

**Microbiological control methods
in the European Pharmacopoeia:
present and future**

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Session I

International harmonisation update

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8:40-09:30



International harmonisation microbiological methods

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Harmonisation forum

- PDG = EP + JP +USP, WHO observer
- ICH: Steering Committee requested harmonisation of 11 general chapters for application of Q6A guideline
- ICH Task Forces: dissolution, disintegration, uniformity of dosage units, microbiological quality
- VICH = EU + JMAFF + USDA/CVB
 - JMAFF= Japanese Ministry for Agriculture Forestry and Fisheries
 - USDA/CVB = US Dept of Agriculture/Centre for Veterinary Biologics

The obstacles

- Legal environment of each pharmacopoeia
- Different traditions in use of pharmacopoeia
- Each region starts from a quite different position

Work programme

- 60 monographs on excipients
- 11 'ICH' general chapters
- Biotechnology methods
- Powder characterisation methods

11 general chapters

- Bacterial endotoxins
- Dissolution, Disintegration
- Uniformity of dosage units
- Extractable volume of parenterals
- Particulate matter in parenterals
- Sterility
- Microbiological quality
- Sulphated ash
- Colour and clarity of solutions

Procedure

- PDG: 7 stages to harmonisation, stage 8 is declaration of harmonisation
- Internal procedure: each pharmacopoeia maintains fully its internal procedure
- VICH: revision of EP carried out in parallel with VICH procedure

PDG procedure

- Stage 1: identification of work item and appointment of
- Stage 2: preparation of harmonisation proposal
- Stage 3: comment on proposal by expert groups (new procedure)
- Stage 4: forum publication

PDG procedure (2)

- Stage 5: consensus
- Stage 6: sign-off
- Stage 7: implementation

- Web page: www.pheur.org

For the user

- Harmonisation is achieved when all 3 pharmacopoeias have implemented the signed-off text
- Regulatory acceptance probably requires declaration of equivalence by the pharmacopoeias
- Transparency has to be ensured

Transparency in Ph Eur

- Statement at beginning of monograph/method
- Residual differences indicated in the text (♦)
- Information chapter 5.8 *Pharmacopoeial harmonisation* will give item-by-item analysis

Progress to date

- Bacterial endotoxins: signed off, published and implemented in all 3 pharmacopoeias
- Sterility test: signed off with residual differences
- Biotech methods: 6 signed off and in press for Ph Eur
- Excipients: $\approx 30\%$ signed off

Sterility test

- Signed off with residual differences 11/2002, publication Ph Eur 6/2003
- Residual differences:
 - Shelf-life of media
 - Media used for preparations with mercurial preservatives
 - Validation of each batch of medium
 - Transfer volume if medium becomes cloudy
 - Details of test validity conditions

Microbiological quality

- Test methods introduced in Ph Eur in 1980s
- Acceptance criteria in monographs were initially in footnotes (non-mandatory)
- After a few years' experience made mandatory
- USP criteria mandatory, JP considers microbiological quality to be part of GMP, criteria non-mandatory

Microbiological quality

- Now at stage 4 (forum publication 2003)
- Completion and sign-off expected during 2004
- Herbals now excluded from harmonisation

Enumeration methods

- Validation described in greater detail
- Single reference medium cited
- Separate counts for 'bacteria' and 'fungi' (moulds and yeasts): TAMC, TYMC
- Interpretation of results: present Ph Eur allows factor of 5, USP and JP have no factor
- Harmonisation proposal: factor of 2

Tests for specified organisms

- Validation described in greater detail
- Test for *Candida albicans* added (at stage 3)
- Single reference medium for each test, others may be used after validation
- Changes in media, prefer commercially available media

Acceptance criteria

- Based on Ph Eur chapter 5.1.4, few changes
- Based on route of administration
- Herbals excluded
- Non-mandatory in Ph Eur, but authorities require compliance unless justified
- Non-mandatory in JP, Mandatory where cited in USP monograph

Consequences

- Revalidation will be needed in many cases
- Transition period of several years may be needed
- Harmonised methods should be acceptable for international use as soon as implemented in all regions
- Ph Eur monographs will need revision

Mycoplasma test

- At VICH step 4 (consultation)
- EP general chapter being revised in parallel
- Culture method (broth — agar)
- DNA staining after growth in cell culture
- PCR not included in harmonisation

Mycoplasma test (2)

- Harmonisation proposal is simplification of Ph Eur test
- Validation micro-organisms reduced
- Micro-aerophilic incubation only
- No minimum number of plates
- Test shortened by 7 days

Mycoplasma PCR

- JP includes for biotech products
- Ph Eur will develop general chapter
- Limit of detection is a serious limitation
- False positives occur
- Useful as a rapid screening method and for confirmation or rapid reading of culture method

In conclusion

- Conference is an opportunity to contribute to the harmonisation process
- Deadline for comments on Pharmeuropa texts October 2003
