PMF NEWSLETTER

A PUBLICATION OF THE PHARMACEUTICAL MICROBIOLOGY FORUM
Distributed Internationally to 7,831 Subscribers over 100 Countries

Volume 13, Number 12 December, 2007

Be sure to check out the upcoming PMF Conferences and Workshops

The Completion of a Second Year

This issue marks the completion of a second year of monthly publication for the *PMF Newsletter*. We have been very fortunate in having many people contribute articles to the newsletter, and in the wide acceptance the newsletter has received in the industry.

In this issue we take a look at the role that the laboratory SOP system plays in a smoothly operating lab, and in providing a means to both train and to document training of laboratory technicians. If properly constructed, the SOP system can be a source of great strength for the lab operation.

Important Links:

Information on the PMFList at
http://www.microbiol.org/pmflist.htm

Past Issues of the *PMF Newsletter* at
http://www.microbiologyforum.org/news.htm

The second article in this December issue is a status report on the PMFList looking at its size of subscribership and the usage of the list over time. This list, supported by PMF, fills a valuable role in the professional microbiologist's job and is make available free of charge by corporate sponsorship. Complete archives of the list from January of 1998 are available for review.

Finally, an updated list of PMF Conference dates is provided for reference. If you have not come to a PMF conference, you might well consider it for 2008. The PMF conference is characterized by excellent speakers, most of whom have recently published in the literature, and intimate conference sizes to encourage discussion and benchmarking of practices.

Scott Sutton scott.sutton@microbiol.org

The Importance of a Strong SOP System

Scott Sutton, Ph.D.

Microbiology in the QC laboratory depends heavily on documentation. This seems obvious, but the affects of this requirement are not always so obvious. One of the major consequences of this situation is the intense requirements for SOPs in the laboratory. This discussion will look at some of the SOPs that should be covered in your laboratory system.

You can break the organization of a logical SOP system down several ways. One way is operational:

- Quality Requirements
- Media
- Cultures
- Equipment
- Training
- Sample Handling
- Lab Operations
- Testing Methodology
- Data Handling/reporting/archiving

You will note that this method does not correlate to the US CFR organization, the Medical Device ISO organization, nor the EU organizational scheme. That's OK, you will not get any organizational structure that matches all Quality system structures, let alone the requirements of the microbiology lab . However, you must be able to correlate your system to one that matches the preferred method of whomever is auditing you at that moment. We will not go into the various organizational schemes here.

In general, I prefer a slight variation on the operational organization scheme listed above. This scheme is shown on the chart below. This scheme has the advantage, in my mind, of being amenable to use as a method to organize your training program as well as a serving as a framework for SOP organization. In brief, the lab SOPs are broken into three main areas with several subsections:

1. Laboratory Support Activities
   - Media
   - Cultures
   - Equipment
   - Operations
   - Safety
   - Quality
2. Environmental Monitoring and EM Support
   - Viable air
   - Non-viable Air Sampling
   - Surface sampling
   - Personnel Monitoring
   - Media Fill Support
   - Qualification of facility after shut-down
   - Gowning (may share with manufacturing)
3. Testing Methodologies
   - Specific test methods
   - Validation of test methods

(Continued on page 3)


(Continued from page 8)

Why is this Scheme Useful?

One word – training.

Training is a very difficult area for the QC laboratory. Aside from the questions surrounding proficiency testing (which will not be discussed here) there are real logistical issues with determining who should be trained in what SOP and how to maintain training as SOPs are revised.

How does this organizational image of a microbiology lab SOP system help in training? Let's start with a new hire – she/he will need to be immediately trained in all the SOPs concerned with documentation, lab hygiene, lab safety and many of the Quality SOPs. The next groups of SOPs will depend on their job function. For example, a technician performing Sterility Tests will need additional training in:

- Test Methods
- Relevant Equipment (Operation and Maintenance – O&M)
- Aseptic Technique
- Media (quarantine and expiry)
- Biohazard disposal
- Validation
- Method
- Preparation of inocula

This also encourages different functional specialization. For example, there is no need for the technician working in the media kitchen to be trained in how to perform an antimicrobial efficacy test. Nor is it particularly efficient for the bench worker to be running back and forth to the kitchen to check on her media. By separating the jobs, the flow of work in the lab is simplified. Major support functions such as media preparation/release, stock culture maintenance, and equipment tracking can each be handled by a suitably trained manager with backup.

Lets look at each of the functions in more detail.

Testing

Each major type of test performed will have an associated SOP. This SOP should list critical pieces of equipment (and training will necessitate familiarity with the "Operation and Maintenance" (O&M) SOP for each critical piece of equipment). The test will also list specific organisms to be used (if appropriate), necessitating training in relevant culture SOPs. Finally, each SOP will list required media, necessitating training in release and expiry requirements for the relevant media (how do you determine which media can be used for your test?). Finally, the test may require training in the department's SOP on how to count CFU on plates, and on the lab's methods of handling basic math operations (rounding, significant figures, $\log_{10}$ conversions, *etc*).

In addition, each test method SOP should be accompanied by an SOP on how to "validate" the method. This usually consists of demonstrating suitable microbial recovery from samples spiked into the sample or into a neutralizing broth (see USP chapter <1227>). Specific tests may have additional validation requirements depending on the region (Sterility Tests, for example, have additional requirements according to the PIC/S guidance document compared to those of the harmo-

(Continued on page 4)

nized test).

In addition to the validation SOP, it may be prudent to develop an SOP on how to handle failing or questionable results. This SOP can be specific to the test method, or a more general one that provides specific instruction for every test type. This is important, as the company's OOS/CAPA (Out-of-Specification/Corrective and Preventative Action) procedures will almost certainly be directed at the Analytical Chemistry group or Manufacturing, and is likely to be inappropriate to the Microbiology lab. Further, an investigation into a putative Sterility Test failure will be fundamentally different from that of a putative failure of the Antimicrobial Effectiveness test. There will, of course, be elements in common, but the investigations will be defined by their differences.

A separate category of testing involves microbial identification. This group should include basic tests (Gram's stain, spore stains, biochemical reactions and the use of selective/differential media) as well as more advanced methods such as the O&M of proprietary identification technologies as equipment, and their use in microbial identification.

Finally, it is frequently useful to have an SOP on what a good test method SOP should include. Each data sheet for the test method should include sufficient information to determine the culture used (tracing back to the initial receipt from the national stock culture), all critical pieces of equipment used, all buffer and media lots used, time and date of activities and who performed them, and date all information was reviewed. This is in addition to the actual data for the test (for example, dilution factor and CFU/plate for plate count methods).

Environmental Monitoring and EM Support

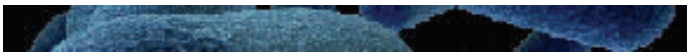
This is set aside as its own group only because of the complexity. In addition to the obvious issues of sampling (and the equipment used for that sampling), gowning and aseptic technique, this area will also have to be concerned with trending of the environmental monitoring data, media fill support and disinfectant qualification.

This area is so complex that many organizations split off the EM group from microbiology altogether. This is, in my opinion, a mistake. It clearly is a huge amount of work for a microbiology department, but not an unmanageable one. The fragmentation of the EM group from the microbiology group serves only to separate the sample acquisition and data analysis functions from the incubation and plate reading/data recording functions, and to limit the influence of subject matter experts. This sets up a situation that encourages avoidance of responsibility for unwelcome results. In addition, this split limits the opportunity of the lab head to shift resources to areas of great, if temporary, need. If the analysts cannot perform EM sampling, they cannot be used if needed. If the EM technicians are not part of microbiology, they cannot help out in the lab.

Laboratory Support Activities

This area is probably the most misunderstood area of the microbiology lab – especially among those in management. We will break the discussion down to Media, Cultures, Equipment, Lab Safety, general Lab Operations and Control of Incoming Samples.

(Continued on page 5)

(Continued from page 4)

Media

The activities that need SOP coverage here include the receipt and acceptance of incoming dehydrated and prepared media, its quarantine, growth promotion confirmation (which may require training in cultures and preparation of inocula), and media release for use. In addition, the mixing and sterilization of in-house media, establishment of its expiry dating and labeling of all media are important. All lab workers who perform testing that involves microbial growth media will require relevant training in how to identify usable media, even if they are not trained in its preparation.

In addition to the direct SOPs on media receipt, preparation and release there are supporting SOPs on relevant equipment O&M procedures, with particular attention to the autoclaves (sterilizers) and their validated cycles and load configuration.

Cultures

The integrity of the culture collection is critical to the QC microbiology lab. This begins with receipt of the culture from the national stock collection and procedures in place to confirm the identity and purity of the sample. SOPs should be in place to govern receipt, quarantine, Quality check, release, and seed lot technique. Many of these functions can be combined into the seed lot technique method (see *PMF Newsletter* 13(11)).

In addition to the seed lot technique out to the working cultures, a specific SOP may need to be in place for preparation of the inocula for the various tests (although this might be included in the test method SOPs).

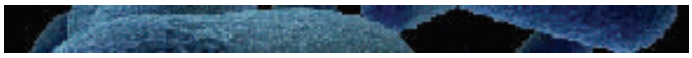
It is frequently found to be useful to have two or three individuals in the lab responsible for maintenance of the culture collection. This relieves others of trying to keep up with the procedures, and allows the specialists to trade off responsibilities in a rotation schedule.

Equipment

I have found equipment to be sufficiently involved to require a dedicated worker (and backup) for the same reasons cited above for media and cultures. Someone needs to maintain the equipment master files (containing vendor qualifications, manuals, certifications, etc), track preventative maintenance (PM) schedules for critical equipment, review performance logs and ensure autoclave cycle records are maintained.

Each critical piece of equipment should have an O&M SOP. There is no need for every technician to have training in every equipment O&M SOP. However, if

(Continued on page 6)



(Continued from page 4)

a particular test method requires that piece of equipment, then training in this SOP is required for all technicians performing the test.

Finally, many pieces of equipment in the microbiology lab have additional requirements beyond the standard PM scheduled work. Equipment designed to maintain temperature (incubators, refrigerators/ cold rooms and water baths, for example) must be monitored to document compliance. In addition, equipment that is used to house "dirty" samples (incubators, refrigerators, water baths, etc) must be cleaned regularly to minimize the potential for contamination. The method and frequency of this cleaning should be described by SOP and documented.

Lab Safety

Many companies have lab safety requirements. These might involve the requirement to maintain available Material Safety Data Sheets (MSDS), what to do in case of spills, fires, earthquake, tornado, or other natural disaster. They may also cover acids, bases, flammables, toxins, equipment, etc. In terms of equipment there is a real need to address the use of autoclaves and compressed gasses in the microbiology lab

An additional, and somewhat unique, requirement for the microbiology lab is to have a Biosafety Manual prepared and ready to handle at least Risk Level 2 microorganisms. This is not too difficult, basic good practices (no mouth pipetting, lab coats, use of containment hoods for operations leading to aerosols, etc), but it is important to formalize the requirements to avoid misunderstandings.

Lab Operations

This is somewhat a catch-all category of SOPs. It isn't that the activities are unimportant, but rather that they are so basic to the operation of the lab that all parties are involved.

Control of Incoming Samples/Materials

The lab should have an SOP governing how to log incoming samples for testing, and beyond that how to track date-on-test, date-off-test, and report date. In addition, the lab should have a general procedure on acquisition and acceptance of perishable consumables.

Documentation Concerns

These can range from version control on data sheets to data entry into lab notebooks and the Laboratory Information Management System and on to record retention for different documents. All should be described by SOP.

(Continued on page 7)

(Continued from page 4)

Training and Proficiency Requirements

An SOP should exist for all job functions in the lab. This should describe the job function in a manner that allows easy categorization of SOP to meet the job requirements (as an aside, if job responsibilities exist for which there is no SOP – I would write the SOP). This allows SOP training be assigned by job function, and allows easy identification of technicians who need retraining when an SOP is revised.

A system should be in place to demonstrate the technician's proficiency in activities critical to their job. This system is, of course, described by SOP. The system should identify critical skills needed, recertification periods, and methods of initial certification and recertification.

Laboratory Hygiene

SOPs should be in place to describe the cleaning and sanitization of the laboratory benches at the beginning and end of each day, the general state of the lab, and expectations of the lab environmental monitoring program (if one is in place). The preparation and expiry dating of sanitizers should be part of this procedure.

The hygiene expectations of the workers should also be addressed. Requirements for clean clothes and bodies, closed-toed shoes, clean lab coats, gloves and other personal protective equipment (PPE) as required should be part of the stated expectations as is the proper use of hand washing equipment.

Biohazardous Waste Disposal

There should be a procedure or procedures for decontamination and disposal of biohazardous waste that is consistent with local (municipal) requirements..

Plate Count Procedures and Basic Math

This type of SOP is designed to standardize common practices in the lab. The plate count SOP seems silly until you realize that the CFU/plate recorded by the technician is really only her interpretation of the CFU, and that estimate is immediately interpreted further (see PMF Newsletter). It is important to establish some consistency in this most basic function in the lab.

The basic math SOP is also critical. This should address at least the topics of rounding issues, significant figures, $\log_{10}$ conversions and the deduction of CFU/mL from the dilution and the CFU/plate. This might also be a good place to define what the lab means when an SOP states a 5 day incubation period vs a 120 hour incubation.

Conclusions

This short article has attempted to describe an SOP system for the QC microbiology lab in a regulated industry. This is not presented as the only SOP system possible, or even that it will be sufficient to your particular needs. It should, however, serve as a starting point or to help with benchmarking your system. A good SOP system should serve as guidance to regulatory compliance and be useful as a framework for training. This article focused on the training aspect rather than trying to link the SOP system to regulatory requirements (although it is the author's belief that the two are by no means exclusionary, regulatory compliance was not the focus of this article).

By looking at the SOP system from a functional perspective we can easily group media, stock culture, equipment, and documentation requirements to test activity making the creation of "job skills" relatively straightforward. This, in turn, simplifies the assignment of SOPs to individuals based on their job functions and simplifies tracking of individuals effected by SOP revisions.

Further information on this topic can be found in Pharmaceutical Quality Control Microbiology by Scott Sutton

PMFList - Status Report

Scott Sutton
Moderator, PMFList

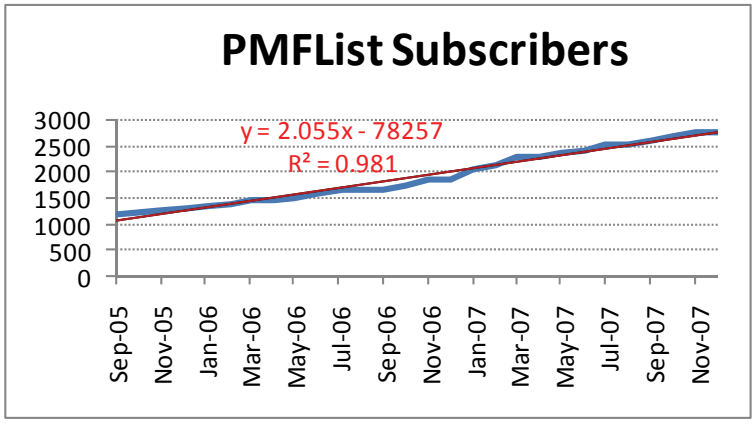
December seems the accepted time to present retrospectives, and I thought it might be a good idea to present some information on the PMFList, the Email discussion group that is offered with the PMF. I am going to look at the status of the list from three perspectives:

- Subscriber enrollment
- Message traffic
- Financial security

Subscriber Enrollment

Subscribers enroll into the PMFList by request. This generally occurs through filling out a web-based subscription form at http://www.microbiologyforum.org/register.htm. The potential subscribers are then screened (you would not believe how many internet sites of questionable integrity and morals want to get on the list!). In any event, after we have had a chance to review the application the new subscriber is entered into the database maintained by the list software—LSoft's LISTSERV. This is the premier service of its type, offering a stable and dependable vehicle for the maintenance of the list.

The subscriber base has shown remarkable growth in the past 15 months as shown in the graph below (linear regression shown for those of you with an interest in that sort of thing). Basically, in September of 2005 the list consisted of 1192 subscribers, at years end 2007 there were 2753. That is remarkable growth!



Message Traffic

A second aspect of the health of the PMFList is the message traffic. To send a message to all the people currently subscribed to the list, a subscriber just sends mail to PMFList@lists.microbiol.org. This is called "sending mail to the list", because you send mail to a single address and LISTSERV makes copies for all the people who have subscribed. The software LISTSERV then sends the emails out to the subscriber base and everyone gets a new Email. Replies

(Continued on page 9)

(Continued from page 8)

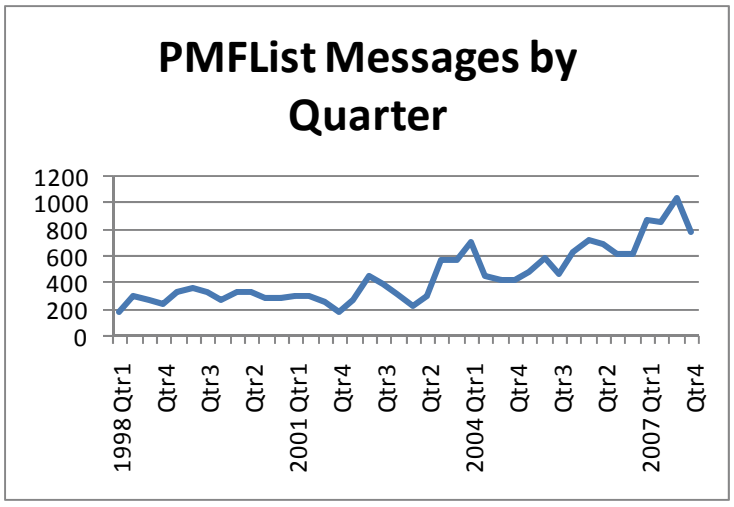
to the Email are handled in the same manner, with replies sent to PMFList@lists.microbiol.org for distribution.

Participation in the list assumes a basic understanding of QC microbiology. Fundamental questions should be answered by study and training, not by Email. There are many books available that are useful for reference purposes on QC microbiology - the PMFList is no replacement for dedicated study.

It is important to remember that the PMFList is NOT moderated for accuracy. Like any professional discussion, a variety of opinions are expressed and many of them may be completely incorrect. Everyone is encouraged to cite references for statements made and questions asked.

Participation in this list is NO SUBSTITUTE FOR A TRAINING PROGRAM. Any company reducing required training as a result of participation in this service does so at their own initiative and without the support or encouragement of the Microbiology Network, the PMF or anyone associated with the list. This service is meant as a communication avenue only .

Having said all that, the communication itself is remarkable. Messages from January of 1998 (when the list was moved from a BBS service to the internet) are archived in a searchable format at http://lists.microbiol.org/archives/PMFLIST.html. The number of messages has increased dramatically over the past ten years (see figure below). These messages break down as below (in approximate numbers):



(Continued on page 10)

(Continued from page 9)

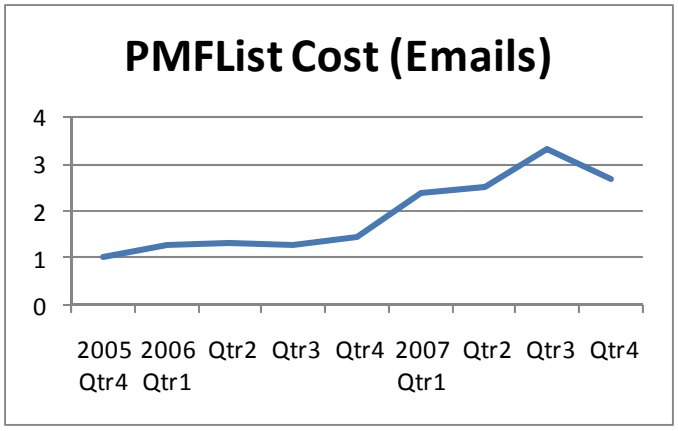
Topic	% Messages
Test and Methods	32%
Microbiology	13%
EM/Media Fills	11%
Laboratory Operations	11%
Sterilization & Disinfection	7%
Equipment	7%
Water	7%
Misc	5%
Manufacturing Support	5%
Jobs	2%

This is a great way to benchmark practices, but you have to take the communications with a grain of salt (as mentioned before).

Financial Security

Like most things in life, the PMFList costs money. LSoft (the vendor) charges on the basis of the number of Emails sent. For example, if there were 1,000 members on the list, and 5 Emails went out, the cost would be for 5,000 Emails.

We can graph the costs of the list based on these considerations from the end of 2005 to the end of 2007 (below). This analysis uses the average number of subscribers during the particular quarter, multiplied by the number of Email messages that went out that quarter, setting Q4 of 2005 as the comparator. The cost of maintaining the service has increased approximately three-fold during this time. While this analysis does not include the annual registration fee, it does show the increased financial obligations of maintaining the list.



These costs are met through the generosity of corporate sponsors, providing the support to make this service free to the users. The PMFList has been very fortunate in having solid sponsors over the years, and I know that all members of the list appreciate their contributions that keep the list financially solvent. The 2007 sponsors were:

- Accugenix - http://www.accugenix.com
- American Type Culture Collection - http://www.atcc.org
- Applied Biosystems, MicroSeq Microbial ID System - http://www.microseq.com/
- BD Diagnostic Systems - http://www.bd.com
- Biolog - http://www.biolog.com
- Biomerieux - http://industry.biomerieux-usa.com
- BTF Precise Microbiology - http://www.btfbio.com
- Dupont Qualicon - http://www.qualicon.com
- EMD Chemicals - http://www.emdchemicals.com
- MIDI, Inc. - http://www.midi-inc.com
- MicroBioLogics, Inc. - http://www.microbiologics.com
- Millipore - http://www.millipore.com
- Pall - http://www.pall.com
- NovaTek International - http://www.ntint.com
- Rapid Micro Biosystems - http://www.rapidmicrobio.com
- Raven Biological Labs - http://www.ravenlabs.com
- Veltek Associates, Inc - http://www.sterile.com

Many of these sponsors have been participating for years, and all deserve our thanks and support. Their participation makes this service available to us all.

Summary

The PMFList has enjoyed significant growth in terms of numbers of subscribers, and in terms of message traffic. This is a clear testament to the value of the service. With this success the cost of maintaining the service has increased dramatically, a cost met by the generosity of our corporate sponsors. Participants in the list should be aware of the sponsors, and of our debt to them in providing the means for the PMFList to remain free to the user.

Upcoming PMF Events

February 18-19 2008 Open Conference on Compendial Harmonization.
Baltimore, MD

March 10-11 - Environmental Monitoring (Susan Schniepp, moderating)

April 7-8 - GMP from the Microbiology Perspective (Scott Sutton, moderating)
Dallas/Ft. Worth, TX

May 19-20 - Microbiology Investigations (Frank Settineri, moderating)

June 9-10 - Validation Issues in Microbiology (Scott Sutton, moderating)
Philadelphia, PA

September 15-16 - Cosmetic Microbiology (Phil Geis, moderating)
Newark, NJ

October 20-21 - 2008 PMF Fall Forum (Scott Sutton, moderating)
Rochester, NY

November 6-7 - Bacterial Endotoxin Summit (Karen McCullough, moderating)
San Francisco, CA

Offering In-House Courses on Microbiology/Aseptic Processing:

- The Microbiology Network/High Peaks Associates http://www.highpeaks.us/in-house.htm
  Experienced in custom-designed courses for the lab or the manufacturing facility, including
  - GMP for the Microbiology Lab
  - Microbiology for Manufacturing
  - Microbiology for Management
  - Auditing the Microbiology Function
  - Investigating Microbiological Data Deviations

USP Corner

Any questions concerning USP documents should be sent to Radhakrishna (Radha) Tirumalai, Ph.D. You can reach Dr. Tirumalai at: (706) 353-4514, via mail at United States Pharmacopeia, 126 Twinbrook Parkway, Rockville, MD 20852 or via e-mail at RST@USP.org. You can write representing your company, or as an individual scientist.

Discussion List Update

PMFList:
Number of Subscribers: 2753
Number of Countries: 88
Number of Messages Last Month: 283

PSDGList (Pharma Stability Discussion Group):
Number of Subscribers: 1071
Number of Countries: 34

Membership is FREE. To **join the PMFList**, visit http://microbiol.org/pmflist.htm and register.

A sister Email is devoted to topics in the **stability testing** of pharmaceuticals, medical devices and personal products. To **join the PSDGList**, visit http://microbiol.org/psdglist.htm and register.

You can ask, answer, or read questions and comments from your colleagues. Archives of the lists are available at:

- http://lists.microbiol.org/archives/PMFLIST.html
- http://lists.microbiol.org/archives/PSDGLIST.html