

# How to participate in the Elaboration and Revision of Monographs

Cathie VIELLE

Head of European Pharmacopoeia Department  
EDQM / CoE

C. Vielle ©2018 EDQM, Council of Europe. All rights reserved.



## 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** (7<sup>th</sup> Edition – 2015) (available on the EDQM website)

C. Vielle ©2018 EDQM, Council of Europe. All rights reserved.



## Creation or revision of a text

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



C. Vielle ©2018 EDQM, Council of Europe. All rights reserved.



## Stages in elaboration or revision (1)

All procedures :

- ✓ 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

C. Vielle ©2018 EDQM, Council of Europe. All rights reserved.



## 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	9 <sup>th</sup> 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	10 <sup>th</sup> Edition	July 2019	1 January 2020

C.Vielle ©2018 EDQM, Council of Europe. All rights reserved.



## Work programme (1)

Based on proposals from:

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

↳ Manufacturers can submit proposals via one of the above

C.Vielle ©2018 EDQM, Council of Europe. All rights reserved.



## 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**

C.Vielle ©2018 EDQM, Council of Europe. All rights reserved.



## 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

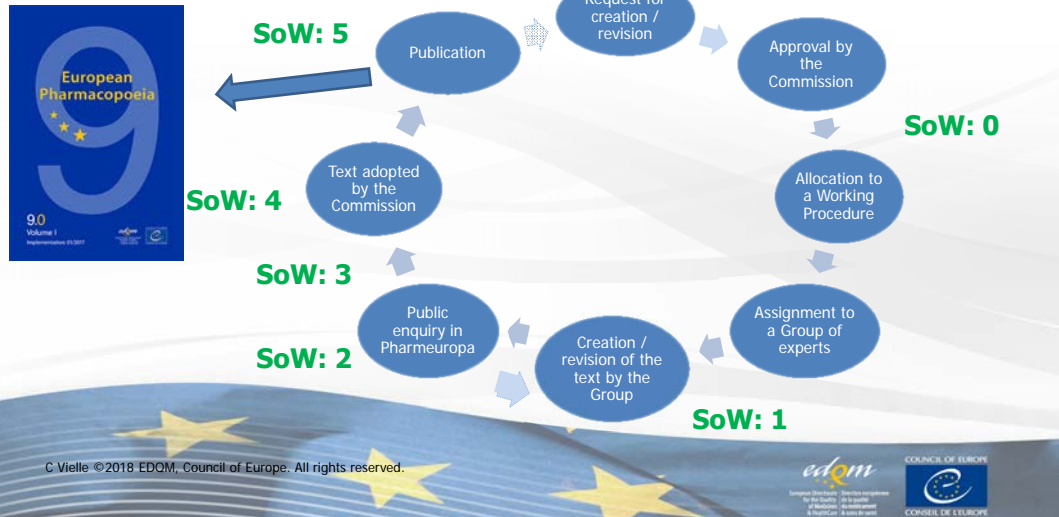
**5** = **published** in the **Ph. Eur.**

C.Vielle ©2018 EDQM, Council of Europe. All rights reserved.



## Creation or revision of a text

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



## 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

C. Vielle ©2018 EDQM, Council of Europe. All rights reserved.

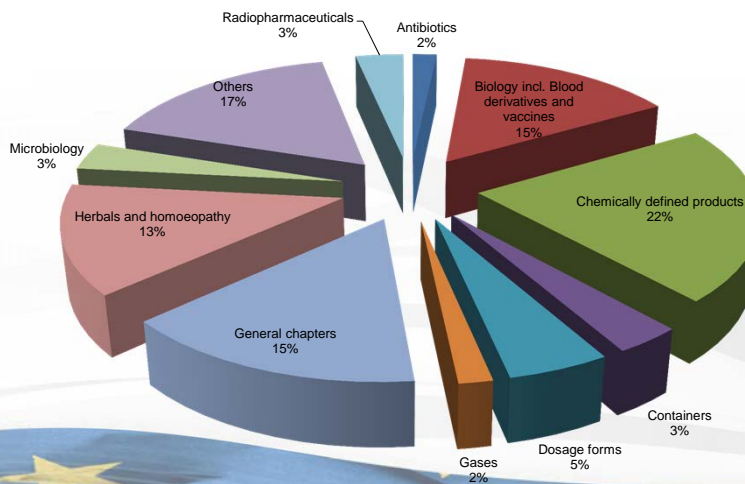
## Groups of experts and working parties

- ✓ **Approx. 800** experts 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>

C. Vielle ©2018 EDQM, Council of Europe. All rights reserved.



## 59 active Groups of experts and working parties



C. Vielle ©2018 EDQM, Council of Europe. All rights reserved.



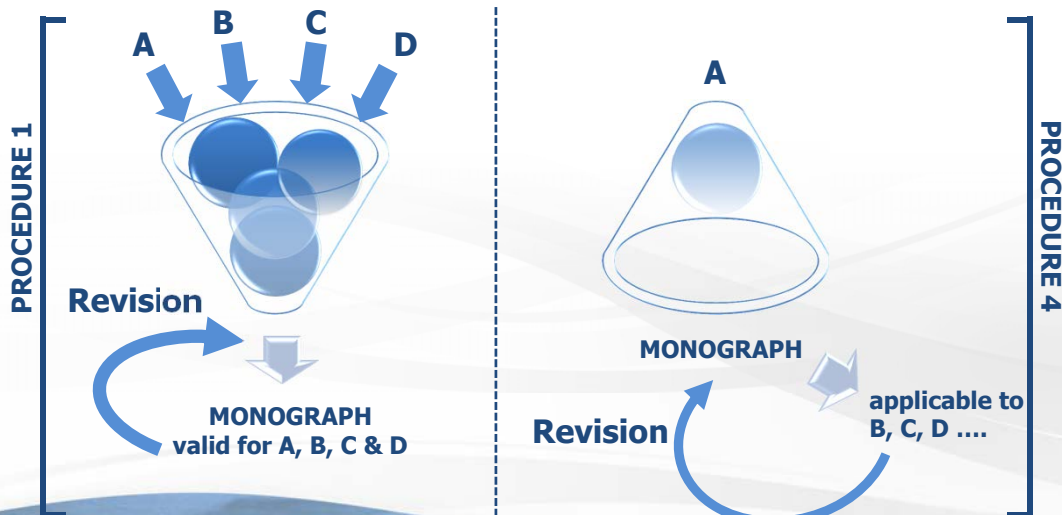
# Monographs: how?

- ✓ **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

C.Vielle ©2018 EDQM, Council of Europe. All rights reserved.



# Monographs: how?



C.Vielle ©2018 EDQM, Council of Europe. All rights reserved.



## 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  $\geq 2$  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

C Vielle ©2018 EDQM, Council of Europe. All rights reserved.



## 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**

C Vielle ©2018 EDQM, Council of Europe. All rights reserved.





## 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](https://www.edqm.eu/medias/fichiers/new_procedure_4_workflow_elaboration_of_a_monograph_updated_sept_2013.pdf)

C.Vielle ©2018 EDQM, Council of Europe. All rights reserved.



## New monographs

Addition to programme depends on:

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

C.Vielle ©2018 EDQM, Council of Europe. All rights reserved.



# 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

© Vielle ©2018 EDQM, Council of Europe. All rights reserved.

edqm

COUNCIL OF EUROPE  
CONSEIL DE L'EUROPE

## Revision: why? (2)

### Developments in Regulatory Environment

e.g. Guidelines, ICH Q3D-  
elemental impurities  
ICH Q8/Q9/Q10/Q11, REACH

### Increased demand for Generic and Biosimilar products

e.g. New sources

**Need to regularly  
review and update  
Ph Eur texts  
need to create  
new texts**

### Scientific / technical evolutions

e.g. Fast LC, PAT,  
new molecules, new therapies  
e.g. CT

### New risks to Public Health

e.g. Genotoxic impurities, TSE,  
contamination/ falsification  
(heparins)

### Developments in Manufacture and Globalisation

e.g. continuous manufacturing,  
changed routes of synthesis

© Vielle ©2018 EDQM, Council of Europe. All rights reserved.

edqm

COUNCIL OF EUROPE  
CONSEIL DE L'EUROPE

## 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)

C.Vielle ©2018 EDQM, Council of Europe. All rights reserved.

edqm

European Directorate for the Quality of Medicines  
et des Produits  
et des Produits  
et des Produits

COUNCIL OF EUROPE  
CONSEIL DE L'EUROPE

## 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**

C.Vielle ©2018 EDQM, Council of Europe. All rights reserved.

edqm

European Directorate for the Quality of Medicines  
et des Produits  
et des Produits  
et des Produits

COUNCIL OF EUROPE  
CONSEIL DE L'EUROPE

## 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

C.Vielle ©2018 EDQM, Council of Europe. All rights reserved.

edqm  
European Directorate for the Quality of Medicines  
et des Produits de Santé  
et des Produits de Santé

COUNCIL OF EUROPE  
CONSEIL DE L'EUROPE

## 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

C.Vielle ©2018 EDQM, Council of Europe. All rights reserved.

edqm  
European Directorate for the Quality of Medicines  
et des Produits de Santé  
et des Produits de Santé

COUNCIL OF EUROPE  
CONSEIL DE L'EUROPE

# 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

C. Vielle ©2018 EDQM, Council of Europe. All rights reserved.

edqm  
European Directorate  
for the Quality  
of Medicines  
& HealthCare

CONSEIL DE L'EUROPE  
COUNCIL OF EUROPE

## 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.

Search Database online | Knowledge Database

Detailed view of Aqua ad inieciabile.

Status	In use
Monograph Number	00169
English Name	Water for injections
French Name	Eau pour préparations injectables
Latin Name	Aqua ad inieciabile
Pinyin Name	
Chinese Name	
Pharmeuropa	27.2
Published in English Supplement	9.1
Published in French Supplement	9.1
Chromatogram	Not available
Additional information	Available
History	View history

### 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  $\pm 2^\circ\text{C}$  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. Arsitto 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 (0.5 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 the stage.

**EDITION 5.0:** corrected

C. Vielle ©2018 EDQM, Council of Europe. All rights reserved.

edqm  
European Directorate  
for the Quality  
of Medicines  
& HealthCare

CONSEIL DE L'EUROPE  
COUNCIL OF EUROPE

## 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 Pharmedropa (see Pharmedropa 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	The number of the last issue of Pharmedropa into which a draft of the monograph was published						
Monograph Number	02987							
English Name	Deferiprone oral solution							
French Name	Défériprone (solution buvable de)							
Latin Name	Deferiproni solutio peroralis							
Pinyin Name								
Chinese Name								
Pharmedropa	29.3							
Published in English Supplement								
Published in French Supplement								
On-going	Elaboration							
State of work	3 - COM							
Pharmedropa	29.3							
Description								
Chromatogram	Not available							
Additional information	Not available							
History								
Interchangeable (ICH_Q4B)	NO							
International Harmonisation chapter 5.8	NO							
Reference standards								
Practical Information	<table border="1"> <thead> <tr> <th>Test(s)</th> <th>Brand Name/Information</th> </tr> </thead> <tbody> <tr> <td>Related substances</td> <td>As Deferiprone is a chelating agent and amber or dark glass contains iron that leaches out of the glass, the glassware should be clear and low acidic but covered with an aluminium foil or other similar material to protect the solutions from light. Column: Symmetry C18 is suitable.</td> </tr> <tr> <td>Assay</td> <td>Column: Discovery C18 and Symmetry C18 are suitable.</td> </tr> </tbody> </table>	Test(s)	Brand Name/Information	Related substances	As Deferiprone is a chelating agent and amber or dark glass contains iron that leaches out of the glass, the glassware should be clear and low acidic but covered with an aluminium foil or other similar material to protect the solutions from light. Column: Symmetry C18 is suitable.	Assay	Column: Discovery C18 and Symmetry C18 are suitable.	
Test(s)	Brand Name/Information							
Related substances	As Deferiprone is a chelating agent and amber or dark glass contains iron that leaches out of the glass, the glassware should be clear and low acidic but covered with an aluminium foil or other similar material to protect the solutions from light. Column: Symmetry C18 is suitable.							
Assay	Column: Discovery C18 and Symmetry C18 are suitable.							

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 Pharmacopoeia, the Japanese Pharmacopoeia 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 (Pharmacopoeia Harmonisation) of the European Pharmacopoeia.

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

C. Vielle ©2018 EDQM, Council of Europe. All rights reserved.



## Monograph under revision

On-going revision

Status	In use	- Aim of the revision - State of work - The number of the last issue of Pharmedropa into which a draft of the monograph was published																
Monograph Number	00288																	
English Name	Pyrimethamine																	
French Name	Pyriméthamine																	
Latin Name	Pyrimethaminum																	
Pinyin Name																		
Chinese Name																		
Pharmedropa	29.3																	
Published in English Supplement	6.0																	
Published in French Supplement	6.0																	
On-going	Revision																	
State of work	3 - COM																	
Pharmedropa	29.3																	
Description	Related substances: replacement of TLC by HPLC method																	
Chromatogram	Not available																	
Additional information	Not available																	
History	<a href="#">View history</a>																	
Interchangeable (ICH_Q4B)	NO																	
International Harmonisation chapter 5.8	NO																	
Reference standards	<table border="1"> <thead> <tr> <th>Available since</th> <th>Cat. No.</th> <th>Name</th> <th>Batch No.</th> <th>Unit</th> <th>Quantity</th> <th>Price</th> <th>SDS Product Code</th> </tr> </thead> <tbody> <tr> <td>P42.00000</td> <td></td> <td>Pyrimethamine</td> <td></td> <td>1</td> <td>250 mg</td> <td>79 EUR</td> <td>201600778</td> </tr> </tbody> </table>	Available since	Cat. No.	Name	Batch No.	Unit	Quantity	Price	SDS Product Code	P42.00000		Pyrimethamine		1	250 mg	79 EUR	201600778	
Available since	Cat. No.	Name	Batch No.	Unit	Quantity	Price	SDS Product Code											
P42.00000		Pyrimethamine		1	250 mg	79 EUR	201600778											
Practical Information	<table border="1"> <thead> <tr> <th>Substance Number</th> <th>Substance</th> <th>Certificate Holder</th> <th>Certificate Number</th> <th>Issue Date</th> <th>Status</th> <th>End date</th> <th>Type</th> </tr> </thead> <tbody> <tr> <td>CEP</td> <td>Pyrimethamine</td> <td>EPCA Laboratoires Limités Pvt. Ltd. 000 067 Mumbai</td> <td>R1-CEP 0009-183-Rev 01</td> <td>20/12/2016</td> <td>VALID</td> <td></td> <td>Chemistry</td> </tr> </tbody> </table>	Substance Number	Substance	Certificate Holder	Certificate Number	Issue Date	Status	End date	Type	CEP	Pyrimethamine	EPCA Laboratoires Limités Pvt. Ltd. 000 067 Mumbai	R1-CEP 0009-183-Rev 01	20/12/2016	VALID		Chemistry	
Substance Number	Substance	Certificate Holder	Certificate Number	Issue Date	Status	End date	Type											
CEP	Pyrimethamine	EPCA Laboratoires Limités Pvt. Ltd. 000 067 Mumbai	R1-CEP 0009-183-Rev 01	20/12/2016	VALID		Chemistry											

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.

C. Vielle ©2018 EDQM, Council of Europe. All rights reserved.



## 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

C.Vielle ©2018 EDQM, Council of Europe. All rights reserved.

edqm  
European Directorate for the Quality of Medicines  
et des Produits de Santé  
& Biotechnologie

COUNCIL OF EUROPE  
CONSEIL DE L'EUROPE

## 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**

C.Vielle ©2018 EDQM, Council of Europe. All rights reserved.

edqm  
European Directorate for the Quality of Medicines  
et des Produits de Santé  
& Biotechnologie

COUNCIL OF EUROPE  
CONSEIL DE L'EUROPE

**Thank you for  
your  
attention!**



C Vielle ©2018 EDQM, Council of Europe. All rights reserved.

*edqm*

Union des Brevets  
de la Courbe  
de la Qualité  
de la Marque  
de la Marque  
de la Marque

CONSEIL DE L'EUROPE



CONSEIL DE L'EUROPE