



Welcome!

Quality of Manufactured Medicines – General Chapters
Performance Testing – Microbiology Topics

Session I, Wednesday, September 24, 2008

10:00 a.m.–12:30 p.m.

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***Microbiology – Overview of Current Activities of the USP Microbiology
and Sterility Assurance Expert Committee Activities***



Compendial Process Improvement Team - History

The Project Team was formed during the 2005-2010 cycle to:

- Open a dialogue between stakeholders and USP to determine ways in which improvements can be made to USP's compendial processes, including:
 - *Pharmacopeial Forum* comment process
 - USP publication topics, including the redesign of USP publications
 - Communication of USP initiatives to pharmaceutical manufacturers and other groups
 - Resolution 12, Expanded Outreach to Stakeholder Groups who are affected by USP Standards*

*Taken from Project Team Charter



USP Microbiology

- Compatible with its overall mission, the role of USP in Microbiology is to develop public standards pertaining to microbiology, that, along with other requirements, ensure the consistent quality of products –pharmaceuticals, excipients and drug substances.



USP Microbiology and Sterility Assurance Expert Committee

- James E. Akers, Ph.D., Chair
- Members:
 - James P. Agalloco, M.B.A.
 - Ivan W. Chin, B.A.
 - Anthony M. Cundell, Ph.D.
 - Joseph K. Farrington, Ph.D.
 - Dennis E. Guilfoyle, Ph.D.
 - David Hussong, Ph.D.
 - Leonard W. Mestrandrea, Ph.D.
 - David A. Porter, Ph.D.
 - Donald C. Singer, M.S.
 - Scott Sutton, Ph.D.
- Scientific Liaison:
 - Radhakrishna Tirumalai, Ph.D.



Areas of Responsibility

- Microbiological Assays
- Microbiological Monitoring
- Not Responsible for:
 - Water
 - Antibiotics
 - Monographs (other than setting Microbial Limits, Sterility and Bacterial endotoxin specifications)



Microbiology as an integral part of Development, processing, and finished product testing

- Microbiological control aspects apply to sterile as well as non sterile products
- Microbiological control is part of a continuum that spans from development of a drug or a biological to manufacture, to final product control
- Integration of all microbiological controls in the continuum will increase the assurance of the final microbiological quality of a product
- USP provides at each part of the continuum, procedures and guidances for microbiological control



New USP Microbiology Chapters- Since 2005 (1)

The following new chapters were published in 2006 (USP 29, 2nd Supplement)

- <1072> *Disinfectants and Antiseptics*
- <1112> *Application of Water Activity Determinations to Non-sterile Pharmaceutical Products*
- <1117> *Microbiological Best Laboratory Practices*
- <1223> *Validation of Alternative Microbiological Methods*



New Harmonized Microbial Limits Chapters Since 2005

New Harmonized Microbial Limits Chapters

- *<61> Microbiological Examination Of Nonsterile Products: Microbial Enumeration Tests*
- *<62> Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms*
- *<1111> Microbiological Quality of Nonsterile Pharmaceutical Products*

Published in 2S to USP 29

To become official on May 1, 2009



Implementation of Harmonized Microbial Quality Chapters-1

- Currently, USP monographs for non-sterile API's, excipients and dosage forms, reference non-harmonized USP<61> Microbial Limit Tests
- Effective May 1, 2009 (USP32), USP monographs will reference either the harmonized USP<61> or the harmonized USP<61> and <62> as appropriate
- In the first phase, only references will change and acceptance criteria will remain as is



Implementation of Harmonized Microbial Quality Chapters-2

- Recommended Minimum microbial quality acceptance criteria are contained in USP<1111>
- In the second phase, a case by case review of microbial quality acceptance criteria will be done *vis a vis* a) the recommendations in USP <1111> , b) other criteria, including, quality of raw materials, method of manufacture, route of administration, target population (immunological status, disease state etc.,)
- USP<1111> recommendations may be used as default criteria, when other information is not available
- As a result of this review, changes to existing monograph microbial quality acceptance criteria may be necessary (addition or deletion of tests)
- Where changes are necessary, a proposal will be published in PF



Revisions to Harmonized Microbial Limits Tests <61>, <62>

Changes to<61>

- Negative control every time that the product is tested

Changes to<62>

- Negative control every time that the product is tested
- Delete indicative property testing of XLD agar with E.coli
- Clarification to Clostridium Testing

Will be published as a direct IRA in PF 34(6) Nov-Dec 2008

Changes effective May 1, 2009



Revised Chapters for 1S to USP 30 (2007)

- Revisions to <1208> *Sterility Testing-Validation of Isolator Systems* and <1222> *Terminally Sterilized Pharmaceutical Products-Parametric Release* that were proposed in *PF* in 2004 were published in 1S to USP 30 with minor changes based on comments received



Revised Chapter for 1S to USP 31(2008)

- Revisions to <55> Biological Indicators-Resistance Performance Tests that were proposed in *PF* in 2004 were approved for publication in 1S to USP 31 with changes based on comments received



Revised <71> Sterility Tests Chapter

- In accordance with ICH Q4B, as a requisite for regulatory interchangeability, <71> Sterility Tests has been revised to eliminate all the eleven discordant foot notes and is now completely harmonized amongst the three pharmacopeias
- Revised Text signed off in November 2007 PDG meeting
- Will be published as a direct IRA in PF 34(6) Nov-Dec 2008
- Implementation- **Effective May 1, 2009**



Revisions to <71> Sterility Tests

- Term validation, has been replaced by the more appropriate term “method suitability” . This is in line with the terminology used in the texts on microbial contamination of non sterile products.
- Alternative thioglycollate medium-a reference to this alternative medium included , with the introduction of the following terms: “Where prescribed or justified and authorized



Revisions to <71> Sterility Tests

- **Growth promotion test frequency**

Test each lot of ready-prepared medium and each batch of medium prepared either from dehydrated medium or from ingredients. In appropriate cases, periodic testing of the different batches prepared from the same lot of dehydrated medium is acceptable.

- **Shelf-life of media**

STORAGE

- If prepared media are stored in unsealed containers, they can be used for 1 month, provided that they are tested for growth promotion within 2 weeks of the time of preparation. If color indicator requirements are met, the shelf-life of such media can be used for 1 year—provided that they are tested for growth promotion within 3 months of the time of preparation. If color indicator requirements are met.

Do not use the medium for a longer storage period than has been validated.



New Monographs for 1S to USP 31(2008)

New monographs on

- Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Non-Paper Carriers
 - Monograph on -Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Liquid Spore Suspensions
- were approved for publication in 1S to USP 31



New Chapter and Monograph Proposals...

New Chapter and Monograph Proposals targeted
for PF 35 (1)

Chapters

- <63>Mycoplasma Testing
- <1113> Microbial Identification

Monograph

- Endotoxin Indicator for Depyrogenation



In the Pipeline of MSA EC.....

New Chapter Proposals

- Microbiological Evaluation of Clean Rooms for Non-Sterile products
- Isolators for Aseptic Processing



In the Pipeline of MSA EC.....

Revisions

<1116> Microbiological Evaluation of Clean Rooms and Other Control Environments

<1211> Sterilization & Sterility Assurance of Compendial Articles

- Short Term fix to eliminate the discussion of the now defunct non-harmonized Sterility Tests and the references to first and second stage Sterility Tests
- Eliminates the older radiation sterilization guidance & directed reader to ISO standards.
- Sets the stage for future changes.



In the Pipeline of MSA EC.....

<1211> Sterilization & Sterility Assurance of Compendial Articles

Long Term fix

- Future chapter will address sterilization at a more basic level as an introduction only section.
- Follow with individual chapters (<1229> series) on each sterilization method



In the Pipeline of MSA EC.....

<1229> series of chapters

- Chemical Sterilization
- Dry Heat Depyrogenation
- Sterilization by Filtration
- Gas Sterilization
- Dry Heat Sterilization in Ovens
- Radiation Sterilization
- Steam Sterilization in Autoclaves
- Terminal Sterilization using Moist Heat
- Vapor Sterilization



Your Involvement with MSA Activities

**Are you reading issues of PF regularly?
Your role is pivotal!**



Development & Revision of Official USP Standards

1. Proposal is published in *Pharmaceutical Forum* (PF) for public review and comment
2. Comments on PF proposal reviewed by USP Scientific Staff and Expert Committee
- 3a. If significant revisions to the proposal are needed, the comments, responses and the revised proposal are published in *PF* for additional public review.
- 3b. If no significant revisions are needed, Expert Committee recommends for official adoption, the proposal becomes official. Comments, if any and responses are published in the *Commentary section* on the USP website





Questions?



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Thank you!



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