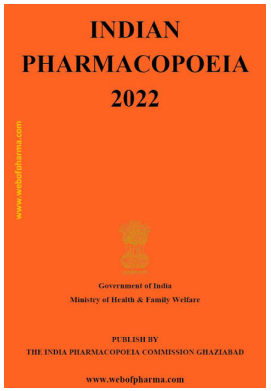
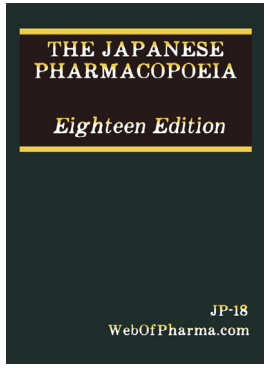
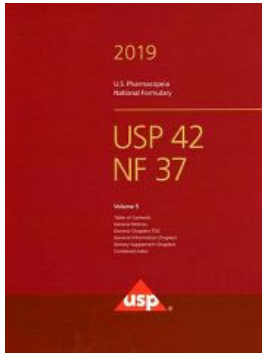
# THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)

# Harmonisierung der Pharmakopöen


## Swissmedic
## Expertentagung Pharmakopöe
## Freitag, 18. Oktober 2024

*Dr Dirk Leutner, EDQM*

# Why do we need harmonisation?

**If each country/region has own pharmaceutical regulation without harmonisation….**

- Pharmaceutical products approved in one country/region that are sold in other countries/regions must meet the quality standards recognized in those countries/regions
- Must conduct similar redundant tests in each country/region, adding no value to the patient or public health

**Pharmacopeial Harmonisation**

→ can align test methods and specifications to a common quality standard

# International Collaboration

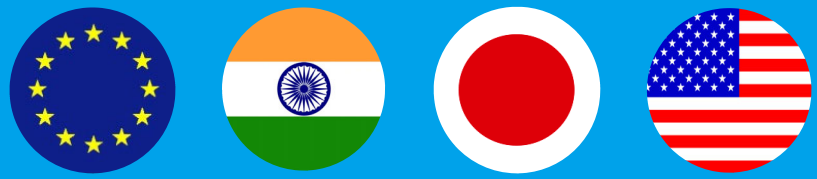
- Ph. Eur.: **successful model of work-sharing and harmonisation between** currently **39 countries**, but based on strong political will and legal commitment
- Ph. Eur., United States Pharmacopoeia, Japanese Pharmacopoeia and Indian Pharmacopoeia, with WHO as an observer, are partners in the **Pharmacopoeial Discussion Group** (PDG)
- **International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)**: EDQM is an observer of the ICH Association and contributes to the development of relevant ICH guidelines; the PDG is tasked by ICH since 2018 to **update the ICH Q4B guideline and its annexes**
- **Global harmonisation (Good Pharmacopoeial Practices)**: EDQM key player in International Meeting of World Pharmacopoeias (IMWP), exchange of pharmacopoeial texts
- **Prospective bilateral harmonisation:** joining forces on new monograph elaboration with other pharmacopoeias (individually with USP, JP and WHO)

# Outline

- **Pharmacopoeial Discussion Group (PDG)**
- Interchangeability through ICH Q4B
- Exchanges through IMWP following GPhP
- Bilateral Harmonisation

# Pharmacopoeial Discussion Group (PDG)

- **Began as an informal group in 1989**; participants include USP, Ph. Eur., IPC, and JP
  - ★ IPC joined as member in 2023
  - ★ WHO joined as observer in 2001
- Focuses on selected official, broad-impact General Chapters and excipient monographs
- Eliminates/minimises need to perform multiple tests and procedures and to comply with multiple acceptance criteria for the same article
- Detailed process, with specific stages and terminology
- One face-to-face meeting a year, with a video conference in the interim



**EP** (EDQM) | **IP** (IPC) | **JP** (MHLW /PMDA) | **USP**

## PDG Mission

To harmonize pharmacopeial standards while maintaining a constant level of science with the shared goal of protecting public health.

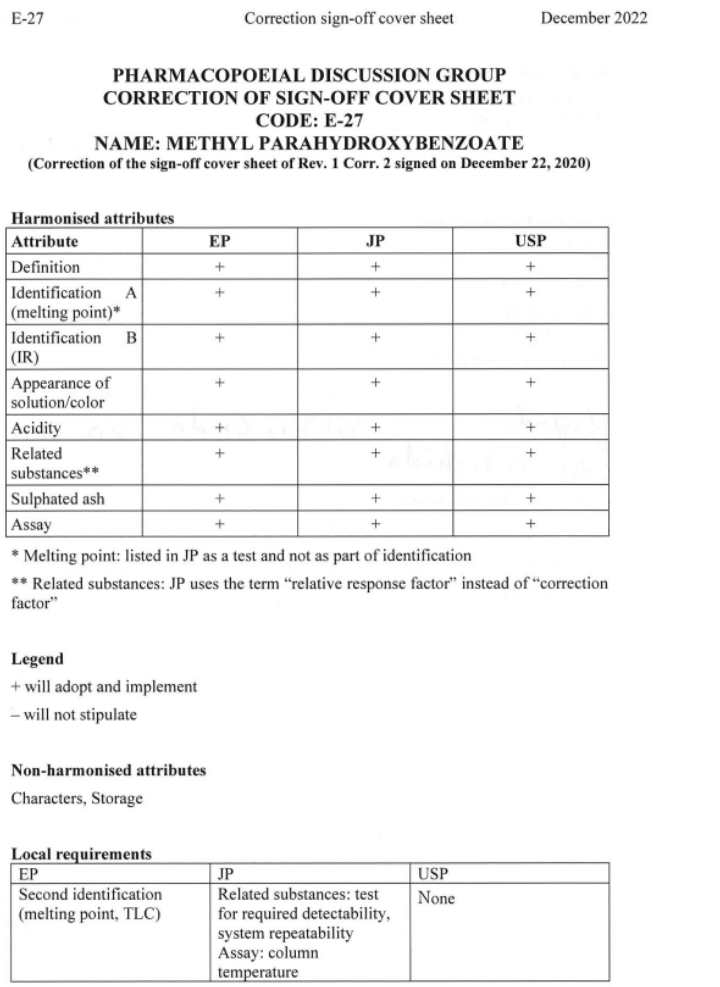
# Harmonisation by Attribute: How PDG moves ahead

For the first 12 years of PDG, **zero** monographs or General Chapters were harmonised!

**Harmonisation by Attribute** was introduced as an acknowledgement that certain attributes simply cannot be harmonised because of:

- ★ (1) Differing **regulatory** or **legal** requirements
- ★ (2) **Non-harmonised** methodology for procedures
- ★ (3) Differences in **scientific** expert opinions

Acknowledgement that **partial harmonisation is preferred to no harmonization**!



E-27 Correction sign-off cover sheet December 2022

**PHARMACOPOEIAL DISCUSSION GROUP**
**CORRECTION OF SIGN-OFF COVER SHEET**
**CODE: E-27**
**NAME: METHYL PARAHYDROXYBENZOATE**
**(Correction of the sign-off cover sheet of Rev. 1 Corr. 2 signed on December 22, 2020)**

**Harmonised attributes**

| Attribute | EP | JP | USP |
|---|---|---|---|
| Definition | + | + | + |
| Identification A (melting point)* | + | + | + |
| Identification B (IR) | + | + | + |
| Appearance of solution/color | + | + | + |
| Acidity | + | + | + |
| Related substances** | + | + | + |
| Sulphated ash | + | + | + |
| Assay | + | + | + |

* Melting point: listed in JP as a test and not as part of identification

** Related substances: JP uses the term "relative response factor" instead of "correction factor"

**Legend**

+ will adopt and implement

– will not stipulate

**Non-harmonised attributes**

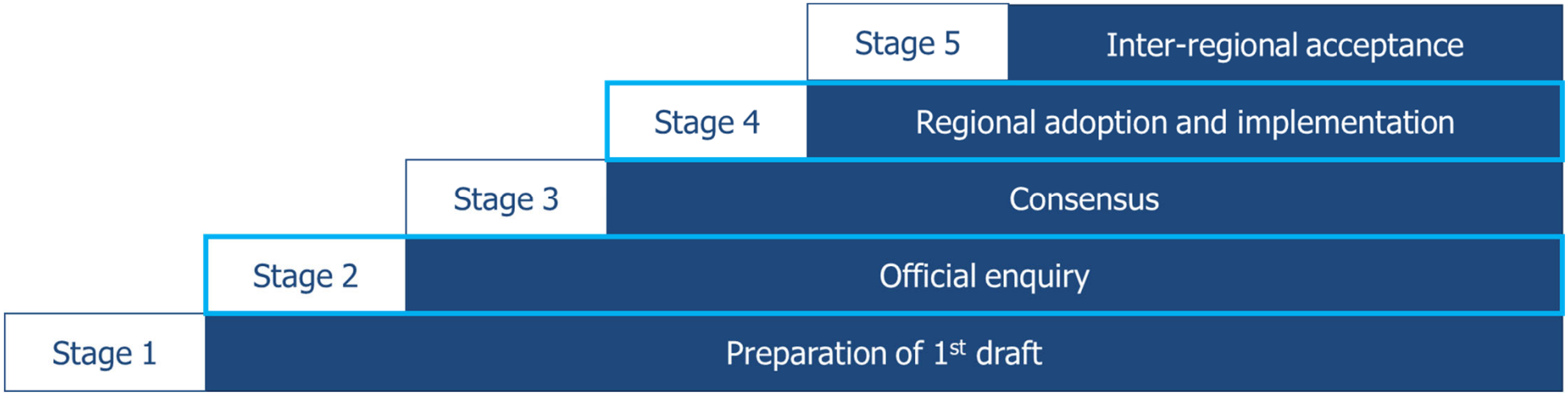
Characters, Storage

**Local requirements**

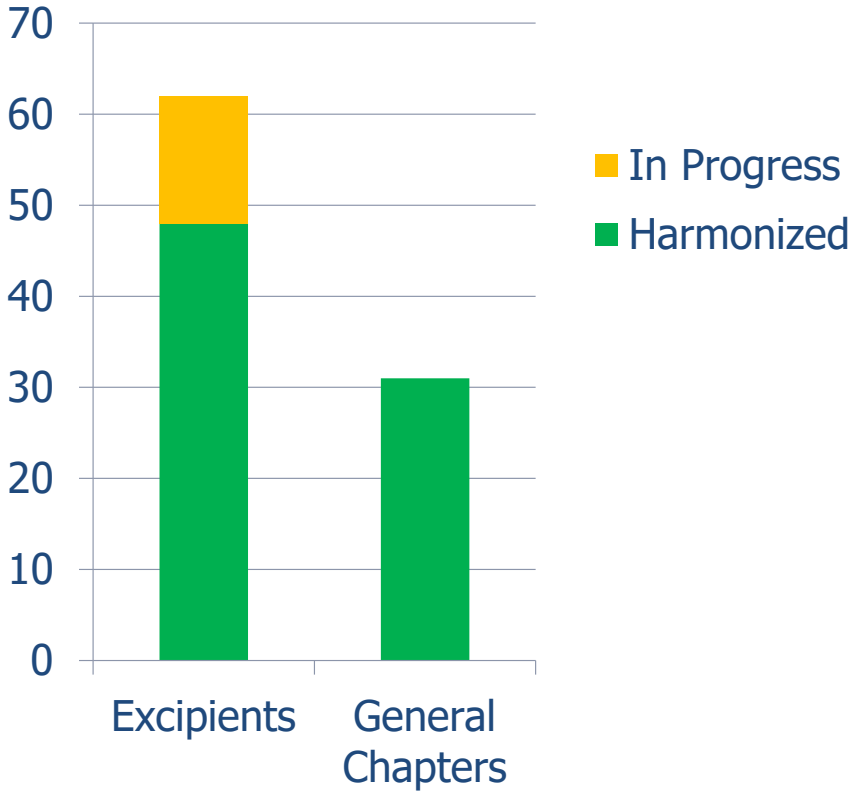
| EP | JP | USP |
|---|---|---|
| Second identification (melting point, TLC) | Related substances: test for required detectability, system repeatability<br>Assay: column temperature | None |

# PDG Harmonization Process

- PDG is an **informal body** but has a formal process
- **Fully embedded in local processes**,
  e.g. through public consultation in each region
- Each text lead by a **Coordinating Pharmacopoeia**



# PDG work programme – many success stories




**All 31 General Chapters harmonised!**



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# PDG Work Program: General Chapters

## General Methods Relevant to Q6A:

Q-01 Dissolution*3
Q-02 Disintegration*3
Q-03/04 Uniformity of Content/Mass
Q-05a Tests for Specified Microorganism
Q-05b Microbial Enumeration
Q-05c Limits for Non-sterile Products
Q-06 Bacterial Endotoxin
Q-07 Color (Instrumental Method)
Q-08 Extractable Volume*3
Q-09 Particulate Contamination*3
Q-10 Residue on Ignition
Q-11 Sterility Test

## General Chapters:

G-01 Analytical Sieving*3
G-02 Bulk Density of Powders
G-03 Conductivity
G-04 Gas Pycnometric Density of Solids
G-05 Powder Flow
G-06 Tablet Friability
G-07 Elemental Impurities*2
G-09 Optical Microscopy*3
G-10 Powder Fineness
G-11 Specific Surface Area
G-13 Laser Diffraction Measurement of Particle Size*3

## General Chapters:

G-14 X-Ray Powder Diffraction
G-15 Water-solid Interaction
G-16 Thermal Analysis*3
G-20 Chromatography*1
G-21 Dynamic Light Scattering*1

## Methods for Biotechnology Products:

B-01 Amino Acid Determination
B-02 Capillary Electrophoresis*3
B-03 Isoelectric Focusing
B-05 Peptide Mapping
B-06 Polyacrylamide Gel Electrophoresis

**All 31 general chapters have now been harmonised!**

*1 : Signed-Off in 2021-2023
*2 : Recent Sign Off in 2024
*3 : Under revision

# PDG Work Program: Excipients

E-01 Alcohols
E-02 Dehydrated Alcohol
E-03 Benzyl Alcohol
E-04 Calcium Disodium Edetate*3
E-05 Calcium Phosphate Dibasic
E-06 Calcium Phosphate Dibasic Anhydrous
E-07 Carmellose Calcium
E-08 Carmellose Sodium*2
E-09 Croscarmellose Sodium*3
E-10 Microcrystalline Cellulose
E-11 Cellulose, Powdered
E-13 Cellulose Acetate Phthalate
E-14 Citric Acid, Anhydrous
E-15 Citric Acid, Monohydrate
E-16 Crospovidone
E-17 Ethylcellulose
E-18 Hydroxyethylcellulose*3
E-19 Hydroxypropylcellulose
E-20 Hydroxypropylcellulose, Low Substituted
E-21 Hypromellose
E-22 Hypromellose Phthalate
E-23 Lactose, Anhydrous*3
E-24 Lactose, Monohydrate*3
E-25 Magnesium Stearate
E-26 Methylcellulose
E-27 Methyl Paraben
E-28 Petrolatum*1
E-29 Petrolatum, White*1
E-30 Polyethylene Glycol*2
E-31 Polysorbate 80*3
E-32 Povidone*3
E-36 Silicon Dioxide*2
E-37 Silicon Dioxide, Colloidal*2
E-38 Sodium Chloride
E-39 Sodium Starch Glycolate
E-40 Starch, Corn
E-41 Starch, Potato
E-42 Starch, Rice
E-43 Starch, Wheat
E-44 Stearic Acid
E-45 Sucrose*3
E-46 Talc *3
E-48 Ethyl Paraben
E-49 Propyl Paraben
E-50 Butyl Paraben
E-51 Glycerin*2
E-52 Carmellose
E-54 Copovidone*3
E-55 Gelatin
E-56 Sucrose
E-58 Mannitol
E-59 Propylene Glycol*2
E-60 Sodium Laurylsulfate
E-61 Starch, Pregelatinized*2
E-62 Sterile Water for Injection*2
E-64 Isomalt
E-65 Isostearyl Alcohol*2
E-66 Myristyl Myristate*2
E-68 Polysorbate 65*2
E-69 Calcium Silicate*2
E-70 Polysorbate 20*2
E-71 Purified Water*2
E-72 Water for injections*2

*1 : Signed-Off in 2021-2023
*2 : Under discussion towards first harmonization
*3 : Under revision

**48 of the 62 excipient monographs have now been harmonized**

# Global Expansion of PDG – Pilot Phase 2022 - 2023

- **2021** Landmark decision by PDG to **launch a pilot** for the first expansion of membership in 32 years.
- **Global Pharmacopeias** interested were **invited** to submit applications to evaluate against objective entry criteria
- 2022-2023 IPC became a **regular participant** in all PDG activities **for one year**
- October 2023: **IPC new 4th member**

# New membership expansion initiative 2024

Newsroom

PDG announces global membership initiative

EDQM | STRASBOURG, FRANCE | 30/08/2024

The Pharmacopoeial Discussion Group (PDG) is excited to announce the launch of the next phase of its global expansion initiative aimed at increasing convergence of harmonised pharmacopoeial standards. This initiative will be the start of a process over the next couple of years to welcome additional pharmacopoeias as new members.

Pharmacopoeias interested in becoming members are encouraged to review the entry criteria, framework and reference information. They are required to submit a statement of intent to the PDG by 15 September 2024 and the formal application by 31 December 2024.

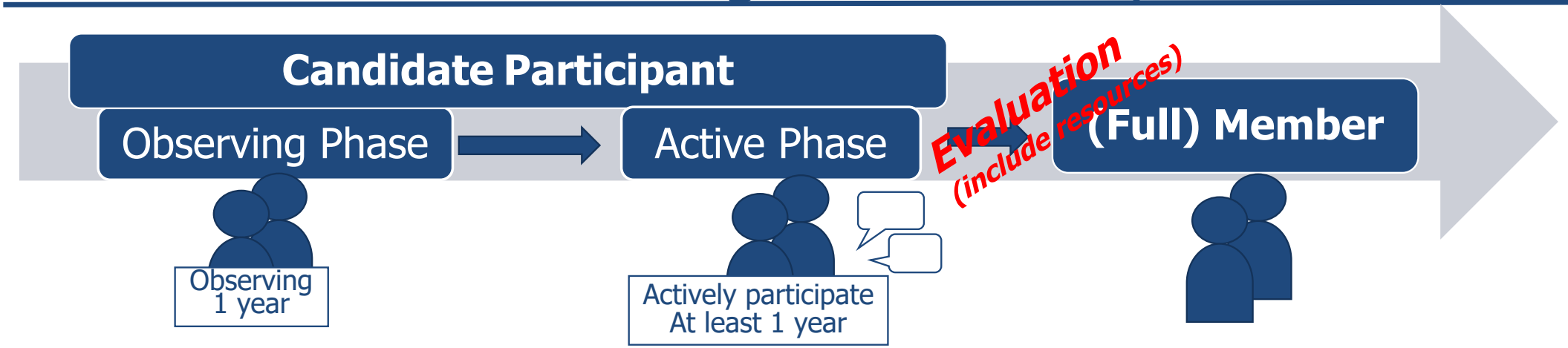
Founded in 1989, the PDG brings together pharmacopoeias to harmonise excipient monographs and selected general texts. Last year, the founding members – the European Pharmacopoeia (Ph. Eur.), the Japanese Pharmacopoeia (JP) and the United States Pharmacopeia (USP) – welcomed the Indian Pharmacopoeia Commission (IPC) as the fourth member. The IPC joining the PDG marked the culmination of a pilot programme launched in 2022 which laid the groundwork for this global initiative.

The PDG has successfully harmonised and maintains 31 general chapters, including key analytical procedures such as chromatography, dissolution testing, sterility and microbiological examination. In addition, the PDG has harmonised 48 excipient monographs and has approximately 20 new texts in its pipeline (general chapters, excipients). The PDG remains committed to promoting the recognition of harmonised pharmacopeial standards to achieve global convergence.

The PDG invites all interested world pharmacopoeias to visit the website for further information regarding the PDG and

- PDG discussed lessons learnt and modified framework and criteria
- PDG sent an invitation to world pharmacopoeias in July 2024
- Possible applicants were asked:
  - to submit application documents **by 31 December 2024.**

# Framework for Next Stage of PDG Expansion

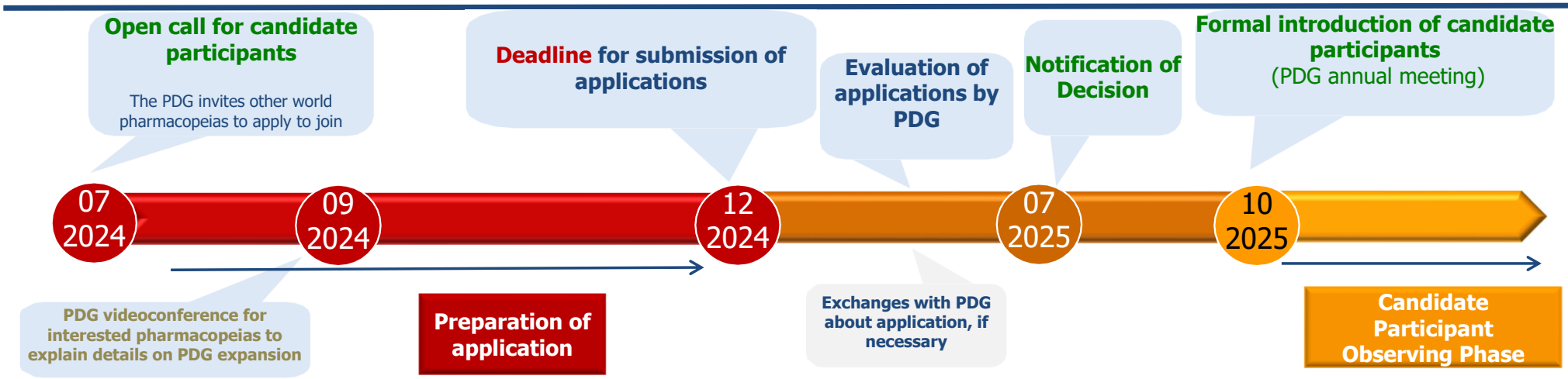



- **Observe** PDG activities and all meetings (including technical meetings and subteam meetings)
- Comments or feedback allowed but not required
- Start implementing PDG harmonized texts
- Gain understanding of PDG's way of working from passive participation

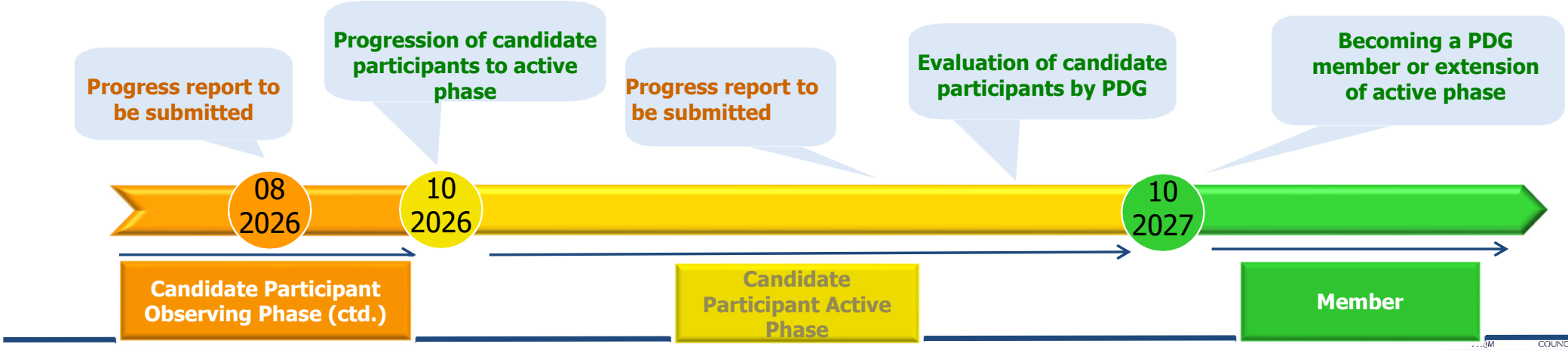
- **Active participation** in PDG activities and all meetings (including technical meetings and subteam meetings
- Required to submit comments and feedback
- Continue implementing PDG harmonized texts
- Actively integrate into harmonization work

- **Full participation**
- Same status as existing members

# Timeline: Application and introduction of candidate participants




# Timeline: Candidate participants towards membership



# Coordination by the secretariat: PDG in numbers

Meetings 2023:

- 1 face-to-face meeting
- 1 stakeholder event

Videoconferences (time zone differences!)

- 10 progress meetings
- 4 technical videoconferences with experts
- 14 other videoconferences

Work programme with 93 items:

- 20 revisions
- 14 excipient monographs under elaboration


# PDG Process fully embedded in Ph. Eur. process

- coordinating pharmacopoeia (CP) lead each topic

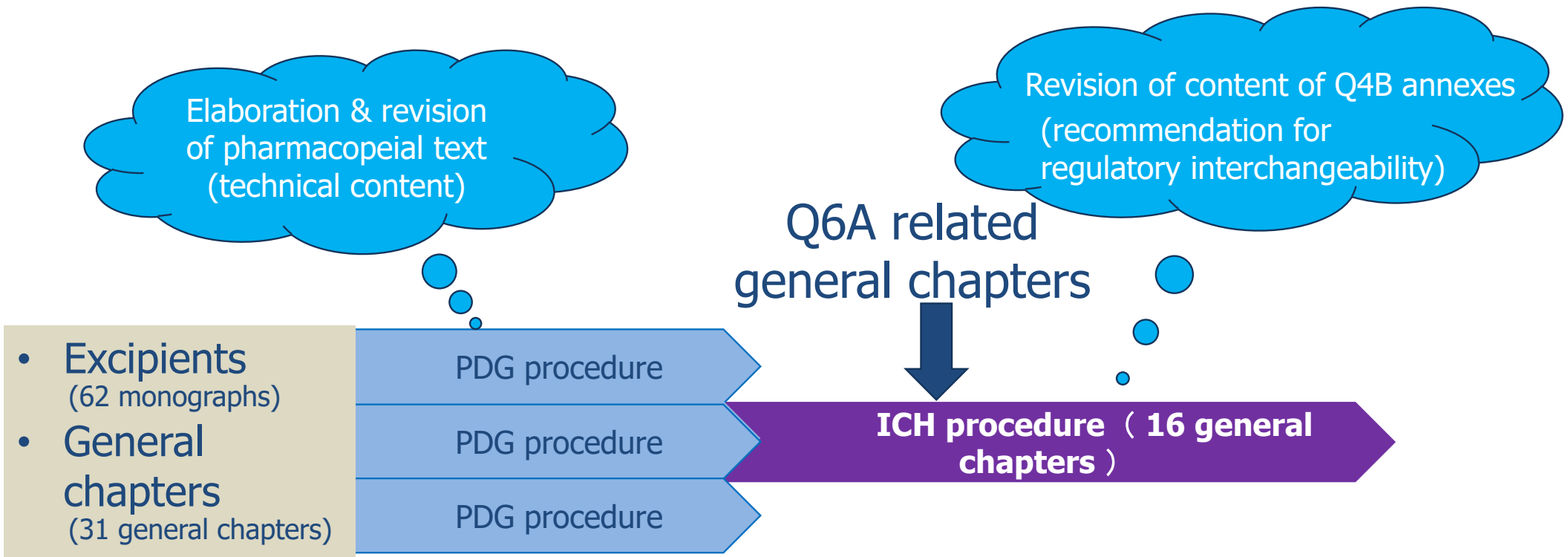
1. Mostly exchanges in writing between the expert groups to get to consensus text
2. Public consultation in each respective forum (Pharmeuropa, PF, JP forum)
3. Again exchanges to build consensus
4. Sign-off after agreement by experts
5. Adoption by Ph. Eur. Commission
6. Publication of sign-off on each homepage
7. Publication of adopted local text

# Outline

- Pharmacopoeial Discussion Group (PDG)
- **Interchangeability through ICH Q4B**
- Exchanges through IMWP following GPhP
- Bilateral Harmonisation

# ICH Q4B – The scope

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



# ICH Q4B - The past

| PDG (since 1989) | | ICH Q4B (**2003 – 2010**) |
|---|---|---|
| Ph. Eur. (EDQM), JP (MHLW/PMDA), USP (USP), IP (IPC, since 2023) | Participant | Regulatory: EC, MHLW/PMDA, FDA<br>Industry: EFPIA, JPMA, PhRMA |
| Harmonisation of Science<br>(Analytical method, Acceptance Criteria) | Activity | Regulatory Harmonisation<br>Regulatory Acceptance for use |
| 31 general chapters, 62 monographs | Target | 16 general chapters |
| Harmonised pharmacopoeial texts | Outcome | Guideline = Recommendation for regulatory use in the ICH regions |

- **ICH Q4B annexes cover 16 harmonised pharmacopoeial general chapters** and were elaborated following an evaluation by ICH of the corresponding texts
- Once in agreement as **interchangeable**, the result was published as an annex to the ICH guideline
- ICH regulatory members are recommended to **accept references to all mentioned pharmacopoeias** in marketing authorisation dossier.

# ICH Q4B – The presence

- **ICH has grown**
- 4 ➔ 17 regulatory members
- 3 ➔ 10 involved pharmacopoeias
- **Pharmacopoeial texts have evolved**

**PDG tasked in 2018 to update GL and annexes**

| ICH regulatory member | Pharmacopoeia |
|---|---|
| ANMAT, Argentina | Argentinian Pharmacopeia |
| 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 | - |
| JFDA, Jordan | - |
| MFDS, Republic of Korea | Korean Pharmacopoeia (KP) |
| MHRA, UK | **European Pharmacopoeia (Ph. Eur.)** |
| NMPA, China | Chinese Pharmacopoeia (ChP) |
| SFDA, Saudi Arabia | - |
| TFDA, Chinese Taipei | Taiwan Pharmacopoeia (TWP) |
| TITCK, Türkiye | **European Pharmacopoeia (Ph. Eur.)** |

# ICH Q4B - The general chapters

| Annex | PDG text covered | Ongoing work |
|---|---|---|
| 1 | Residue on Ignition / Sulfated Ash | No action since 2005 |
| 2 | Extractable Volume | Rev. 2 stage 2 |
| 3 | Particulate Contamination: Sub-visible particles | Rev. 2 stage 3A |
| 4A | Microbial Enumeration Tests | No action since 2023 (rev. 1 corr. 2) |
| 4B | Tests for Specified Micro-organisms | No action since 2008 (rev. 1) |
| 4C | Acceptance Criteria for Preparations and Substances | No action since 2005 |
| 5 | Disintegration | Rev. 2 stage 2 |
| 6 | Uniformity of Dosage Units | No action since 2015 (rev. 2) |
| 7 | Dissolution | Rev. 5 stage 1 |
| 8 | Sterility Test | No action since 2009 |
| 9 | Tablet Friability | No action, Rev. 1 signed 2022 – not in Q4B annex |
| 10 | Polyacrylamide Gel Electrophoresis | No action, Rev. 1 Signed 2014 – not in Q4B annex |
| 11 | Capillary Electrophoresis | Rev. 1 stage 2 |
| 12 | Analytical Sieving | Rev. 2 stage 1 |
| 13 | Bulk Density of Powders | 2024: Rev. 4 corr. 2 signed |
| 14 | Bacterial Endotoxins | No action since 2011 |

# ICH Q4B – The revision

- **Q4B(R1) and Annex 5 of ICH SOP approved by ICH Assembly**
  at June 2024 meeting in Fukuoka
  ICH press release 12/06/2024:

**Revision of Q4B(R1) to Reflect Maintenance by PDG**

The Assembly approved the revision of the Q4B(R1) Guideline on *"Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions"*. The revision reflects that responsibility for the maintenance of Q4B and its annexes is handed over to the Pharmacopoeial Discussion Group (PDG). The new procedure takes account of the growth in ICH Regulatory Members in recent years and will give non-PDG pharmacopoeias the option to harmonise their method with the PDG method or to implement the PDG method in parallel of a local method.

# ICH Q4B – The 2 implementation approaches

- 7 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

# ICH Q4B - The next steps

- PDG will **update all 16 Q4B annexes stepwise** 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 **10 pharmacopoeias involving all 17 ICH regulatory members**

- **Work is performed by the secretariats of the involved pharmacopoeias**

# Outline

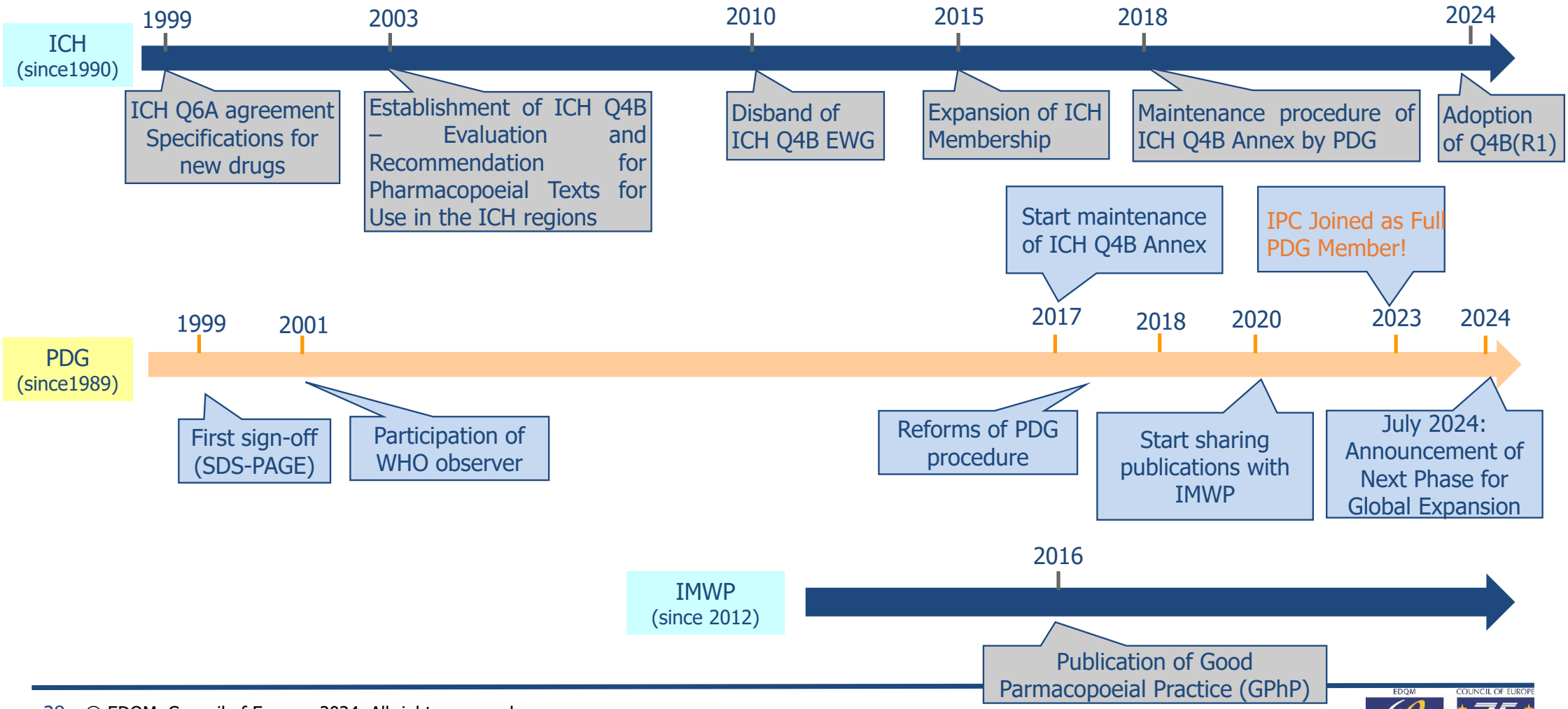
- Pharmacopoeial Discussion Group (PDG)
- Interchangeability through ICH Q4B
- **Exchanges through IMWP following GPhP**
- Bilateral Harmonisation

# Int. Meeting of World Pharmacopoeias

- **discussion forum** (14 meetings since 2012) to
  - **get to know** peers
  - **build trust** among pharmacopoeias
  - **exchange information, knowledge and expertise**, e.g. to inform each other of recent challenges and share solutions found, **pharmacopoeial alert system**

- PDG committed to **support pharmacopoeial harmonisation** of quality standards by **liaising** with other world pharmacopoeias (e.g. via IMWP) and by **sharing PDG texts** with all IMWP ph. :
  - **for comments at public consultation** stage and
  - **after sign-off** for optional implementation following **Good Pharmacopoeial Practices**

# Summary: Timeline of Multilateral Collaborative Activities



# Outline

- Pharmacopoeial Discussion Group (PDG)
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- **Bilateral Harmonisation**

# Bilateral vs. PDG harmonisation

| | PDG Harmonisation | Ph. Eur. Bilateral Prospective Harmonisation |
|---|---|---|
| Goal | Align test procedures and limits to a common quality standard<br>Texts do not have to be identical | |
| Launched | 1989 | 2008 (USP), 2024 (JP), Ph. Int. (WHO) |
| Participating pharmacopoeias | Ph. Eur., USP, JP, WHO (joined as observer in 2001), IPC (joined 2022 as pilot participant) | Ph. Eur. and USP<br>Ph. Eur. and JP<br>Ph. Eur. and Ph. Int. (WHO) |
| Focus | Excipient monographs and general chapters (method) | New active substance and medicinal product monographs for products mainly still under patent |
| Process | Official procedure embedded in internal processes | Respective internal processes for monograph elaboration |
| Work initiation | Determined by the PDG | Manufacturers' request<br>(subject to the agreement of the Ph.) |
| Revisions | Commitment not to unilaterally revise | No commitment |

# Monographs to date (Ph. Eur./USP)

**Pilot phase** launched in 2008

## Pilot phase

Celecoxib
Montelukast sodium
Rizatriptan benzoate
Sildenafil citrate

## Post-pilot active substance monographs

Aprepitant
Dronedarone HCl
Fingolimod HCl
Lacosamide
Prasugrel HCl
Raltegravir potassium
Regorafenib
Riociguat
Rivaroxaban
Sitagliptin phosphate
Sorafenib tosilate

## Post-pilot Medicinal product monographs

Dronedarone tablets
Lacosamide infusion
Lacosamide oral solution
Lacosamide tablets
Raltegravir chewable tablets
Raltegravir tablets
Riociguat tablets
Rivaroxaban tablets
Sitagliptin tablets
Sorafenib tablets

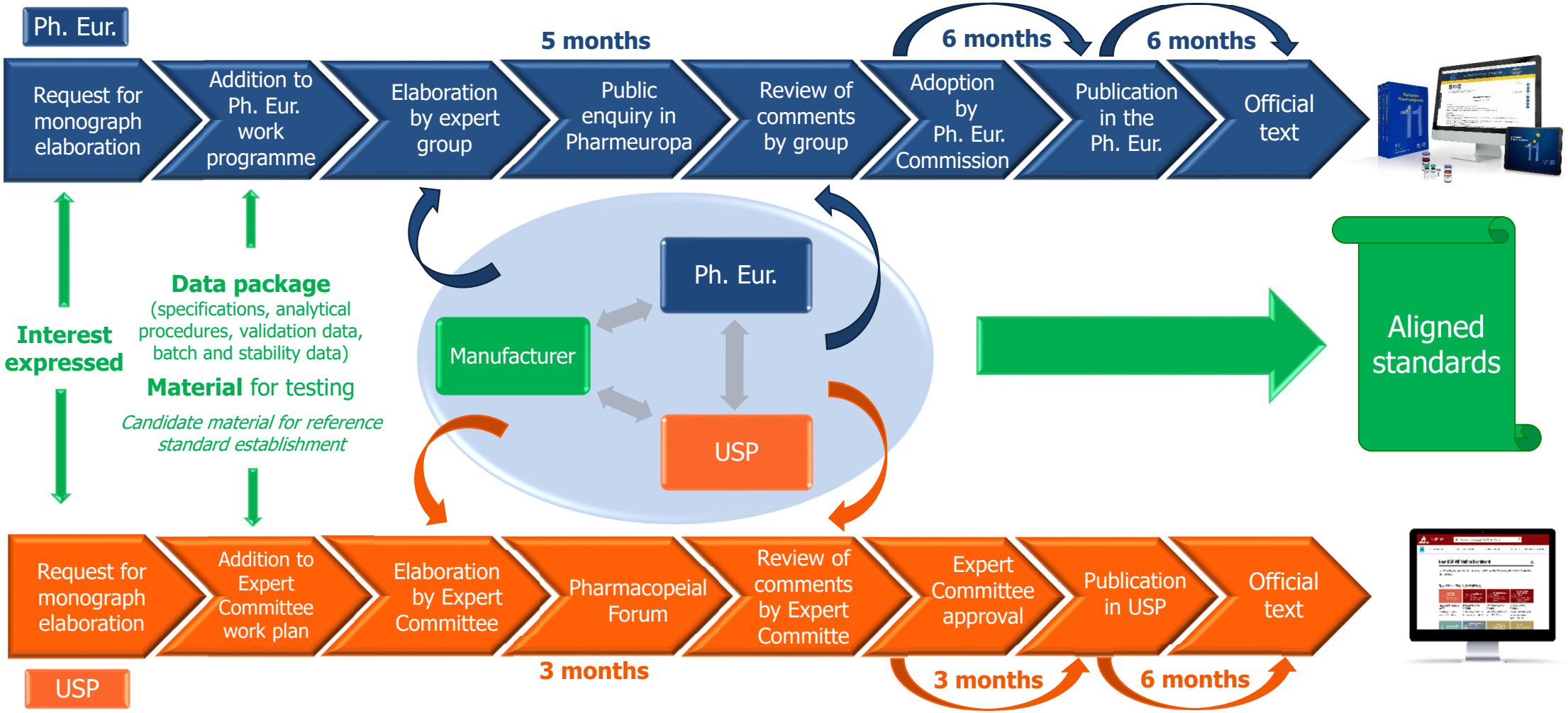
## Ongoing projects

Alectinib HCl – A. capsules
Brivaracetam – B. tablets –
B. injection or infusion – B. oral solution
Cabazitaxel acetone – C. concentrate for infusion
Dapagliflozin propanediol – D. tablets
Deferasirox
Etravirine – E. tablets
Fulvestrant injection
Mirabegron
Plerixafor – P. injection
Regorafenib tablets
Teriflunomide – T. tablets
Ticagrelor – T. tablets

**Post-pilot**
22 official monographs (11 active substances and 10 medicinal products)

22 **Ongoing**
in various stages of development

# Ph. Eur. and USP monograph elaboration



# Some differences between Ph. Eur. and USP

## Limits as approved by competent authorities
(e.g. content, dissolution, impurities)

| USP | Ph. Eur. |
|---|---|
| Specific to the US market | Specific to the European market |

## Limits as set in the individual pharmacopoeias

| USP | Ph. Eur. |
|---|---|
| Generally based on FDA approved limits | Based on limits approved in Ph. Eur. member states (may be adapted based on batch/stability data) |

## Dissolution test

| USP | Ph. Eur. |
|---|---|
| Several tests | One test |

## Solutions

| USP | Ph. Eur. |
|---|---|
| Concentrations and/or exact amounts to be used (masses, volumes) | Generally exact amounts to be used (masses, volumes) |

## System suitability tests
(Tests for impurities / Assay)

| USP | Ph. Eur. |
|---|---|
| Resolution, sensitivity, RSD in monographs | Resolution or p/v ratio in monographs<br>Generally, sensitivity & RSD rely on *2.2.46* |

## Impurity identification

| USP | Ph. Eur. |
|---|---|
| Relative retentions and/or reference standards for impurities | Reference standards for specified impurities and those used for SST<br>No relative retentions for unspecified impurities |

# Thank you for your attention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