PMFNewsletter

A quarterly publication of the Pharmaceutical Microbiology Forum

Volume 4, Number 2 Summer 1997

President's Message

The Sixth Annual PMF Membership Meeting was held in Wilmington, NC on April 16, 1997, following the annual Board of Directors meeting that was held the day before.

This year, we are planning to increase our membership and our international exposure. We will also conduct two surveys, one on salaries, as it was concluded that industry salary surveys do not reflect the common lower salaries of Microbiologists, when compared to other scientists. The second survey will be on microbial identification methods currently used in your laboratory. The first survey is included in this newsletter. A pre-survey was conducted at our meeting in Wilmington. The results of the pre-survey and the survey will be combined and published in our next issue. Please take time to fill out the survey and return it to us. The more information we can obtain, the more valuable the results will be.

We are also planning to get our membership involved in participating in an e-mail discussion group where you will be able to post technical questions (exclusively regarding Microbiology) and receive answers from various members in a rapid fashion. Our long-term goal is to also conduct one or two chats a year. During a chat session, everyone will log-in at a scheduled time and date, and via e-mail, we will have live cyberspace conversations on the chosen topics.

Stay tuned, we will provide you with more information as we develop the systems, with the assistance of The Microbiology BBS.

Laura

Come Visit Our Website at http://microbiol.org/PMF.htm We also welcome you to visit the Microbiology BBS site at http://microbiol.org

The Pharmaceutical Microbiology Forum is proud to have members in the following countries: United States, Canada, The Netherlands, Belgium, Germany, Israel, Puerto Rico and Japan.

IN THIS ISSUE:

USP Workshop

Below are notes from the USP Workshops on Water and Microbiology held in San Juan, Puerto Rico April 6-8, 1997:

New Water Monographs for Purified Water and Water for Injection (WFI).

- Source water must meet EPA Drinking water Standards.
- EP, JP, and EPA drinking water standards are currently considered equivalent, therefore, test only using one of these three standards.
- There are and will be different standards and monographs for processed water (BULK) AND PACKAGED WATER. Packaged water is sterile. This is why there are different monographs.
- Total Organic Carbon (TOC) test can be set as a simple pass/fail test. If you do not validate the equipment, the standard check can be considered a one-point validation and it will give a pass/fail result. Although, this will be considered a qualitative test.
- Ninety percent of the problems associated with TOC are due to glassware. ULTRA cleaned glassware should be used. This glassware (all of it excluding flasks, pipettes, etc.) should be *dedicated* glassware. This glassware should never go through your glass washer, or you may have detergent residue interferences.
- Conductivity is a 3-stage test, also called the chloride-ammonia model. This test rewards you for having good water. This means that the better your water is, the less testing you do. If you pass stage 1, you will pass stages 2 and 3. For this reason, there is no need to do all the parts.
- Conductivity - there was no one (1) value considered typical, since the pH range from 5 to 7 allows for tremendous differences in conductivity.
- Due to the fact that micro results are variable, it will continue to be an informational chapter <1231>, *not* a monograph. There is a legal impact of a monograph.
- Note that your company has filed water specifications with their drug applications at the FDA. If USP changes, your company needs to also change the specifications in the drug application.
- Having water pass EPA standards *does not* mean that the water is free of objectionable organisms.
- Water isolates should be identified.
- There is no requirement for absence of *Pseudomonas* sp. in water.
- Oxidizable Substances will be deleted as of May 15, 1998 (for Purified and WFI only). Packaged water will continue with this test.
- Changing to TOC can take a company approximately 6 months. The company may need to change resins, frequency of testing, and frequency of preventative maintenance. The sampling program may need to be upgraded (i.e. re-train personnel who collect samples).
- Harmonization with EP and JP will be next. Attributes to argue about are: nitrate/nitrite, lower level of ammonia, are these needed?
- There will be a stimulus article coming up in PF on the topic of harmonization.

Sterility Testing <71> Proposed Changes

- Adds *Staphylococcus aureus* for Fluid Thioglycollate and *Aspergillus niger* for Soybean Casein Digest Broth.
- *A. niger* may present problems with breaking of the mycelia. Keep USP informed if you see problems here.
- *Bacillus subtilis* may be removed as a test organism, since it is a strict aerobe, but it is a test organism for FTM.
- *Pseudomonas aeruginosa* is being considered as a test organism.
- The current proposal will be revised again. There are a few printing errors. The revision will also clarify that canister systems, such as Steritest, are suitable for sterility testing.
- Direct transfers will be allowed with maximum volume of medium of 2000 mL.
- Membrane filtration can be done with up to 5 rinses of 500 mL each.
- Sterility test is a very limited test due to the small number of samples tested. Finding contamination is a *challenge*. For this reason, stage 2 is eliminated.
- CFR will still allow stage 2 testing. Harmonization with FDA seems *necessary*.

Antimicrobial Effectiveness

- This proposal is expected to become official prior to any others discussed.
- Editorial changes/clarifications were published in PF23 (2) Mar-Apr 1997.
- Category (2) for anhydrous bases or vehicles is not recognized by EP, therefore, USP will have 4 product categories while EP has only 3.
- Bacterial and yeast suspensions are to be used within 24 hours of harvest; EP allows only 8 hours as the age of the inoculum suspension.

(cont pg. 3)

- EP allows use of cultures from other depositories other than ATCC. USP only allows use of ATCC cultures.
- USP will define no increase in population as not more than 0.5 $\log_{10}$. EP defines no increase as 0.3 $\log_{10}$.
- Kill ratios (how fast an antimicrobial should reduce populations) will be different between the new USP and the EP. EP will still have more stringent requirements than USP.

Soon to come is an informational chapter on antimicrobial effectiveness.

Bacterial Endotoxins Test

There are no changes or proposals pending.

- There are a few differences between USP and the FDA guideline in terms of handling standards. Per FDA guideline, the standard does not need to be run with each test, only when a new lot is obtained.
- It is recommended that you validate the gel clot assay for all your products, as it is the referee test. Users need to know of any problems *before* the FDA runs the test.
- Inhibition can be caused by anything that can inhibit enzymatic reactions (i.e. chelators, heavy metals, pH). Inhibition is more common than enhancement. The most common way to overcome it is by adding water (i.e. dilution). Dilutions give rise to the maximum valid dilution. If inhibition is not overcome in gel clot, another method is then chosen (turbidimetric, chromogenic).

Microbiological Attributes of Pharmacopoeial Articles

- This is an informational chapter (page 1939 in USP 23). The proposal is to expand its scope and change the name to Microbiological Attributes of Non-sterile Pharmaceutical Products.
- Water used in manufacturing for cleaning could be tap or purified, but should be at 80°C.
- The new proposed monograph has only one table with limits for Total Aerobic Microbial Counts and Total Combined Yeast and Mold Counts, based on the route of administration of the product. Each class of product also has objectionable organisms. The standard four indicators are included. Screening for *Candida albicans* in vaginal products will become a requirement.
- The table indicates that it is impossible to list every microorganism that may be objectionable. An example was given where a Class 1 recall was done on an inhalation solution for the presence of *Pseudomonas gladioli* and *P. cepacia*. However, the product was free of the standard organisms called for in USP. USP reminded people that FDA *does not use USP methods*. FDA uses the Bacteriological Analytical Manual (BAM) methods, which include the use of 10 gram samples, enrichment broth for 5-7 days, followed by isolation and identification of *all* isolates.
- It is recommended that you use the BAM methods during the validation stage in order for your company to know what FDA can *possibly* find.
- The current microbial limits test is faster and less sensitive than the FDA's method.
- The following are considered objectionable organisms, per *Formulation of Pharmaceutical Dosage Forms Disperse Systems*, Volume 2:
  - *Pseudomonas multivorans*
  - *Klebsiella* spp.
  - *Proteus mirabilis*
  - *Candida parapsilosis*
  - *Pseudomonas putida*
  - *Serratia marcescens*
  - *Penicillium* spp.
  - *Saccharomyces* spp.

Upcoming USP Events

Dr. Joseph Knapp – Chair of the Microbiology Subcommittee announced the following:

1) New chapter on sterility of isolators
2) Changes in calculations of Biological Indicators
3) Chapter on parametric release
4) <1106> Microbial Integrity of Container/Closure Systems
5) Informational chapter on endotoxins
6) Changes to the MLT chapter
7) Informational chapter on seed lot technique is under consideration

The PMF recommends that you *write to the USP with your comments on all proposals*. You can write representing your company, or as a single *scientist*.

Any questions concerning USP documents should be sent to Dr. Roger Dabbah. You can reach Dr. Dabbah at (301) 816-8336, or via e-mail at RD@USP.org. When communicating with Dr. Dabbah, let him know you are a PMF member.

Summary of AAI Seminar Series

The following is a summary of a presentation at the seminar entitled "Taking Microbiology into the 21st Century," held in Wilmington, NC April 15-16, 1997:

Assessing Sterile Product Container/Closure Integrity

- USP, FDA and PDA are each working on container closure guidelines. The number of containers to be tested is not currently addressed by any of these 3 documents.
- PDA has a task force and they have worked on the topic since 1994.
- Physical tests are more sensitive than the microbiological test.
- PDA will revise Technical Bulletin #4. This is currently in draft form.
- PDA funded a study awarded to the University of Iowa to perform gas studies using Mass Spectrometry. One of the purposes of the study was to correlate dye testing with microbial ingress. A correlation was found.
- The PDA task force conducted an information search by soliciting the information from publications and other industries. The search revealed that very few of the publications dealt with the microbiological challenge.

Current Container/Closure methods include:

1) Static ambient challenge
2) Vacuum ionization
3) Capacitance
4) Mass Spectroscopy
5) Internal Pressure
6) USP Sterility
7) Media Fills (no challenge)
8) Microbial Immersion
9) Microbial Aerosol Ingress

The New PDA bulletin will include:

1) Introduction
2) Package Design, QC and assembly
3) Decision Tree
4) Methods
5) Comprehensive Bibliography

The new document is expected to be released in the Fourth quarter of 1997.

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.

AAI MICROBIOLOGY SEMINAR SERIES-HALFDAY SESSIONS USP UPDATES 1997 AND METHOD VALIDATIONS

SAN FRANCISCO, CA, SEPTEMBER 23, 1997
SAN DIEGO, CA, SEPTEMBER 24, 1997
Contact Leslie Clapp, (800-575-4AAI).

MICROBIOLOGICAL UPDATE

ISLAMORADA, FL
NOVEMBER 11-13, 1997
Microbiological Update (305-664-8513).

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.

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.

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 is the professional opinions of our members and does 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.

Current Compendia

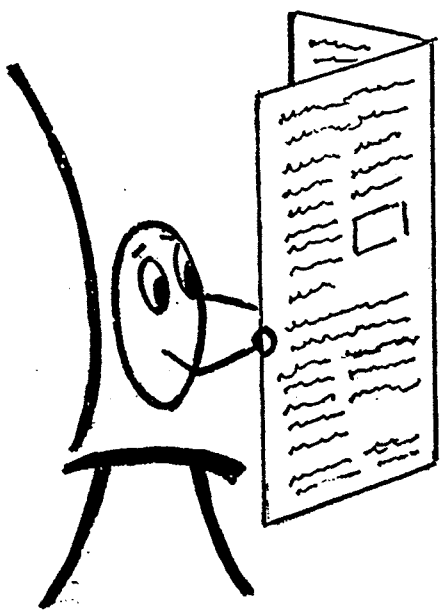
US Pharmacopeia (USP) 23 Supplement 6

European Pharmacopoeia (EP) 1997

Japanese Pharmacopoeia XIII (JP) 1996

*If you use any other compendia, let us know for inclusion in this corner

MICROTOONS



E.coli reading the newspaper today

The following Internet Sites may be of interest to you

Internet Address	Description
http://law.house.gov/cfr.htm	Code of Federal Regulations
http://microbiol.org/	Microbiology BBS
http://microbiol.org/pmf.htm	PMF Home Page
http://fda.gov/cber/cberftp.html	CBER Information
http://ww.fda.gov/cder/cgmpnotes.htm	Paul Motisse Human Drug CGMP Notes
http://www.fda.gov//guidance/index.htm	FDA Guidance Documents
http://www.fda.gov/cder/index.html	CDER Home Page [21 CFR, Fed Register, Policies, etc.]
http://www.fda.gov/cdrh/topindx.html	General Index of all CDRH Documents
http://www.fda.gov/cgi-bin/ice-form.pl	Index Gateway of all FDA Documents – To Search
http://pda.org	PDA Home Page
http://www.pharmweb.co.uk/hypermail/0068	Catalog of Prior Messages of the PDA Sci Tech Discussion Group
http://www.pharmweb.net/pharmweb/pwq/pharmwebq2.html	Sci Tech Discussion Group – To join
http://www.pharmweb.net/pwmirror/pwq/pharmwebqc.html	Biotech Discussion Group/Drug Discussion Group
http://sunsite.unc.edu/pwmirror/pharmweb94.html	PDA on Pharmweb
BETList @ micorbiol.org @ External	To reply to/join ACC-LAL Discussion Group
Pharm Tech @ pharmweb1.man.ac.uk @ External	To reply to PDA Sci-Tech Discussion

If you have found an interesting site related to pharmaceutical microbiology, please let us know.

Benchmarking Survey Results – Routine Microbial Sampling Frequency

Water Systems		Environmental Monitoring				Operator Gowning		Compressed Gases *(clean air, CO_2, N_2, etc).*	In process Bioburden *(media, buffers, product stream)*
Purified Water USP	Water for Injection	Controlled Unclassified	Class 100,000	Class 10,000	Class 100	Entry	Exit		
Daily Weekly *Production units daily, use points weekly*	Daily Weekly *Production units daily, use points weekly*	Monthly	Monthly	Weekly Monthly *weekly in fill facility*	Each lot Monthly *each lot: air only*	Quarterly *operators requalified annually*	Each lot Monthly *each lot in fill facility only*	Quarterly Semi-annually *particulates quarterly, viables semi-annually*	Each lot
Daily Weekly	Daily Weekly	Weekly	Weekly	2x/week	Each lot 2x/week	Quarterly	Each lot	Quarterly	Each lot
Not applicable	Daily Weekly *Use points daily if something attached (e.g. hose)*	Not monitored	Monthly Quarterly	Each lot Daily Weekly Fill areas *daily(static, pre-processing)*	Each lot *Prior, during, & end of each lot*	Quarterly *Operators requalified quarterly*	Each lot *Each operator tested monthly at minimum*	Monthly Quarterly	Each lot *Equip rinses monthly*
Daily *micro: all points weekly* *chem: in-line*	Daily *Micro all points weekly. Chem in-line*	Not monitored	Weekly *Aseptic area, each lot*	2x/week *aseptic area, each lot*	Each lot *Variable, process dependent*	Qual/validation *Prior to media fills only*	Each lot	Not monitored *P.O.U filters used*	Each lot
Daily Weekly *1-2 critical points daily. all use points weekly*	Daily Weekly *1-2 critical points daily. All use points weekly.*	Weekly Monthly *Air viables weekly, particulates monthly*	Weekly Monthly *Air viables weekly, particulates monthly*	Each lot Monthly *Surfaces & air viables each lot, particulates monthly*	Each lot Monthly *Surface & air viables & particulates during filling*	Each lot	Each lot	Monthly *Hydrocarb monthly. Micro after maintenance. P.O.U. filters used*	Weekly Monthly
Daily Weekly *Daily: micro at beg, mid & end of loop; chem&endotoxin at beg only. Weekly: micro at all use points*	Daily Weekly *Same as purified. Chem & endotoxin at additional use points weekly*	Monthly	Weekly	Each lot Weekly	Each lot Weekly	Each lot *Fill facility only*	Each lot *Fill facility only*	Quarterly	Each lot
Each lot	Each lot Daily Weekly	Not monitored	Daily	Each lot	Each lot	Annually *Operators requalified annually*	Each lot	Monthly	Each lot *During validation at minimum*
Daily Weekly	Daily Weekly	Weekly Monthly	Weekly Monthly	Weekly	Each lot Monthly	Annually *Operators requalified annually*	Annually *Operators requalified annually*	Monthly	Each lot
Weekly	Daily Weekly *Use points daily, all points weekly*	Quarterly	Daily Weekly *Daily whenever work being performed*	Each lot 2x/week Weekly *High activity areas, each lot*	Each lot *STA only*	Annually			Each lot

A fellow microbiologist conducted an informal survey of 9 biopharmaceutical firms in Spring 1997, relative to the frequency of their environmental monitoring in the industry. The results are tabulated in this table.

The survey form included in this newsletter will compile very valuable information regarding salary ranges among microbiologists. Have you ever seen salary surveys published and realize your pay scale is not in accordance with the survey? This is our chance to tabulate what really happens in our profession. Please take the time to fill the survey and return it to PMF. Feel free to make copies of the form and ask your colleagues to fill them out and send them, also. Let us make this a useful tool for our profession! Thank you in advance for your cooperation. NOTE: If you filled out a similar survey in Wilmington, NC, please do not fill out the one here, as it is the same survey.

PMF Salary Survey

CIRCLE ALL THAT APPLY TO YOUR CURRENT EMPLOYMENT

Education: (Highest Degree) AA BA/BS MA/MS Ph.D.

Geographic Area: Eastern (N) (S) Central (N) (S) Pacific (N) (S)

Total Years of Experience: <5 5-10 11-15 16-20 21-25 >25

Work Area: QA QC (Micro) (Analytical) Regulatory Manufacturing Research/Development Sales
Other:_____

Type of Product: sterile dosage non-sterile dosage Diagnostics Medical Devices Cosmetics Food
Contract (lab) (manufacturer)

Current Title: Analyst/technician Scientist Supervisor Manager Director
Other _____

Number of Company Employees: <50 50-100 101-200 201-500 501-1000 >1000

Salary Range in Thousands: <20 21-25 26-30 31-35 36-40 41-45 46-50 51-55 56-60 61-65 66-70
71-75 76-80 81-85 86-90 >90

Comments:

DO NOT sign your name, or use your company name. Send your completed survey (no later than **September 26, 1997**) to:

Sharon Wood
755 Wimbleton Lane
Livermore, CA 94550-1749

The results will be tabulated and published in the next newsletter.

Pharmaceutical Microbiology Forum
Membership Application
or
Change of Information Form

MISSION: The 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.

THIS APPLICATION IS:

A New Member Application	
To Update my information, as indicated	

Name:
Company:
Department:
Position (title):

Phone:
Fax:
e-mail Address:

Preferred Mailing Address
Co.:
Address:

City, State
Country:
Zip

Please tell us how you heard about us:

The PMF mailing list is private, not for sale.
Membership dues are a one time fee of $15.00. Please send check or money order to the address below.

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

FAYETTEVILLE NC 283 #1 09/11/97 21:55

Pharmaceutical Microbiology Forum
c/o L. Valdes-Mora
3166 Wood Valley Road
Panama City, Florida 32405

Address Correction Requested

02142-1401 31