Ph. Eur. and other pharmacopoeias - The ICH harmonization process of compendial texts

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Workshop Pharmacopeias: overview, uses and related activities - A guide towards a correct use

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Dichiarazione di trasparenza/interessi*

Le opinioni espresse in questa presentazione sono personali e non impegnano in alcun modo l'AIFA

Interessi nell'industria farmaceutica	NO	Attualmente	Da 0 a 3 anni precedenti	oltre 3 anni precedenti
INTERESSI DIRETTI:				
1.1 Impiego per una società: Ruolo esecutivo in una società farmaceutica	X	☐	☐	☐ obbligatorio
1.2 Impiego per una società: Ruolo guida nello sviluppo di un prodotto farmaceutico	X	☐	☐	☐ obbligatorio
1.3 Impiego per una società: altre attività	X	☐	☐	☐ facoltativo
2. Consulenza per una società	X	☐	☐	☐ facoltativo
3. Consulente strategico per una società	X	☐	☐	☐ facoltativo
4. Interessi finanziari	X	☐	☐	☐ facoltativo
5. Titolarità di un brevetto	X	☐	☐	☐ facoltativo
INTERESSI INDIRETTI:				
6. Sperimentatore principale	X	☐	☐	☐ facoltativo
7. Sperimentatore	X	☐	☐	☐ facoltativo
8. Sovvenzioni o altri fondi finanziari	X	☐	☐	☐ facoltativo
9. Interessi Familiari	X	☐	☐	☐ facoltativo

* Eugenia Cogliandro, secondo il Regolamento per la disciplina dei conflitti di interesse all'interno dell'Agenzia Italiana del Farmaco approvato dal CdA AIFA con Delibera n. 37 del 13 ottobre 2020.

N.B. Il compenso ricevuto per questo intervento è regolato dalla contrattazione collettiva.

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European Pharmacopoeia Commission Priorities for 2023-2025

- 1. Non-technical priorities
- 1.1. Rules of procedures and guides
- 1.2. Modernisation of ways of working
- 1.3. Stakeholder engagement
- **1.4. Harmonisation and international collaboration**
- 2. Technical priorities
- 2.1. Modernisation of analytical procedures and integration of new technologies
- 2.2. Biologicals
- 2.3. Alternatives to animal testing
- 2.4. Impurities
- 2.5. Herbal drugs and herbal drug preparations
- 2.6. Excipients
- 2.7. Nanomedicines
- 2.8. Medicinal product monographs for chemically defined APIs
- 2.9. European Paediatric Formulary https://www.edqm.eu/en/d/1280675

Ph. Eur. Commission Priorities for 2023-2025-1.4

International collaboration is in the DNA of the Ph. Eur.: decisions are taken by consensus by the EPC, which represents the 39 states and the European Union that form the current Ph. Eur. membership, and the texts adopted are enforced in all of them. The Ph. Eur. also means collaboration with experts from beyond the frontiers of the member states, from observer and other countries. **Collaboration with other pharmacopoeias is also important**. In this context, it is worth mentioning the **Pharmacopoeial Discussion Group (PDG)**, which brings together the **US Pharmacopeia (USP), the Japanese Pharmacopoeia and the Ph. Eur.**, with the recent addition of the Indian Pharmacopoeia as part of a pilot expansion programme, together with the WHO as observer. The aim of the PDG is to harmonise pharmacopoeial standards while maintaining a constant level of science with the shared goal of protecting public health. The PDG's recent plan to expand membership to pharmacopoeias currently not yet represented will be further supported to enlarge its global footprint.

In addition, **bilateral initiatives with the USP**, and the **International Pharmacopoeia (WHO**), as well as more global discussions in the framework of the **International Meeting of World Pharmacopoeias (IMWP)** are ongoing to enhance pharmacopoeial co-operation and harmonisation. The Ph. Eur. and the EDQM also collaborate with a number of institutions, such as – to name but a few – the **EMA, HMA, the EU Commission and ICH**, to ensure that Ph. Eur. texts are aligned with current regulations and to provide input for guidelines and future regulatory requirements. All this international activity is highly relevant for harmonisation, but it also ensures that the Ph. Eur. remains current and pertinent, aligned with the constantly changing regulatory landscape and influential in countries beyond its member states.

The need for international harmonisation

Globalisation and the ever-increasing expansion in international trade reinforce the need to develop and maintain global quality standards for medicines.

Pharmacopoeial standards are a vital cog in the smooth functioning of marketing authorisation and market surveillance processes as well as in the free movement and trade of medicines across the globe.

As such, the European Pharmacopoeia (Ph. Eur.) is actively engaged in a number of international harmonisation initiatives, including:

- bilateral harmonisation efforts with pharmacopoeias from other regions or countries;
- working in an informal structure called the Pharmacopoeial Discussion Group (PDG);
- actively participating in the International meeting of world pharmacopoeias (IMWP).

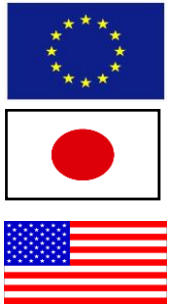
If each country/region has own pharmaceutical regulation without harmonisation…

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

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

The Pharmacopoeial Discussion Group

The PDG, began as an informal group in 1989, brings together:



- European Pharmacopoeia (Ph. Eur.) EDQM
- Japanese Pharmacopoeia (JP) MHLW/PMDA
- United States Pharmacopoeia (USP) USP
- World Health Organization (WHO) joined as an observer in 2001
- Indian Pharmacopoeia Commission (IPC), recently welcomed as a pilot global expansion participant*

*27 October 2023, Strasbourg, France Pharmacopoeial Discussion Group achievements - The Pharmacopoeial Discussion Group (PDG) held its annual autumn meeting from **3 to 4 October 2023**. The group **welcomed the Indian Pharmacopoeia Commission (IPC) as a new member** during the meeting. The addition of the IPC, a first in the over 34-year history of the PDG, facilitates the reach and enhances the impact of pharmacopoeial standards harmonisation.

The Pharmacopoeial Discussion Group - Purpose and process

Purpose

Harmonisation **excipient monographs and general chapters**, reducing the burden placed on manufacturers to perform **multiple tests and procedures** and to comply with multiple **acceptance criteria** for the same article depending on the jurisdiction.

The PDG works to reflect the latest scientific advancements while championing public health protection

Process

- **Topic selection:** PDG selects candidate texts for its work programme after assessing proposals received (for example, from associations of manufacturers of pharmaceuticals and excipients).
- Since 2001, the PDG has organised, on request, ad hoc meetings with industry representatives.
- **Drafting:** each topic is assigned to one of the participating pharmacopoeias, which takes the lead in co-ordinating the drafting of the text in question.
- **Publication for comments:** the harmonised text is then published for comment on the respective forums of the three pharmacopoeias.
- **Implementation:** once all member pharmacopoeias have agreed on a final, harmonised text, it is signed-off by the PDG and implemented according to the usual procedure employed by each member.

The Pharmacopoeial Discussion Group – Harmonisation definition

The PDG's mandate covers the technical harmonisation of the text; each pharmacopoeia is free to adapt the style and format to its own requirements.

A pharmacopoeial general chapter or other pharmacopoeial document is harmonised when a pharmaceutical substance or product tested by the harmonised procedure as published in EP, JP and USP yields the **same results**, and the **same accept/reject decision** is reached.

- Text does NOT have to be identical
- Each Pharmacopeia can adapt the text to local style, and take into consideration of local reference standards and reagents

Each pharmacopoeia does not revise unilaterally after harmonisation. When necessary, revision should be conducted according to the PDG Working Procedures.

Ph. Eur. General chapter 5.8. Pharmacopoeia harmonisation provides essential guidance to users on the PDG's harmonisation efforts and how information is presented in respective Ph. Eur. texts. This chapter helps users to understand and correctly apply harmonised texts.

An Example of PDG Success Story: Chromatography

- The harmonised general chapter Chromatography was signed-off by the Pharmacopoeial Discussion Group (PDG) on September 28, 2021.
- During a joint PDG-industry meeting in 2009, the PDG was encouraged to add harmonisation of the three regional chapters on chromatography to the PDG work program. Although the chapters in question differed in content and format, it was considered feasible to develop a chapter describing core requirements applicable for TLC, HPLC and GC.
- These harmonised requirements promote the development of individual monographs with a consistent approach and enhance understanding of basic requirements by users in all three regions.

PDG Work Program: General Chapters

General Methods Relevant to Q6A:	General Chapters:	Methods for Biotechnology products:
Q-01 Dissolution Q-02 Disintegration 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 Q-09 Particulate Contamination Q-10 Residue on Ignition Q-11 Sterility Test	G-01 Analytical Sieving G-02 Bulk Density and Tapped Density 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 G-10 Powder Fineness G-11 Specific Surface Area G-13 Laser Diffraction Measurement of Particle Size G-14 X-Ray Powder Diffraction G-15 Water-solid Interaction G-16 Thermal Analysis G-20 Chromatography*1 G-21 Dynamic Light Scattering*2	B-01 Amino Acid Determination B-02 Capillary Electrophoresis B-03 Isoelectric Focusing B-05 Peptide Mapping B-06 Polyacrylamide Gel Electrophoresis

29 of the 31 general chapters have now been harmonised

*1 : Signed-Off in 2021

*2 : Under discussion towards first harmonisation

International Meeting of World Pharmacopoeias (IMWP)

- First convened by WHO in 2012.
- IMWP brings together national and regional pharmacopoeias, from across the globe, with the aim of fostering international co-operation and harmonisation by promoting fruitful discussions and information exchanges.
- The IMWP is an ideal platform to emphasize the role and importance of quality aspects when speaking about access to medicines worldwide.
- Pharmacopoeias set quality standards for manufacturers to produce medicines and vaccines which are safe and of good quality. Regulators ensure that manufacturers comply with these quality standards before medicines are authorized to be on the market and throughout the product's shelf life.
- Regular meetings attended by representatives from national, regional and international pharmacopoeias, all of which committed to working towards harmonisation and strengthening WHO's role in the development of global standards for the production and testing of medicines.

Fourteenth International Meeting of World Pharmacopoeias

8 – 10 November 2023

Good Pharmacopoeial Practices (GPhP)

- GPhP were developed by pharmacopoeial representatives under the auspices of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP).
- The development of GPhP to promote prospective harmonisation is perhaps the IMWP's greatest achievement to date.
- The primary aim was to define approaches and policies for establishing pharmacopoeial standards in general, with a particular focus on harmonisation.
- The set of principles laid down in the GPhP provide guidance on the design, development and maintenance of pharmacopoeial standards for national, regional and international pharmacopoeias. Initially focussed on pharmaceutical ingredients and medicinal products, two new chapters – monographs for compounded preparations and monographs on herbal medicines – have since been added.

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)

- The ICH is a unique organisation that brings together regulatory authorities and the pharmaceutical industry to discuss scientific and technical aspects of drug registration.
- Since it was founded in 1990, it has been the ICH's mission to **promote and support harmonisation worldwide** to ensure that safe, effective and high quality medicines are developed and registered efficiently.
- Like other organisations, the ICH has had to adapt to an increasingly **globalised drug development industry**.
- Its main vehicle for achieving harmonisation is the **development of ICH guidelines** that are established through a process of scientific consensus and collaboration between regulators and industry experts.
- As an observer, the **EDQM** contributes to the development of ICH guidelines in a number of relevant areas, including the control of impurities, the development and validation of analytical procedures and continuous manufacturing.

ICH Q4B

- Q4B is an ICH Expert Working Group (EWG) established in November 2003.
- As with all of the ICH EWGs, it is **composed of regulators and industry representatives** of the three ICH regions, with some observers.
- The **subject** of Q4B is "Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions".
- The **texts** evaluated by Q4B are primarily the result of harmonisation by the Pharmacopoeial Discussion Group (PDG).
- The **aim** of Q4B is to recommend that the texts published in the three pharmacopoeias (Ph. Eur., JP and USP) can be used as interchangeable.
- Texts determined to be interchangeable, can be used by industry and accepted by the regulators of the three regions.
- The recommendation of interchangeability is provided in a series of topic-specific **"Annexes"** as published on the ICH website (www.ich.org).

The Q4B Process - Value of the Q4B Activity

- A component of international harmonisation efforts to assist in common specifications
- A savings in time, effort and cost
  - Industry: to globally unify testing strategies [for applications and other regulatory (compliance) needs] – one test rather than three
  - Regulators: to reduce or eliminate the need to go through a justification procedure as to the use of other compendial methods (done one time to eliminate repetitive justifications)

Interaction of PDG with ICH

ICH Q4B evaluates and recommends pharmacopoeial texts for use in the ICH regions. Once in agreement as interchangeable, the result was publicised as a guideline.

PDG (since 1989)		ICH Q4B (2003 – 2010)
Ph.Eur. (EDQM), JP (MHLW/PMDA), USP (USP)	Participant	Regulatory: EU, MHLW/PMDA, FDA Industry: EFPIA, JPMA, PhRMA
Harmonisation of Science (Analytical Method, Acceptance Criteria)	Activity	Regulatory Harmonisation Regulatory Guideline
General chapters, excipients monographs	Target	General chapters
Harmonised pharmacopoeial texts	Outcome	Guideline = Recommendation for regulatory use in the ICH regions

Maintainance ICH Q4B Annexes

The annexes of the ICH Q4B guideline covered 14 harmonized pharmacopoeial general chapters and were initially elaborated following an evaluation of the corresponding texts by an ICH expert working group.
Once the ICH Regulatory Members had agreed that the texts were interchangeable, the result was published as an annex to the ICH guideline.

The four ICH Regulatory Members at that time accepted references to the three PDG pharmacopoeias in marketing authorisation (MA) dossiers received in their region.

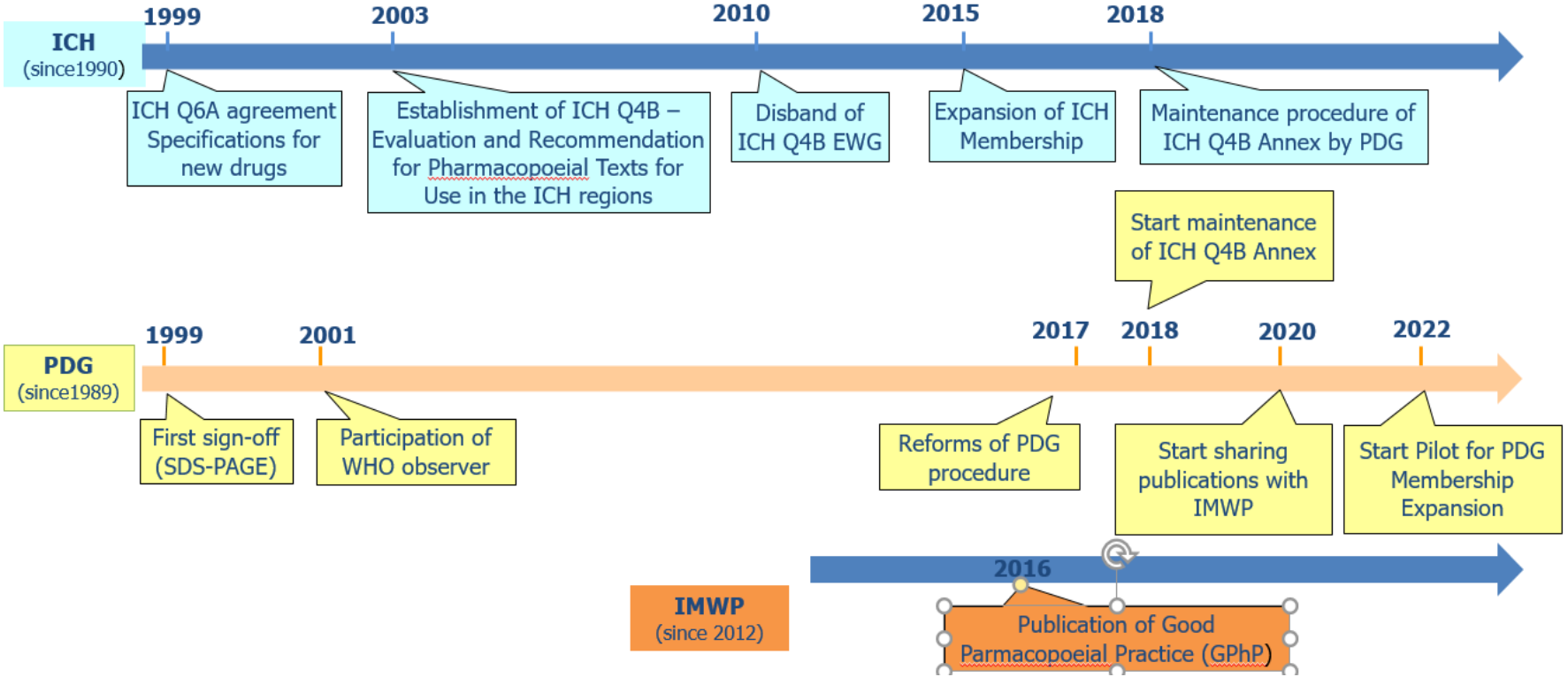
The ICH expert working group had been discontinued in 2010 and the intervening period had seen a growth in ICH membership and an evolution in the pharmacopoeial texts.

The PDG had been entrusted by ICH with updating the Q4B annexes and developing a new maintenance procedure to reflect the current situation, which now involved 15 ICH Regulatory Members and eight pharmacopoeias.

ICH Q4B Annexes

Q4A - Q4B Pharmacopoeias	
Q4A	Pharmacopoeial Harmonisation
Q4B	Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions
Q4B Annex 1(R1)	Residue on Ignition/Sulphated Ash General Chapter
Q4B Annex 2(R1)	Test for Extractable Volume of Parenteral Preparations General Chapter
Q4B Annex 3(R1)	Test for Particulate Contamination: Sub-Visible Particles General Chapter
Q4B Annex 4A(R1)	Microbiological Examination of Non-Sterile Products: Microbial Enumeration Tests General Chapter
Q4B Annex 4B(R1)	Microbiological Examination of Non-Sterile Products: Tests for Specified Micro-Organisms General Chapter
Q4B Annex 4C(R1)	Microbiological Examination of Non-Sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use General Chapter
Q4B Annex 5(R1)	Disintegration Test General Chapter
Q4B Annex 6	Uniformity of Dosage Units General Chapter
Q4B Annex 7(R2)	Dissolution Test General Chapter
Q4B Annex 8(R1)	Sterility Test General Chapter
Q4B Annex 9(R1)	Tablet Friability General Chapter
Q4B Annex 10(R1)	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

PDG Collaborative Activities with ICH and IMWP



Concluding remarks

- Globalisation and the ever-increasing expansion in international trade reinforce the need to develop and maintain global quality standards for medicines.

- Pharmacopoeial standards are a vital cog in the smooth functioning of marketing authorisation and market surveillance processes as well as in the free movement and trade of medicines across the globe.

- Harmonisation is essential for savings in time, effort and cost:

  - Industry: to globally unify testing strategies
  - Regulators: to reduce or eliminate the need to go through a justification procedure as to the use of other compendial methods

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