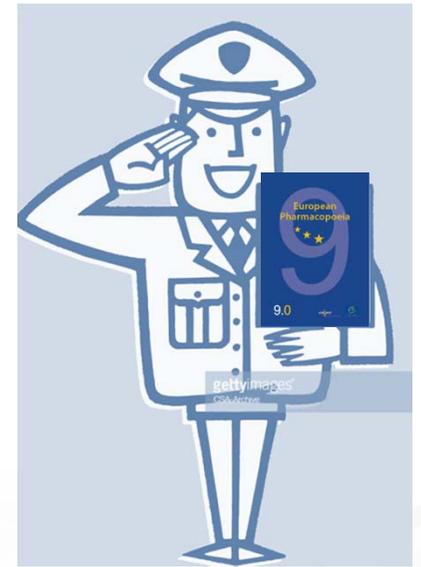


At your command... General Methods in the Ph. Eur.



Swissmedic Expertentagung Pharmakopöe 2018

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European Pharmacopoeia, EDQM



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



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 the basic human right of access to good quality medicines and healthcare



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 on 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 materials, 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); 28 Observer countries plus 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.
- Meets three times a year in closed sessions.
- Draft texts are published for public consultation; all technical decisions are taken by unanimous vote.
- EDQM/EPD provides the technical secretariat.



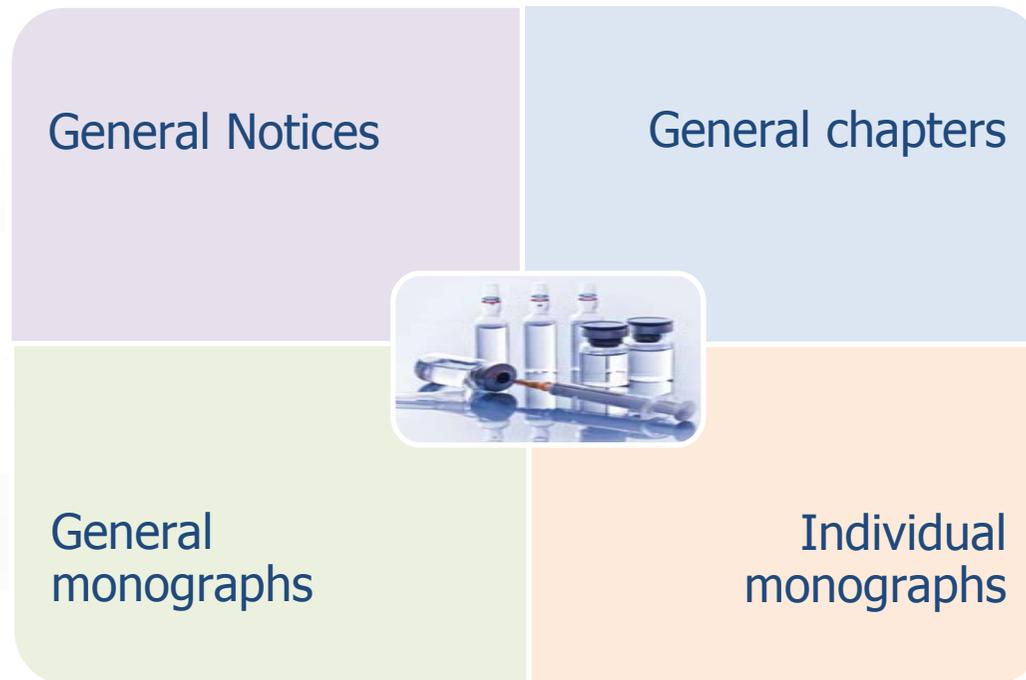
Ph. Eur. network



- **Currently 59 active groups** of experts and working parties (+ 13 “dormant”) elaborating and revising texts, meeting up to 3 times a year.
- **More than 800 experts**, mainly from Competent Authorities (NPAs, Assessors, OMCLs, Inspectors), Industry, Universities.

Mainly from Ph. Eur. member states but also from abroad (Brazil, US FDA, Australia, India, Korea, etc.).

Content and structure of the Ph. Eur.



General notices



- Apply to **all** texts
- Provide basic information for users and rules on how to understand texts, conventional expressions
- Address general issues

General chapters 1/2



1. General methods (GM):

- 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

General chapters 2/2

- Not mandatory on their own
- When referred to in a monograph (general or individual), they become part of the standard
- Some chapters are only informative or provide examples → this is clearly indicated

General monographs 1/2



1. General monographs on dosage forms:

- Classified by pharmaceutical form/route of administration
- Applied during licensing (if relevant)

2. General monographs on classes of substances

- “Classes” defined by production method, origin, risk factors (e.g. fermentation, TSE risk)
- Aspects not treated in each individual monograph such as residual solvents, bacterial endotoxins, etc.
- Shared quality aspects

General monographs 2/2

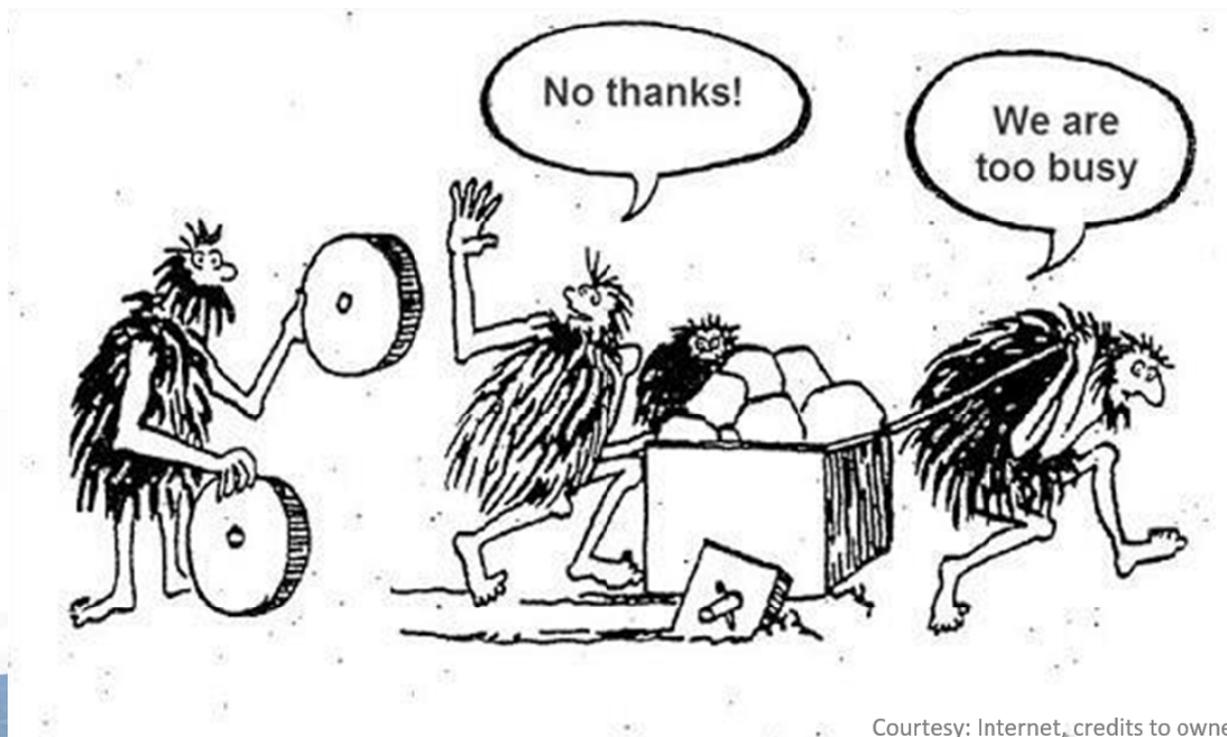
- Complementary to the individual monograph (unless otherwise indicated)
- ALL general monographs are mandatory and apply to ALL substances and preparations falling within the scope of the Definition section of the general monograph
- No cross-reference in individual monographs: check the Introduction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

Individual monographs



- Substance/Product based
- Specific
- But... not stand-alone

General methods modernisation program



Courtesy: Internet, credits to owner

Why was it needed?

- Need for more flexibility for GM revision process
- More than 300 GMs and texts to maintain
- Most texts had not been revised since 1st publication (> 15 years)
- Increasing amount of Helpdesk queries
- Problem of some standard methods (e.g. LOD): all groups concerned but no direct responsibility
- Impact on individual monographs
- Working on new general methods or general texts

What is the objective?

- ✓ To move from an essentially reactive approach to a pro-active approach
- ✓ To include recent techniques and produce a Pharmacopoeia which is scientifically state-of-the-art
- ✓ To improve existing methods to take into account recent progress in analytical technology and regulatory practice
- ✓ To standardise the content and format of the texts
- ✓ To introduce and/or improve elements of equipment performance and qualification -> increase user-friendliness
- ✓ To introduce and/or improve universal system suitability tests
- ✓ To suppress toxic reagents or materials

How?



Creation of a dedicated working party, "MG", mandated to:

- ✓ Create a template for GM texts
- ✓ Develop a more flexible approach for revision of GMs:
 - ✓ Work by correspondence
 - ✓ Status of ad hoc specialists
 - ✓ Creation of sub-groups
- ✓ Identification and prioritisation of revisions
- ✓ Use the momentum created by other working parties also active with GMs (e.g. VSADM, CST)
- ✓ Step-up communication on revisions and new publications (e.g. press releases, social media)

First achievements

Recently revised chapters:

- Standardisation of volumetric solutions 4.2.2
- Melting point 2.2.14
- X-Ray fluorescence spectrometry 2.2.37
- Clarity and degree of opalescence 2.2.1
- Infrared absorption spectrophotometry 2.2.24
- Raman spectroscopy 2.2.48
- Conductivity 2.2.38
(in international harmonisation)





Melting point 2.2.14

Revision adopted in March 2016 (Supp. 9.1)

- Capillary method with manual determination
- In 2002 an instrumental method 2.2.60 was developed, but no reference was added to monographs (unlike method 2.2.14)
=> method 2.2.60 was not used
- With revision, both methods, i.e. 2.2.14 & 2.2.60, merged to allow the use of instrumental determination
- Impact on 270 monographs



IR absorption spectrophotometry, 2.2.24

Revision adopted in March 2018 (Supp. 9.7)

- Extended description of ATR measurement
- Control of equipment performance modified
- Removal of monochromator instruments
- New sections on applications and limitations
- Guidance on the use of spectra libraries
- Description of procedures for the comparison of spectra



Ongoing revisions

- Chromatographic separation techniques 2.2.46 (PDG)
- Elemental impurities 2.4.20 (PDG)
- UV-VIS spectrophotometry 2.2.25
- Loss on drying 2.2.32
- Osmolality 2.2.35





Chromatographic separation techniques, 2.2.46

- Provides definitions and calculation methods for common parameters (peak, retention time, resolution, etc.)
- Defines bounds within which chromatographic conditions could be adjusted without revalidation, e.g. composition of mobile phase, column length, particle size,
- Provides universal system suitability parameters, not repeated in monographs, e.g. minimum S/N ratio at reporting threshold, limits of symmetry factor
→ become mandatory part of the monograph

Public consultation stage complete, draft now being further discussed within PDG and with regulators

➔ If adopted, would mean major changes, e.g. LC to UHPLC, symmetry factor 0.8 to 1.8, and harmonisation of parameters



Absorption spectrophotometry, ultraviolet and visible, 2.2.25

To be presented for adoption in June 2018

- Now also covers UV-Vis detectors used in liquid chromatography and in PAT applications
- Equipment qualification section improved
- Clarification of requirements
- Replacement of potassium dichromate (REACH regulation)
➔ Nicotinic acid for equipment qualification CRS will be available to test absorbance accuracy and linearity



Loss on drying, 2.2.32

To be presented for adoption in June 2018

- Diphosphorous pentoxide (toxic, obsolete) replaced by molecular sieve as drying agent
- Use of "high vacuum" discouraged
- Other instruments allowed with validation (microwaves, halogen lamps, etc.)
- Since Ph. Eur. 9.4, new CRS material: *sodium aminosalicylate for equipment qualification CRS*

General texts

For information and guidance.
But may also be subject to revision



Examples:

- 5.4 Residual solvents (keeping up-to-date with ICH guideline)
- 5.12 Reference standards
- 5.1.6 Alternative methods for control of microbiological quality
- 5.20 Elemental impurities

New general texts

✓ 5.21 Chemometric methods applied to analytical data (Supp. 8.7)

- chemometrics well suited for PAT applications
- provide alternative analytical tools
- allow for investigation of large data tables and treatment of intricate signals

✓ 5.24 Chemical imaging (Supp. 9.3)

- can be used to support PAT applications
- CI measures spatial distribution and contributes to understanding the properties of materials such as finished products, excipients, APIs and starting materials
- represents a versatile tool used in process development and may enhance process understanding.



Some new texts in the pipeline

- Evaporative light scattering detection 2.2.62
- Direct amperometric and pulsed electrochemical detection 2.2.63
- Scanning electron microscopy 2.9.52
- Implementation of pharmacopoeial methods 5.26
- Cross-validation 5.27
- Multi-variate statistical process control 5.28

Challenges

- Increasing visibility before and during the revision process (≠ monographs for which users are notified)
- Finding reliable information on instruments
- Enrolling method specialists
- Versatility of instruments and methods
- Finding the right balance to not turn the GM into a textbook
- Perform lab testing or not
- Impact on many existing monographs
 - Loss on drying: ~1100 monographs
 - IR: ~1200 monographs
- Revision of some of the historical methods (wet chemistry)
- It takes time to come up with a good quality text !

But together let's...

★ ★ ★ ★ ★
**MAKE
GENERAL METHODS
GREAT AGAIN!**
★ ★ ★ ★ ★



Thank you for your attention!

