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

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EDQM – Ph. Eur. Information Session

GENERAL METHODS IN THE Ph. Eur. CONCRETE EXAMPLES

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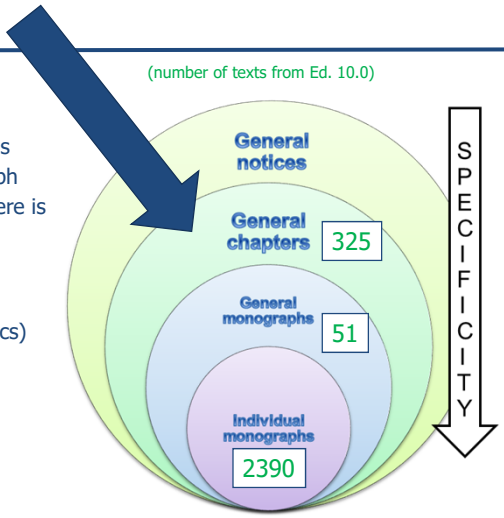
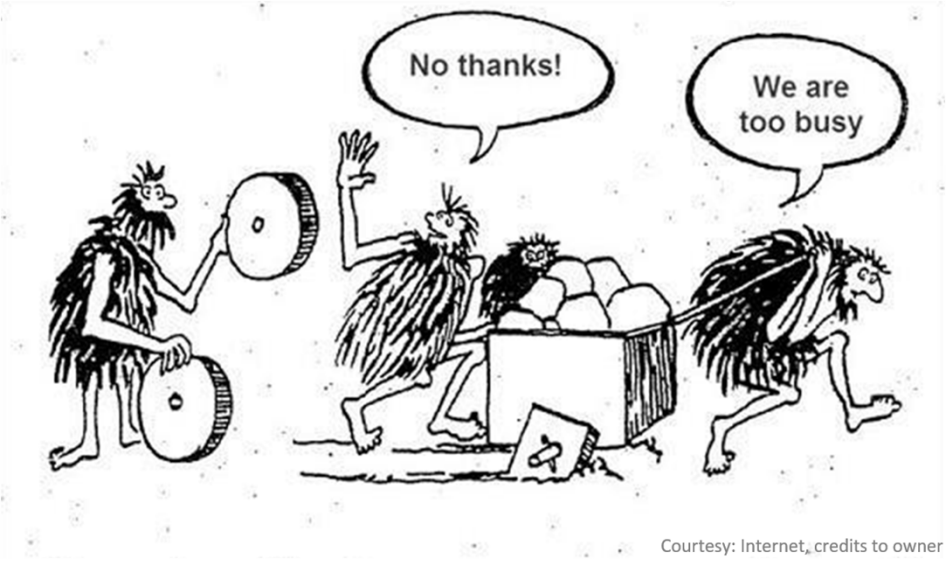
Focus on General chapters

- Section 2: Methods of analysis (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
- Section 5: General texts:
  - Informative texts
  - Specific to certain topics (e.g. microbiology, chemometrics)
  - In some cases, reproduces the principles of regulatory guidelines



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

General methods modernisation programme



Courtesy: Internet, credits to owner

Why was such a programme needed ?

Going ahead with the revision process of General Methods (GM) :

- More than 300 GMs and texts to maintain up-to-date
- Most texts were not reviewed since first publication (> 15 years)
- Facing increasing interest raised by users via the Heldpesk
- Tackling revisions of some standard methods (e.g. LOD) : all groups are concerned, but none has the responsibility in up-dating the chapter

And :

- Impact assessment on individual monographs needed
- New methods and texts are usually out-of-scope of regular groups, unless really dedicated to the field

What is the objective ?

- To shift from a reactive approach to a pro-active approach
- To include recent progress in analytical technology and produce a Pharmacopoeia which is scientifically state-of-the-art
- To follow development in regulatory practice
- To standardise the content and format of general texts (template)
- To introduce and/or improve elements of equipment performance and qualification
- To introduce and/or improve universal system suitability tests
- To suppress toxic reagents or materials
- To increase user-friendliness

Recent achievements : revised/new GMs

(Not exhaustive)

- X-ray fluorescence spectrometry, 2.2.37
- Optical rotation, 2.2.7
- Conductivity (Int. Harm.), 2.2.38
- Osmolality, 2.2.35
- Loss on drying, 2.2.32
- Infrared absorption spectrophotometry, 2.2.24
- UV/Visible spectrophotometry, 2.2.25
- Degree of coloration of liquids (Int. Harm.), 2.2.2
- Test for BET using recombinant factor C, 2.6.32

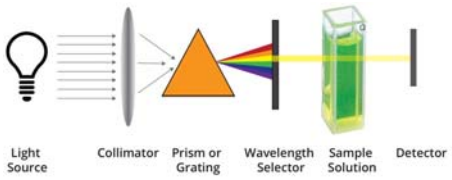
Loss on drying, 2.2.32

- Diphosphorous pentoxide (toxic and obsolete) replaced by molecular sieves as drying agent
- Definition of « constant mass » added
- Clarification of the requirements
- Use of "high vacuum" discouraged (problem of equipment availability)
- Other equipment allowed with validation (microwaves, halogen lamps, etc.)
- Since Ph. Eur. 9.4: *sodium aminosalicylate for equipment qualification CRS*

  ➢ Impact on about 1100 monographs !

UV-Vis absorption spectrophotometry, 2.2.25

- Addition of UV-Vis detectors used in liquid chromatography and in PAT applications
- Equipment qualification section improved
- Clarification of requirements: link to the intended use
- Fixed performance criteria but flexibility in the use of certified material
- *Nicotinic acid for equipment qualification CRS* as alternative to potassium dichromate (REACH regulation) for test of absorbance accuracy and linearity



BET using recombinant factor C, 2.6.32

- The classical BET (2.6.14) is based on limulus amoebocyte lysate (LAL) from the horseshoe crab (endangered species)
- Chapter 2.6.32 describes a method using recombinant factor C (synthetic reagent) and fluorimetric detection
- More sustainable, reduce the pressure on animal resources
- Revised general text *5.1.10. Guidelines for using the test for bacterial endotoxins,* clarifies conditions for the introduction of rFC-based methods by users of the Ph. Eur.

Some updates in the pipeline

★ International harmonisation

★Chromatographic separation techniques, 2.2.46 (after Pharmeuropa)

★Determination of elemental impurities, 2.4.20 (after Pharmeuropa)

- Balances, 2.1.7 (after Pharmeuropa)
- N-Nitrosamines in active substances, 2.4.36 (Pharmeuropa 32.2)
- Raman spectroscopy, 2.2.48 (Pharmeuropa 32.3)

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

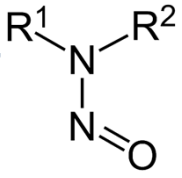
Public consultation stage complete, draft now being further discussed within PDG and with regulators

➡ When adopted, will mean major changes, e.g. transfer to UHPLC, symmetry factor 0.8 to 1.8, and harmonisation of parameters such as resolution calculation

Balances, 2.1.7

- Added project after repeated user requests and survey with stakeholders
- Scope: balances for analytical purposes (not manufacturing)
- Builds upon already published guidance to fit in the regulatory landscape
- Recommendations for performance checks on main contributors to measurement error (sensitivity and repeatability)
- Definition of minimum weight

N-Nitrosamines in active substances, 2.4.36



- angiotensin-II-receptor antagonists (sartans) containing a tetrazole group; in the Ph. Eur.: valsartan, losartan potassium, candesartan cilexetil, irbesartan and olmesartan medoxomil
- Limit test at 0.03 ppm
- 7 N-Nitrosamines in total: NDMA, NDEA, NDBA, NMBA, NDiPA, NEiPA and NDPA
- Set of 3 validated analytical procedures relying on different chromatographic separation techniques (GC and LC) and mass spectrometry detection
- varied set of procedures using different instruments, thus covering the needs of many quality control laboratories in Europe and beyond

In public consultation (32.2)

New chapters recently published or adopted

✓Scanning electron microscopy, 2.9.52 (Ed. 10.0)

- Imaging and chemical characterisation capabilities to evaluate morphology, size, shape and elemental composition of pharmaceutical products

✓Process analytical technology, 5.25 (Ed. 10.0)

- general approach to the integration of analytical techniques in the process environment

✓Recommendations on testing of particulate contamination: visible particles, 5.17.2 (Supp. 10.3)

- provides guidance on how users can establish that their product is "practically free from particles".

✓Multivariate statistical process control, 5.28 (Supp. 10.4)

- analyse data with potentially correlated variables and generation of control charts for control and improvement of manufacturing processes.
- tool for continuous manufacturing (CM), real-time release testing (RTRT).

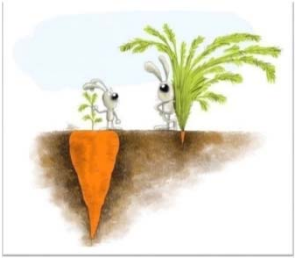
Recent major additions on the work program

- Implementation of pharmacopoeial methods, 5.26
  - ➢ Guidance to assess to which extent the pharmacopoeial method is suitable and adequately performing for its intended purpose given the actual conditions of use in the laboratory of concern
- Comparability testing of alternative methods, 5.27
  - ➢ Guidance for equivalence testing when the official method (i.e. the pharmacopoeial method), is replaced by an alternative method for control purposes
- General procedures for analysis of recombinant therapeutic mAbs, 2.5.43, 2.5.44 & 2.7.26
  - ➢ Development of general SEC, cIEF procedures for mAbs and biological assays for anti-TNF-alpha product class
- Evaporative light scattering detection, 2.2.62

Challenges

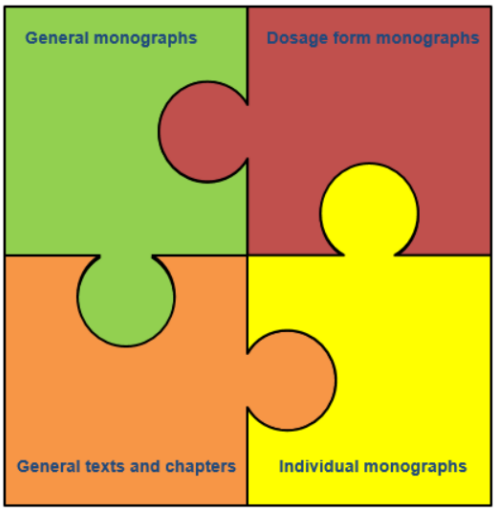
- Number (300+) and diversity of methods
- Build-in of paradigm shifts: QbD, RTRT, data treatment …
- Enrolling method/instrument specialists
- Generation of representative data, laboratory studies
- High impact on many existing monographs (transversal view)
  - Loss on drying: ~1100 monographs
  - IR: ~1200 monographs
- Revision of some historical methods (long-lost expertise)
- Obtaining reliable up-to-date information on instruments
- Finding the right balance to not turn the GM into a textbook
- Ensuring maximum visibility before and during the revision/elaboration process
- Communication with all stakeholders (internal and external)

It takes effort to come up with good quality, well balanced texts…



… while keeping pace with the evolution in the technology and regulatory environment

An essential piece of the puzzle !



Great general texts will help build clear requirements and support development of appropriate monographs

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