PMF Newsletter

A quarterly publication of the Pharmaceutical Microbiology Forum

Volume 3, Number 1 Winter, 1996

Letter from the President

A technology that has been known for years is infiltrating the pharmaceutical microbiology arena. The bioluminescence technology is the detection of microorganisms by their Adenosine Triphosphate (ATP). ATP in the presence of luciferin and the enzyme luciferase, produces bioluminescence (light). There is now equipment that can convert the light produced into a response that allows you to detect contaminated lots. Currently, the technology does not quantify low numbers of microorganisms. However, it can be used as a screening tool. You can test production lots using this technology. If no bioluminescence is produced, that lot can be released to the market. If bioluminescence is detected, you will perform the classical microbial limits (MLT) method for final release. The advantage of this technology is that once you have cross-validated it with your classical MLT, you can release the good lots in 24-48 hours while only the questionable lots stay on quarantine for the full 7 days. Drop us a note and let us know if you would like to see technical information and data on this technology in a later issue of this newsletter. For vendor information, you can contact Celsis, Inc. at 1-800-222-8260. In Europe, call (44) 1223-426-008.

As this year begins, the Organizational Board of the PMF hopes you had a very nice holiday season. We hope to see you at the PMF Annual General Assembly meeting scheduled for Sunday, April 21, 1996 in Wilmington, NC. Following is a listing of the PMF Staff for 1996:

PMF ANNUAL MEETING

Sunday, April 21, 1996

Wilmington Hilton

Wilmington, NC

Inside This Issue

Summary of the AAI Microbiology Series

From April 26-April 28, 1995, the AAI Microbiology Series Validation in the Pharmaceutical Microbiology Laboratory, What's New in 1995 was held at the Wilmington, NC Hilton. A summary of several sessions was included in the Summer Newsletter. Below is a summary of the remaining sessions.

Microbiological Methods Used for Cleaning Validation

The presenter discussed the requirements for conducting cleaning validations of process equipment. This type of validation is the process by which we assure that the methods used to clean process and packaging equipment are effective and reliable. The results are work systems that are in compliance with the FDA and cGMP regulations.

This type of validation requires that the microbiologist associated with the validation have considerable experience in evaluating disinfectants. The microbiologist on the validation team has to be involved in all aspects of the cleaning validation including: review of equipment cleaning SOP's, disinfectant preparation, storage conditions, and times for prepared disinfectants, and sampling plan development. The sampling plan includes: selection of sampling sites, selection the sampling method(s), number of samples, when in the process to collect the before and after cleaning samples, and what constitutes an acceptable and unacceptable result. After the initial review of the process in question, the team has to generate a protocol. The protocol includes a title, the purpose, any background data or information pertinent to the validation, the finalized sampling plan, test methods and acceptance criteria. Also, the protocol must include a plan of action if specifications are not met.

Disinfectants are selected based on flora and compatibility with equipment. The test should be conducted using ATCC cultures and environmental isolates. This will help determine if the active ingredient and contact time chosen are appropriate or if changes are needed. Below are examples of disinfectants and inactivators:

Disinfectant	**Inactivator**
Halogens	0.1% Sodium Thiosulfate
Phenolics	Tween
Aldehydes	0.2% Sodium Sulfite
Quaternary	Lecithin and Tween

If you filter the disinfectant during the testing, this helps in inactivating it.

Prior to sampling and testing, the testing laboratory should perform an antimicrobial effectiveness test on the disinfectant being used in the cleaning process to ensure they are capable of acceptable reduction or elimination of contaminants. Neutralizing agents, appropriate to the disinfectants used in the process may be incorporated in the microbial isolation media to allow detection of the maximum number of organisms. It must be demonstrated that inhibitors are inactivated and that procedure does remove bioburden.

The methods commonly used are contact plates for flat surfaces, swabs for hard to reach locations, and rinse samples for large containers. As with most laboratory procedures, the ability of the media to support growth must be confirmed. The cleaning validation procedure in the Microbiology Laboratory can be run as follows:

Apply inoculum and let it dry. You can place it in an incubator for 15-30 minutes to expedite drying. Recovery should be in the same log that you apply it. Example: If you add 100cfu, you should remove at least 90cfu. Recovery problems are common. You need to work with it and optimize inoculum application, drying time and sampling method.

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(Cleaning Valdation, cont)
Isolates should be subcultured to provide 24 hour pure cultures. Older cultures have been shown to give inaccurate results. The cultures are to be Gram stained and identified. The following are sample acceptance criteria for product contact sites. Specifications should be set based on the intended use of the product.

Type of Sample	*Acceptance Criteria*
Contact Plates	0-5 cfu/25cm2
Swabs	0-5 cfu/25cm2
Rinse Samples	<1cfu/mL

If you obtain higher counts after sanitization, there may be people introducting contaminants. Aseptic steps may need to be included in the process to resolve the situation.

Validation of a Water for Injection System

Water for Injection is water purified by distillation or reverse osmosis. This type of water does not have any added substances. The importance of WFI stems from the fact that it is the most widely used drug product ingredient and it is absolutely essential to the quality of the product. The validation program should include:

1.Written validation procedures
2.Validation protocols
3.Summary of data

As with any other validation, one must conduct IQ, OQ, and PQ. Revalidation is to be conducted annually and when significant system modifications are implemented.

The maintenance of the system should include preventive maintenance, repairs, sanitization/sterilization, and passivation.

Routine testing procedures should state the locations to be sampled and the frequency. All subloops should be tested. Trending of the data should be conducted. Testing of the system per USP includes the nine USP analytical tests: pH, heavy metals, total solids, chlorides, ammonia, sulfate, carbon dioxide, oxidizable substances, and calcium. The microbiology requirements are for total counts, coliforms, and bacterial endotoxin.
Editorial Note: It has been proposed and accepted to date to eliminate the coliform testing. This is a controversial issue among pharmaceutical microbiologists.

The analytical chemistry requirements are proposed to be changed. The calcium, sulfate, chloride, ammonia and carbon dioxide tests will all be replaced by a conductivity test. Oxidizable substances will be replaced by total organic carbon (TOC). Heavy metals and total solids will be deleted. A guideline for microbial counts will be added to the USP as part of a General Information Chapter.

PharmComm Online Information Service

The PharmComm Online information service provides information specifically tailored to pharmaceutical, biotechnology, and medical device industry subscribers. PharmComm Online is pulling together a broad range of related information including regulatory documents, journals and publications, technical discussion forums, vendor-specific support areas and documents, and even 10K's for pharmaceutical/biotechnology/medical device companies.

The PharmComm Online is **not** an internet service. It is available to subscribers only, through modems attached to the public switched telephone network and through telnet for those who wish to use the internet rather than dialing in.

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(PharmComm cont.)
PharmComm Online's goal is to present in one place, solid, useful information for access whenever it's needed. This information currently includes Standard Operating Procedures developed by AAI over the past sixteen years; Computer System Validation SOP's, Protocols, Test Procedures, and Reports; meeting and seminar announcements; proceedings from technical meetings; questions and answers; Federal Register updates in pharmaceutically related areas; and much more.
PharmComm Online also provides a platform for Vendor Partners who serve the pharmaceutical industry. Through PharmComm Online, these Vendor Partners can provide access to equipment manuals, publications, technical information and support, and ordering information for equipment and services.
The information we are making available initially is just the beginning. As subscribers use the Online service, they will request information and services that are most useful to them. We expect growth in areas and ways currently not imagined.

PharmComm Online Features

- Multimedia client software based on Microsoft Windows for ease of use
- Download and upload files while you work online in other areas
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- Adobe Acrobat Portable Document Format (PDF) files for use on Windows, DOS, MacIntosh, and UNIX systems

•Access to public or private discussion areas (chat areas)

•Access to all public Forums, User Registry, and Polls & Questionnaires

•The User Registry is like a telephone book, only with more information. Its use is entirely optional.

•Polls and Questionnaires are available for use by anyone who wants to collect opinions or statistical information on specific topics. Subscriber responses are optional.

Please contact Dr. Bruce Rudy at (910) 256-4146 for additional information.

Reader Questions

Is it necessary to test tablets for microbial content since it delays the release of the products. Would environmental sampling, cleaning validation and three validation batches should be enough, even though no historical data is available on the products. What is the trend in the industries? Do they routinely perform microbial release testing? Are preservatives sometimes added to the tablets? Can desiccants be used in the containers to keep the products dry?
The second question is in regards to the use of benzyl alcohol and parabens as a preservative system. These are two common preservatives, but are any products using such as system. Have they been used together before? If not, are they incompatible?

Response:
Different pharmaceutical companies will approach this situation differently. Some companies will check the microbial content of the finished product, particularly if the

(cont pg. 5)

(Reader Question cont.)
manufacturing involves wet granulation. If there will be a compression step, most people will feel secure that this process will destroy microorganisms. There are many tablet and capsule formulations that do have preservatives. In tablets, the concern is the growth of molds, as most bacteria will die from desiccation, except sporeformers. Some manufacturers even go to the extreme of performing antimicrobial preservative testing on solid dosage forms that contain preservatives. This is not a USP requirement, as USP currently reads. Because of this, the USP pass/fail criteria may not be appropriate and the analyst reports results for information only.
Benzyl alcohol and parabens, according to formulators we consulted with, are compatible. Benzyl alcohol has been paired with phenol, potassium sorbate, benzoic acid or sodium bisulfite. Methyl and propyl paraben have been used with benzoic acid or benzalkonium chloride. For a more comprehensive list, look for a section on the use of preservatives in compendial articles that the USP will publish in the near future. A draft of this was included in the USP Open Conference (Jan. 1996). Details of the conference will be in our next issue.

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, 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.

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

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.

March 3-8, 1996, *Pittcon '96*, Chicago, IL.

March 11-18, 1996, *AAI Pharmaceutical Laboratory CGMP Trainers Program*, Wilmington, N. C.

March 19-24, 1996, *Water Quality Association*, Indianapolis, IN.

April 22-23, 1996, *AAI Pharmaceutical Microbiology Conference, Microbiology Requirements and Regulatory Compliance in the Pharmaceutical Industry*, Wilmington, N. C..

April 22-25,1996, *CleanRooms '96 East, The 11th International Conference on Advanced Technologies and Practices for Contamination Control*, Boston, MA.

May 19-23, 1996, *96th General Meeting, American Society for Microbiology*, New Orleans, LA

ONLINE

Would you be interested in having on-line information on Pharmaceutical Microbiology? If so, please respond via e-mail and tell us what you would like to see. Send your e-mail note to nlmoral@aol.com (all lowercase letters)

PMF Newsletter is published quarterly by the Pharmaceutical Microbiology Forum. 2850 Harrison Avenue, Suite C, Panama City, FL 32405. Telephone (904) 763-5453. 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.

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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 are a one time fee of $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

PMF Newsletter Comments

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

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Address Correction Requested