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

EDQM in International Harmonisation Initiatives

2019 Training Session
"The European Pharmacopoeia"
Mrs Cathie Vielle
EDQM Head of European Pharmacopoeia Department

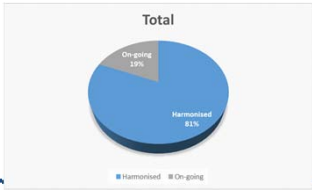
10 – 11 September 2019, Iselin, New Jersey, USA

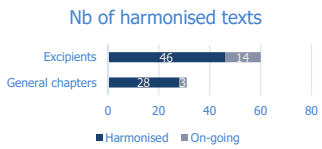
Update on Recent PDG Developments

PDG meeting

Pro memoria, PDG reforms approved in 2017 :

- Restructuring meeting format to engage more at the technical level and introduce more direct exchange between the experts in the regions
- Streamlining of working procedure, reducing complexity => elimination of two stages to increase efficiency and improve focus.
- Strategic review of harmonization areas and individual work items currently in progress and for future consideration still ongoing.
- Cleaning of the work programme => identification of items to be considered outside of PDG (e.g. bilateral discussion)





Work programme => the review continues

Prioritisation scheme for excipient monographs and general chapters:

- Strategic review conducted on 10 excipient monographs and 5 general chapter
- Extension to remaining general chapters
- Need for further discussion for excipient monographs

Transparency => another PDG priority

- Towards other Pharmacopoeias:
  - Discussion on how information on progress made by the PDG should be shared amongst the PDG member pharmacopoeias and other pharmacopoeias participating in the International Meeting of World Pharmacopoeias (IMWP) => to be continued at the next face-to-face meeting which will be hosted by the JP on 1-2 October 2019 in Tokyo (Japan)
- Towards other harmonisation initiatives:
  - New Maintenance Procedure on the ICH Q4B Annexes Adopted by the ICH Assembly
- Towards users:
  - PDG harmonization policy to be further updated to provide additional clarity to users.

How can you know if a monograph is harmonised ?

Indication of harmonisation:

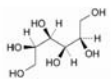
(1) This monograph has undergone pharmacopoeial harmonisation. See chapter 5.8. *Pharmacopoeial harmonisation*

The non-harmonised attributes/provisions are placed between black diamonds (♦♦)

The local requirements are placed between white diamonds (◇◇)

MANNITOL (1)

Mannitolum



$C_6H_{14}O_6$ [69-65-8] M_r 182.2

DEFINITION

D-Mannitol.

Content: 97.0 per cent to 102.0 per cent (dried substance).

♦CHARACTERS

Appearance: white or almost white crystals or powder.

Solubility: freely soluble in water, practically insoluble in ethanol (96 per cent).

It shows polymorphism (5.9).♦

IDENTIFICATION

First identification: C.

◊*Second identification*: A, B, D.

A. Specific optical rotation (2.2.7): + 23 to + 25 (dried substance).

Dissolve 2.00 g of the substance to be examined and 2.6 g of *disodium tetraborate R* in about 20 mL of *water R* at 30 °C; shake continuously for 15-30 min without further heating. Dilute the resulting clear solution to 25.0 mL with *water R*.

B. Melting point (see Tests).◊

C. Infrared absorption spectrophotometry (2.2.24).

Comparison: *mannitol CRS*.

Ph. Eur. Chapter 5.8 Pharmacopoeial harmonisation

MANNITOL (0559)

Harmonised attributes

Attribute	Ph. Eur.	JP	USP
Definition	+	+	+
Identification by IR	+	+	+
Appearance of solution	+	+	+
Conductivity	+	+	+
Melting point	+	+	+
Reducing sugars	+	+	+
Related substances	+	+	+
Nickel	+	+	+
Loss on drying	+	+	+
Microbial contamination	+	-	+
Bacterial endotoxins	+	-	+
Assay	+	+	+
Labelling	+	-	+

LEGEND
+: will adopt and implement
–: will not stipulate

Non-harmonised attributes

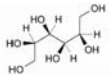
Characters/Description, Heavy metals, Container and storage/Packaging and storage

Local requirements

Second identification (specific optical rotation, melting point, TLC) (Ph. Eur.), Absence of *Salmonella* (Ph. Eur.)

MANNITOL (1)

Mannitolum



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B. Melting point (see Tests).◊

C. Infrared absorption spectrophotometry (2.2.24).

Comparison: *mannitol CRS*.

(sign-off date: 6 June 2012)

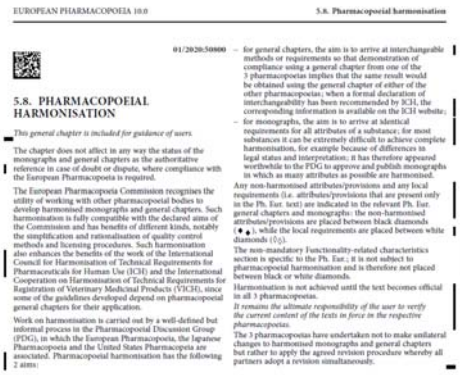
Chapter 5.8 : will change in 10th Edition

10th Edition:

NOTE ON THE GENERAL CHAPTER

With a view to increasing transparency on the texts harmonised by the PDG, it is proposed to stop mentioning the harmonised and non-harmonised items, as well as the local requirements, in this chapter; conversely sign-off coversheets signed off by the PDG will be made available on the EDQM website. This chapter has been revised accordingly.

- Chapter 5.8 will no longer give details on harmonisation of individual monographs, PDG process explained in general
- List of harmonised monographs will be published separately
- It remains the ultimate responsibility of the user to verify the current content of the texts in force in the respective pharmacopoeias



EUROPEAN PHARMACOPOEIA 10.0 — 5.8. Pharmacopoeial harmonisation

01/2020:50800

5.8. PHARMACOPOEIAL HARMONISATION

This general chapter is included for guidance of users.

The chapter does not affect in any way the status of the monographs and general chapters as the authoritative reference in case of doubt or dispute, where compliance with the European Pharmacopoeia is required.

The European Pharmacopoeia Commission recognises the utility of working with other pharmacopoeial bodies to develop harmonised monographs and general chapters. Such harmonisation is fully compatible with the declared aims of the Commission and has benefits of different kinds, notably the simplification and rationalisation of quality control methods and licensing procedures. Such harmonisation also enhances the benefits of the work of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH), since some of the guidelines developed depend on pharmacopoeial general chapters for their application.

Work on harmonisation is carried out by a well-defined but informal process in the Pharmacopoeial Discussion Group (PDG), in which the European Pharmacopoeia, the Japanese Pharmacopoeia and the United States Pharmacopeia are associated. Pharmacopoeial harmonisation has the following 2 aims:

– for general chapters, the aim is to arrive at interchangeable methods or requirements so that demonstration of compliance using a general chapter from one of the 3 pharmacopoeias implies that the same result would be obtained using the general chapter of either of the other pharmacopoeias; when a formal declaration of interchangeability has been recommended by ICH, the corresponding information is available on the ICH website;

– for monographs, the aim is to arrive at identical requirements for all attributes of a substance; for most substances it can be extremely difficult to achieve complete harmonisation, for example because of differences in legal status and interpretation; it has therefore appeared worthwhile to the PDG to approve and publish monographs in which as many attributes as possible are harmonised.

Any non-harmonised attributes/provisions and any local requirements (i.e. attributes/provisions that are present only in the Ph. Eur. text) are indicated in the relevant Ph. Eur. general chapters and monographs: the non-harmonised attributes/provisions are placed between black diamonds (♦ ♦), while the local requirements are placed between white diamonds (◊◊).

The non-mandatory Functionality-related characteristics section is specific to the Ph. Eur.; it is not subject to pharmacopoeial harmonisation and is therefore not placed between black or white diamonds.

Harmonisation is not achieved until the text becomes official in all 3 pharmacopoeias.

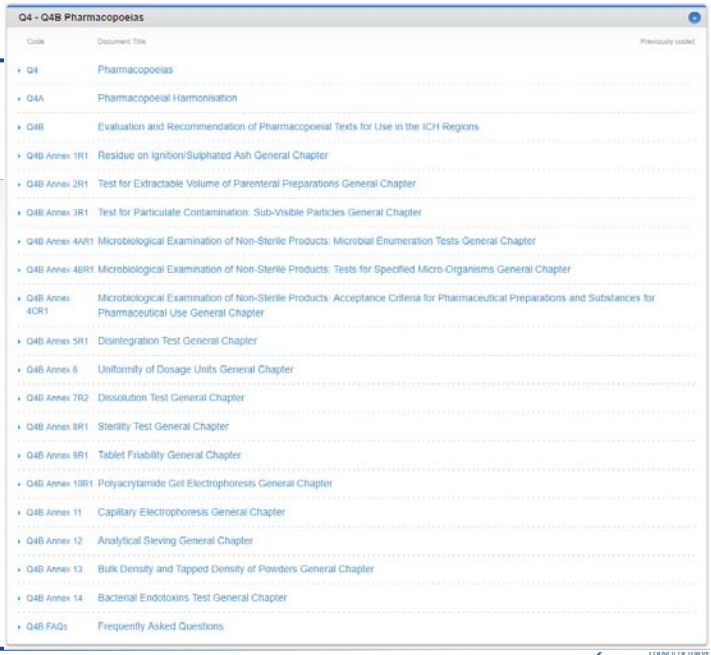
It remains the ultimate responsibility of the user to verify the current content of the texts in force in the respective pharmacopoeias.

The 3 pharmacopoeias have undertaken not to make unilateral changes to harmonised monographs and general chapters but rather to apply the agreed revision procedure whereby all partners adopt a revision simultaneously.

5. General texts

New Maintenance Procedure on the ICH Q4B Annexes Adopted by the ICH Assembly

ICH website:



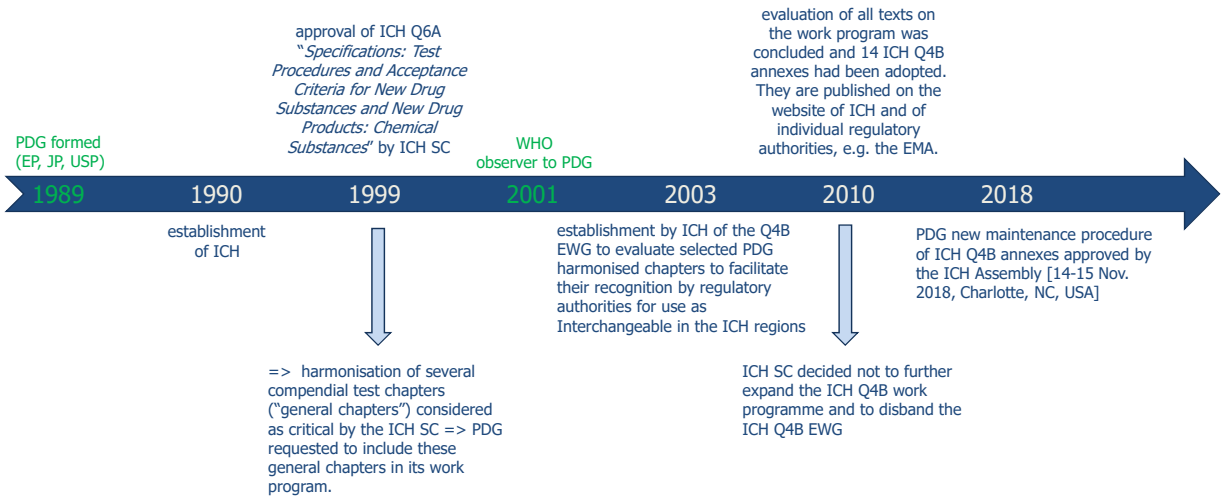
Q4 - Q4B Pharmacopoeias

Code	Document Title	Previously coded
Q4	Pharmacopoeias	
Q4A	Pharmacopoeial Harmonisation	
Q4B	Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions	
Q4B Annex 1R1	Residue on Ignition/Sulphated Ash General Chapter	
Q4B Annex 2R1	Test for Extractable Volume of Parenteral Preparations General Chapter	
Q4B Annex 3R1	Test for Particulate Contamination: Sub-Visible Particles General Chapter	
Q4B Annex 4AR1	Microbiological Examination of Non-Sterile Products: Microbial Enumeration Tests General Chapter	
Q4B Annex 4BR1	Microbiological Examination of Non-Sterile Products: Tests for Specified Micro-Organisms General Chapter	
Q4B Annex 4CR1	Microbiological Examination of Non-Sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use General Chapter	
Q4B Annex 5R1	Disintegration Test General Chapter	
Q4B Annex 6	Uniformity of Dosage Units General Chapter	
Q4B Annex 7R2	Dissolution Test General Chapter	
Q4B Annex 8R1	Sterility Test General Chapter	
Q4B Annex 9R1	Tablet Friability General Chapter	
Q4B Annex 10R1	Polyacrylamide Gel Electrophoresis General Chapter	
Q4B Annex 11	Capillary Electrophoresis General Chapter	
Q4B Annex 12	Analytical Sieving General Chapter	
Q4B Annex 13	Bulk Density and Tapped Density of Powders General Chapter	
Q4B Annex 14	Bacterial Endotoxins Test General Chapter	
Q4B FAQs	Frequently Asked Questions	

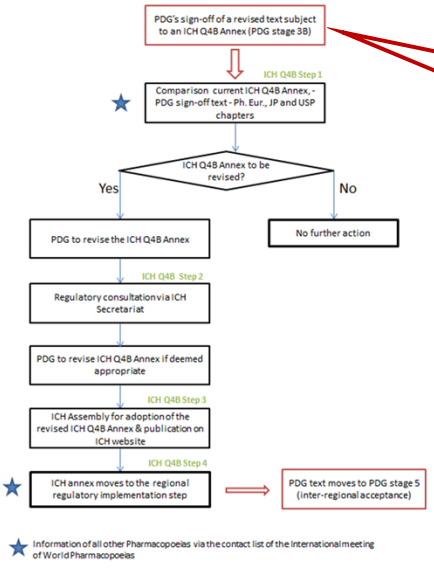
PDG Chapter ⇔ ICH Q4B Annex

CP	PDG Number	PDG Name	Q4B Annex
JP	Q-10	Residue on Ignition	Q4B Annex 1R1 Residue on Ignition/Sulphated Ash
EP	Q-08	Extractable Volume	Q4B Annex 2R1 Test for Extractable Volume of Parenteral Preparations
EP	Q-09	Particulate Contamination	Q4B Annex 3R1 Test for Particulate Contamination: Sub-Visible Particles
EP	Q-05a	Test for Specified Microorganism	Q4B Annex 4AR1 Microbiological Examination of Non-Sterile Products: Microbial Enumeration Tests
EP	Q-05b	Microbial Enumeration	Q4B Annex 4BR1 Microbiological Examination of Non-Sterile Products: Tests for Specified Micro-Organisms
EP	Q-05c	Limits for Non-sterile Products	Q4B Annex 4CR1 Microbiological Examination of Non-Sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use
USP	Q-02	Disintegration	Q4B Annex 5R1 Disintegration Test
USP	Q-03/04	Uniformity of Content/Mass	Q4B Annex 6 Uniformity of Dosage Units
USP	Q-01	Dissolution	Q4B Annex 7R2 Dissolution Test
EP	Q-11	Sterility Test	Q4B Annex 8R1 Sterility Test
USP	G-06	Tablet Friability	Q4B Annex 9R1 Tablet Friability
EP	B-06	Polyacrylamide Gel Electrophoresis	Q4B Annex 10R1 Polyacrylamide Gel Electrophoresis
EP	B-02	Capillary Electrophoresis	Q4B Annex 11 Capillary Electrophoresis
USP	G-01	Analytical Sieving	Q4B Annex 12 Analytical Sieving
EP	G-02	Bulk Density and Tapped Density	Q4B Annex 13 Bulk Density and Tapped Density of Powders
JP	Q-06	Bacterial Endotoxins	Q4B Annex 14 Bacterial Endotoxins Test

Why a new maintenance procedure? Some history

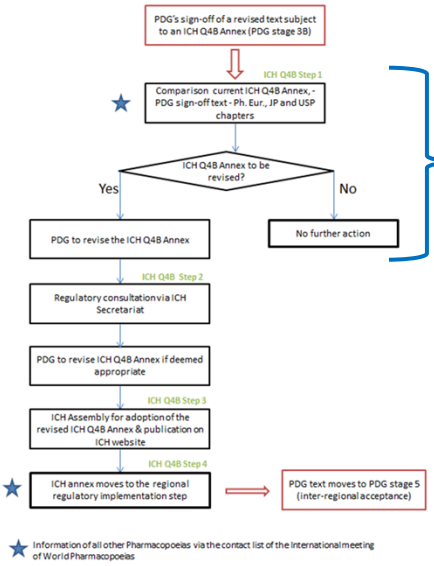


Future Maintenance process of the ICH Q4B Annexes



As with the former ICH Q4B process, the need to revise a Q4B annex would be triggered by PDG's sign-off of a revised text subject to Q4B. Potentially non-harmonised and/or local requirements are highlighted in the sign-off coversheet.

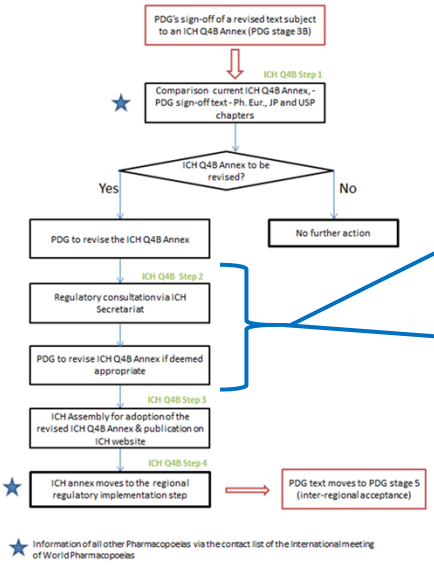
Future Maintenance process of the ICH Q4B Annexes



Step 1:

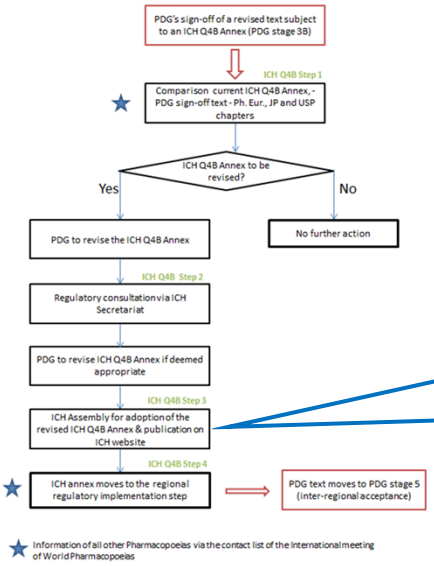
- PDG compares the corresponding current ICH Q4B Annex, the PDG sign-off text as well as the corresponding Ph. Eur., JP and USP chapters as published in the respective Pharmacopoeias. All other pharmacopoeias are informed of the ongoing review via the contact list of the International meeting of World Pharmacopoeias (IMWP).
- Based on this review, the PDG prepares a revised Q4B annex, which is submitted to the ICH Secretariat for proceeding to Step 2. Depending on the case, revision could be limited to an update on the pharmacopoeial reference texts (i.e. updated versions of the pharmacopoeia).

Future Maintenance process of the ICH Q4B Annexes



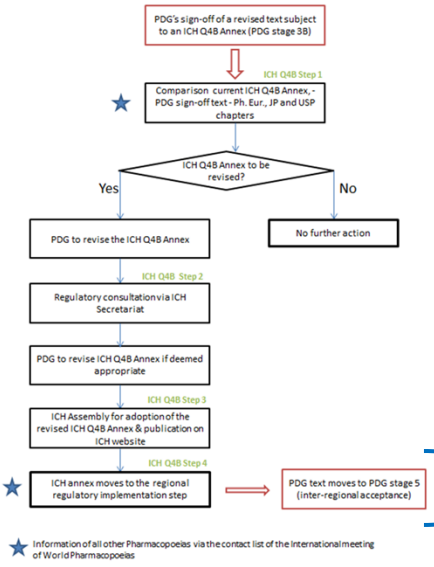
Step 2 (*former ICH Q4B Step 3*):
The draft Q4B annex is submitted to the ICH Secretariat to initiate regulatory consultation (generally for 3 months). The regulatory consultation and discussion should focus on the Q4B Outcome in the annex, i.e. regulatory interchangeability; comments on the harmonised pharmacopoeial text itself are not expected. Comments will be evaluated by PDG and the annex revised by PDG, where necessary.

Future Maintenance process of the ICH Q4B Annexes



Step 3 (*former ICH Q4B Step 4*):
PDG submits the revised annex to the ICH Assembly for adoption and publication on the ICH website.

Future Maintenance process of the ICH Q4B Annexes



Step 4 (*former ICH Q4B Step 5*):
The annex moves to the regional regulatory implementation step. The corresponding PDG chapter moves to PDG stage 5 (inter-regional acceptance). All other pharmacopoeias are informed via the contact list of the International meeting of World Pharmacopoeias (IMWP).

Some other inititatives

Quick walk through

Sharing Vs Harmonisation & Convergence ….

PDG

Informal
Prospective Harmonisation

MoU

IMWP

Sharing Vs Harmonisation & Convergence ….

PDG

Informal
Prospective Harmonisation

Retrospective harmonisation of general chapters and excipient monographs - JP, Ph. Eur, USP (& WHO as observer)

IMWP

Sharing Vs Harmonisation & Convergence ….

PDG

Informal
Prospective Harmonisation

Informal prospective harmonisation
Ph. Eur. & USP : 19 monographs harmonised: 13 monographs on API and 6 on finished products

➢Further 15 monographs on the work program

Monograph	Mono. No.	Adopted	API/FP
Aprepitant	2757	COM 153, November 2015	API
Celecoxib	2591	COM 140, June 2011	API
Dronedarone hydrochloride	3039	COM, 163 Nov 2018	API
Everolimus	2918	COM 160, March 2018	API
Fingolimod hydrochloride	2988	COM 160, March 2018	API
Lacosamide	2992	COM 158, June 2017	API
Lacosamide infusion	2991	COM 160, March 2018	FP
Lacosamide oral solution	2990	COM 160, March 2018	FP
Lacosamide tablets	2989	COM 161, June 2018	FP
Montelukast sodium	2583	COM 138, November 2010	API
Prasugrel hydrochloride	3040	COM, 163 Nov 2018	API
Raltegravir chewable tablets	2939	COM 158, June 2017	FP
Raltegravir potassium	2887	COM 157, March 2017	API
Raltegravir tablets	2938	COM 158, June 2017	FP
Regorafenib monohydrate	3012	COM 161, June 2018	API
Rizatriptan benzoate	2585	COM 138, November 2010	API
Sildenafil citrate	2270	COM 141, November 2011	API
Sitagliptin phosphate monohydrate	2778	COM 151, March 2015	API
Sitagliptin tablets	2927	COM 151, March 2015	FP

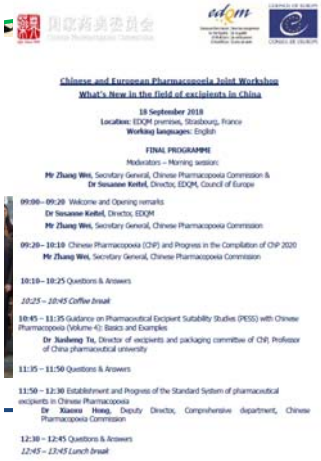
Sharing Vs Harmonisation & Convergence ….

PDG

MoU on collaboration and exchanges e.g. EDQM – ChP; EDQM – IPC; EDQM – ANVISA etc… ;

=> involvement of observers in the elaboration/revision of texts.

=>Information sharing (of data, know-how…) ; co-organisation of events



Sharing Vs Harmonisation & Convergence ….

PDG

Informal
Prospective Harmonisation

International Meeting of World Pharmacopoeias

cf information provided by WHO at the last PDA conference

International Meetings of World Pharmacopoeias

- Opportunity for greater collaborative work
- Opportunity for sharing of information between world pharmacopoeias
- Development of good pharmacopoeial practices (GPhP), applying WHO's standard-setting processes and procedures
- Outcome presented to WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) → through ECSPP also to WHO's 194 Member States

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IMWP

Call for experts 2019

Provide a vital and invaluable contribution to the elaboration and maintenance of Ph. Eur. texts by taking part in the work of the Ph. Eur.

- Expand your knowledge of the Ph. Eur. and the European regulatory system
- Network with peers and other professionals with various backgrounds and from all over Europe and beyond
- Help shape Ph. Eur. texts, internationally-recognised quality standards for medicines
- Share information and experience

Nomination process now open to all experts!

- Ph. Eur. member states: via your respective National Pharmacopoeia Authorities.
- Non Ph. Eur. member states: via EDQM Helpdesk service.

Thank you for your attention

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Thank you for your attention

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