmeuropa

Text adopted by the Ph. Eur. Commission

Publication in the Ph. Eur.



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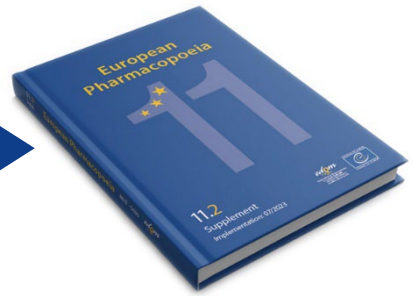
Ph. Eur. monograph elaboration/revision: main steps

Once published, texts need to be regularly renewed

Request for monograph elaboration/ revision (0) → Agreement by the Ph. Eur. Commission (0) → Assignment to a Group (1) → Elaboration or revision of the text by the Group (2) → Public enquiry Pharmeuropa (3) → Text adopted by the Ph. Eur. Commission (4) → Publication in the Ph. Eur.



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State of work : the figures are to be interpreted as follows :
- 0 – The monograph has been authorised but work has not started yet
- 1 - Draft work has started
- 2 - Pharmeuropa the monograph has been authorised for publication in Pharmeuropa (see below)
- 3 - COM the monograph has been submitted for adoption to the European Pharmacopoeia Commission
- 4 - DEF the monograph has been adopted

Ph. Eur. monograph elaboration/revision: main steps

Search Database online | Knowledge Database

Detailed view of Corpora ad usum pharmaceuticum.

Status	In use
Monograph Number	02034
English Name	Substances for pharmaceutical use
French Name	Substances pour usage pharmaceutique
Latin Name	Corpora ad usum pharmaceuticum
Pinyin Name	
Chinese Name	
Pharmeuropa	35.1
Published in English Supplement	11.3
Published in French Supplement	11.3
On-going	Revision
State of work	2 - Pharmeuropa
Pharmeuropa	35.1
Description	Deletion of the test for Pyrogens (2.6.8) and introduction of a reference to the new general chapter 5.1.13 Pyrogenicity.
Chromatogram	Not available
Additional information	Not available
History	View history
Interchangeable (ICH_Q4B)	NO
Pharmacopoeial harmonisation	NO
Reference standards	
Practical Information	**Test(s)** **Brand Name/Information**
CEP	

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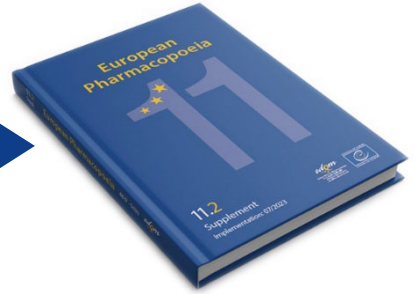
Ph. Eur. monograph elaboration/revision: main steps

Industry, OMCLs, assessors…

Request for monograph elaboration/ revision → 0 → Agreement by the Ph. Eur. Commission → 0 → Assignment to a Group → 1 → Elaboration or revision of the text by the Group → 2 → Public enquiry Pharmeuropa → 3 → Text adopted by the Ph. Eur. Commission → 4 → Publication in the Ph. Eur.



Invitation of interested parties to participate

Interested parties can check the feasibility for authorised products

Responding to the Pharmeuropa enquiry is a must

Monographs are based on quality described for **approved products**

Once a monograph is published, MAHs of authorised products have to ensure that their products meet the requirements of the monograph… ***at the implementation date at the latest***

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)

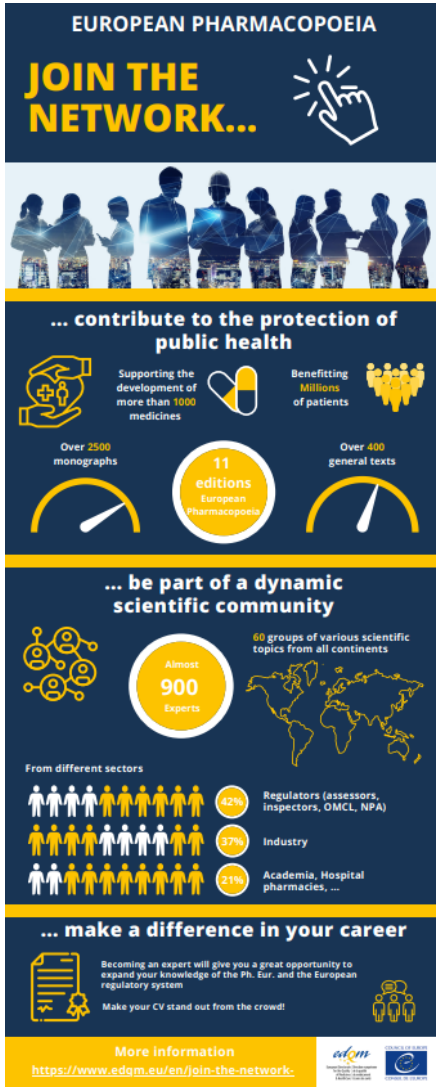
Ph. Eur. reference standards

- 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.

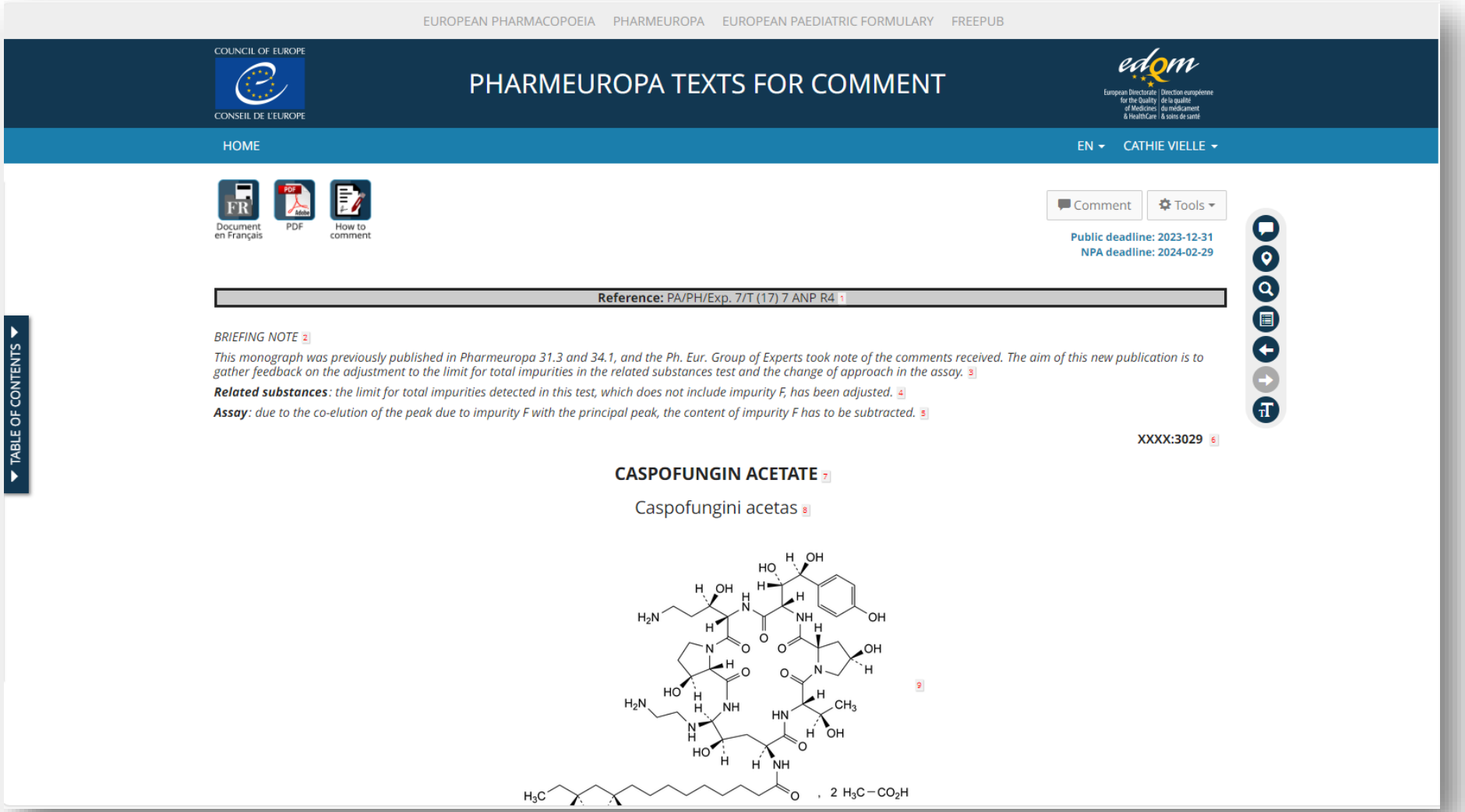
☐ Other:

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 ….

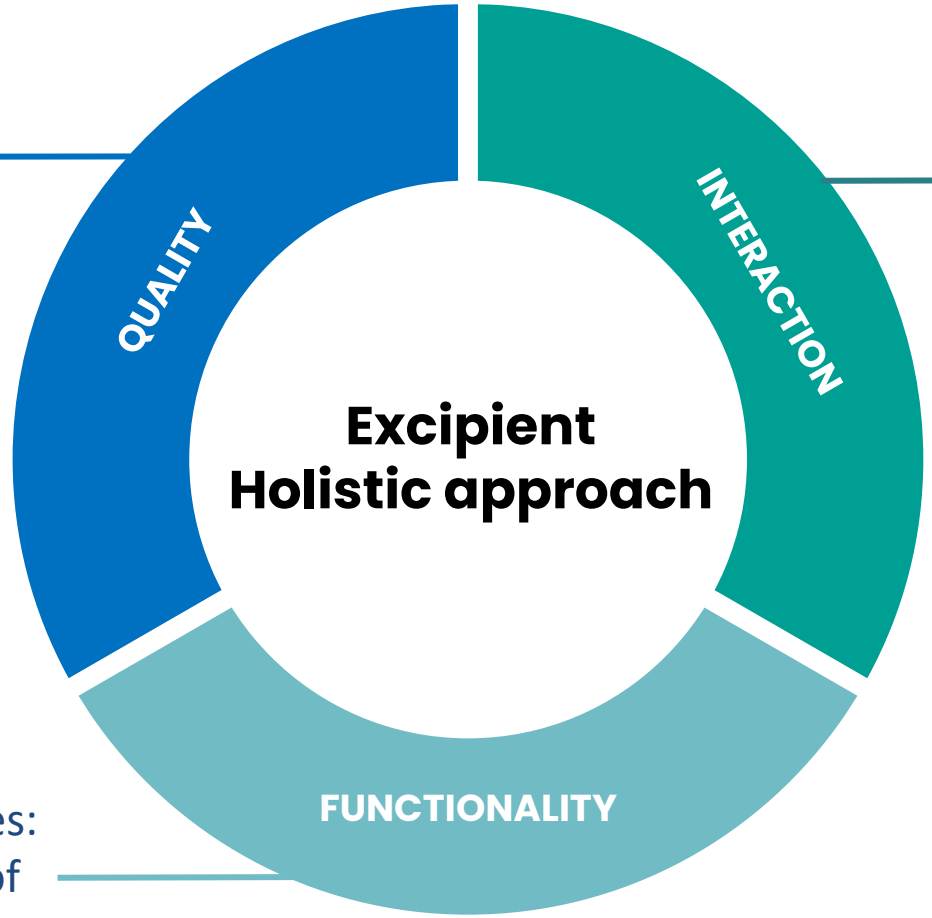


https://pharmeuropa.edqm.eu/home

Excipient Strategy WP

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

WATCH THE SPACE

New Excipients Strategy Working Party (EXS)

► More information: EDQM News

- Approved the creation of a **new Excipients Strategy Working Party (EXS WP)** at Ph. Eur. Commission in June 2022
- Address specificities of standard setting for excipients (Terms of reference)
- End 2022: **Experts appointed**
- March 2023: **work started**
- **Stock taking of the current situation and reflection** on potential areas for development and opportunities for the Ph. Eur. took place
- ► first outcome expected 2024
- Stakeholders will be involved and updated on the outcome of the discussions

European Paediatric Formulary

Critical availability of Paediatric medicinal products

- Needs of paediatric patients are not met despite all efforts
  - ⇒Prescription of off-label and unauthorised medicine for children is widespread in Europe. (45-60 % of total prescription, EMA survey 2006)
  - ⇒Cause?: Small patient group, lack of business case, hard to set up clinical trials

- To fill the gap, paediatric drugs may be prepared extemporaneously
  - ⇒There is a **need for** clinicians and pharmacist to have **appropriate formulations** in the absence of licensed, marketed alternative.
  - ⇒Pharmacists have documented those formulation at local and national level but no standardisation effort at the European level had been undertaken : Work has been done, some national data is available

- A European Paediatric formulary was envisionned (2013) to share knowledge on standardised formulations throughout Europe and beyond

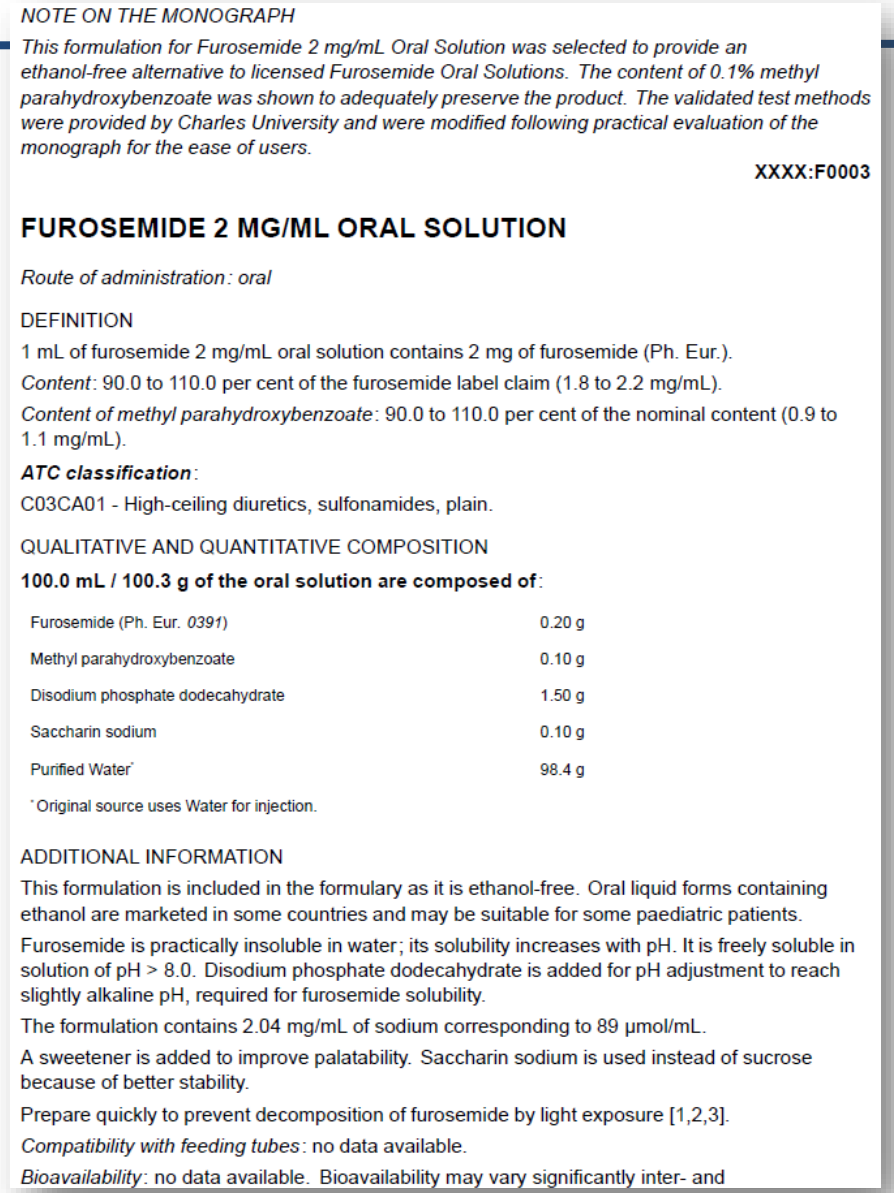
Concept of a European Paediatric Formulary

- General idea is to:
  - **Collect** on European level formulations that are described in national formularies or whose use is well-established.
  - **Select** formulations of appropriate quality
  - **Elaborate** the monographs in a standardised format
  - **Verify** practically preparation method and analytical procedures
  - **Publish** on central platform for clinicians and pharmacists for easy and free access

- The formulary would give **access to formulations of appropriate quality**, allowing preparation of an unlicensed medicinal product when no licensed alternative is available to the patient.
- The formulary would NOT be legally binding nor part of the Ph. Eur. It is up to the member states to use according to national legislation and practices

Process and status

- All texts undergo **public consultation**
- Pharmeuropa PaedForm open for direct **comments by all**
- Final texts approved by both EPC and CD-P-PH
- 9 monographs were in public consultation (+2 since 12/23)
- 5 monographs finalised (+2 by 02/24)



NOTE ON THE MONOGRAPH

This formulation for Furosemide 2 mg/mL Oral Solution was selected to provide an ethanol-free alternative to licensed Furosemide Oral Solutions. The content of 0.1% methyl parahydroxybenzoate was shown to adequately preserve the product. The validated test methods were provided by Charles University and were modified following practical evaluation of the monograph for the ease of users.

XXXX:F0003

FUROSEMIDE 2 MG/ML ORAL SOLUTION

Route of administration: oral

DEFINITION

1 mL of furosemide 2 mg/mL oral solution contains 2 mg of furosemide (Ph. Eur.).

Content: 90.0 to 110.0 per cent of the furosemide label claim (1.8 to 2.2 mg/mL).

Content of methyl parahydroxybenzoate: 90.0 to 110.0 per cent of the nominal content (0.9 to 1.1 mg/mL).

ATC classification:

C03CA01 - High-ceiling diuretics, sulfonamides, plain.

QUALITATIVE AND QUANTITATIVE COMPOSITION

100.0 mL / 100.3 g of the oral solution are composed of:

Furosemide (Ph. Eur. *0391*)	0.20 g
Methyl parahydroxybenzoate	0.10 g
Disodium phosphate dodecahydrate	1.50 g
Saccharin sodium	0.10 g
Purified Water*	98.4 g

*Original source uses Water for injection.

ADDITIONAL INFORMATION

This formulation is included in the formulary as it is ethanol-free. Oral liquid forms containing ethanol are marketed in some countries and may be suitable for some paediatric patients.

Furosemide is practically insoluble in water; its solubility increases with pH. It is freely soluble in solution of pH > 8.0. Disodium phosphate dodecahydrate is added for pH adjustment to reach slightly alkaline pH, required for furosemide solubility.

The formulation contains 2.04 mg/mL of sodium corresponding to 89 µmol/mL.

A sweetener is added to improve palatability. Saccharin sodium is used instead of sucrose because of better stability.

Prepare quickly to prevent decomposition of furosemide by light exposure [1,2,3].

Compatibility with feeding tubes: no data available.

Bioavailability: no data available. Bioavailability may vary significantly inter- and

European Drug Shortages Initiatives

Overview of the EDQM actions on Shortages

Governance

- Certification Steering Commitee
- OMCL Network
- CD-P-PH
- European Pharmacopoeia Commission (EPC)

(*EDQM Secretariat*)

Certification procedure	OMCL Network	Methodological Guide	European Drug Shortages Formulary
Shortage related to shortage of API	**Measures in place** ►fast-tracking CEP assessment for API affected by shortages ►Providing information on reliable source of API	**Similar medecines to the one affected by shortage**	Ad hoc support from the OMCL network for testing of medicines non authorised in EU for potential importation	Support national competent authorities and healthcare professionals in **identification and selection of medicines that can be in short supply under certain circumstances and can be prepared in hospital (and/or community) pharmacy**	**Publish a European Formulary**, a compilation of texts (monographs) describing **methods for the preparation and quality control** of standardised unlicensed pharmaceutical preparations that could be used as a temporary replacement of potentially unavailable, essential licensed medicines

Shortages initiative

PREPAREDNESS PHASE

AIM: Mitigate effects of shortages, including shortages occurring during public health emergencies

SHORTAGES CRISIS SITUATION

Governance

- European Committee on Pharmaceuticals and Pharmaceutical Care (CD-P-PH)
- European Pharmacopoeia Commission

(*EDQM Secretariat*)

Methodological Guide

Support national competent authorities and healthcare professionals in **identification and selection of medicines that can be in short supply under certain circumstances and can be prepared in hospital (and/or community) pharmacy**

Other existing sources

- **EMA's lists - Essential and critical medicines**
- **WHO lists**

Enablers

European Shortages Formulary

Compilation of non legally binding texts (monographs) describing **methods for the preparation and quality control** of standardised unlicensed pharmaceutical preparations could be used [1] as a temporary replacement of potentially unavailable, essential licensed medicines

► Formulary available to be used by pharmacists

For consideration

► Working group to provide technical guidance if medicines not covered,

[1] Depending on national legislation

EPC Priorities

If you wish to 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

European Pharmacopoeia future programme/directions

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

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2.6. Excipients

2.7. Nanomedicines

2.8. Medicinal product monographs for chemically defined APIs

2.9. European Paediatric Formulary

2.10. European Drug Shortages Formulary

3. Environmental sustainability & Alternative to animal testing

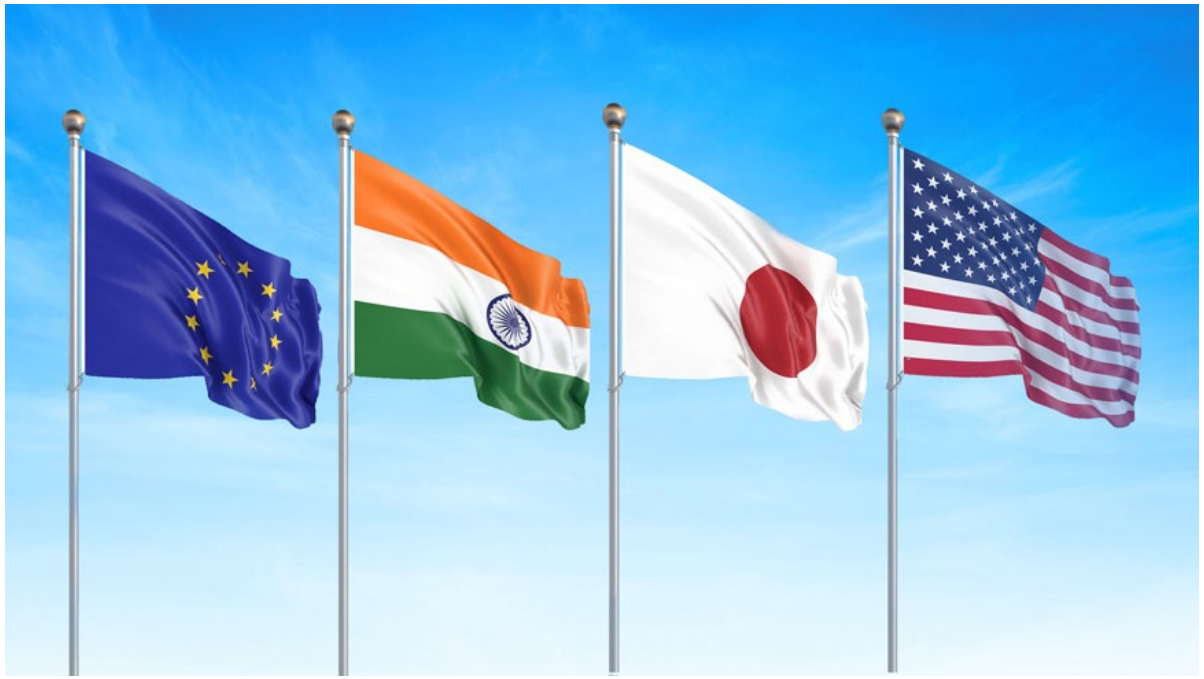
Changes soon to come

Update on PDG:

1. PDG expansion
2. ICH Q4B Annexes

PDG expansion

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



Update on PDG:

1. PDG expansion
2. ICH Q4B Annexes

Scope of Q4B and its 16 annexes

Reminder

- **Declarations of Interchangeability by ICH regulatory members**
- **Relevant for pharmacopoeias from ICH regulatory members**

Concerning ICH Q4B annexes

Elaboration & revision of pharmacopeial text (technical content)

Revision of content of Q4B annexes (recommendation for regulatory interchangeability)

Q6A related general chapters

- Excipients (62 monographs)
- General chapters (31 general chapters)

PDG procedure

PDG procedure

PDG procedure

ICH procedure（16 general chapters）

ICH Q4B: general chapters covered

Reminder

Annex number	PDG text covered
1	Residue on Ignition / Sulfated Ash
2	Extractable Volume
3	Particulate Contamination: Sub-visible particles
4A	Microbiological Examination of Non-Sterile Products: Microbial Enumeration Tests
4B	Microbiological Examination of Non-Sterile Products: Tests for Specified Micro-organisms
4C	Microbiological Examination of Non-Sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use
5	Disintegration
6	Uniformity of Dosage Units
7	Dissolution
8	Sterility Test
9	Tablet Friability
10	Polyacrylamide Gel Electrophoresis
11	Capillary Electrophoresis
12	Analytical Sieving
13	Bulk Density and Tapped Density of Powders
14	Capillary Electrophoresis

Why a new maintenance procedure? Reminder

- **ICH has grown**
- 4 ➔ 15 regulatory members
- 3 ➔ 9 involved pharmacopoeias

- **Pharmacopoeial texts have evolved**

ICH regulatory member	Pharmacopoeia
EC, Europe	European Pharmacopoeia (Ph. Eur.)
FDA, United States	United States Pharmacopeia (USP)
PMDA/MHLW, Japan	Japanese Pharmacopoeia (JP)
Health Canada	-
Swissmedic, Switzerland	European Pharmacopoeia (Ph. Eur.)
ANVISA, Brazil	Brazilian Pharmacopoeia (FB)
COFEPRIS, Mexico	Mexican Pharmacopoeia (FEUM)
EDA, Egypt	Egyptian Pharmacopoeia
HSA, Singapore	-
MFDS, Republic of Korea	Korean Pharmacopoeia (KP)
MHRA, UK	European Pharmacopoeia (Ph. Eur.)
NMPA, China	Chinese Pharmacopoeia (ChP)
SFDA, Saudi Arabia	-
TFDA, Chinese Taipei	TW Pharmacopoeia (TWP)
TITCK, Türkiye	European Pharmacopoeia (Ph. Eur.)

Proof of Concept for a new maintenance procedure

- **PDG had been entrusted in 2018 by ICH to update the Q4B annexes**
- PDG conducted a **pilot phase** → proof-of-concept on 3 annexes
- **Constraints** were discussed and **general agreement found** in June 2023
- **End of pilot phase was envisaged** with revised ICH Q4B guideline and SOP presented to ICH in November 2023
- **Again concerns raised** by ICH members (to the wording and process)

Two different implementation approaches

- Non-PDG pharmacopoeias have two options for implementation:

  - **standard implementation** approach:

  1) The ph. will harmonise their text with the PDG text
  2) The regulatory authority accepts reference to all pharmacopoeias found harmonised

  - **parallel implementation** approach:

  1) The pharmacopoeia will implement the PDG text in parallel to a local version
  2) Manufacturers may use for products in this region the harmonised text or the local text
  3) Products for export to other ICH regions use the harmonised text

Next steps

- **PDG is clarifying remaining issues with ICH members**
- **Foreseen close of proof-of-concept phase** in 2024 with approval of revised ICH Q4B guideline and ICH SOP by ICH Assembly
- PDG will **update all 16 Q4B annexes subsequently** together with ICH
- maintenance will be triggered by
  1) revision of the PDG text
  2) new involved pharmacopoeia having harmonised its text

- This work aims for **regulatory interchangeability** of **16 important pharmacopoeial texts** between **9 pharmacopoeias**

Thank you for your attention

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