How to participate in the Elaboration and Revision of Monographs

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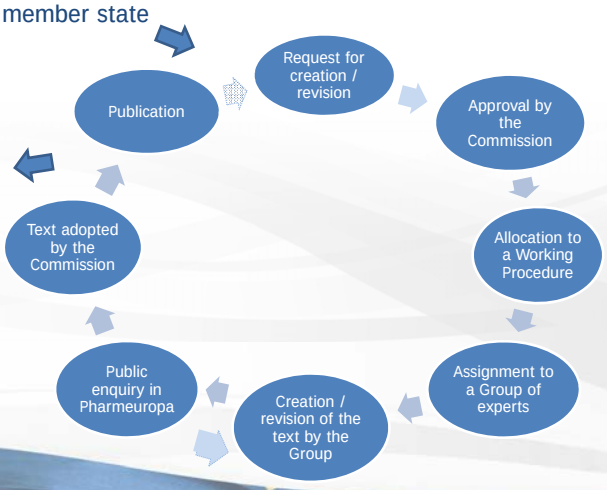
Basis for monographs

- ✓ 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 regulatory authorities at Pharmeuropa stage
- ✓ Policy for monograph development is given in:
  Technical Guide for the Elaboration of Monographs
  - just revised (7th Edition – 2015) (available on the EDQM website)

Creation or revision of a text

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



Stages in elaboration or revision (1)

<u>All procedures</u> :

- ✓ Addition to work programme by the Ph. Eur. Commission: public announcement
- ✓ Interested parties can **(and should!)** express an interest
- ✓ Elaboration, experimental verification of the draft
- ✓ Publication in Pharmeuropa
- ✓ Study of comments by group of experts/working party

Stages in elaboration or revision (2)

- ✓ Submission to 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

Commission Sessions		Edition Supplement	Publication schedule	Implementation date
Session No.	Date			
153	November 2015	9th Edition	July 2016	1 January 2017
154	March 2016	9.1	October 2016	1 April 2017
155	June 2016	9.2	January 2017	1 July 2017
156	November 2016	9.3	July 2017	1 January 2018
157	March 2017	9.4	October 2017	1 April 2018
158	June 2017	9.5	January 2018	1 July 2018
159	November 2017	9.6	July 2018	1 January 2019
160	March 2018	9.7	October 2018	1 April 2019
161	June 2018	9.8	January 2019	1 July 2019
162	November 2018	10th Edition	July 2019	1 January 2020

Work programme (1)

Based on proposals from:

- ✓ National delegations
- ✓ Groups of experts
- ✓ EDQM

↳ Manufacturers can submit proposals via one of the above

Work programme (2)

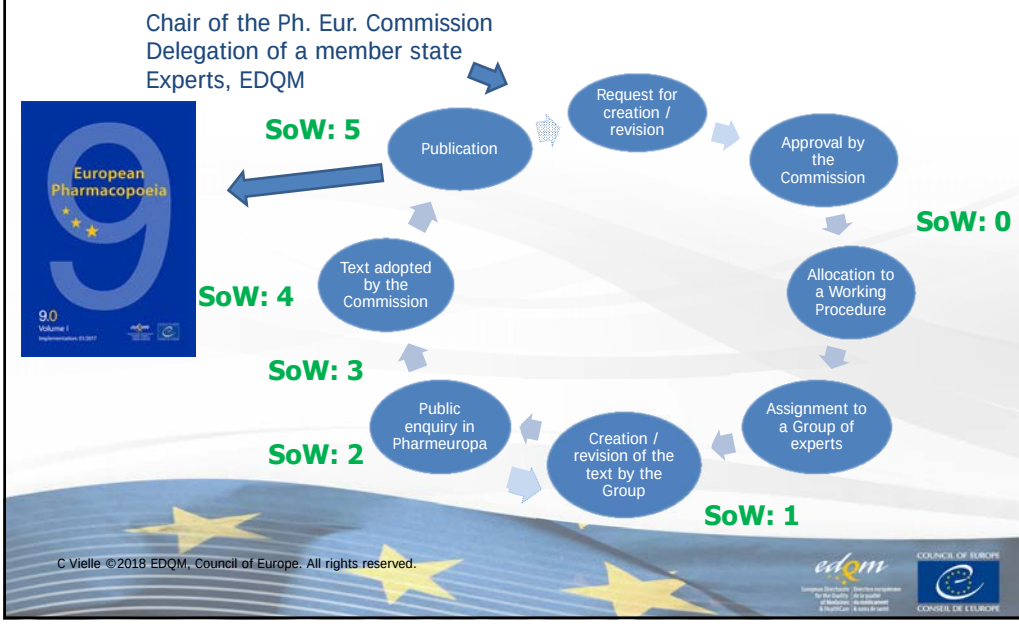
- ✓ Additions announced on:
  - EDQM website (http://www.edqm.eu/en/european-pharmacopoeia-work-programme-607.html)
  - Pharmeuropa-on-line (http://pharmeuropa.edqm.eu/home/) under "*useful information*"
- ✓ Status (steps 1-5) displayed on the website

Work status: see Knowledge database

Key to information on State of Work (SoW):

0 = on the work programme, no first draft
1 = first draft (new or revised monograph)
2 = published (or in press) in Pharmeuropa
3 = submitted to the Commission
4 = adopted by the Commission, ready for publication
5 = published in the Ph. Eur.

Creation or revision of a text



Monographs: how?

✓ **Procedure 1** (Group of experts):

Multi-source products and monograph revisions

On request, data are handled confidentially by EDQM

✓ **Procedure 4** (Group of regulators):

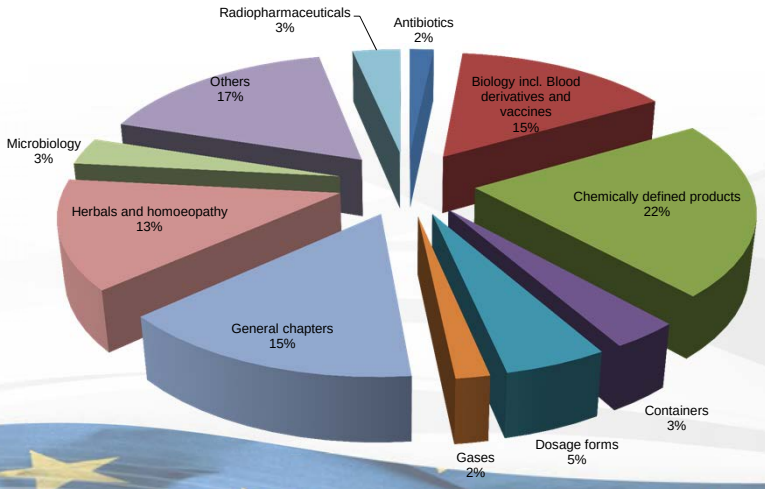
Single-source products, direct co-operation with innovator

Data are handled confidentially by EDQM

Groups of experts and working parties

- ✓ Approx. 800 experts from the Ph. Eur. members states and observers
- ✓ he 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

59 *active* Groups of experts and working parties



Monographs: how?

✓ **Procedure 1**

Multi-source products and monograph revisions

On request, data are handled confidentially by EDQM

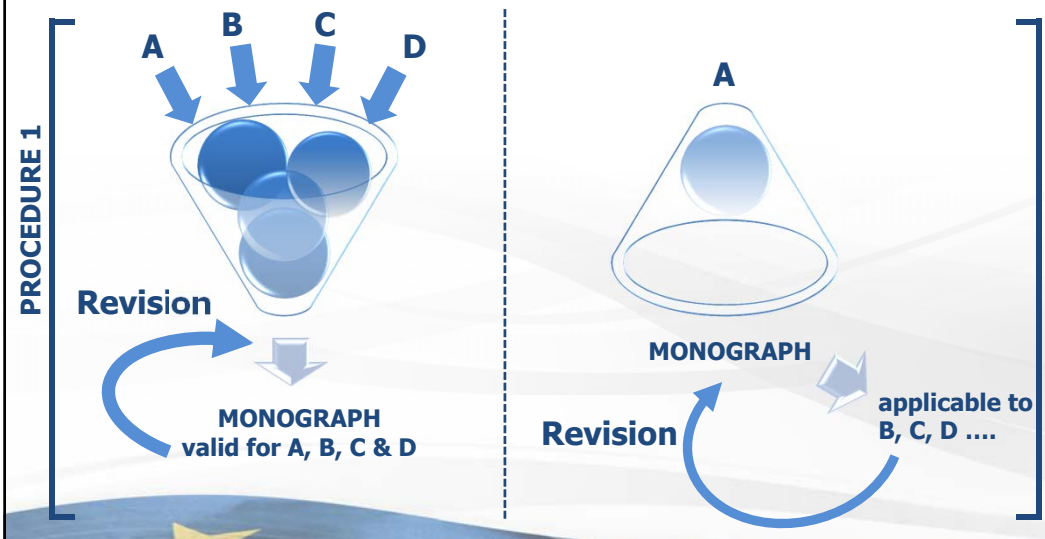
✓ **Procedure 4**

Single-source products, direct co-operation with innovator

Data are handled confidentially by EDQM

Group of solely composed of regulators

Monographs: how?



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

P4 procedure: steps (1)

1. Ph. Eur. Commission: addition to work programme
2. Manufacturer: submits data package/samples
3. Rapporteur from expert group P4 and EDQM staff member prepare first draft
4. Discussion with manufacturer
5. Experimental verification (EDQM/OMCL(s))
6. Report and questions to manufacturer
7. Rapporteur/EDQM: draft for Pharmeuropa

P4 procedure: steps (2)

8. Group P4 approves draft for public consultation
9. Comments collected via National Pharmacopoeia Authorities
10. EDQM compiles comments
11. Rapporteur and EDQM examine comments, prepare revised draft, after approval by group P4
12. Presented for adoption (or republication)

https://www.edqm.eu/medias/fichiers/new_procedure_4_workflow_elaboration_of_a_monograph_updated_sept_2013.pdf

New monographs

Addition to programme depends on:

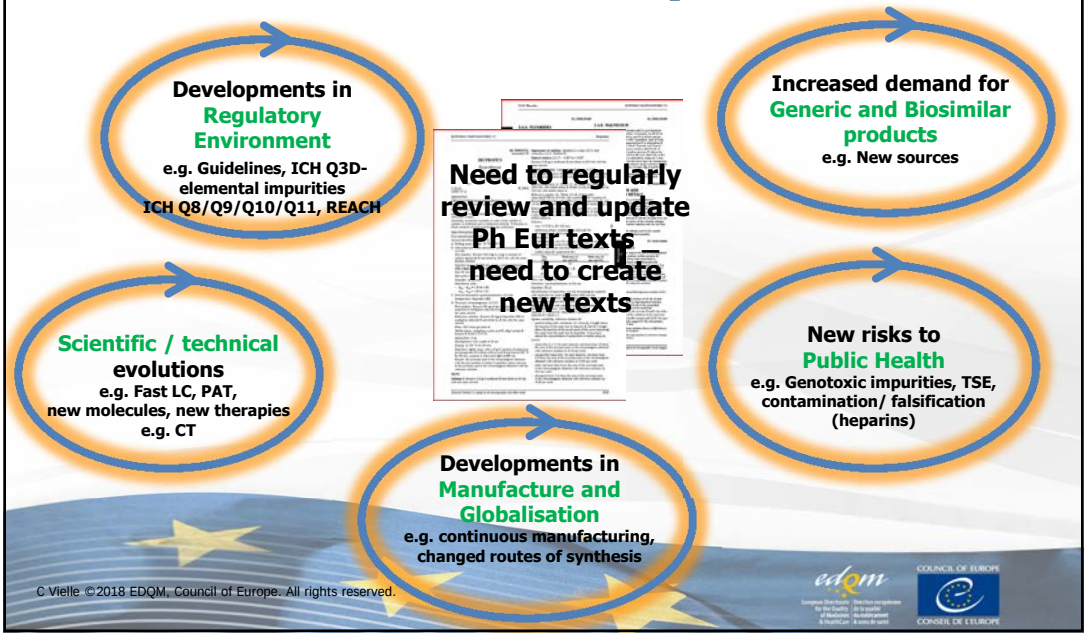
- ✓ Therapeutic importance
- ✓ Extent of use
- ✓ Number of countries in which product is approved

Proposing a new monograph

Contact your National Pharmacopoeia Authority (in Europe) or EDQM (outside Europe)

- ✓ **Initial data**: countries 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

Revision: why? (2)



Revision: why? (2)

- ✓ New sources have new impurity profiles
- ✓ New quality issues arise
- ✓ Analytical methods change / development: more convenient methods, more powerful/sensitive methods, more reliable methods become available
- ✓ International harmonisation (PDG, ICH, VICH)

How can manufacturers request revision?

- ✓ Europe: via National Pharmacopoeia Authority
  (address list on EDQM website and in Pharmeuropa)
- ✓ Outside Europe: contact EDQM which will refer the matter to a group of experts or to the Commission

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

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

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 you see Pharmeuropa for revision proposals
  - Provide samples, test draft proposal

After revision: why ?

FAQ: “Why did you revise the monograph on…?”

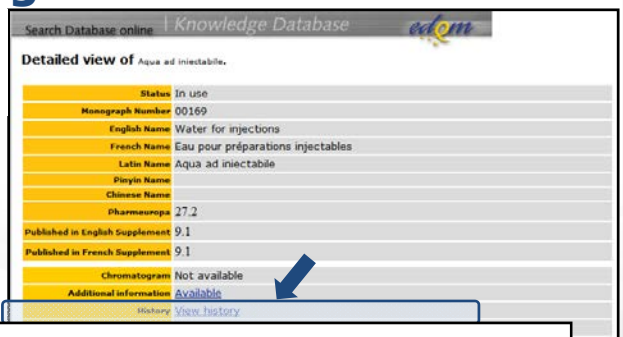
The answer can be find out via:

- ✓ 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

Knowledge database

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.



SUPPLEMENT 9.1
Production: revision to include purification processes equivalent to distillation (such as reverse osmosis coupled with appropriate techniques) for producing water for injections (WFI), in addition to distillation; use of non-distillation technologies for the production of WFI requires that notice be given to the supervisory authority of the manufacturer before implementation.
A requirement for regular monitoring of total organic carbon has been added to further emphasise the specific test controls required in the Production section.
The revision of the monograph is supported by the evidence provided in the document 'Reverse osmosis in Ph. Eur. monograph *Water for injections (0169)*', published in the Knowledge database under 'Additional information'.

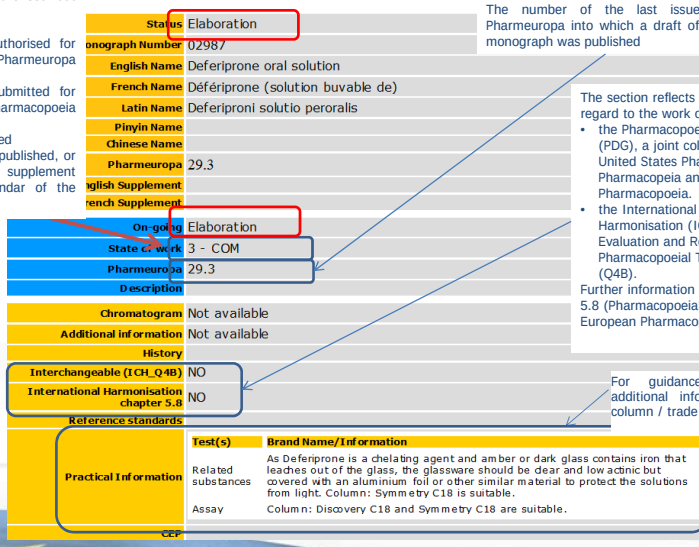
SUPPLEMENT 7.3: corrected

SUPPLEMENT 6.3
Microbiological monitoring: the 5-day incubation time has been replaced by a more practical requirement of not less than 5 days; addition of criteria for growth promotion of the R2A medium used for microbiological monitoring; such criteria are routinely included for media in the Ph. Eur. to ensure suitability. Requirements similar to those stated in the harmonised chapter (2.6.12 and 2.6.13) are mentioned.
Conductivity: this section has already been revised for harmonisation with the USP draft; in view of changes to the USP, the Ph. Eur. monograph is revised again; the changes are also intended to clarify the text, which has been the subject of numerous enquiries from users; a tolerance of ± 2 °C for temperature measurement has also been added for harmonisation with the USP.
Heavy metals: (Water for injections in bulk): in view of the conductivity requirements, the test for heavy metals is now superfluous (see G. Torres, A. Arsitio and C. Genovesi, Comparison of EP 'Heavy metals' test with USP 'Conductivity' test, Pharmaceutical Technology, January 2005, 80-81).
Oxidisable substances: (Sterilised water for injections): the present requirement is too strict for containers with a volume less than 50 ml; although these containers may comply at release, containers that have been found to be suitable for pharmaceutical use are frequently non-compliant by the end of the shelf-life; a relaxed limit is included for these containers.
Ammonium (Sterilised water for injections): for the same reasons as stated for the test for Oxidisable substances, a relaxed limit (0.6 ppm) is included for containers with a volume less than 50 ml.
Heavy metals: (Sterilised water for injections): the test for Water for injections in bulk is deleted, and since there is no possibility of contamination during the preparation of sterilised water for injections from water for injections in bulk, the test is also deleted at this stage.

EDITION 5.0: corrected

Monograph 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)



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

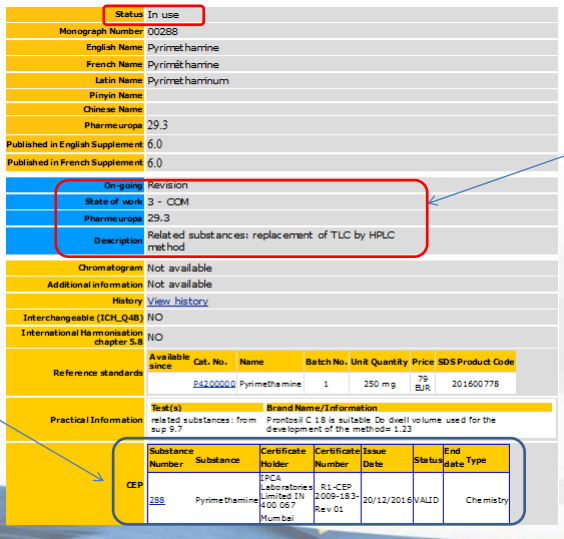
The section reflects the status of the text with regard to the work of:
- the Pharmacopoeia Discussion Group (PDG), a joint collaboration between the United States Pharmacopeia, the Japanese Pharmacopeia and the European Pharmacopoeia.
- the International Conference on Harmonisation (ICH) Quality Guideline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

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

Monograph under revision

On-going revision



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

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.

How to participate ?

- ✓ Participation depends on the procedure used
- ✓ For all procedures ⇨ provide samples for testing and participate as early as possible

  (i.e. before the text is published in Pharmeuropa)
- ✓ Only information on APIs and excipients used in already approved products licensed in Europe is considered

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!