PMF Newsletter

A quarterly publication of the Pharmaceutical Microbiology Forum

Volume 3, Number 4 Winter , 1996

President's Message

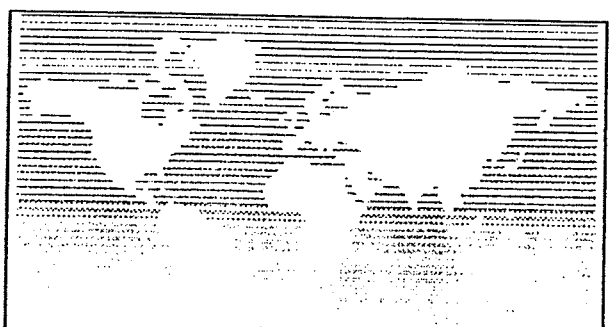
Another year will come to an end very shortly. We hope that you have enjoyed reading our newsletter this year and that we have stimulated technical discussions and new ideas.

This year we have once again increased our membership by at least 25%. Our goals for 1997 will include continued growth of our membership and conducting technical discussions on-line via the Microbiology BBS.

We are now a global organization! PMF has members from the Netherlands, Canada, and Japan. We will now have a highlighted box in the newsletter listing the countries of origin of our members. As we communicate with different countries, this will help in understanding regulations and practices around the world. At the end, we should have one set of rules and regulations and only one pharmacopoeia.

Happy Holidays,

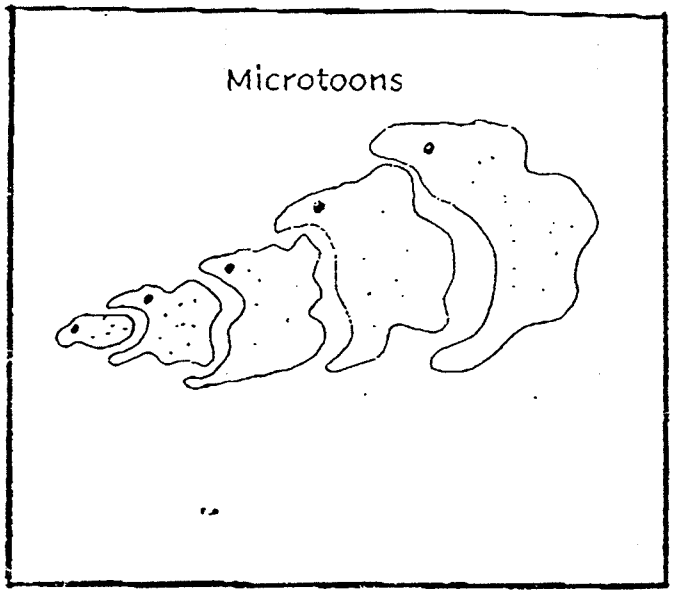
Laura



The Pharmaceutical Microbiology Forum is proud to have members from the USA, Canada, The Netherlands, Belgium, Germany, Israel, Puerto Rico and Japan.

MICROTOONS

Draw your impression of bacteria, or send your favorite Microtoon Send to L. Valdes-Mora. We will use them in future newsletter issues.



"It's a bug-eat-bug world out there"

COME VISIT OUR WEBSITE AT
http://www.microbiol.org/pmf.htm

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The following is a continuation of the summary of presentations given at AAI's Microbiology Seminar Series held in Wilmington, NC in April 1996.

Microbiological Requirements for Stability Studies

The objective of a stability program is to provide evidence on the variability of a drug substance or drug product influenced by environmental factors (temperature, humidity, light). Based on the results, the storage conditions, retest periods and shelf life are established.

- Stability data should be submitted for all sizes.
- The preservative (if present) should be monitored for concentration at the beginning and end of the expiration date of the product. This can be done with microbial challenges or by chemical assays.
- Non-sterile formulations that require control of microbial populations where preservatives are not used, should be tested at specific intervals throughout the expiration dating period.
- Topicals should be tested for Pseudomonas cepacia, Aspergillus niger, and Candida albicans. A wider number of microorganisms may be potentially pathogenic for immumo-compromised patients.
- Simulated use challenges may be used. For example, re-challenging a sample after 14 days. The decision to conduct this type of test is based on the use of the drug.
- Metered dose aerosols used in the respiratory system should be monitored for the absence of pathogenic organisms and for total counts.
- Ophthalmic preparations are to be tested for sterility.
- Parenterals are to be tested for sterility, pyrogenicity, container closure integrity, and preservatives (if present).
- Sterility testing for biological products or container closure integrity should be performed minimally at the beginning and end of shelf life.
- Preservative effectiveness testing in relation to stability protocols should be conducted using the first three production batches and testing occurring at the beginning and end of the stability period.
- Drug products that are labeled pyrogen free are to be tested via pyrogen (rabbit) or endotoxin tests at the beginning and end of the stability study. *(cont pg. 3)*

NEW PRODUCT ANNOUNCEMENT

PML Microbiologicals recently launched a new packaging style for isolator environmental testing media called Barrier $_{tm}$ Wrap. There are several advantages to the new package style, one of which is safety. Also, these bags are impervious to hydrogen peroxide. Contact PML Microbiologicals at 800-435-5693 for information.

- Stability studies will have a variety of storage conditions with different temperatures, humidities, freeze/thaw, and/or light cycles. Microbiological testing will only be conducted at the storage condition that matched the use or labeled conditions.

The following tests are usually conducted:

Product Form	Test
Dry Powder, Capsules, Tablets	Microbial Limits
Liquids, Creams, Ointments, Aerosols (non-sterile)	Microbial Limits Preservative Effectiveness
Parenterals, Other Sterile Products	Sterility, Endotoxin, Container Closure Integrity, Preservative Effectiveness(multi-use containers only)
Ophthalmics	Sterility and Preservative Effectiveness (multi-use containers)
Intrauterine Devices	Sterility Container Integrity

Examples of Stability Intervals for Microbiological Testing

Test	Interval
Microbial Limits	0, 6, 12, 18, 24, 36, 48, 60 months
Preservative Effectiveness	Beginning and End (expiration)
Sterility	Beginning, Annually, and End (expiration)
Container Closure Integrity	Beginning, Annually and End - Inverted*
Endotoxin	Beginning, Annually and End - Inverted Beginning and End - Upright

*Inverted is tested more as it is considered worst case

JAPAN REGULATORY AND COMPENDIAL ISSUES

- Japan is the second largest pharmaceutical market.
- The country has extremely productive R&D.
- Most Japanese pharmaceutical manufacturing is in Tokyo and Osaka.
- The Koseisho is the Ministry of Health and Welfare. This is equivalent to FDA, but is not responsible for food. The Koseisho is also in charge of the Japanese Pharmacopoeia.
- The country is behind in validations the way we do them in the United States.
- In 1996, the government gave the industry 2 years to comply with validation. Validation requirements started in Japan in 1994.
- The Japanese Pharmacopoeia is in its 13th edition (1996).
- The JP is working towards harmonization with USP and EP.

Sterility

- Retests are very common for sterility failures.
- The JP only has peptone water as rinsing fluid.
- Procedures do not mention penicillinase or isopropyl myristate , even though Japan is the main developer of cephalosporins.

Media Storage and Growth Promotion

- Media is to be stored in a cold place.
- Storage for up to one year is acceptable.
- Growth promotion is to be repeated every three months (USP is more restrictive).

Bacteriostasis/Fungistasis

- Method is not specific
- No agents (neutralizers) are mentioned.
- Organisms used need to be known to be resistant to antimicrobials, but guidance is not given as to how to identify these organisms, the level of resistance, or how to perform the challenge.
- Membrane filtration requires the entire contents to be tested, unless it is greater than 500mL.
- 14 day incubation
- A second retest is permitted if the first retest is shown to be inadequate.

Particles

- Tests are very stringent about freedom from particulates.

(cont. pg 6)

(Japan cont.)

WFI

- Purity is determined by TOC and chemical tests similar to the old USP 23 tests. No specifications for microbial content are given.

Sterilization

- Allows for use of dry heat, steam under pressure, flowing steam, and use of boiling water and tyndalization-like methods.

- The dry heat temperatures can vary. Some of the low ones (135-145°C for 3-5 hours) may not be sporicidal and will not depyrogenate.

- The intermittent moist heat methods will not be sporicidal and are considered unconventional in the USA.

Overall Comment

- Harmonization will take time.

- Japan does not have strong regulatory enforcement.

Japan Goals

- Gain access to international markets.

- Achieve harmony with Europe and North America.

- Define equivalency of methods with international trading partners.

ENVIRONMENTAL MONITORING

The PDA held a dinner meeting at Rhone Poulenc in Rorer, Pa focusing on environmental monitoring. Points of interest were handling out of specification (oos) results and international regulations. They stressed the importance of trending that is in line with FDA interests. It is very important to pay attention to the current or proposed European regulations, especially if your company will sell products overseas. These regulations may have an effect on future US regulations. The focus should be on the proposed chapter 1116 in the Pharmacopoeial Forum.

Future Topics

The purpose of the Newsletter is a sharing of information among Microbiologists. Your contributions to *PMF Newsletter* are needed in the form of short articles, letters to the Editor, job openings, comments, or suggestions. Please direct your correspondence to *PMF Newsletter,* c/o L. Valdes-Mora, 3166 Wood Valley Road, Panama City, FL 32405 [Tel (904) 763-5453]. 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.

A Look at Pharmaceutical Microbiology in Japan (contributed by a member)

I had the pleasure of working with the microbiology departments in a couple of Japanese pharmaceutical companies.

Cleanliness is very important in this country and this was very apparent in the laboratories I visited. All employees wore uniforms, the women were dressed in skirts with matching vests, a white blouse and a tie that matched the skirt and vest. The men wore short jackets, trousers and white shirts with ties.

Full clean room gowning is required to enter Class 10,000 or better. All microbial ID's are done in Class 10,000 areas. They have Vitek equipment to help with the workload.

The sterility and water testing are performed in laminar flow cabinets (Class 100) within Class 10,000 rooms. Environmental monitoring is performed within the cabinet and in the room during testing.

The analysts doing the testing had been trained well, but were somewhat restricted to the type of work they were allowed to do. Very few had degrees in Microbiology, but one of the analysts doing sterility testing had a degree in pharmacy. Degrees in chemistry were more common.

Pictures were taken of all the incubated culture plates, positive and negative. These were filed with their work sheets.

The laboratories were relatively new and had ample space for working. In many of the micro labs that I have worked in, I think management allocates space on the basis of size, and microbes are very small.

One very traditional practice was to have visitors leave their outdoor shoes behind. We did so when we entered the controlled environmental areas (Class 100,000). This is a good practice, but the shoes were replaced with open-heeled bedroom slippers. These were difficult to walk in and kept coming off. We made a suggestion to provide shoe covers, instead.

The cafeterias were most interesting. All food servers wore face masks and gloves. There was a nice variety of interesting dishes. I wish I could have tried them all. The meals are subsidized by the company, so they were very good bargains for the workers. Food is very expensive in Japan.

In our discussions, we covered most of the topics that concern the pharmaceutical microbiologist. We focused heavily on environmental monitoring, validation of methods, writing SOP's, etc. I found the people friendly and interested, but not afraid to speak up, or ask questions. I felt I learned a lot and would like to return sometime and continue some of these discussions.

Advertisements:

The PMF newsletter will accept advertisements for both those seeking employment, as well as those with current job openings. We also encourage any advertisements for products or items that are new and of interest to microbiologists. Please send these to Laura Valdes-Mora.

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.

January 13-14, 1997, *Enhancing the Efficiency of a Quality Assurance Unit*, Center for Professional Advancement, New Brunswick, New Jersey. Also to be held in Chicago, IL March 6-7, 1997.

January 13-15, 1997, *Preparing and Conducting Installation, Operational and Process Qualifications, IQ/OQ/PQ*, Center for Professional Advancement, New Brunswick, New Jersey

January 13-16, 1997, *International Symposium on Product Quality and Integrity*, Philadelphia, Pennsylvania, Institute of Environmental Sciences.

April 13-15, 1997, *Taking Microbiology into the 21st Century*, Applied Analytical, Inc., Wilmington, North Carolina

The Pharmaceutical Microbiology Forum thanks Applied Analytical Industries, Inc. For their continued support.

Pharmaceutical Microbiology Forum (PMF) 1996 Organizational Board

PMF Newsletter is published quarterly by the Pharmaceutical Microbiology Forum.

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

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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.**

PLEASE PRINT

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_____

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Home Phone: _____

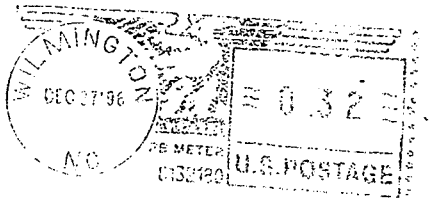
Do you have access to E-mail? _____

Please tell us how you heard about us. _____

Membership Dues for one year are $15.00. Please send a check or money order to:

Pharmaceutical Microbiology Forum
c/o Elizabeth Darner
223 Sunnymead Road
Somerville, NJ 08876

**The PMF mailing list is private, not for sale



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