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

How to Participate in the Elaboration and Revision of Monographs

European Pharmacopoeia Training Session on Biologicals
4-5 February 2020

Dr Mihaela Buda
European Pharmacopoeia Department
EDQM, Council of Europe

Basis for Monographs

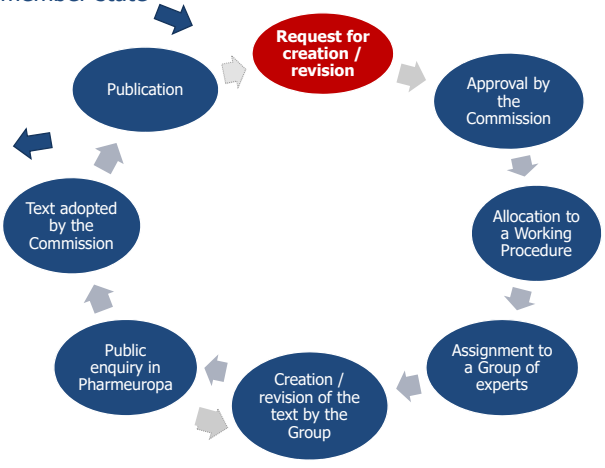
- ✓ Monographs must take account of all currently approved products
- ✓ Approved specification(s) are the main basis backed up by batch data
- ✓ Draft monographs are checked by users including regulatory authorities at Pharmeuropa stage
- ✓ Policy for monograph development is given in:

  Technical Guide for the Elaboration of Monographs
  (available on the EDQM website)

and specific Technical Guides:

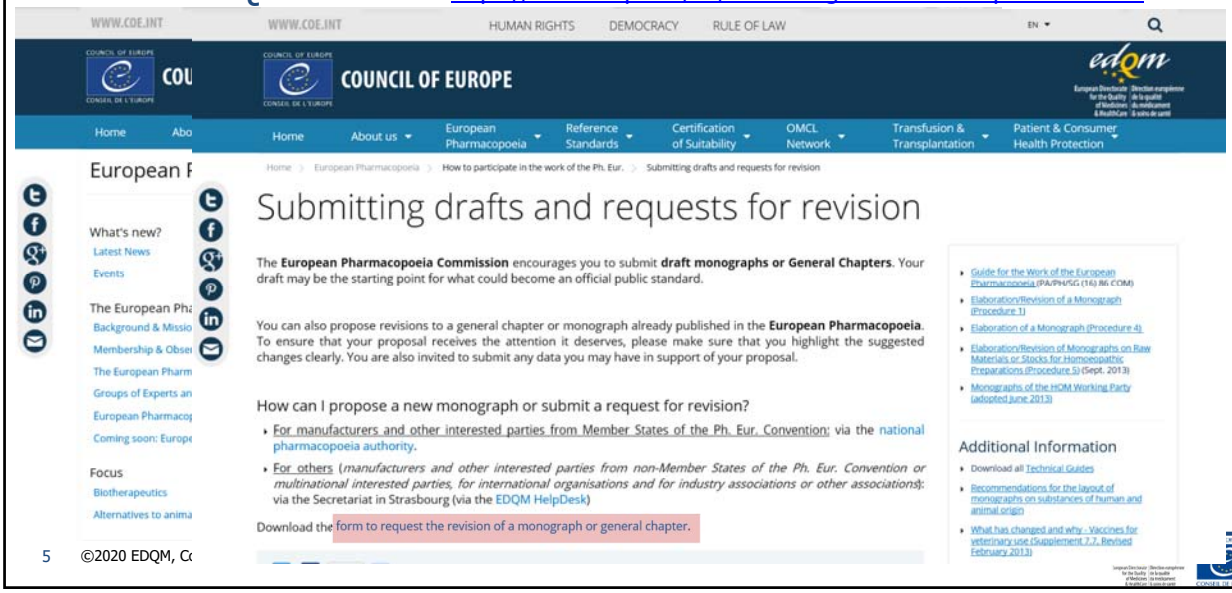
Creation or Revision of a text

Chair of the Ph. Eur. Commission
Delegation of a member state
Experts, EDQM



How to Request a Revision?

- Go the EDQM website: https://www.edqm.eu/en/submitting-drafts-and-requests-revision



Proposing a New Monograph

⇨ Contact the EDQM *[in Europe: National Pharmacopoeia Authority]*

- ✓ **Initial data**: countries (in Europe) where the product is approved
- ✓ **Data package**:
  - Current specifications
  - Analytical procedures (SOPs)
  - Method validation reports
  - Batch and stability data
  - Samples of the finished product, substance and impurities
  - Full description of data package is available

Request for Revision of a Ph. Eur. Text

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 a MONOGRAPH, SECTION TO BE REVISED:

☐ Title ☐ Definition ☐ Production ☐ Characters

☐ Identification ☐ Tests ☐ Assay ☐ Storage

☐ Labelling ☐ Impurities ☐ Functionality-related characteristics ☐ Other

DATA ATTACHED TO SUPPORT THE REQUEST FOR REVISION

Sufficient data must accompany the request to enable the group of experts and/or the Commission to decide whether revision of the monograph is necessary. The data should be evaluated in this light by the requester. Wherever possible, a concrete proposal should be made for amendment of the monograph.

☐ validated method of analysis (comparison with the existing method should be provided wherever possible):

☐ batch data ☐ typical chromatogram (if applicable)

☐ other

Please indicate where samples of the product and any necessary *Reference Substance* for testing of the revision proposal can be obtained:

Where useful, please indicate suppliers for reagents/equipment:

Manufacturer(s) identified (name, address ...):

If urgent revision is requested, please indicate why this is justified.

Page 2/2 FORM/339 – Rev. 03 [25/03/2013]

Data for Revision

- ✓ Revision can only be undertaken if the request is backed up by sufficient data
- ✓ Provide **batch data**, sample chromatograms, etc. to enable a decision on the need for revision
- ✓ Supply **validated methods** (if possible, cross-validated against official Ph. Eur. method) and samples notably for all impurities controlled by the new method

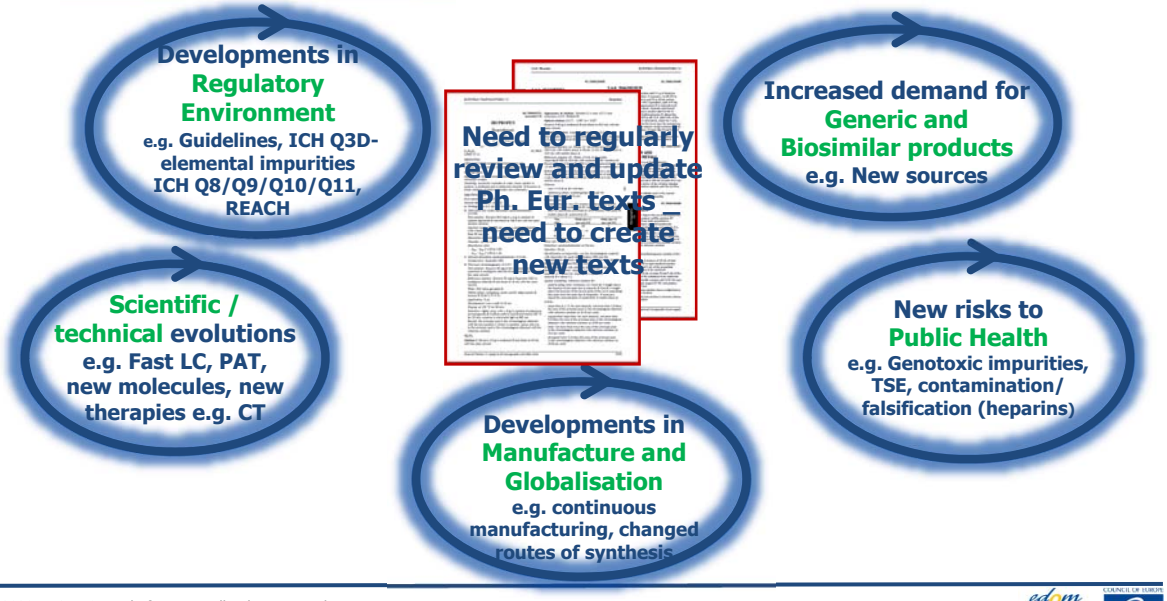
And then?

- **Outside Ph. Eur. Member states**:
  - ⇨ contact EDQM which will refer the matter to a group of experts or to the Ph. Eur. Commission

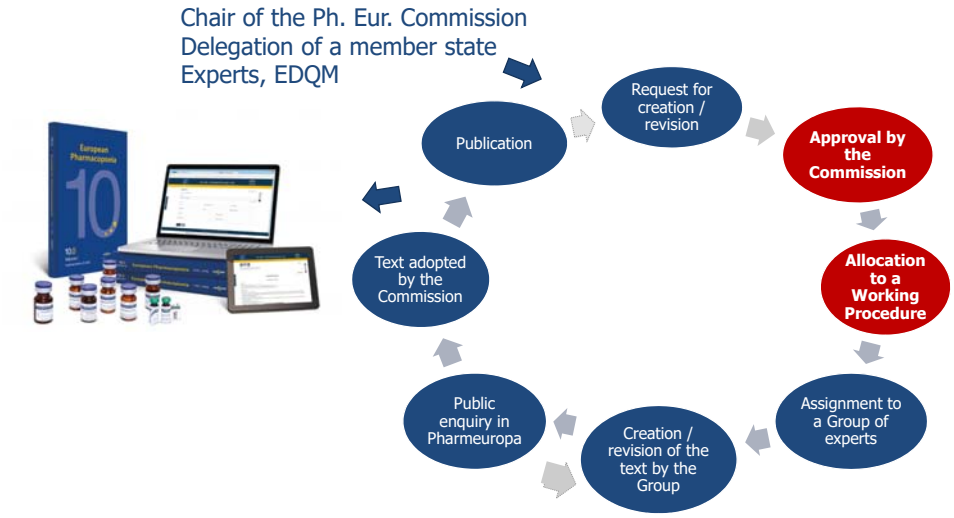
- **Ph. Eur. Member states:**
  - ⇨ via National Pharmacopoeia Authority (address list on EDQM website and in Pharmeuropa)

Make clear what needs revising and, if possible, make a concrete proposal

Revision: Why?



Creation or Revision of a Text



Revision Programme

- ✓ **Work programme** is announced via EDQM website and to industry associations and pharmacopoeia liaison contacts (http://www.edqm.eu/en/european-pharmacopoeia-work-programme-607.html)

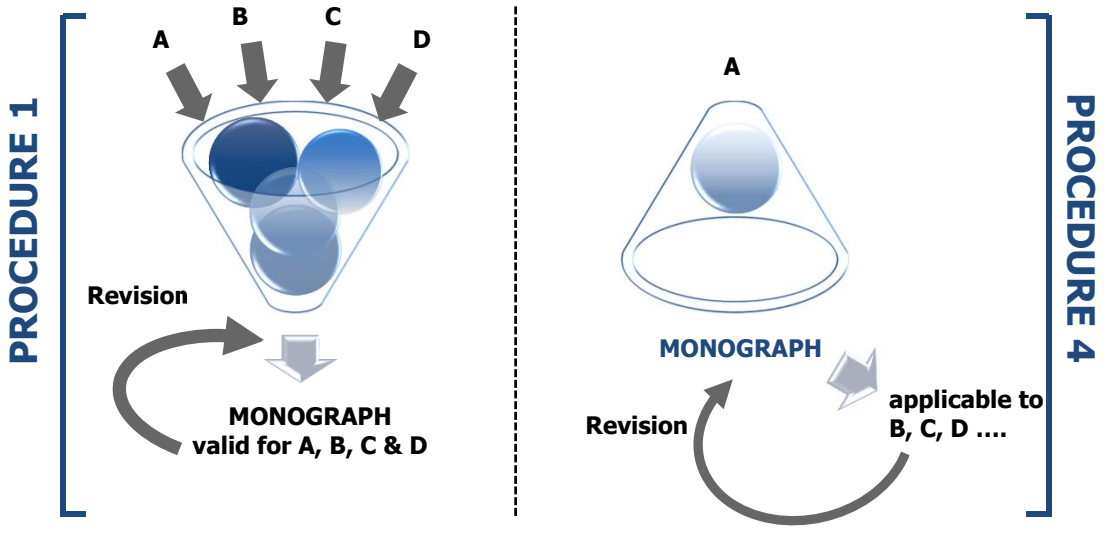
- ✓ **Stakeholders to**:
  - Declare an interest for relevant items
  - Make sure Pharmeuropa is seen for revision proposals
  - Provide samples, test draft proposal

How are Texts Elaborated / Revised?

- **Procedure 1** (Group of experts):
  Multi-source products and monograph revisions
  On request, data are handled confidentially by EDQM

- **Procedure 4** (Group of regulators):
  Single-source products, direct co-operation with innovator
  Data are handled confidentially by EDQM

How are Texts Elaborated / Revised?

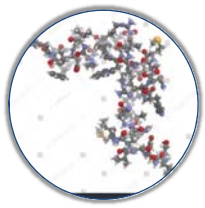


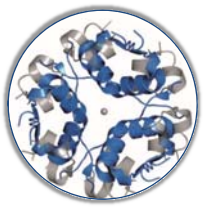
P4 Procedure: Aim

- ✓ Create monographs for single-source substances/finished products (still under patent) with a potential for further generics
- ✓ Based on authorised products
- ✓ Monograph ready ≥ 2 years before patent expiry (ideally)
- ✓ Possibility of starting elaboration work 5 years after first MA approval
- ✓ Protection of proprietary information: expert group P4 solely composed of regulators, OMCLs and EDQM

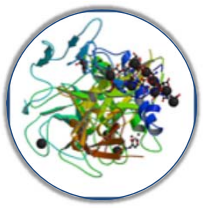
Ph. Eur. Monograph Elaboration: P4 Examples

PROCEDURE 4 (single-source)

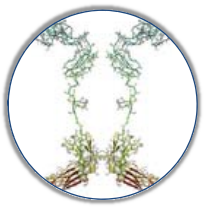

Teriparatide (2829)


Insulin glargine (2571)

currently under revision (**P1**)

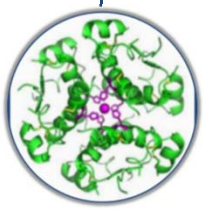

Human coagulation factor VIIa (rDNA) concentrated solution (2534)


Human coagulation factor VIIa (rDNA) concentrated solution (2522)

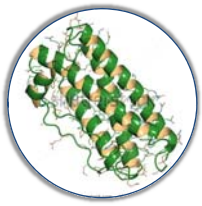

Etanercept (2522)

Ph. Eur. Monograph Elaboration: P1 Examples

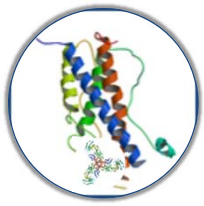
PROCEDURE 1 (multi-source)



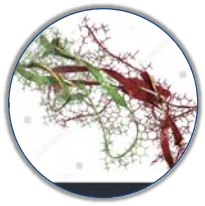
Insulin, human (0838)



Filgrastim concentrated solution (2206)



Somatropin (0950, 0951, 0952, 2370)



Follitropin concentrated solution (2206)

Infliximab concentrated solution (2928)

Creation or Revision of a Text

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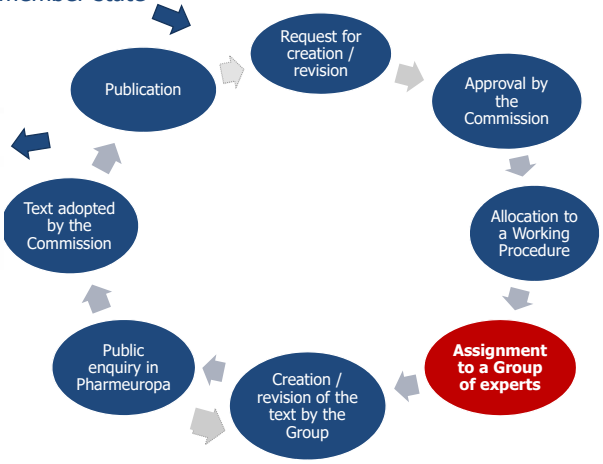
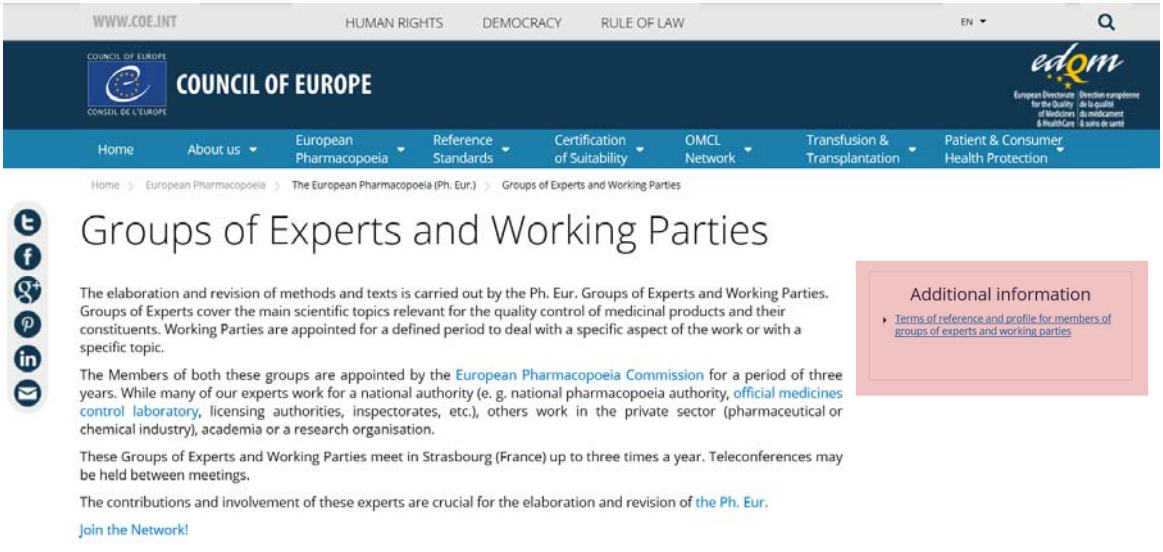
Experts, EDQM



By Whom?

- ✓ **Groups of experts and working parties** – appointed by the Ph. Eur. Commission
- ✓ 800 **experts** in pharmaceutical sciences from the Ph. Eur. members states and observers
- ✓ The Ph. Eur. Commission has revised its working procedures to open up to the nomination of experts from non-European Pharmacopoeia member states and non-observers states
- ✓ EDQM web site: https://www.edqm.eu/en/join-network



Example:

Group of Experts No. 6B (Human Plasma and Plasma Products)

Terms of reference

- Drafting and revision of texts in the field of blood products

Profile for experts

- Current expertise in the field of blood products, notably related to quality control of and development of control methods
- Access to laboratory facilities for verification and validation of methods proposed for inclusion in monographs, Essential: Active involvement in laboratory verification of test methods and drafting of texts
- Several years of experience in one or more of the following fields:
  - Quality control of blood products in a pharmaceutical or bulk manufacturing setting
  - Batch release or market surveillance of Human Blood, Plasma and Plasma Products in a regulatory authority
  - Assessment of the relevant parts of applications for marketing authorisation within a medicines agency
  - Quality control of blood products in an independent testing laboratory
  - Method development and verification in a regulatory authority
  - Development of methods for control Human Plasma and Plasma Products in a research and development environment

CTP Working Party (Cell Therapy Products)

Terms of reference

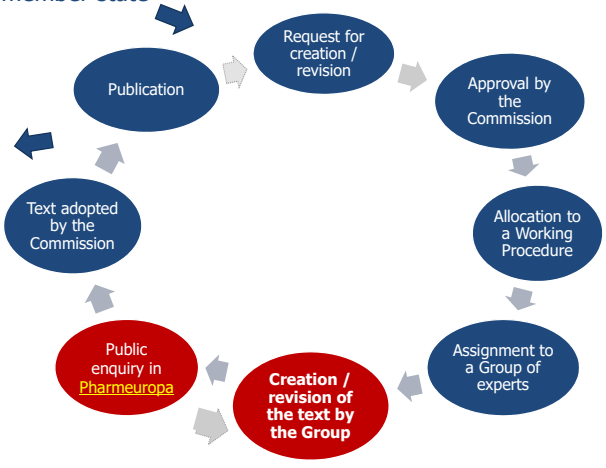
- Revision of general chapter *2.7.29 Nucleated cell count and viability* in order to update it with new automated technologies for cell enumeration (e.g. image cytometry)
- Revision of Ph. Eur. texts (monographs or chapters) where it might be necessary to account for chapter *5.2.12 Raw materials of biological origin for the production of cell-based and gene therapy medicinal products*
- Evaluation of the need to revise the introductory statement of the monograph on parenteral preparations (0520) by adding cell-based preparations to the list of preparations to which the monograph does not necessarily apply, and if so, evaluation of the need for a general Ph. Eur. text dealing with cell-based preparations
- Drafting and revision of other texts in the field of cell therapy products

Profile for experts

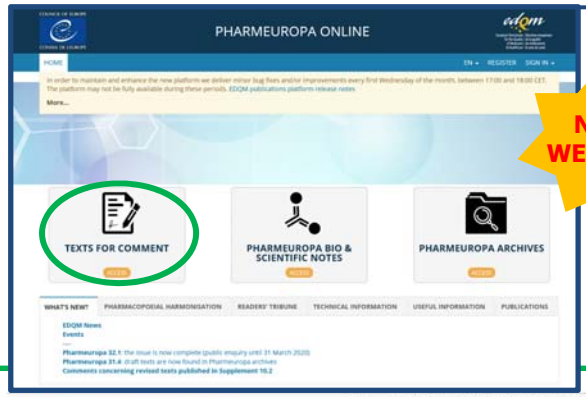
- Current expertise in analytical methods related to the development and quality control of cell therapy products and/or tissue-engineered products and/or to the quality control of tissues for human use
- Several years of experience in one or more of the following fields:
  - Development of cell therapy products and/or tissue-engineered products
  - Quality control of cell therapy products and/or tissue-engineered products in a pharmaceutical manufacturing setting or in a hospital environment and/or microbiological control of tissues and organs used for human transplantation
  - Assessment of applications for marketing authorisation of cell therapy and/or tissue-engineered products
  - Market surveillance of the quality of cell therapy products, tissue-engineered products and/or tissues and organs used for human transplantation in a regulatory authority
  - Pharmaceutical quality control in an independent testing laboratory
  - Development of methods (e.g. microbiological methods) to control cell therapy products and/or tissue-engineered products and/or tissues and organs used for human transplantation in a research and development environment

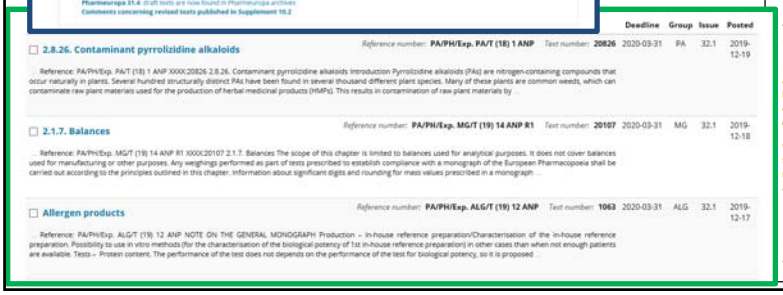
Creation or Revision of a Text

Chair of the Ph. Eur. Commission
Delegation of a member state
Experts, EDQM



How to Comment?!





How to comment

The Texts for comment database contains proposals for new and revised monographs and general texts that are intended for inclusion in the European Pharmacopoeia and are submitted for public comment. In the case of proposals for revision, text to be deleted is crossed out and replacements or additions are underlined.

According to the Guide for the work of the European Pharmacopoeia:

- for manufacturers and other interested parties from member states of the Ph. Eur. Convention:
  - comments on Pharmeuropa texts should be submitted via the national pharmacopoeia authority;
- for manufacturers and other interested parties from non-member states of the Ph. Eur. Convention, and for multinational interested parties:
  - comments on Pharmeuropa texts should be submitted preferably via the national pharmacopoeia authority of the member state where the product is authorised;
  - in cases where comments are submitted to the EDQM Helpdesk (preferably as attachments to the enquiry form), please indicate the member state(s) where the product is authorised;
- for industry associations or other associations:
  - communications should be made via the EDQM secretariat.

The addresses of the national pharmacopoeia authorities and of the EDQM are published on the Pharmeuropa website under the tab *Useful information*.

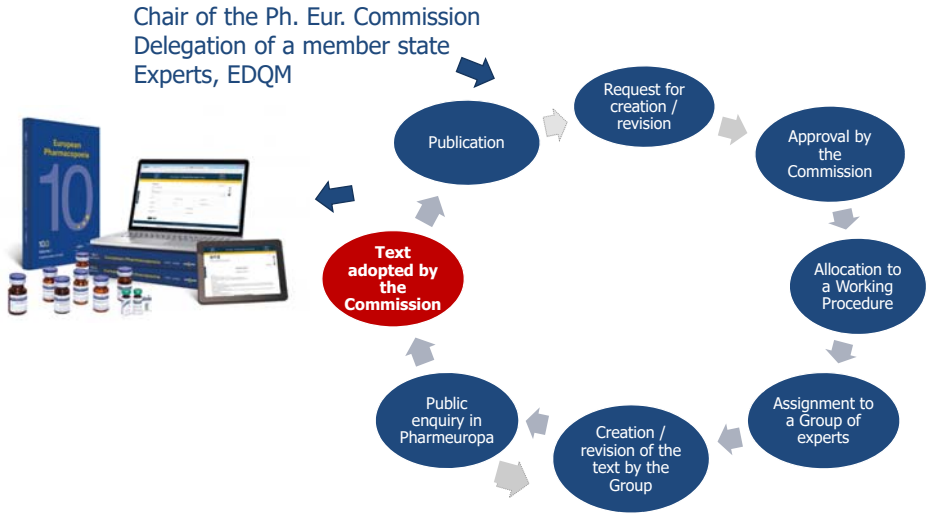
In order to facilitate the processing of comments received by the secretariats of the national authorities and the EDQM, please mention in any correspondence the PA/PH reference number indicated at the beginning of each text. If the comment refers to a specific part of the text, please also mention the corresponding line number. This number can be found in the HTML version of the text on Pharmeuropa online, in the Texts for comment database.

Comments that propose modifications of limits should be supported by analytical data obtained on a significant number of batches. Proposed changes of methodology should be supported by experimental results of a comparative trial of the method published in Pharmeuropa for comment and the proposed alternative.

Only comments sent before the deadline indicated at the top of each text will be considered for the preparation of the final version.

It is stressed that these proposals have not been adopted by the European Pharmacopoeia Commission and must not be regarded as official texts.

Creation or Revision of a Text

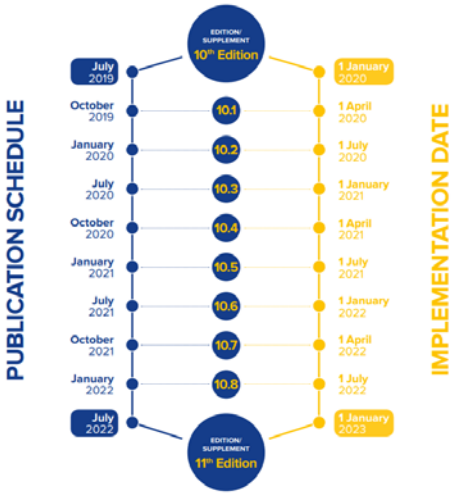


Adoption of the Text (New or Revised)

- ✓ Submission to Ph. Eur. Commission for adoption
- ✓ Publication in the Ph. Eur.
- ✓ Implementation 1 year after adoption (see publication schedule available on website)

Overall timescale: minimum 2 years

Including 5 months for public enquiry and at least 6 months between adoption and publication



After Revision: Why ?

FAQ: "Why did you revise the monograph on…?"

⇨ The answer can be found out via:

- ✓ Briefing notes in Pharmeuropa
- ✓ Collected briefing notes posted on the website for each new edition/supplement (http://pharmeuropa.edqm.eu/home/menupage/English/Useful%20Information/Supplementcomments82.pdf)
- ✓ Knowledge database (monograph history)

No briefing notes for corrections

Text under Elaboration

0 The monograph has been authorised but work has not started yet
1 Work has started (first draft)
2 The monograph has been authorised for publication in Pharmeuropa (see Pharmeuropa number)
3 The monograph has been submitted for adoption to the European Pharmacopoeia Commission
4 The monograph has been adopted
5 The monograph is about to be published, or has been published (see the supplement number indicated and the calendar of the editions below)

Status	Elaboration
graph Number	20632
English Name	Test for bacterial endotoxins using recombinant factor C (2.6.32.)
French Name	Essai des endotoxines bactériennes par la méthode du facteur C recombinant (2.6.32.)
Latin Name	
Pinyin Name	
Chinese Name	
Pharmeuropa	31.1
Published in English Supplement	
Published in French Supplement	
On-going	Elaboration
State of work	4 - DEF
Pharmeuropa	31.1
Description	
Chromatogram	Not available
Additional information	Not available
History	
Interchangeable (ICH_Q4B)	NO
Pharmacopoeial harmonisation	NO
Reference standards	
Practical Information	Test(s) / Brand Name/Information
CEP	

The number of the last issue of Pharmeuropa into which a draft of the monograph was published

The section reflects the status of the text with regard to the work of:
- the Pharmacopoeia Discussion Group (PDG), a joint collaboration between the United States Pharmacopeia, the Japanese Pharmacopeia and the European Pharmacopoeia.
- the International Conference on Harmonisation (ICH) Quality Guideline on Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH (Q4B).

Further information can be found in chapter 5.8 (Pharmacopoeial Harmonisation) of the European Pharmacopoeia.

Text under Revision

On-going revision

Status	In use
Monograph Number	00780
English Name	Oxytocin
French Name	Oxytocine
Latin Name	Oxytocinum
Pinyin Name	
Chinese Name	
Pharmeuropa	21.3
Published in English Supplement	10.0
Published in French Supplement	6.0
On-going	Revision: impurities
State of work	1 - Draft
Pharmeuropa	21.3
Description	
Chromatogram	Not available
Additional information	Not available
History	View history
Interchangeable (ICH_Q4B)	NO
Pharmacopoeial harmonisation	NO

Reference standards

Available since	Cat. No.	Name	Batch No.	Unit Quantity	Price	SDS Product Code
	00700000	Oxytocin CRS	6	41 mg	90 EUR	
	00770000	Oxytocin/Desmopressin validation mixture CRS	5	20 mg	79 EUR	

Practical Information

Test(s)	Brand Name/Information

CEP

Substance Number	Substance	Certificate Holder	Certificate Number	Issue Date	Status	End date	Type
780	Oxytocin	ASPEN OSS B.V. NL 5349 AB Oss	R1-CEP 2000-150-Rev 03	07/04/2016	VALID		Chemistry
780	Oxytocin	HEMMO PHARMACEUTICALS PVT. LTD. IN 400 613 Mumbai	R1-CEP 2008-029-Rev 00	16/10/2015	VALID		Chemistry
780	Oxytocin	SHANGHAI SOHO-YIMING PHARMACEUTICALS CO., LTD. CN 201 707 Chenggu Town	R1-CEP 2011-002-Rev 00	25/08/2017	VALID		Chemistry
780	Oxytocin	SHENZHEN JYMED TECHNOLOGY CO., LTD. CN 518 057 Shenzhen	RO-CEP 2015-376-Rev 00	27/11/2017	VALID		Chemistry
780	Oxytocin	Joint Stock Company "Grindeks" LV 1057 Riga	R1-CEP 2002-200-Rev 02	21/09/2018	VALID		Chemistry

- Aim of the revision
- State of work
- The number of the last issue of Pharmeuropa into which a draft of the monograph was published

History: contains information concerning certain technical modifications to some revised/corrected texts published since Ph. Eur. 5.0. This information complements the modifications indicated by lines in the margin in the supplements and is not necessarily exhaustive.

For guidance purposes: provides additional information to users e.g. column / trade names

If certificate(s) of suitability have been granted for the substance in question, their list is shown. This is an excerpt from the online List of CEP.

Ph. Eur. Monograph Elaboration/Revision: to Summarise

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

Call for interest

Participation of interested parties

Responding to Pharmeuropa enquiry is a must

OMCLs, assessors, companies

1. Request for monograph elaboration/ revision
2. Endorsement by the Ph. Eur. Commission
3. Assignment to a Group of Experts
4. Creation/ revision of the text by the Group
5. Public enquiry in Pharmeuropa
6. Text adopted by the Ph. Eur. Commission
7. Publication in the Ph. Eur.

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

- **Review of data package**
- **Draft monograph development**
- **Laboratory study/ collaborative testing – <u>all</u> preparations** (protocol preparation; method verification; data analysis)

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

Once a monograph is published and implemented, MAH's of registered products have to assure their product meets the requirements of the monograph

Pharmacopoeia Liaison

- ✓ EDQM wishes to have a pharmacopoeia liaison contact for each major manufacturer/user
- ✓ Channel information and requests from manufacturer to EDQM
- ✓ Reception point for contact by EDQM
- ✓ Benefits for both sides

Thank you for your attention

Stay connected with the EDQM

EDQM Newsletter: **https://go.edqm.eu/Newsletter**
LinkedIn: **https://www.linkedin.com/company/edqm/**
Twitter: **@edqm_news**
Facebook: **@EDQMCouncilofEurope**