PMF Newsletter

A quarterly publication of the Pharmaceutical Microbiology Forum

Volume 3, Number 1 Summer, 1994

1994 PMF Annual Meeting

Current Issues in Pharmaceutical Microbiology

On April 25th and 26th, a seminar on *Current Issues in Pharmaceutical Microbiology,* sponsored by AAI was held in Wilmington, North Carolina. This seminar provided not only highlights of critical issues in the Microbiology QC lab, but also provided a forum for interaction with over one hundred microbiologists from other companies. The highlights of topics covered were as follows:

Isolation Technology Overview

Carmen M. Wagner, Ph.D. Lederle-Praxis Biologicals

This technology reduces the human factor in product contamination. The important features include visibility, manipulation, ventilation and filtration of air, and transfer of equipment. Its primary application is in the handling of potent powders and filling of sterile products. State of the art QC labs may also use this technology.

Computer System Validation of Automated Speciation Systems

Dr. Ray Miller, AAI

Laboratory computer systems consist of hardware, software and people. To validate the system, it is not only necessary to perform IQ for hardware and OQ/PQ for software, but also have SOP's and proper training for the people using it.

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Inside This Issue

Sterility Failure Investigations

A sterility test failure is a dreaded event. It not only causes an enormous amount of additional work for the people involved in its investigation, it almost always results in the rejection of the material in question due to the lack of a clear assignable cause in the test laboratory. As a microbiologist that has conducted a fair share of sterility failure investigations in the course of a career, I offer the following checklist to our readers in the hopes that it may make their sterility failure investigations go smoother, however minutely.

The investigation process is divided into 4 main sections:

a) The specific lot information which serves to set boundaries on the material DIRECTLY associated with the sterility failure.

b) The process specific information which serves to identify OTHER lots which might be implicated should this cause of the failure be identified to be systemic in nature. (i.e. Discovery of a ruptured vent filter in a production autoclave raises a question regarding other lots sterilized in that particular autoclave from the time that filter was last integrity tested).

c) The lab related information documents and the test-specific details would serve to invalidate the initial failure if an assignable cause in the laboratory be found.

d) The conclusion which recommending release or rejection of the lot, based on the findings of the investigation.

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Annual Meeting (continued from page 1)

Validation of Bioburden Testing & Microbial Limits Testing

Ms. Gayle Borovian, J&J Consumer Products

- Use of own environmental isolates for validation of test methods was suggested
- A double validation was recommended
- The general rule for duplicate plate variation is within 0.5 log
- Documented evidence of innate hostility of a formulation may eliminate the need for test method development
- FDA does not like temperature changes, but rather a specific temperature (±)
- Incubation temperature should be optimum for the organism used
- Revalidation may be needed when a substantial change occurs, e.g. new manufacturing site, new raw materials, etc.

Current Issues Related to Water Quality in the Pharmaceutical Industry

Dr. Richard Wood, Pfizer

The following topics were discussed:

- The microbiologist should become familiar with the types of organisms found in each particular system. Identification is more important than the actual numbers present.
- The microbiological quality of feed water
- The ideal way to prevent the occurrence of biofilm in an ambient, recirculating USP water system.
- The USP proposed changes to chemical tests and specifications for Pharmaceutical Ingredient Waters.
- The USP will add a general information chapter on Pharmaceutical Water System Validation
- Trending of data should be performed both during validation and routine testing.
- Validation requirements of USP Purified Water System.
- Establishment of sampling methods for pharmaceutical water systems.
- Microbial recovery from individual systems

USP Issues and Initiatives in Microbiology-A Progress Report

Dr. Rodger Dabbah, US Pharmacopeia

Open Conference on Water/Microbiology 1993

- During the conference, there was a request that the micro specs for USP water not be included in the monograph and the sub-committee agreed that they would only be included in the guidelines
- It was established that blanket ID's for all bacteria recovered from water systems is not required. But it is important to establish a baseline and know your system.
- Water system trending should be included in the validation protocol to help establish variations in the system.
- For water system validation purposes, the subcommittee feels that membrane filtration of a 100ml sample is a much more sensitive test. If you use the plate count method and continuously have 0 counts then you are not learning anything about your system.
- USP 23 will contain some new general information chapters on Total Organic Carbon, validation of water systems, pharmaceutical water systems, water system components, installation/materials of construction component selection, sanitization, operation, maintenance, control, sampling considerations, and microbial considerations.

<51>Preservative Effectiveness

The proposed AET is in the process of being rewritten

<1211>Sterilization and Sterility Assurance

- Chapter is being updated. Clarification of retesting procedures and sampling.
- Incubation period for membrane filtration is changing from 7 to 14 days.

Microbial Attributes of Excipients/Drug Substances

- Issue of indicator organisms will be revised

Cleaning Validation in the Pharmaceutical Industry-Some Microbiological Issues

Dr. Bill Hall, Burroughs Wellcome

Some common strategies for setting limits included:

- Potency of the substance being cleaned
- Toxicity of the substance
- Allergenic nature of the substance
- Assay detection limits
- Safety factors
- Process capability of the cleaning

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Future Topics

Your contributions to *PMF Newsletter* are needed in the form of short articles, letters to the Editor, comments, or suggestions. Please direct your correspondence to *PMF Newsletter*, c/o L. Valdes-Mora, 1206 North 23rd Street, Wilmington, NC 28405 [Tel.(910) 251-6786 or FAX (910) 251-6755]. Submit any articles with your name and phone number in case we need to contact you. Your name and company will not appear without prior written authorization.

Calendar of Events

The Calendar of Events is provided as a service to PMF Newsletter readers. Submission of complete and accurate information will be published on a space-available basis.

1994

September 19-21, *Pharm Tech Conference*, Atlantic City, NJ (503) 343-1200

September 19-21, *PDA/FDA Joint Conference,* Hyatt Regency Hotel, Bethesda, MD.

October 30-November 1, *PDA Annual Meeting Courses*, Wyndham Franklin Plaza, Philadelphia, PA

November 2-4, *PDA Annual Meeting and Exhibition*, Wyndham Franklin Plaza, Philadelphia, PA.

November 6-10, *AAPS Annual Meeting Symposium on Advances in Parenteral Manufacturing*, San Diego, CA

Sterility *(continued from page 1)*

I. Lot Specific Information

1. Date/time manufacturing started and ended. The investigation is usually limited to the lot-related activities bracketed by this time period.

2. No. of sections in the lot. Refers to distinct "sub-sections" of a lot(e.g. autoclave or freeze drier loads). These become important if/when a partial rejection of the lot can be justified.

3. Section of the lot where growth was observed. Again, this information becomes useful when there might be a chance of saving portions of a lot.

4. Lot of bulk material used. In the case of aseptically filled sterile powders, a review of the bulk lot used may be appropriate.

5. Other lots filled with the same bulk. Although each lot is released or rejected on its own merits, lots coming from the same bulk lot yielding sterile results may serve as good "support data".

II. Process-Related Information

1. Line Validation by media fill-when was the last one done? Is one due?

2. The sterilization records of the primary packaging components (i.e. dry heat ovens or tunnels for glass; autoclaves for stoppers; ETO for plastics, etc.). Were all cycles acceptable?

3. The environmental monitoring data associated with the shift(s) when the lot in question was produced:

   a. Viable particle counts (air sampling and surface testing). Note number of samples at of above ALERT levels for both methods. Note number of samples at or above ACTION level for both methods. If an action level was exceeded, was the appropriate action taken?

   b. Comparison of the flora isolated from the test failure with the environmental isolates obtained in the production suite- Is there a correlation? Has the test isolate EVER been found in the manufacturing area?

   c. Non-viable particulates- Were these found to be within current operating guidelines?

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Sterility *(continued from page 3)*

d. Pressure differentials between rooms- Were they satisfactory? Was the air determined to be flowing in the right direction?
e. Temperature and humidity charts- Were they between acceptable operating parameters?

4. HEPA filter certifications for filters in the aseptic manipulation zones- Are the HEPA filters within the required certification cycle? Are they due for a recertification? Were filters performing within specifications at the time of their last certification?

5. Sanitization logs- Did sanitizations take place as required? Were any discrepancies noted?

6. The bioburden of all product-contact utilities(i.e. water, steam, compressed air, etc.)-Were they all acceptable for the period in question?

7. The bioburden of all raw materials- Were they acceptable?

8. Sterilizing filter integrity test results(for product sterilization as well as the filters servicing the compressed air and vacuum systems)-Did all the filters pass the integrity test?

9. Preventive maintenance and calibration records of the critical parameter instruments of the process equipment(i.e. autoclave, Strunck tunnel, hot air oven, freeze drier, etc.)-Were all instruments performing within the correct specifications and tolerances at the time of their last calibration?

10. Corrective maintenance records- Were there any repairs done on the equipment, before or during the manufacture of the lot, which may have had an impact on the sterility of the product or the accuracy of the instruments used to manufacture the lot?

11. Exception or discrepancy reports- Did any occur during the production of the lot? Did anything transpire during the lot's manufacture that required more than usual operator intervention?

12. Operator garment/glove monitoring- Was it performed? Were results typical?

13. Operator training- Did all operators working on the production of this lot receive proper training(i.e. aseptic technique, gowning, etc.)?

III. Sterility Test Laboratory Data

1. General Information
   a. Analyst performing the test-by unique identifier
   b. Hood Number
   c. Date test was performed
   d. Date test was found to have growth
   e. Failed test medium
   f. Identity of the test isolate
   g. Total tests completed same day and other tests showing contamination same day

2. Test Controls
   a. Manipulative negative control
   b. Equipment/Media sterility check
   c. Positive Control-(growth promotion

3. Environmental Controls
   a. Operator/Garment/glove monitoring results
   b. Air sample results
   c. Historical data-When was this organism last detected in the lab?

4. Sterilization Records and BI Results for:
   a. Media
   b. Equipment
   c. Diluting Fluids

5. Sanitization logs for the test suite or sterilization documentation for users of barrier technology.

6. HEPA filter certifications

7. Analyst training records

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Sterility *(continued from page 4)*

8. Lab sterility retest data
    a. Total failures
    b. Total tests
    c. % positive
    d. Total failures for this type of presentation

9. Sterility Retest Information for Lot (2x samples, if justified)
    a. Analyst
    b. Date on Test
    c. Results

IV. Conclusion and Recommendation This section summarizes the findings of the investigation for the material in question based on those findings. If a repetition of the first stage sterility test (or proceeding to a second stage sterility test) is warranted, it is in this section that the reasons for this decision are discussed. This section might also serve to document the recommendation to reject the affected material if the failure is identified to be manufacturing related.

The foregoing list is intended to serve as a GUIDE to our readers; by no means is it intended to be all inclusive. The contents of the list should be evaluated for its relevance to a given product or process and tailored accordingly. For example, if the product in question is terminally sterilized, it may be appropriate to determine the sterility test isolate's D-value to compare it with the sterilization cycle received by the section of lot showing microbial growth. Or perhaps an audit into the sterilization processes of a vendor that provides your company with a particularly difficult to sterilize component may be appropriate. Only YOU can determine what elements of the previous list are relevant to your operation and which sterility impacting elements should be incorporated into you investigations due to the uniqueness of your product or operation.

Coming in PMF

Current Issues in Microbiology, Methods Development, Regulatory Trends, Book Reviews, Career Development, Job Opportunities

Annual Meeting *(continued from page 2)*

Documentation Requirements in the Microbiology Laboratory

Ms. Tara Sams, AAI, Inc.

Documentation should contain sufficient detail to provide a complete record of events sufficient to recreate the activity. SOP's and Documented Records are required for the following:

- Personnel: Monitoring, Training
- Facilities: Certification/Validation, Cleaning, Monitoring
- Equipment
- Materials
- Documentation Review and Storage

An FDA Perspective of Microbiological Quality Control Laboratories

Mr. Robert Coleman, US FDA

Areas of interest to the FDA with regards to the Microbiology Laboratory are as follows:

- Facilities
- Equipment
- Systems
- Media
- Testing Procedures
- Personnel
- SOP's

Handling of Aberrant Data in the Microbiology Lab

Ms. Lucia Clontz, AAI, Inc.

The objective of this workshop was to establish the rationale for evaluation of results based on current FDA interpretations (U. S. vs Barr) and to implement the required investigation procedures and action steps.

The Pharmaceutical Microbiology Forum would like to express its appreciation and thanks to AAI (Applied Analytical Industries, Inc.) for their continued support.

Water Activity and its Relation to Product Contamination

Water activity, a_w, is an index of the availability of water for chemical reactions and microbial growth. It has been defined as the ratio of vapor pressure of water above a material and the vapor pressure of pure water and can be measured on a Sina-scope instrument. In a material, water is either "bound" or "free". Bound water is held by physical forces to macromolecules and is not available to act as a solvent or participate in chemical reactions. . . including the metabolic activity of microorganisms.

Microorganisms have a maximum, optimum, and minimum a_w for growth. None can grow in pure water (a_w=1.00), and minimum level for growth of select molds is a_w=0.67. In general, bacteria (min 0.90-0.91) require a higher a_w for growth than yeast(min. 0.87-0.94), which require a higher a_w than molds (min. 0.70-0.80). Organisms will not grow below the minimum a_w. As the a_w is lowered, the lag phase is increased and the growth rate decreases.

Besides influencing the growth, some other effects of lowering the a_w is an increased resistance of microorganisms to heat. Also, the lower the a_w, the longer organisms survive during storage. Controlling the amount of available water is a good means of preservation, and is most often associated with food preservation. Dehydration, adding solutes (salt, sugar, etc.), and freezing are the most common means of lowering the a_w.

Decreasing the amount of available water with the addition of excipients such as NaCl, glycerol, glucose, or sucrose, is also a promising approach to increasing the stability of drug and cosmetic products. When using this means of preservation, however, there are important things to consider. Although organisms present in the material may not grow . . . they are less apt to die. Strict adherence to GMP's would, therefore, be essential. Additionally, preservatives may or may not work well in the absence of water. Packaging is another consideration . . . can the product pick up moisture from the surrounding air?

Writer's Comments

Although decreasing the water acitivity of a product reduces the opportunity for microbial growth, it also, in some cases, reduces the rate of kill. Available water is necessary for the antimicrobial action of preservatives to occur. For example, a cough syrup containing Potassium Sorbate as the preservative has a slower decline of molds when the glycerine level is increased. To some extent, we are "preserving" the organisms by decreasing the water activity. We have, however, reduced its abilty to grow. does this mean the sample with a slower rate of kill is better preserved?

Reader's Comment for Writer

A sample with slower kill rate may not be better preserved. A preservative system in intended to be bacteriocidal and fungistatic. If the preservative does not kill in 14 days, it is not considered an adequate preservative per USP. Also note per British and European Pharmacopeias, preservatives need to kill even faster.

QUESTIONS FROM PMF MEMBERS

Questions will be posed in the newsletter so that other PMF members can respond. Responses will appear in the next issue.

1. Have you had an autoclave problem? If so, how did you solve it?

2. How do you test clean steam?

3. How do you do sterility tests for mammalian cell cultures?

4. Have you experienced variability in kill times for biological indicators from different vendors, with the same D-value?

Newsletter is published by the Pharmaceutical Microbiology Forum, 1206 North 23rd Street, Wilmington, NC 28405. Telephone (910) 251-6786. Send all inquires, letters, and comments to the above address, c/o L. Valdes-Mora.

PURPOSE: To provide a forum for discussion of microbiology issues in the pharmaceutical industry.

Reminder
HAVE YOUR DUES BEEN PAID???

Pharmaceutical Microbiology Forum
Membership Application

MISSION: PMF provides a forum for pharmaceutical microbiologists to exchange information on microbiological issues in the pharmaceutical industry and interact with the USP and regulatory agencies.

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PMF Newsletter Comments

We value your input.
Please write your comments or questions below and send to:

Laura Valdes-Mora
AAI
1206 North 23rd Street
Wilmington, NC 28405

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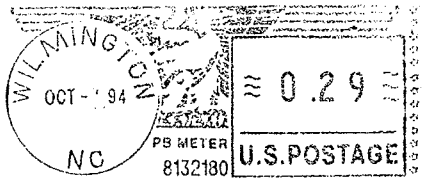

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Address Correction requested