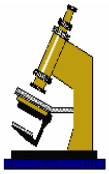
PMF
Pharmaceutical Microbiology Forum



PMF NEWSLETTER

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Inside this issue:

President's Message

As the year of 2003 came to an end, I reflected upon the changes in the PMF during this past year. We not only started a successful sponsorship program but also re-designed the newsletter which is now virtual and published on our new and very own website. **http://microbiologyforum.org**

In 2003, the PMF officers networked with key individuals from companies in our industry in order to increase the membership and exposure of our organization. As a result, special events are in the works for 2004 which we hope will elevate the technical impact that the PMF has and can provide to the pharmaceutical and biotechnology industries. This newsletter is a good example of how we interact with other companies not only to gather and disseminate valuable information but also to provide a forum for members to voice their opinions on issues that can affect the operations and business decisions at our companies.

I appreciate your continued interest in the PMF organization and I am certain that with your support, we will have a great and successful 2004.

Lucia Clontz

Environmental Monitoring

By Lucia Clontz, Diosynth-RTP

Environmental monitoring (EM) continues to be one of the hot topics of discussion in the pharmaceutical and biotechnology industries. The fact that the regulatory agencies routinely include review of EM programs and trended data during inspections only adds to the attention given by companies to this area of the business. The field of monitoring of controlled environments is also changing at a fast pace. New pieces of equipment are being introduced to the market and new ideas on how one should manage an EM program have also been brought to light.

This article summarizes the discussions on EM that took place at the PDA Southeast Chapter meeting in April of 2003 in Raleigh, North Carolina and at the PDA/FDA Joint Conference in September of 2003 in Washington, DC.

Topic: How does FDA view EM data in relation to batch release?

The recent approach to this issue is to de-link routine EM data from batch release criteria where applicable (i.e., non-sterile manufacturing). In order to do so, a company must have a robust EM program and effective in-process controls, such as sterile filtration steps. Even when EM data are not directly linked to batch release, companies do investigate Alert and Action Level excursions and attempt to correlate the data generated to what was going on in the room at the time of sampling so that proper root causes for excursions can be established.

For non-sterile processes that flow to sterile processes, the level of scrutiny of EM data gradually increases and eventually, the review of EM data does become part of the batch release evaluation (for example: bulk fill operation).

Some non-sterile manufacturing companies stated that out-of-trend (OOT) or Action Level excursions for non-viable particulates are not taken into consideration as far as batch release is concerned since non-viable EM testing, in non-sterile manufacturing areas, is considered to be more of a room classification/facility issue.

For sterile manufacturing, all excursions, even the ones nowhere near the fill area, are still considered and properly evaluated and investigations completed prior to batch disposition/release.

The general consensus was that a Master Plan should be created to rationalize the company's approach to the connection between EM data and batch release for certain steps of the process or types of processes. In addition, regardless of whether the data should be part of batch release evaluation or not, many investigators do expect to see a product impact statement when Action Level excursions occur.

One must remember that EM is used as a tool to detect adverse trends in the environment and to ensure microbiological and particulate control in the manufacturing areas. One FDA inspector mentioned that companies are too quick to panic when Action Level excursions are detected instead of looking for adverse trends.

Topic: How do you set Alert and Action Levels?

Most companies have chosen a harmonized approach using the recommendations from the EU and the FDA, to include applying the most stringent criteria where applicable, although some companies stated that they use the most stringent criteria across the board. However, the regulators prefer to see Alert and Action Levels based on historical data once the EM program has been established for a minimum of 12 months.

Typically, based on historical data, Alert Levels are set at the 95^{th} percentile (cut-off value approach), or at a tolerance limit of $\gamma = 0.95$ and $P = 0.95$ (non-parametric tolerance limit approach), or at 2 x SD from the mean value. Action Levels are typically set at the 99^{th} percentile (cut-off value approach), or at a tolerance limit of $\gamma = 0.99$ and $P = 0.99$ (non-parametric tolerance limit approach), or at 3 x SD from the mean value. Yet, there are companies that have chosen to establish only the Alert Levels based on historical data and keep the action levels based on industry/compendial recommendations. Such approach is also acceptable and these companies have successfully defended their position with the regulatory agencies.

Some companies also stated that they have effectively explained and implemented Action Levels less stringent than the industry recommended ones based on their operations. Again, the purpose of an EM program is to look for trends!

It is important to note that all participants agreed that the rationale for how the Alert and Action Levels are established must be captured in a governing EM SOP or Master Plan.

Topic: Should Alert and Action Levels be re-evaluated on a periodic basis?

Most companies re-calculate Alert and Action Levels annually since the FDA expects these values to be based on historical data. One company pointed out that the USP only states that a company must have Alert/Action Levels and re-evaluate them periodically. Another company indicated that

(Continued from page 2)

the Alert Levels were re-calculated annually at 80% of previous and already established level. Regardless of the frequency and method chosen, the expectation is that the calculated levels should go down with time and that adverse trends are timely detected and addressed.

Topic: EM for non-sterile operations

The issue whether EM for non-sterile manufacturing needs to be performed at all was discussed. Although some companies and, believe it or not, one FDA investigator stated that EM for non-sterile manufacturing was not required, most non-sterile manufacturing companies do have an EM program in order to ensure microbiological control of the environment. My experience is that an EM program IS a regulatory expectation even for non-sterile manufacturing sites.

Topic : Non-viable particulate monitoring issues

At the PDA Southeast Chapter meeting, one company mentioned that they received a citation by the Medicines Control Agency (MCA) for not cleaning the interior of a non-viable particle counter instrument. This company is currently struggling with the challenge of figuring out how to clean the inside of the equipment to avoid cross-contamination. Another company stated that they are in the process of acquiring Met-One units with HEPA filters since an inspector was concerned with the quality of the air exhausted from the unit.

The issue of whether one should evaluate non-viable results based on each value or based on an average of the replicate results was also discussed. The responses were mixed: some do not average at all and others do not average in Class 100 but do so in Class 1,000 or Class 10,000 areas.

One comment was made to the fact that ISO documents do not address routine monitoring for non-viable particulates. This type of monitoring is required only for room classification verification.

It was clear though that non-viable particulate monitoring is a crucial part of an overall EM program and the regulators view control of particulates essential to the microbiological control of the environment. Therefore, inspectors do expect to see an emphasis on particulate control, i.e., equipment in place to reduce the level of particles in the environment, such as dust collection systems for weigh & dispense areas and HEPA filtration systems for controlled environments.

Topic: How to handle mold isolates: What does the FDA say about molds?

FDA expects firms to control the environment for microorganisms in general and set Alert and Action Levels based on counts only. However, if the product being manufactured has a specific requirement for absence of objectionable organisms, selective screening for the specified organism(s) must be included in the EM program. Isolation of mold, unless considered objectionable to the product/process, SHOULD NOT be elevated to Action Level status.

Topic: Is it necessary to perform specific fungal and/or anaerobic monitoring?

Most companies do not perform specific fungal or anaerobic monitoring as part of the routine monitoring of the facilities, unless such types of organisms are deemed objectionable. However, it is recommended that an initial evaluation be performed in order to demonstrate that the facility does not have a contamination problem with strict anaerobes or fungi that would require the use of selective media/screening methods. This can be accomplished by performing EM using specific fungal medium and/or specific anaerobic medium/incubation alongside aerobic incubation using an all-purpose medium, such as TSA, for a given period of time. This exercise will most likely provide the data (proof/ qualification) that the company can reduce or eliminate the use of special fungal and/or anaerobic medium. Most companies also perform routine EM using dual incubation (same medium incubated at both temperature ranges of 30–35°C and 20–25°C) for recovery of both bacteria and fungi. Others indicated that they perform EM using specific anaerobic medium/incubation once a quarter because they use *Clostridium* biological indicators and they want to make sure they are not contaminating the environment.

Topic: Qualification of EM equipment. Is it necessary? How do go about qualifying EM equipment?

Qualification of environmental monitoring equipment/ method is required. One method is to perform media growth promotion before and after exposure to the test environment to ensure media is not being desiccated and is still suitable for recovery of viable organisms. Also, one must ensure equipment is pulling the correct amount of air and that the timer is calibrated.

Performing a side-by-side study using two or more instruments/media was also recommended as a tool for choosing a method prior to implementation of an EM program. However, since EM instruments for viable particle monitoring have different mechanisms of air collection, a true data output comparison cannot be made and one cannot expect results to be the same. Such type of exercise is useful primarily to support the choice of equipment/method and whenever changing instruments/methods already

(Continued from page 3)

established, since in the latter case, a new baseline would have to be established for trending purposes.

Europe has always required settling plates with a recommended maximum of a four-hour exposure time. If the use of settling plates is part of an EM program, it is expected that the exposure times be qualified.

As far as acceptance criteria goes, a 70 percent recovery for growth promotion challenges and as a comparison criterion between new and existing unit/method is typical. Using 0.3 – 0.5 log variability as a measure to indicate no difference in methodologies is also acceptable.

It is important to note that if a company changes methods/ equipment, Alert and Action Levels which are based on historical data must be re-evaluated. Do not expect such levels to hold true and trends to stay the same!

One FDA inspector made an observation that the choice of site to be monitored and times when routine monitoring should take place (dynamic monitoring) are still areas of deficiency and reasons for regulatory observations. Therefore, choice of sites for placement of equipment must be carefully evaluated not only during equipment qualification/comparison studies but also during the initial set up of an EM program.

Dynamic monitoring is in fact a regulatory expectation not only in the US but also in Europe.

Topic: Data Trending: What type of program do you have for trending EM data?

Most companies either trend once a quarter or once a month. All agreed that management must be involved and review/ approval of trend reports. The use of a software program is essential to expedite data reporting and to detect adverse trends.

Trending is performed most often by either area classification or manufacturing area/room. Trending by site within an area is not the norm unless a problem area has been identified.

When evaluating excursions, it is important to note that Alert Level is a red flag only. Most companies have established that three Alerts constitute one Action. Other companies stated that multiple Alerts in the same area and consecutive Alerts for the same site constitute Action. For both, Alert and Action Levels excursions, area manager must be notified.

Topic: Data Trending: How do you choose what to trend? Do you trend zeros? How do you handle TNTC in a trend?

Yes, zeros are included in the trends. Some companies perform month-to-month comparisons.
Comments were made to the fact that percent normalization of data is much better and that graphs are better than tables. As far TNTC goes, most people establish 300 or another number to reflect TNTC.

Topic: How many people identify Alert and/or Action Level isolates?

For excursions in an aseptic fill area, all Alert and Action Level isolates are identified, since such isolates may have a direct impact on batch quality/release. Most companies Gram stain representative Alert Level isolates and perform full identification for representative and predominant Action Level isolates. The goal is to maintain a trend on the typical microbial flora in the environment, especially the type of flora that is recurring and resistant to the disinfection/ cleaning program.

Topic: How many people are using software to capture and trend EM data?

All companies use some type of software to evaluate EM data. Some indicated that they use LIMS but it is difficult to trend and data must be exported to another program for graphing/trending purposes. Validating the exporting of data to the other system is also required. The EMSS software by Compliance Solutions was discussed. It was mentioned that this system does site-to-site trends very well but does not export data very well. However, EMSS can be customized and new upgrades will address customer concerns, to include customized reports. Other companies indicated they are in the process of evaluating the software from Novatek. Others who had already done so, were pleased with this product.

Topic: How often do you use sporicidal agents?

The frequency of use of sporicidal agents varies. Some companies use such chemicals on an “as needed” basis to eradicate contamination by spore-forming organisms. However, most companies have chosen to use sporicidal chemicals more frequently (monthly or even quarterly) to prevent contamination by spore-forming organisms. These companies also complained about corrosion problems that occur with the frequent use of such harsh chemicals. It is worth noting that recent FDA warning letters included citations for rust on equipment and items such as chairs, in the manufacturing areas.

Come Visit Our Website at

http://microbiologyforum.org

Are you aware of our on-line discussion group? Membership is FREE. To join, send an e-mail to Listserv@peach.ease.lsoft.com. Write ['Subscribe PMFlist' Firstname Lastname] as the first line of text. (message). You can ask, answer, or read questions and comments from your colleagues.

USP Corner

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

Any questions concerning USP documents should be sent to David Porter, Ph.D. You can reach Dr. Porter at: (706) 353-4514, via mail at United States Pharmacopeia, 126 Twinbrook Parkway, Rockville, MD 20852 or via e-mail at DAP@USP.org. When communicating with Dr. Porter, let him know you are a PMF member.

Current Compendia

US Pharmacopeia (USP) 27
Supplement 1, 2004
European Pharmacopoeia (EP) 4
Supplement 4.4 April, 2003
Supplement 4.5 July, 2003
Supplement 4.6 January, 2004
Supplement 4.7 April, 2004
Supplement 4.8 July, 2004
Japanese Pharmacopoeia (JP) XIV 2001
Supplement 1, 2003
Chinese Pharmacopoeia (1995)
* If you use any other compendia, let us know for inclusion in this corner.

Letters and 483s

October/November 2003

"“Failure to follow written procedures for the cleaning and maintenance of equipment, including utensils, that are used in the manufacture, processing, packing or holding of a drug product as required by 21 CFR 211.67(b). For example, no validation has been performed on the equipment cleaning and sanitizing procedure, Test Method XXX. This procedure is used for the cleaning of all tanks, totes and filling equipment after the manufacture of all products, including industrial cleaners, cosmetics and OTC pharmaceutical products”.

“The quality control unit also failed to adequately investigate the possible correlation between sterility failures found in two of the thirteen lots produced with the incorrect filling parts. According to your annual product review, lots of XXXX injection were manufactured from January 1, 2001 through September 30, 2002. There were three sterility failures resulting in lot rejections during this time period. Two of these lots were manufactured with the incorrect filling parts. The quality control unit also failed to investigate issues such as container closure integrity or low fill volumes observed by production personnel during the manufacture of lot # XXXXXX”.

“Inadequate Standard Operating Procedures that are not always available, lack appropriate details, or contain contradictory information. For example, the written procedure for method validation lacks detailed instructions and acceptance criteria for each test and conflicts with the protocol. Additionally, some software application and microbiology lab autoclave procedures have not been validated adequately. [21 CFR 211.160(b)]”

Internet Address	Description
http://www.learningstream.com/cder_fda	FDA Education Training Seminar
http://www.doctorfungus.org	Information site on fungi including photos

If you have found an Internet site that contains information of relevance to pharmaceutical microbiology, please let us know.

PMF THREAD

Environmental Monitoring

Question 1

My company manufacturers clinical trial batches of non-sterile solid dosage forms (caplets, tablets, capsules, etc.). The facility is relatively new and we are putting together an environmental monitoring plan. We have already performed a baseline engineering study of all wall surfaces (RODACs), floor surfaces (RODACs) and air samples (M Air T unit from Millipore) from a number of locations within each room within the manufacturing area.

Additionally, we looked at each room during static and dynamic conditions. We also performed each test on three days about a week apart. From this data we will determine the future locations of testing and frequency of testing. Now, here is my question. We feel strongly that we need to ID the isolates recovered, but how often do we need to ID them? Do we ID everything we isolate for the first "X" number of months and then ramp down to another frequency or do we ID everything we find for a year or do we not ID anything we find if the numbers are low. Do we care what the organism is if there aren't many that we recover especially, if we remind ourselves that this is a non-sterile environment? Any information, guidance or opinions offered will be appreciated.

Answer 1

We always established alert and action limits based on our earlier results. We ID anything over the alert and the action limits and during the first year of a new clean room, we ID one sample of air and surface per sampling period (tested once a week, once a month, quarterly) for a full year to get the normal flora of the room.

Answer 2

I also work in a non-sterile facility. We ID only when an action level is exceeded.

Answer 3

I think the first action of your question should be to realize what your Specs. are for the product. E.g.: tablets, absence of E. coli. So you must be certain that no E. coli is encountered in the cleanroom. You can verify this by ID of all colonies at t=0. After this you perform it on quarterly frequency (every three months).In the meantime you can distinguish the micro-organisms on morphology. If you do this, you'll notice that most of the isolated flora contains bacilli and micrococcaceae, so no need for ID, as you product is not in danger.

Trending Environmental Monitoring Data

Question 1

I would like to know how other firms define and review for Environmental monitoring trends. With so many test results having "zero" CFUs, I am having some difficulty determining an appropriate way to assess for trends. A single spike hardly seems like a trend, and with presence of any level of microorganisms so infrequent, I would like to know how others are measuring for trends. It is easy to say a trend exists if there is growth at a specific site for three consecutive samples, but what is currently being done regarding comparisons to the previous month, quarter or year's data? Are you tending by single site, filling room, or both parameters? If you are using a manual system instead of computer program, how are you accomplishing this and how are you reporting it?

Answer 1

We defined an Environmental trend to be out of the normal for three consecutive months. Any individual spike that is still within alert limits is placed on a list to watch for during the next testing cycle.

If the spike if above alert but within action, we would provide a warning to the group where the spike is, to clean the site and to watch for reasons that they may be getting higher organisms in that area.

Our trending is pretty significant, each site is trended as a separate line on a room trend that way I can look at individual sites as well as the room as a whole. I use a microsoft access database to capture my data but then use excel to run my trend charts.

PMF thanks its 2003 sponsors, Diosynth and Biolog for their support

Diosynth Biotechnology is a full service provider of process development and cGMP manufacturing services for recombinant human therapeutic proteins and monoclonal antibodies to the pharmaceutical and biotechnology industries worldwide.

Biolog's ongoing commitment to innovation for our Pharmaceutical customers started over six years ago with our comprehensive validation manuals and was followed by releasing the first system based method for identifying filamentous fungi, introducing the OmniLog Automated Identification System, and launching 21CFR Compliant software in 2001. We have recently expanded our field based Technical Services to include optional on-site validation assistance.

Article Review

Environmental Monitoring for Aseptic Processing

David Hussong, Ph.D., FDA, American Pharmaceutical Review, Volume 6, Issue 2, Summer 2003

The author in this article reviews the current review perspective of an environmental monitoring plan in support of an aseptic process to manufacture a sterile drug product. The development of the review process stemmed from a few events in the early 1970's involving non-sterility of some large volume parenterals. The formation of a microbiology-specific-review program, designed to assess the

Article Review continued

safety of sterile drug products, was the beginning of the FDA's initiative to help all of industry understand the concepts of sterile drug manufacturing and to work with industry to apply these concepts to the sterile drug manufacturing process. Guidance documents, such as the 2003 Guideline on Sterile Drug Products Produced by Aseptic Processing were also the result of these initiatives.

Microbiology monitoring for aseptic manufacturing should be described in drug applications. The Guideline for Submitting Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products discusses topics to be addressed by applicants. The elements of a monitoring program must be defined; these include frequency, methods, defined sites and acceptance criteria. Once the elements are defined, approved by the FDA and implemented by the firm, FDA field investigators would then audit the raw data to confirm compliance.

Sampling and cultivation methods have an influence on monitoring data. Since there is no single monitoring procedure that will yield perfect results, the chosen method should be appropriate and followed without deviation. New methods for monitoring processes related to drug manufacture have been developed since the 1970's. When a firm wishes to change to use these new methods, they should clearly describe and justify the new method in the appropriate regulatory document. Since newer methods often use different parameters, other than CFU's, then established acceptance criteria may change and should be discussed in the report.

Firms may use any method for setting environmental alert and action levels. A good starting point for microbial count values is listed in guidance documents. Subsequent values should then be determined by dynamic averaging of results in the specific facility. Greater importance should be placed on directional trend of the data rather than a single discrete value. Environmental monitoring is a process indicator and should not be viewed as a product release criteria. Non-conforming results should be noted and investigated with findings retained. Procedures related to investigations of non-conforming results should be defined in SOP's.

Astute Microbiologists are always aware that environmental monitoring is viewed as an intrusive event in aseptic processing. As a result, these Microbiologists should give careful consideration when defining sampling techniques and evaluating results.

Effective Communications with the USP Microbiology Committee

Laura Valdes-Mora, MS
Elite MicroSource Corporation

The Pharmaceutical Microbiology Forum (PMF) has recommended since its inception in 1992 to communicate with the Analytical Microbiology Committee of the United States Pharmacopeia (USP). This is a group of 12 microbiologists who are appointed for a 5 year period to work on setting microbiology standards. The group is coordinated *via* a *Liaison*. The incumbent *Liaison* since the year 2000 is Dr. Dave Porter who replaced Dr. Roger Dabbah, who moved to a higher position at the USP.

The USP seeks feedback from its users regarding new proposals or even existing chapters. There are two major modes of communication with the USP: Attending a USP Open Conference and sending written feedback.

USP Open Conferences are planned by the USP when a committee or committees have many outstanding proposals. The group wants to get a better feel of the overall acceptability of any new methods or concepts prior to bringing them to closure by publishing them as official in an edition of the USP compendium or a Supplement to the same. There is no specific frequency to these meetings.

The easiest mode of communication for an individual scientist or a company is to send written comments, primarily in a letter format. According to Dr. Porter, the feedback letters will be quite helpful if we were to include the following:

1. Indicate the Chapter or Monograph you are writing about.

2. Where was the material published? Include volume, number of the publication and pages.

3. Overall impression of the Chapter or Monograph being critiqued.

4. Offer observations and comments regarding the document. Refer to specific sections of the publication. Present comments in the **same** order the sections were published. Add data to support your views, whenever possible. This will be extremely beneficial.

5. Provide a summary of your comments.

6. Indicate how the USP can contact you.

In summary, the USP can use your feedback more effectively if you follow the above recommendations by Dr. Porter to include an Introduction, General Comments, Specific Comments, a Summary and Conclusions. Although some of the points may seem simple, they are extremely helpful when there are dozens or hundreds of letters on the same subject. Can you imagine? Remember that the USP is used as the official standard for drugs in at least 46 countries in the world. People from all over the globe interact with the USP.

It is crucial that we all send feedback to USP, particularly when we do not agree with one or more recommendations or methods proposed in either an Information Chapter or a General Chapter (also known as Referee Chapters). Do keep in mind that if USP does not hear from you and others alike, the silence will be interpreted as concurrence (agreement) and the proposal will move forward and end in the USP.

What are you waiting for? Put down this newsletter and compose your letter to USP. The Analytical Microbiology Committee anxiously awaits your input.

As always, remember that you can reach Dr. Porter at the USP. See the USP Corner of this newsletter where his address, phone and e-mail are always published.

I will see you around the bench!

Pharmaceutical Microbiology Forum
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or
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MISSION: *The PMF provides a forum for pharmaceutical microbiologists to exchange information on microbiological issues in the pharmaceutical and related industries and interact with the USP and regulatory agencies.*

THIS APPLICATION IS:

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Pharmaceutical Microbiology Forum
C/o Laura Valdes-Mora
3166 Wood Valley Road
Panama City, FL 32405

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3166 Wood Valley Road
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