The 9th Edition of the Ph. Eur. & current hot topics

Japanese Pharmacopoiea 130th Annivsersary Symposium
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Toyko, Japan

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Agenda

- The Council of Europe and its EDQM
- The 9th Edition of the European Pharmacopoeia or how to turn challenges into opportunities and success
- Some examples of recent developments
- Collaboration with Japan

The Council of Europe

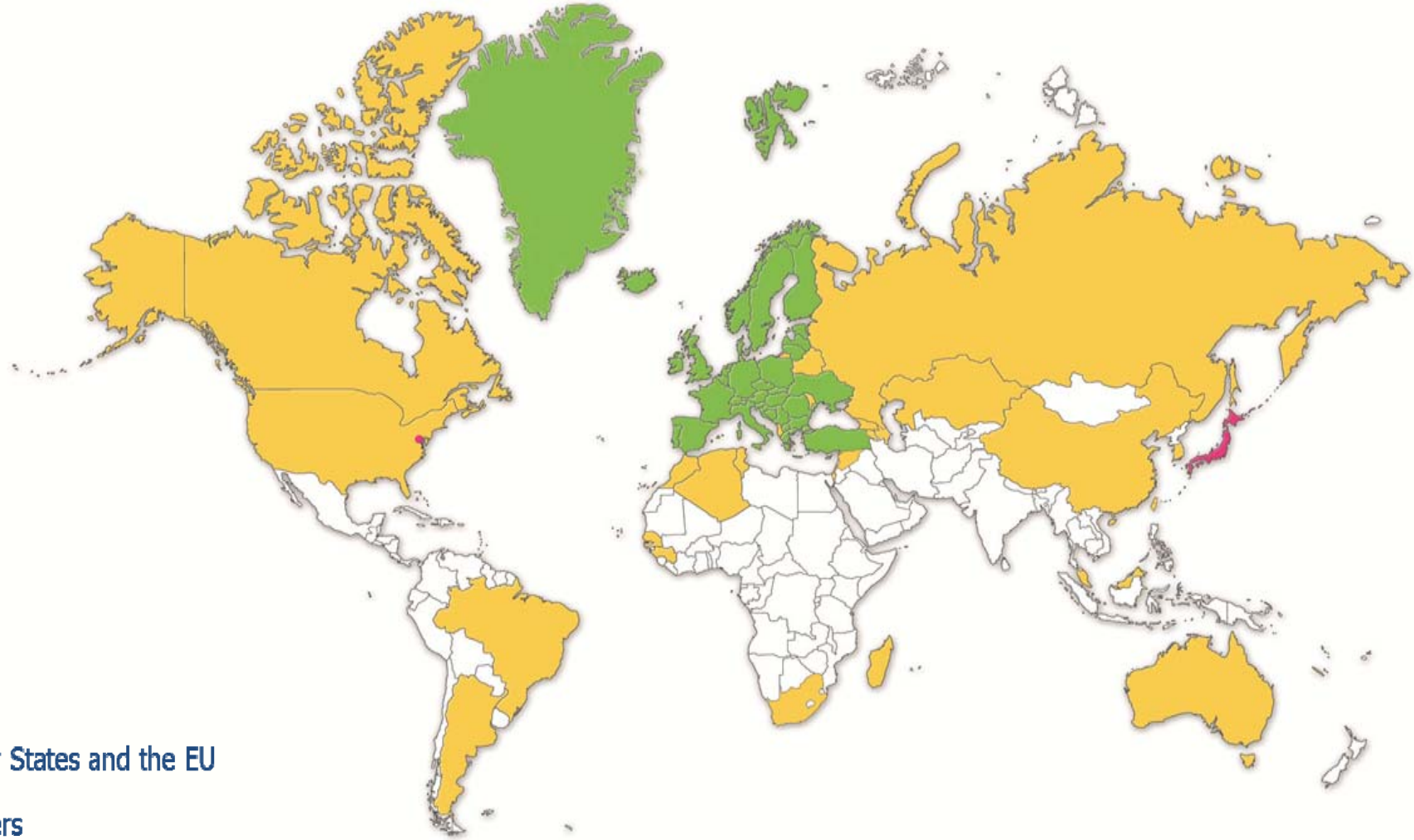
- Founded in 1949
- Headquarters in Strasbourg, France
- 47 member states > 820m citizens
- The oldest international organisation dedicated to fostering co-operation in Europe.
  - ➢ Promotes democracy
  - ➢ Protects human rights
  - ➢ Protects the rule of law

Member states

European Directorate for the Quality of Medicines & HealthCare (EDQM)

A Directorate of the Council of Europe (DG II)

Member states and observers



37 Member States and the EU

28 Observers

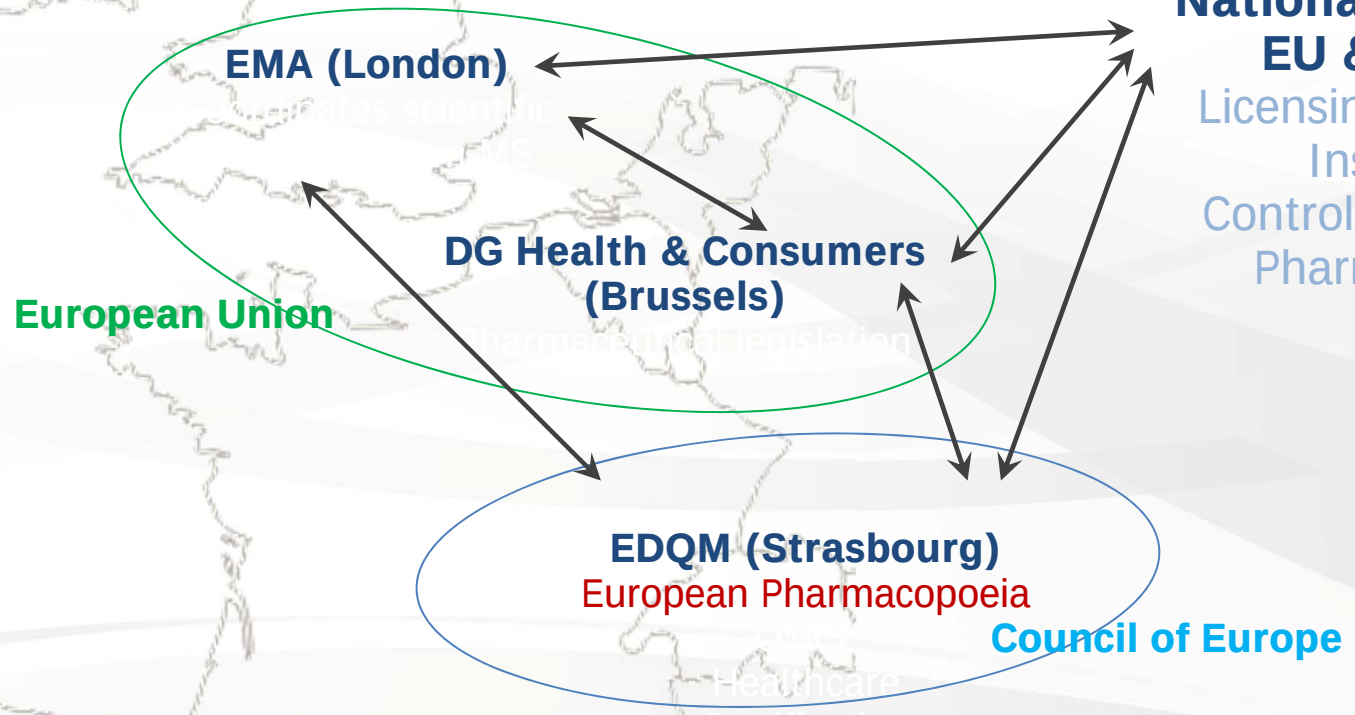
The 9th Edition of the Ph. Eur.

- Europe's legal and scientific benchmark for pharmacopoeial standards
- applicable in 37 European countries and used in over 100 countries worldwide.
- 121 new and 1403 revised texts compared to the 8th Edition => over 50% of the 9th Edition's content is new.

The Ph. Eur. network: An asset!

- More than 700 members in Ph. Eur. Groups
- Appointed by the Ph. Eur. Commission
- With a well balanced expertise:
  - Approx. 1/3 from Health Authorities including EMA => relationship with European regulators is a strength!
  - Approx. 1/3 from Industry
  - Approx. 1/3 from University, Hospital
- and the support of nearly 60 observers (from e.g. Algeria, Armenia, Australia, Belarus, Canada, Israel, Malaysia, Russian Federation, TFDA, USFDA)

Relationship with European Regulators: A strength of the Ph. Eur.!



The European Pharmacopoeia: a transparent process

- All revised and new texts published online in Pharmeuropa (the European pharmacopoeial forum, free access) for public enquiry
- Work programme available on EDQM website
- Style guide and technical guides freely available and downloadable on EDQM website
- Knowledge database (free access) ➔ useful information
- Organisation of hearings with interested parties
- .....

Basis for monographs

- Monographs must take account of all currently approved products on the European market
- 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 published in:

  Technical Guide for the Elaboration of Monographs

  recently revised (7th Edition – 2015) (available on the EDQM website)

In the field of …
Finished Product Monographs (FPM)

- With some exceptions, historically, focus on API and excipient monographs (e.g. monographs on immunosera for human use, immunosera for veterinary use, some biological preparations such as insulin preparations, radiopharmaceutical preparations, vaccines for human use and vaccines for veterinary use)
- Introduction of the general monograph Pharmaceutical preparations (2619)
- Guidance document on the elaboration of FPM available on EDQM website
- Monograph on Sitagliptin tablets published in Suppl. 8.7
- 16 FPM on the work programme *(1 FPM (Rosuvastatin tablets) on the P1 work programme)*

Current focus in FPM

Follows critical assessment and discussions: Takes into account usefulness of Ph. Eur. monographs and impact on registered products

- Priority on Single-source monographs on products that are potential future generics
- Immediate release dosage forms
- Solid and liquid formulations
- Will be expanded subsequently

In the field of … Biologicals

- New general chapter 5.2.12 *Raw materials for the production of cell-based and gene therapy medicinal products* (Publication in 9th Edition):
  - ✓ is non-mandatory
  - ✓ harmonises current practices
  - ✓ helps users to identify the critical quality attributes of raw materials
  - ✓ helps users to manage batch-to-batch variability and change control for raw materials
  - ✓ encourages raw material manufacturers to record and share information on the origin and quality of the raw material
- New general chapter 2.6.34 *Host Cell Protein assays* (Publication in Suppl. 9.1):
  - ✓ Provides guidance for the development and validation of HCP assay used to test products obtained by recombinant DNA technology
  - ✓ Use of alternative approaches acceptable to CA not excluded

In the field of … Biologicals

- Monograph on Teriparatide, elaborated under P4Bio procedure, (9th Edition)
- Elaboration of a monograph on human coagulation factor IX (rDNA) powder for solution for injection (2994) (Pharmeuropa 28.1), and of additional drug substance monographs pegfilgrastim (146th session – Pharmeuropa 28.2), Etanercept (147th session) and Darbepoietin alfa (151st session) as part of P4Bio
- Addition of a new monograph on Infliximab pilot phase on the MAB work programme (148th session) → public enquiry to come soon

In the field of … General Methods

Recently revised chapters:

- Water: micro determination 2.5.32
- Potentiometric titration 2.2.20
- Approximate pH of solutions 2.2.4
- Amperometric titration 2.2.19
- Potentiometric determination of ionic concentration using ion-selective electrodes 2.2.36
- Potentiometric determination of pH 2.2.3
- Raman spectroscopy 2.2.48
- Melting point 2.2.14

⇨ **Important elaboration/ revision program currently ongoing**

Just adopted (June 2016 → Ph Eur Suppl. 9.2):

- Primary standards for volumetric solutions 4.2.1. & Volumetric solutions 4.2.2
- Clarity and degree of opalescence 2.2.1

Underway (some examples only!):

- Chromatographic separation techniques 2.2.46
- Conductivity 2.2.38 **PDG**
- Dynamic Light Scattering (New for Ph Eur)
- Determination of elemental impurities (2.4.20)
- X-Ray fluorescence spectrometry 2.2.37
- IR absorption spectrophotometry 2.2.24
- Loss on Drying, 2.2.32
- UV-VIS spectrophotometry 2.2.25

In the field of … Control of Impurities

Organic impurities: ***A strength of the Ph. Eur.***

- Represents an essential part of individual monographs
- Control strategy follows ICH Q3 A
- Principles are laid down in general monograph 2034 « Substances for pharmaceutical use »
- « Transparency list » at the end of a monograph: provides list of the impurities which are controlled by the test(s) described in the monograph
- Limits defined for « specified », « unspecified » and the total of impurities

In the field of … Control of Impurities

EMA guideline on the specification limits for residues of metal catalysts or metal reagents
In force since 01/09/2008 (for new products)

Chapter 5.20 *Metal catalyst or metal reagent residues*
Chapter 2.4.20 *Determination of metal catalyst or metal reagent residues*

EU

Ph Eur

ICH Q3D for elemental impurities
Implementation schedule as decided by CHMP:
For new products: June 2016
For already existing products: December 2017

Decision taken by the Ph. Eur. Commission to align revision of Ph Eur texts with latest implementation schedule of ICH Q3D in Europe i.e. Dec 2017:

- *Individual monographs with cross-reference to Chapter 2.4.8 Heavy metals ➔ deletion of the cross-reference with the 9th Edition (01/01/17)*
- *General monograph Pharmaceutical preparation (2619) ➔ will refer to Chapter 5.20 ➔ ICH Q3D will become legally binding in all Ph Eur signatory parties (Pharmeuropa 28.2)*
- *General monograph Substances for pharmaceutical use (2034) => to clarify how to handle substances used in drug products outside of the scope of ICH Q3D guideline (Pharmeuropa 28.2)*
- *Chapter 5.20 ➔ revision to reproduce the principles of ICH Q3D instead of EMA GL*
- *Chapter 2.4.20 ➔ 1,- revision to align with ICH wording ; 2- harmonisation with USP & JP*
- *Discussion ongoing: impact on monographs for substances of natural origin (e.g. mined excipients) where elemental impurities are potentially present and not intentionally added.*

ICH
[EU, JP, US FDA, Health Canada, Swissmedic]

In the field of …
Water for Injections (0169)

current status

Ph. Eur.
WFI monograph

- **Quality standard**
- Defines quality of WFI in terms of **microbiological** & **physico-chemical requirements**

PRODUCTION section
revision:

- include **reverse osmosis coupled with suitable techniques** for producing WFI in addition to distillation;
- a requirement for '*regular total organic carbon monitoring*' is added to further emphasise the specific test controls required.

System design, operation, maintenance (validation and monitoring)

→ ***GMP requirements***

European Pharmacopeia Commission
Decision on work program – 146th Session, June 2013

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WAT Working Party
Preparation of draft revision – 7th Meeting, October 2014

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Public consultation on Pharmeuropa 27.2 (April 2015)
(Comments by 30 June 2015)

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WAT Working Party
Examination of comments

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Adopted by the Ph. Eur. Commission March 2016 → publication in Suppl. 9.1

Cooperation with JP

- JP is a long-standing and valued partner for the Ph. Eur. and the EDQM
- Long-time partnership in the context of PDG, established in 1989
- Informal prospective harmonisation of APIs → JP joined recently
- Informal exchange of knowledge and experience between Ph.Eur. and JP staff
- Signature of a Memorandum of Understanding to further strengthen cooperation on 13. Sept. 2016

Thank you for your attention

European Directorate for the Quality of Medicines & HealthCare (EDQM)