

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

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General Chapters

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Content of the presentation



- Types of general chapters
- Modernisation program
- Important revisions
- New chapters

Types of general chapters

- General Methods:
describe analytical methods (2-series)
- General Texts:
of more general character, often for information
and users' guidance, sometimes reproduction of
guidelines

Both become mandatory when referred to in a monograph

Modernisation program: what is the objective?

- ✓ To include recent techniques and ensure that the European Pharmacopoeia 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 system suitability tests
- ✓ To minimise or eliminate use of toxic materials (see REACH)

What have we done?

Recently newly elaborated / revised general methods

- ✓ Melting point 2.2.14 (Supplement 9.1)
- ✓ Standardisation of volumetric solutions 4.2.2 (Supplement 9.2)
- ✓ Clarity and degree of opalescence 2.2.1 (Supplement 9.2)
- ✓ Functionality Related Characteristics 5.15 (Supplement 9.2)
- ✓ X-Ray fluorescence spectrometry 2.2.37 (Supplement 9.3)
- ✓ Nickel in hydrogenated vegetable oils 2.4.31 (Supplement 9.4)
- ✓ Water: micro determination 2.5.32 (Supplement 9.4)
- ✓ Infrared Absorption Spectrophotometry 2.2.24 (Supplement 9.7)
- ✓ Loss on drying 2.2.32 (Supplement 9.8)
- ✓ Osmolality 2.2.35 (Supplement 9.8)
- ✓ UV-VIS spectrophotometry 2.2.25 (Edition 10.0)
- ✓ Scanning electron microscopy 2.9.52 (Edition 10.0)

What have we done?

Recently newly elaborated / revised general texts

- 5.15 Functionality Related Characteristics (Supplement 9.2)
- 5.1.6 Alternative methods for control of microbiological quality standards (Supplement 9.2)
- 5.24 Chemical imaging (Supplement 9.3)
- 5.20 Elemental impurities (Supplement 9.3)
- 5.21 Chemometric methods applied to analytical data (9.0)
- 5.4 Residual solvents (*keeping up-to-date with ICH guideline*) (Supplement 9.5)
- 5.12 Reference standards (Supplement 9.5)
- 5.25 Process Analytical Technology (Edition 10.0)



Some examples in detail

UV-Vis absorption spectrophotometry (2.2.25)

- Extended description of equipment and its operation
- Now covers UV-Vis detectors for chromatography
- Now covers PAT applications
- Includes diffuse reflection mode


Some examples in detail

UV-Vis absorption spectrophotometry (2.2.25), contd.

- Absorbance accuracy for equipment qualification: Nicotinic acid introduced as alternative to potassium dichromate
- More comprehensive description of equipment qualification
- Requirements for equipment qualification now distinguish between qualitative and quantitative application
- New section on system suitability testing

Some examples in detail

IR absorption spectrophotometry (2.2.24)

- Extended description of ATR instruments and related criteria for equipment performance
- Monochromator instruments no longer described
- New section on applications; e. g. use for qualitative and quantitative analysis
- Accuracy of wavenumber scale: 



Some examples in detail

IR absorption spectrophotometry (2.2.24), contd

- Accuracy of wavenumber scale:



Now 4 instead of 7 band positions



Shifted positions for ATR instruments

Table 2.2.24.-1 - Band positions and associated acceptable tolerances of the polystyrene film used to verify wavenumber accuracy

Band position (cm ⁻¹)		Tolerance (cm ⁻¹)
Transmission	ATR	
906.6	906.1	± 1.0
1028.3	1027.7	± 1.0
1601.2	1601.0	± 1.0
3060.0	3059.7	± 1.0

Some examples in detail

IR absorption spectrophotometry (2.2.24), contd

- More user-friendly:

- ✓ Sample preparation described in more detail
- ✓ More guidance on the use of stored spectra and in-house libraries
- ✓ Description of procedures for comparison of spectra

Any difficulties ?

Revisions of chapters which are widely used must be done carefully !

- ➔ Application is retrospective for maybe hundreds of monographs
- ➔ Essential to get input of many involved stakeholders and users, i. e. manufacturers, control laboratories, assessors
- ➔ Revisions of existing individual monographs may become necessary,
e. g. revised chapter on Loss on drying:
- suppression of high vacuum, replacement of diphosphorous pentoxide

New General Chapters - Examples



- Chromatographic Separation Techniques 2.2.46
- Implementation of pharmacopoeial methods 5.26
- Equivalence testing of alternative methods 5.27
- Balances

and others

Chromatographic separation techniques 2.2.46

- ✓ Important revision ongoing within the PDG process (USP-JP-Ph. Eur.)
- ✓ New limits for symmetry factor
- ✓ Calculation of resolution harmonised (measurement at half height)
- ✓ R_t and R_{Rt} only for information, not for SST
- ✓ System repeatability in assays: now for APIs **and** excipients
- ✓ Discussion with assessors (QWP) is still ongoing

Chromatographic separation techniques 2.2.46

- Revised adjustments of stationary phase, column dimensions, mobile phase flow rate, injection volume (isocratic and gradient)



- Modification of column dimensions now based on L/d_p ratio (L = column length, d_p = particle size)
- L/d_p remains constant or in the range of -25 per cent to +50 per cent
 - > For TPP
 - > For SPP: other L/d_p provided N within -25 and + 50 % of original N
- When there is change of particle size, flow rate has to be adjusted
- Valid for isocratic and gradient systems
- **This means: change from HPLC to UHPLC is possible**

Chromatographic separation techniques 2.2.46

- BUT:

- « *These changes are acceptable provided system suitability requirements are fulfilled, and selectivity and elution order of the specified impurities to be controlled are demonstrated to be equivalent* »

In addition general SSTs:

- ✓ *Symmetry factor of peak used for quantitation OK*
- ✓ *Sensitivity (S/N) at reporting threshold not less than 10*


- This means higher flexibility but more requirements to be fulfilled!

Implementation of pharmacopoeial methods 5.26

- Ph. Eur. General Notices:

"When implementing a pharmacopoeial method, the user must assess whether and to what extent the suitability of the method under the actual conditions of use needs to be demonstrated according to relevant monographs, general chapters and quality systems."

In view of many users' questions it became obvious that more explanation of « implementation » was required

 New chapter is being elaborated which is based in ICH Q2 nomenclature and risk based approach, differentiation between methods and uses (e. g. qualitative and quantitative).

Examples will be provided.

Equivalence testing of alternative methods 5.27

- Ph. Eur. General Notices:

« **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.* »

Users and assessors often requested the EDQM to be more precise.



The new chapter will provide explanations, examples and statistical evaluation.

Conclusion

- Further chapters will be revised and new ones elaborated
- e. g. General methods on wet chemistry (identification reactions of ions and functional groups, 2.3.1)
- Chapters shall become more user-friendly
- Chapters to be scientifically state-of-the-art
- Any proposals, wishes?



Thank you for your attention



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