PMF Newsletter

A quarterly publication of the Pharmaceutical Microbiology Forum

Volume 3, Number 2 Spring , 1996

Letter from the President

This year the PMF will continue with our goal of increasing communications among the pharmaceutical microbiologists. In order to get the most out of the organization, we need to enlist as many pharmaceutical microbiologists as possible. We do obtain new members every month, however, we know that there are many more that are not members, yet.

The PMF carries a very small membership fee ($15.00), set to cover our minimal expenses, based on the fact that we are a not-for-profit organization. Most members allow their company to pay for their membership. For those less fortunate, the low fee enables them to pay from their own pocket.

We know that some of you share the newsletter with others, and are glad that more and more people in USA and Europe know about us. However, to make the PMF a bigger and stronger organization, we propose that each and every pharmaceutical microbiologist joins the organization.

If you are not a member, please consider joining. Also, we recommend you have the newsletter delivered to your home instead of to your office. This will help you remember to send in any address changes and will get the newsletter forwarded instead of being passed on to your successor, or being destroyed.

Last, but not least, I would like to encourage you, as a member, to let our organization be known to your peers and any colleagues you may have in any other companies, such as past coworkers or people you meet at a national meeting, seminar, or workshop. The more people we have in our group, the more resources we will have to prevent some of us from reinventing the wheel! By sending questions, answering questions, or by sending articles to the PMF, we help each other increase our knowledge of microbiology.

Following is a listing of the PMF Staff for 1996:

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Inside This Issue

USP Open Conference

The USP Open Conference covering Microbiological compendial issues was held in Ft. Myers, Florida from January 11-13, 1996. This type of conference is held to provide outsiders to the USP an opportunity to comment on proposals published in the Pharmacopeial Forum (PF), and a few unpublished drafts. Anyone can send comments to USP either as an individual, or representing the view of a company.

This year's conference was attended by more than 240 people from 34 states and 8 countries. The discussion topics were chosen in advance. There were six topics and six discussion groups. Each participant was assigned to a group which rotated through each topic. The format was a round table and those assigned to the group were at the table. Others attending were to sit away from the table. Each topic had a discussion leader, but each discussion was different, because the group participants were different with each session. The topics under discussion were: Antimicrobial Efficacy, Sterility Testing, Microbial Evaluation of Controlled Environments, Sterilization, Water and Raw Materials/Products. The USP summarized all topics and on the last day presented the most common comments per topic. A summary of those comments was mailed to the attendees during the month of March. Below is a set of comments heard at this conference.

Antimicrobial Efficacy

Leader: Scott Sutton, Ph. D.

- Anhydrous products should not be tested using this method. You would need to introduce the inoculum containing liquid, thus changing the product. This will make this test invalid.

- Oral products mentioned in USP means liquid and suspensions. The wording was criticized since it quotes "oral products and oral dosage forms" this verbiage does include solid forms.

- Pseudomonas aeruginosa was indicated not to be a good challenge organism for antacids because it is known to grow copiously. P. cepacia or other environmental pseudomonads would be more valuable. You may be able to show some control over pseudomonads, even though P. aeruginosa will grow. Because of this you should show that Pseudomonas spp. are under control in your water system.

(cont. pg 3)

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.

June 3-7, 1996, PDA Baltimore Course Series (IV), Baltimore, Maryland

June 18-21, 1996, *PDA Baltimore Course Series (V)*, Baltimore, Maryland

PMF Newsletter is published quarterly by the Pharmaceutical Microbiology Forum.

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

The information contained in this newsletter are the professional opinions of our members and do not represent the policies or operations of any corporation or government agency to which members may be associated. *PMF Newsletter* is intended to serve as an open forum and confidentially will be maintained. The information in *PMF Newsletter* is solely for information purposes and is developed from sources believed to be reliable. Statements expressed constitute current opinions derived through analysis of available information and professional networking. Articles or opinions are for information only for PMF members to stimulate discussion and are not the views of the PMF board or regulatory agencies. The *PMF Newsletter* cannot make any representations as to the accuracy or completeness of the information presented and the publisher cannot be held liable for errors.

Test organisms are a concern in order to achieve consistency in testing. We should have a specific way of handling inocula. This was considered to be a major key on the quality of the suspension, and should be addressed first. Then we can determine if a test for stock cultures antimicrobial resistance suitability, as proposed in PF 21 (4) July-August, 1995, is necessary.

A representative of the European Pharmacopoeia (EP) indicated that in Europe, most pharmaceutical companies will meet criteria A or at least B. The American companies indicated they have products that will not meet even the B criteria. The EP representative also indicated that the zero time point in the EP is a data point. The initial count is taken from the inoculum count and calculated, not from the zero point. This is usually misunderstood.

Rebounding of organisms is usually seen between days 14 and 21, not later. S. aureus and P. aeruginosa are the two organisms that usually "come back". The US may need to move to shorter intervals (less than 7 days). Europeans are concerned that products are used daily, therefore a 7 day time point is not that valuable. That is the reason they perform a 6 hour count.

Attendees indicated that USP must provide a very clear definition of "no increase". Attendees also suggested USP should consider adding an explanation on validating preservatives in different ways. Examples: chemical inactivation, dilutions, filtrations, etc.

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, 2850 Harrison Avenue, Suite C, 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.

Sterility Testing

Leader: Murray Cooper, Ph. D

- The chapter has a comment in the media section indicating to determine the pH after sterilization and during its shelf life. Attendees pointed out that pH checks in shelf life are not necessary. This is addressed during validation of the media, not during regular use.

- It was noted that wording 10-100 viable microorganisms needed to be changed to 10-100 cfu. Colony forming units is the appropriate term.

- The 10-100 cfu inoculum was recommended for review. Attendees suggested to change it to less than 100 cfu or leave it as 10-100 cfu with an explanation that if you have less than 10 cfu and growth is obtained, the test does not need to be repeated.

- The bacteriostasis/fungistasis (B/F) section has new organisms proposed. This may invalidate B/F already in place. This section is not harmonized with BP or EP. USP has a new draft with more choices for organisms. A major issue is Micrococcus luteus or Staphylococcus aureus. Which one is better for the B/F? Attendees expressed having problems with both. No species seemed better.

- Growth promotion is proposed to be changed to a 7 day incubation. Membrane filtration will change from 7 to 14 day incubation (all attendees in a specific session were opposed to this). B/F incubation will be not more than 7 days for membrane filtration and direct transfer. As soon as product test compares to control, you can stop the test.

- Obtaining a sterile beta lactamase from a manufacturer was reported as a problem. Most people are preparing vs purchasing it.

(cont. pg 4)

(Sterility cont.)

- Direct transfers - The maximum volume should be 1 liter. If product is still showing antimicrobial properties, continue sterility using 1 liter.

- The rinses for membrane filtration need to be explained. Water does not need to be rinsed while other products may need more than 3 rinses to overcome any antimicrobial properties.

- Second stage testing will be eliminated. If a test is invalidated it will be the only case for repeating a test. This is not considered a retest.

- Negative controls need to be clarified. Is this referring to known negatives or to exposing media during testing?

Microbiological Evaluation of Controlled Environments

Leader: Barry Garfinkle

The table presented on frequency of sampling is too specific with no allowance for tailoring the environmental monitoring program to the site and/or products. The attendees recommended that the table be retitled as example of frequency of sampling. It was also recommended that documents be written with examples and using the words "should" instead of will. This will soften the documents and perhaps lower the chances of a 483. The table also includes values for terminally sterilized products , even though the chapter states at the beginning that it is for aseptic fill processes. This chapter was written by several people and does not show tight links from one section to another. The section on terminally sterilized products is there because it refers to medical devices that will be aseptically packaged after being terminally sterilized. Due to the variety of authors, there are contradictions in this chapter. One section indicates to test during the operation, while another section clearly states not to disrupt the manufacturing operation.

The value of settling plates was discussed. FDA does not see value of them, but the Europeans do. The group consensus was that settling plates, even though qualitative, can be placed at various sites in the operations. This includes critical areas (areas where product is exposed) without harming the operation.

Attendees indicated that this type of sampling may have more value than volumetric samples because organisms that can settle are the ones that will get into the product. A comparison of the size of the plate to the size of the orifice of your product container will be appropriate. this will give a better idea of the probability for contamination. The media fill section was recommended to be taken out and placed in a separate chapter. Media fill comments are as follows:

The chapter recommends dual incubation temperatures, first low, then high temperature. The incubation temperature is not as for sterility 22.5 ±2.5 and 32.5 ±2.5 for 48-72 hours. It was recommended that incubation temperature and time be the same as used for sterility.

Growth promotion for media fills is written to be done before the media fill. This is not how the industry does it. Media fills are conducted, all units are incubated, then growth promotion is performed. An attendee indicated that if you pull some units to perform growth promotion, the investigator may think you pulled the "bad units" and called them growth promotion. Because of this, growth promotion needs to be performed at the end of the incubation time of the media fill.

Some companies use the media from the fills for their regular sterility tests. This is done for Soybean Casein Digest Medium, only.

To perform media fills in a worst case scenario, it was suggested that the media fill be "piggy backed" to a regular production run. Media fill is conducted right after the regular production, without changing the line, the operators, the gowning, or disinfecting.

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Sterilization

Leader: Henry Avallone

Biological Indicators

Population specifications are proposed to be changed from 50-300% of label claim to label claim up to 0.48. It was recommended that this new specification be modified since it will be too tight at the lower end. Differences in plating, analysts, media and other variables are not allowed for. It was recommended that 1/2 log plating variability be adopted here, as well as in all USP chapters to make them uniform.

During this roundtable, media fills came up again and the attendees again indicated that media fill should be put into a separate section.

A chemical indicator that changes with temperature **precisely** when 121°C is reached may be needed. This does not exist! Attendees indicated that perhaps an integrator or computer chip may be a better choice. USP may describe the device needed and its characteristics. The comment to this was that USP can write many things that we would like to obtain from the manufacturers of indicators, but this may not be realistic. For years, the pharmaceutical industry has requested a self contained biological indicator with a population of $1x10^6$ spores/ampule. However, this indicator does not exist!

The sterility test section under sterilization is different from section <71> and does allow for second stage. It was recommended that it will be written the same way as the one under sterility.

Revalidation of moist heat is written to be done every 12-14 months. Attendees recommended re-evaluation vs revalidation. If you have had no problems with your sterilizer, you may just re-evaluate all data/records and accept it as "no need for revalidation at this time." Re-evaluate annually. However, if there is a significant change, then revalidation must be conducted.

The guideline also calls for using 20 BI's in the PQ phase. This number was challenged. The attendees recommended changing verbiage to "use a minimum of 10 BI's.

The proposal for container/closure integrity is presented with the goal of having it replace sterility tests performed during stability. It was noted that antimicrobial products cannot be tested via immersion tests (for integrity testing). Cytotoxic products may need to have immersion tests not on the product itself, but on the media fills. This will be a problem. If this test is to be performed for stability, you need to use a medium that is stable at various stability conditions throughout the shelf-life of your product. Some could be 5 years. The feasibility of this approach was questioned.

Microbial Limits/Microbial Attributes/Water

Leader: Henry Avallone

WATER:

Attendees asked which reference was used to establish the requirement for source water as ≤500 cfu/mL. Mr Avallone agreed to check on this. Attendees indicated that a distinction needed to be made between incoming water and source water. The leader indicated that FDA does not use the pour plate method. FDA filters 100mL aliquots. Attendees indicated that 100 cfu/mL as a standard was criticized as a high number. Numbers are important but species is even more important. The EP limit for water is 10^2 cfu/mL. This means that you can have 5X this number, therefore the real upper limit is 500 cfu/mL.

Recovery differences when using TSA, R2A and R4A were commented on. Overall, attendees agreed that at the first stage, one must check the water with various media and decide which one is more suitable for the particular water testing. Medium richness, injured organisms, incubation temperature and incubation times need to be considered during the decision making process.

The proposed chapter was heavily criticized for getting into IQ, OQ and PQ guidelines. Attendees indicated that those 3 items needed to be left open for the various companies to tailor them to their specific operations and products.

The reference to Standard Methods 18th edition needs to be revised since the 19th edition is available.

(cont pg. 6)

There is no harmonization in the various pharmacopoeias in terms of water testing. However, some international pharmacopoeias are gearing to change current chemistry requirements to TOC, pH and conductivity, just as USP is doing.
The issue of absolute numbers came up again. Attendees suggested that the 1/2 log variation be applied all throughout the USP microbiology sections.

RAW MATERIALS/PRODUCTS:

It is recommended that finished products have the same limits as raw materials. A limit of 1000 cfu/g is being proposed for oral solids, but some raw materials are proposed as 1000-5000 cfu/g. Also, natural and synthetic materials have the same specifications. This should be corrected because the objectionable organisms are more likely to be found in natural sources, not in synthetics. It was mentioned that natural products can be sterilized using ethylene oxide. The section on indicator organisms needs to be expanded because its purpose is misunderstood, primarily by upper management eager to release products to market. All microorganisms present in a product need to be known. New proposed indicators are Candida albicans for vaginal products and Pseudomonas fluorescens for inhalants. It was commented that Dennis Guilfoyle of the FDA tends to subject topicals and inhalants to enrichment broths. After this, samples are plated using various media and every colony found is identified. They perform population counts. However, the main goal is to determine which species of microorganisms are present.
Mr. Avallone indicated that FDA does not use USP tests for topicals. They use Bacteriological Analytical Tests. This reference uses 7 day enrichment tests. It was recommended that incubation times be given in USP as minimum of X hours to allow for longer incubation time instead of having ±2 hours. This is, again, to soften the document and prevent regulatory issues. Some people did not agree with this recommendation because organisms such as S. aureus may lose their typical colony color with longer incubation times. The proposal is written requiring subculturing of S.aureus using 3 different media in duplicate. This was found to be excessive. The attendees recommended rewriting of this portion requiring use of one of the media as USP 23 currently states.
NOTE: In order to make a USP conference productive for anyone, people must be up to date on all pertinent proposals in the PF or at best read the book that is sent by the USP for the conference. The proposals are not formally presented.

Addendum to Validation of a WFI System

These are interesting notes not published in our last newsletter:

- The MCA (British "FDA") looks at LAL levels in feed water.
- Most WFI systems have 80°C loops. Very few companies have validated WFI systems at lower temperatures. Running loops at lower temperatures is a cost savings idea.
- If a system is held under nitrogen, screening for anaerobic organisms is necessary. Testing should be conducted in the tank, the return loop and some drops.
- A retroactive system review is recommended. Do not refer to it as retroactive validation, since FDA does not like this term.
- During the review all data are evaluated. Look at preventative maintenance, work orders, calibration, drawings, SOP's and sampling and place in a package. If a problem is found with the data, then a physical revalidation must take place, otherwise, system revalidation is not necessary.
- A change control system should require an order (request) submission of the work to be done. The validation team will evaluate if the package will be affected by the work order. If work is approved, a report detailing work done should be required from people making the changes, because in many cases, more work than originally requested is performed.

(cont pg 7)

(Water cont.)

- If you have alert limits of 5 cfu/mL, action limits of 10 cfu/mL and your counts are always 0 cfu/mL, then your alert and action limits are too high. Scale them down by determining where are 95% of the counts falling.
- During the method validation for hot water, you must inoculate hot water and ensure microorganisms survive in order to be recovered, otherwise, your method will not be validated.

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.

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

Microtoons

PMF's Regulatory Corner

PMF will have a new section in the PMF Newsletter that will include:

1. What questions were asked by the agency?
2. What did the agency recommend?
3. What were the citations?
4. Recent responses from USP.
5. ISO questions/comments.

Please share any of the items above that have occurred either at your company, or at a colleagues company. Do not use names or company names. Thank you for your assistance. We will publish all collected comments. Please forward to:

Laura Valdes-Mora
AAI
2850 Harrison Avenue, Suite C
Panama City, Florida 32405

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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.**

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

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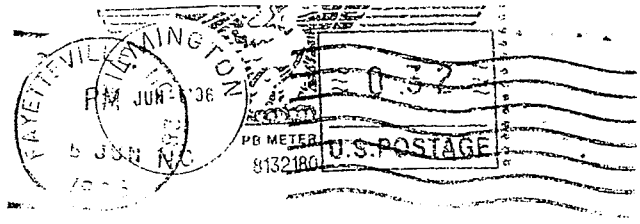

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