European Regulations for Medicines

Place and Role of the European Pharmacopoeia in Europe – Ph. Eur. concept

Cathie VIELLE

Head of the Ph. Eur. Department, EDQM

THE PLACE OF THE PH. EUR. IN EUROPE

The Council of Europe

Founded in 1949

Development of European common and democratic principles

47 member countries

Headquarters in Strasbourg

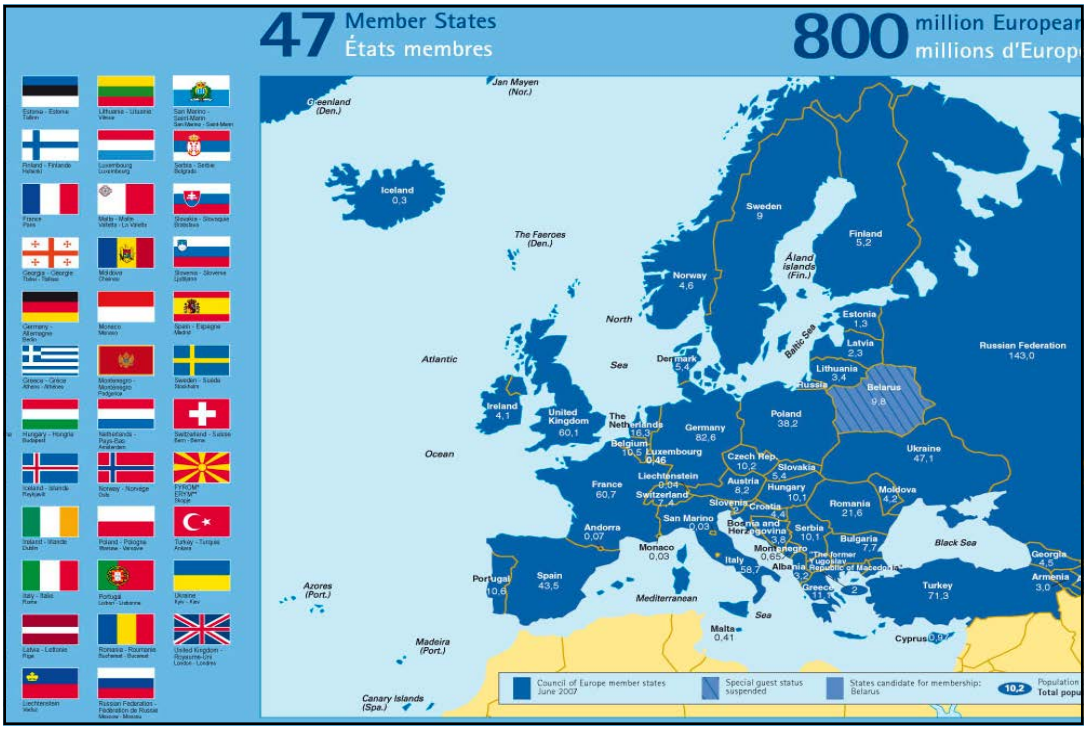
Core values:

– protection of human rights

– pluralist democracy and the rule of law

The Council of Europe is not the European Union!

- **European Union (EU):** a unique economic and political partnership between currently 28 European countries ⇒ more than 500 million citizens.
- **European Council:** the EU's main decision-making body. It defines the general political direction and priorities of the European Union.

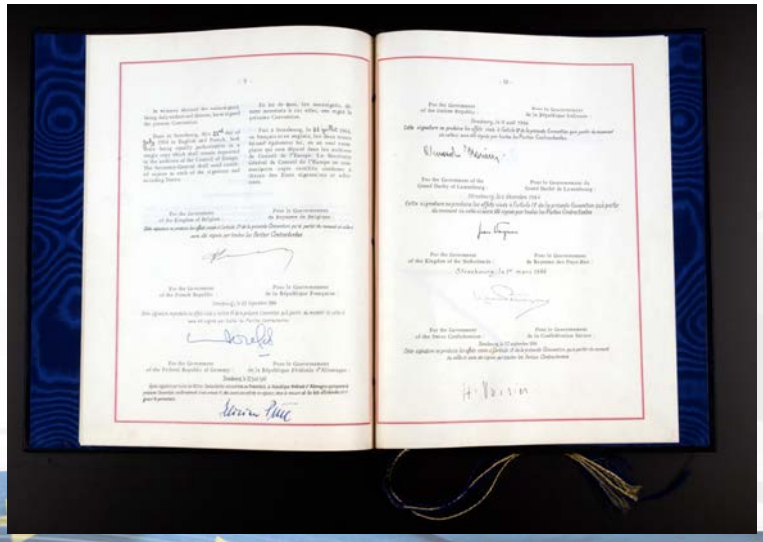


European Directorate for the Quality of Medicines & HealthCare

- A Council of Europe Directorate, based on the Convention on the Elaboration of a European Pharmacopoeia (PA, 1964)
- Mission: to contribute to a basic human right: access to good quality medicines and healthcare

6

European Pharmacopoeia Convention



European Pharmacopoeia Convention

Article 1:

The Contracting Parties undertake

a) Progressively to elaborate a Pharmacopoeia which shall be common to the countries concerned and which shall be entitled “European Pharmacopoeia”;

b) To take the necessary measures to ensure that the monographs which will be adopted... and which will constitute the European Pharmacopoeia shall become the official standards applicable within their respective countries.

Strasbourg, 22 July 1964

Why still national Pharmacopoeias?

- For texts of interest to one Member State only; for texts out of the scope of the Ph. Eur. (e.g. national formularies)
- Three main approaches (country specific):
  - ➢ Discontinuation of the national pharmacopoeia (e.g. Sweden, Finland, the Netherlands), Ph. Eur. as the only pharmacopoeia, potentially translated into national language
  - ➢ Maintenance of a national pharmacopoeia to complement the Ph. Eur.:
    - Inclusion of the Ph. Eur. in the national pharmacopoeia (e.g. British Pharmacopoeia, Royal Spanish Pharmacopoeia)
    - Publication of a National pharmacopoeia in addition to the Ph. Eur. (e.g. France, Germany, Switzerland, Austria)

Ph. Eur. / National Pharmacopoeia / 3rd country Pharmacopoeia in the EU

Ph. Eur.

With respect to the quality part (chemical, pharmaceutical and biological) of the dossier, all monographs including general monographs and general chapters of the European Pharmacopoeia are applicable.

Nat. Ph.

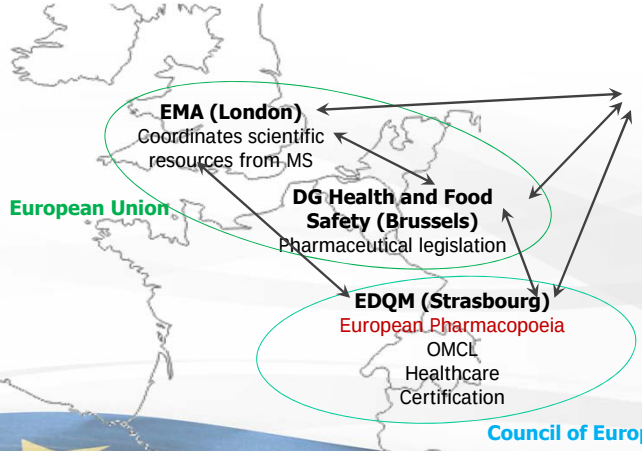
The monographs of the European Pharmacopoeia shall be applicable to all substances, preparations and pharmaceutical forms appearing in it. In respect of other substances, each Member State may require observance of its own national pharmacopoeia.

3rd country Ph.

In case where starting and raw materials, active substance(s) or excipient(s) are described neither in the European Pharmacopoeia nor in the pharmacopoeia of a Member State, compliance with the monograph of a third country pharmacopoeia can be accepted. In such cases, the applicant shall submit a copy of the monograph accompanied by the validation of the analytical procedures contained in the monograph and by a translation where appropriate.

Directive 2003/63/EC, 3. MODULE 3: CHEMICAL, PHARMACEUTICAL AND BIOLOGICAL INFORMATION FOR MEDICINAL PRODUCTS CONTAINING CHEMICAL AND/OR BIOLOGICAL ACTIVE SUBSTANCES, 3.2 Content and Basic Principles

Key players for the quality of medicines



National Authorities EU & non-EU
Licensing Authorities
Inspection
Control Laboratories
Pharmacopoeia

11

The Pharmacopoeia in the EU Legislation

The Ph. Eur. is legally binding, but the legislation foresees a mechanism to provide the pharmacopoeia authority with information on the quality of products on the market; an excellent tool to ensure that monographs are not cast in stone but routinely updated to reflect the state-of-the-art.

12

ELABORATION AND MAINTENANCE OF THE PH. EUR.: PRINCIPLES

European Pharmacopoeia (Ph. Eur.)

- Protecting public health - one common compulsory standard.
- The Ph. Eur. is the official pharmacopoeia in Europe – complemented by national pharmacopoeias for texts of interest to only one Member State.
- Mandatory at the same date in 38 Member States (CoE) and the EU (decision of Ph. Eur. Commission).
- Legally binding quality standards for ALL medicinal products in its member states, i.e. raw material, preparations, dosage forms, containers must comply with the Ph. Eur. requirements when they exist.

Ph. Eur. Commission

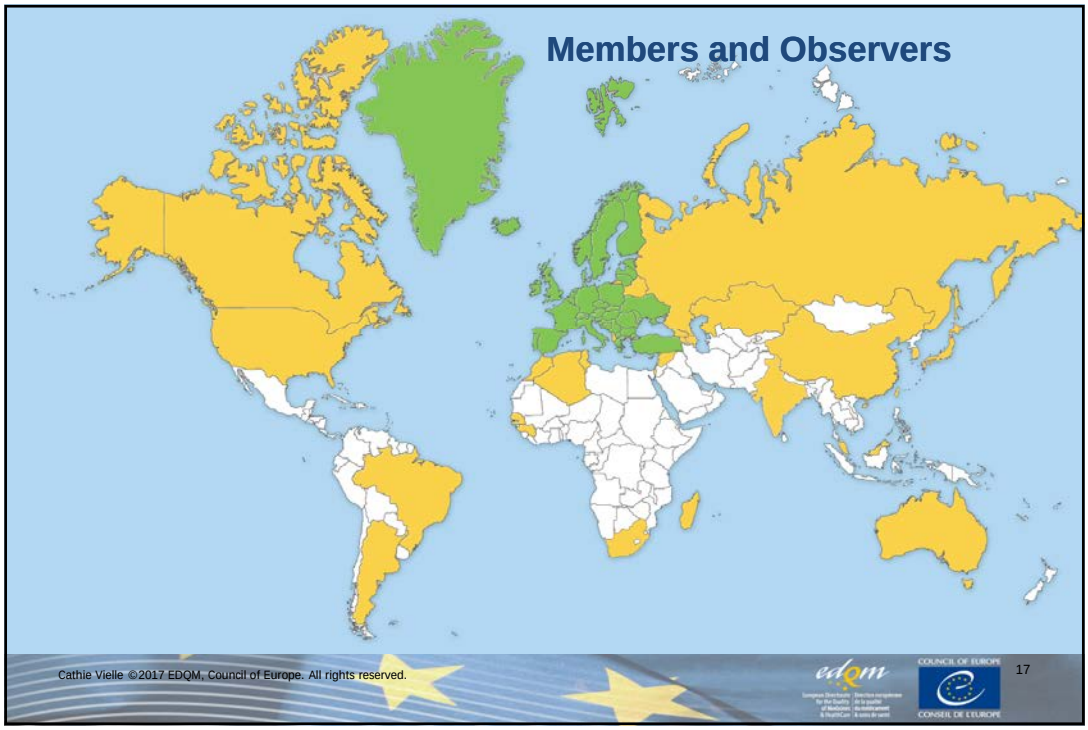
- One delegation per member state or observer;
- 38 Member States plus a delegation from the EU (a representative from DG Health & Food Safety and the EMA);
  Observers: 27 countries (incl. 7 European countries), Taiwan Food and Drug Administration (TFDA) and World Health Organization (WHO);
- Delegates mainly come from health ministries, health authorities, pharmacopoeias and universities and are appointed by the national authorities on the basis of their expertise;
- Three sessions a year;
- Draft texts are published for public consultation and adopted by unanimous vote;
- EDQM/EPD provides the secretariat.

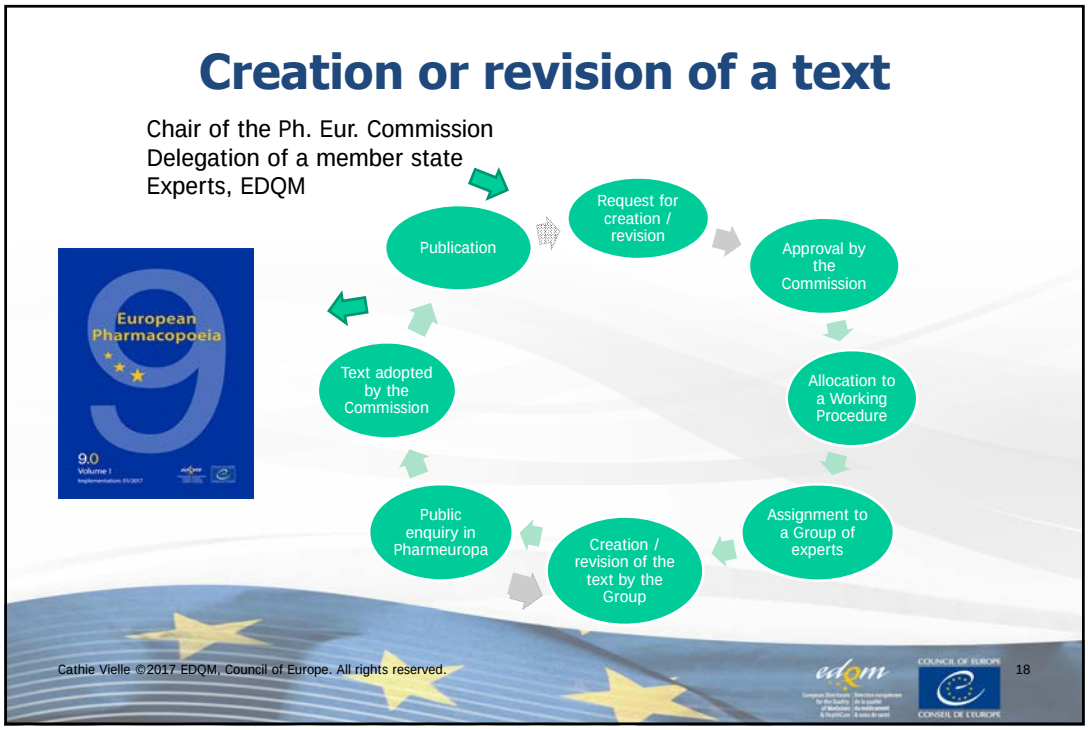
15

Ph. Eur. network

- 59 active Groups of experts and working parties (+ 13 “dormant”) elaborating and revising texts, meeting up to 3 times a year;
- More than 700 experts, mainly from Competent Authorities **(NPAs, Assessors, OMCL, Inspectors)**, Industry, Universities;
- Mainly from Ph. Eur. member states but also from abroad (Brazil, US FDA, Australia, India, Korea, Madagascar, etc.).

16





CONCEPT OF THE PH. EUR.

Content and structure of the Ph. Eur.

General Notices

General chapters

General monographs

Individual monographs

General notices

- Apply to **all** texts
- Provide basic information to the user and rules to understand texts, conventional expressions
- Address general issues

21

General Notices

At the very beginning of the Ph. Eur. (page 3)

- address general issues
- aim at providing basic information to the user
- apply to **all** texts
- include rules to understand texts, conventional expressions

Essential reading before starting to use monographs and chapters

22

Conventional terms: meanings

'competent authority': the national, supranational or international body / organisation vested with the authority for making decisions concerning the issue in question. May be a national pharmacopoeia authority, a licensing authority or an official control laboratory.

'unless otherwise justified and authorised' means that the requirements have to be met, unless the competent authority authorises a modification or an exemption where justified in a particular case.

Etc...

23

Flexibility in the Ph.Eur. Alternative methods

24

Alternative methods

- Ph. Eur. tests = reference methods, alone authoritative in cases of doubt or dispute.
- Compliance required, but alternative methods may be used: same pass/fail decision
- Users' responsibility to demonstrate their suitability. Approval of *competent authority* needed in any case
  The EDQM does not decide if acceptable or not!

Alternative methods

"The tests and assays described are the official methods upon which the standards of the Pharmacopoeia are based. With the agreement of the competent authority, alternative methods of analysis may be used for control purposes, provided that the methods used enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official methods were used. In the event of doubt or dispute, the methods of analysis of the Pharmacopoeia are alone authoritative."

Flexibility in the Ph. Eur.
Waiving of tests

Compliance to Ph. Eur. ≠ Performance of tests

↓ requisite

↓ not prerequisite

- In some cases, some tests may be omitted based on validation data or other suitable justification
- Tests for process-specific impurities may be omitted if it is demonstrated that they will not occur with the particular process used.

27

Waiving of tests

"(1) *An article is not of Pharmacopoeia quality unless it complies with all the requirements stated in the monograph. This does not imply that performance of all the tests in a monograph is necessarily a prerequisite for a manufacturer in assessing compliance with the Pharmacopoeia before release of a product. The manufacturer may obtain assurance that a product is of Pharmacopoeia quality on the basis of its design, together with its control strategy and data derived, for example, from validation studies of the manufacturing process."*

28

Flexibility in the Ph.Eur. PAT

"(2) *An enhanced approach to quality control could utilise process analytical technology (PAT) and/or real-time release testing (including parametric release) strategies as alternatives to end-product testing alone. Real-time release testing in circumstances deemed appropriate by the competent authority is thus not precluded by the need to comply with the Pharmacopoeia.*"

General chapters 1/2

1. General methods:
   - Give general requirements for equipment and procedures
   - Editorial convenience: avoid repetition in each monograph
   - Provide standard procedures that can be used where there is no monograph
2. General texts:
   - Informative texts
   - Specific to certain topics (e.g. microbiology, chemometrics)
   - In some cases, reproduces the principles of regulatory guidelines

Why general chapters?

Analytical methods:

- Editorial convenience: avoid repeating standard methods in each monograph
- Provide standard methods that can be used when there is no monograph
- Give general requirements for equipment, equipment qualification or calibration

General chapters

- Not mandatory "*per se*"
- When referred to in a monograph, they become part of the standard
- Can be used for substances not covered by monographs → may need validation
- Some general chapters are not referred to in any monograph useful guidance, can be referred to in applications

General monographs

1. General monographs on dosage forms:
   - Classified by pharmaceutical form/route of administration
   - Applied during licensing (if applicable)
2. General monographs on classes of substances
   - "Classes" defined by: production method, origin, risk factors (e.g. fermentation, TSE risk)
   - Aspects that cannot be treated in each individual monograph such as residual solvents, bacterial endotoxins ...
   - Quality aspects that are common to a class of products

General monographs

- Complementary to the individual monograph (unless otherwise indicated)
- General monographs are ALL mandatory and apply to ALL substances and preparations within the scope of the Definition section of the general monograph
- No cross-reference in individual monographs: Check in the Introduction & Definition which monograph applies!

Individual monographs

- Substance based
- Specific
- But… not stand-alone

Thank you!