PMF NEWSLETTER

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The Skill and Art of QC Microbiology

There have been a couple of events that helped shape this particular newsletter. The first was the completion of the transcript record from the PMF Open Conference last February. Yes, I know that it has been three months spent in releasing this document and this is too long. We have learned from the experience and will not repeat that delay. However this is not what I am referring to as a motivating event for this newsletter. Rather there were a couple of comments made in the discussion section on one of the topics about the role of the practicing microbiologists in shaping USP policy. These comments were along the vein that is was absurd for USP to charge for the *Pharmacopeial Forum* and then expect everyone to comment on the drafts. If USP wanted comments (continues the argument), then the *PF* should be free. I will forebear discussion about the impact of MP3 file sharing on our perceptions of what should be free, but this Open Conference participant's comment got us thinking about the USP practices of continuous improvement. David Porter has contributed an analysis of the USP process as a review. Clearly no one need participate in making the USP chapters better, but how can you withhold assistance and then complain about the result?

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 event was a short Email chain recently on the PMFList about "Who is a Microbiologist?" This was a very entertaining exchange, but in the end the question was unresolved. I have taken a swing at trying to answer it this month. By the way, if you feel strongly about this question please do not hesitate to contribute an analysis yourself. All commentary will be published in the newsletter (subject to editorial review) in an attempt to reach some consensus on this critical question.

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The USP Process

David Porter, Ph.D.

I don't think there's any doubt that the readers of the PMF Newsletter are familiar with the *United States Pharmacopeia* (*USP*). If not familiar, I suspect you have all heard of it. It is also likely, although less so, that if you know about the *USP*, you have at least passing familiarity with the *Pharmacopeial Forum* (*PF*). Recent events with a number of recently published *USP* general chapters suggests that the interplay between the *PF* and the *USP*, and the critical role the readers of *PF* are meant to play, suggest that this role is less well understood. The purpose behind this article is to describe the role as it was intended, followed by a description of what seems to be the reality of the situation, and possible remedies.

The *USP* itself principally contains numerous monographs for many types of products and APIs, and general chapters providing either methodologies as called for from within monographs (these are considered to be mandatory general chapters, associated numbers in angle brackets are < 1000), or general information chapters that, as the name suggests, are intended to be informative and not mandatory (associated numbers in angle brackets are ≥ 1000). The reality is that the USP does not enforce any of its material, be they monographs or general chapters. The regulatory agencies such as the FDA serve that function. Therefore, the agencies may consider content of informational chapters to be enforceable.

The USP process whereby it develops official content (that which is published in *USP* is official content) is stated as being one of continuous revision. Viewed in that light, the latest official version of *USP*, *USP 30*, is simply the latest in a series of revisions dating back to volume 1 of *USP* published in 1820. Below is the process used by USP, at least in theory, whereby material goes from draft form to eventually arrive at official status. This process can be found in the front matter of any issue of *PF*. The figure on the next page was redrawn from *PF* Volume 33(3) [May-June 2007].

The revision process at USP is designed to rely on input from the "public" (the second box from the top) in large part as a means of assuring that the proposed monograph or general chapter as published in *PF* as an *In-Process Revision* (and therefore, not yet official) is acceptable. The thinking is that the readers will be alert to proposals in *PF* that may impact upon their capabilities to produce product that will be in compliance, or remain in compliance, with the compendial requirements. The next three boxes all serve to amplify the importance this process places upon receipt of comments from the "public." Incidentally, "public" refers to any interested party, but for all practical purposes, the term refers to pharmaceutical

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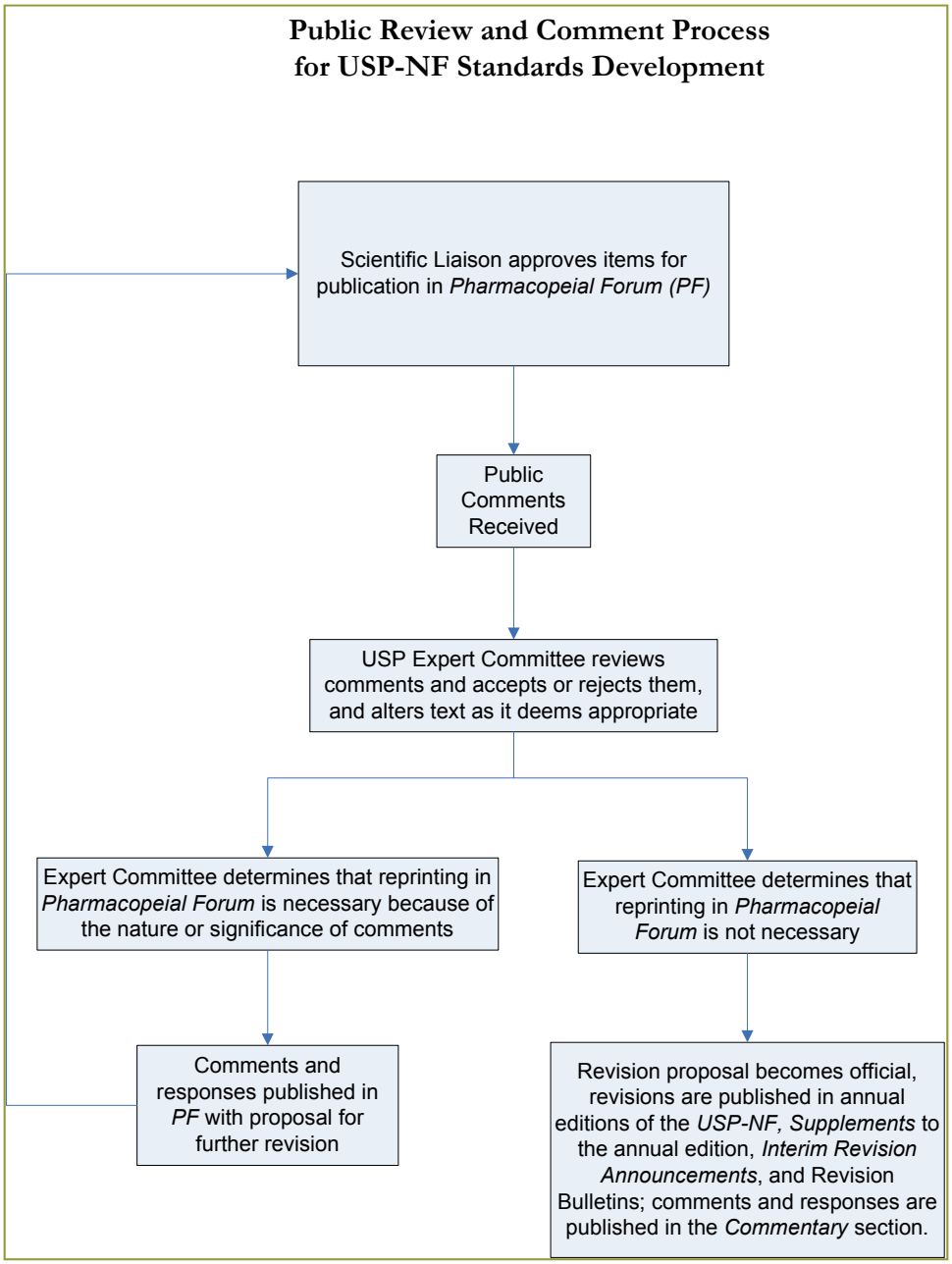

Internet Address	Description
http://commtechlab.msu.edu/sites/dlcme/	The Digital Learning Center for Microbial Ecology is an educational resource about ecology and microbiology. The DLC-ME includes the Microbe Zoo, Microbes in the News, Meet the Scientists, and more.
http://swbic.org/outbreak/	Outbreak! is an interactive teaching tool for use by students and science educators. Players must use microbial identification techniques to identify the causative agent of an illness outbreak.
If you have found an Internet site that contains information of relevance to professional microbiology in the industrial sector, please let us know.	

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manufactures and contract laboratories. The intended impact of the comments is substantial, with the comments leading potentially to republishing the proposal revised in such a manner as to address to comments, or potentially leading to the publishing of the proposal as official in the next *USP*, a Supplement, or as an *Interim Revision Announcement* in *PF*. If no comments are received at USP in response to a proposal in *PF*, the presumption has been that no readers have substantive issues with the proposal. In that case, the proposal most often is then published as official.

Apparently the reality is that the process as envisioned by USP has been breaking down more often than in previous times. Whether this is due to the increased rate of publication within *PF*, less time for available staff to read the *PF* and forward it to relevant members of their companies for review, lack of *PF* itself in companies where the *USP* is present, a combination of these possibilities or other possibilities not considered here, problems do seem to exist.

Some recent examples serve to illuminate the general problem. Chapter <231> *Heavy Metals* was published in 2006 with a revised *Method II*. After its publication previously in *PF*, relatively few comments of a substantive nature were received, and therefore the chapter was published in *USP* as official. It was only after that time when many companies found themselves needing to comply with the revised method that problems arose. For many, the method did not work. Why hadn't the USP heard about these problems when the chapter with the revised procedure was still in *PF* as a proposal, and therefore not yet official?

Another example is chapter <62>, currently official as *Microbial Limit Tests*, which was published in *USP 29 Second Supplement* as a harmonized chapter titled *Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms*. This chapter appeared in *PF* back in 2004, and few changes were made from that proposal which then was published with the intention of making it official August 1, 2007. Only after this chapter was published with the intended date by which it was to become official did USP hear about various, evidently costly, difficulties with the chapter. Again, why hadn't the USP heard about these problems when the chapter with the revised procedure was still in *PF* as a proposal, and therefore not yet official?

After these occurrences, it became apparent that the assumption that hearing no substantive comments meant that the readers had reviewed the proposals and had no serious issues was incorrect. This author has had a

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number of opportunities to quiz audiences as to how many read *USP* and how many read *PF*. These informal surveys never fail to indicate that many people who read *USP* do not also read *PF*. In fact, more than a few companies apparently subscribe to *USP* but not to *PF*. Given the critical role intended for the "public" by USP to ensure that its standards (monographs and general chapters) are suitable, the lack of more readership of *PF* seems to be a critical problem.

How could this problem be remedied? One idea proposed by various people this author has discussed the issue with was to provide the *PF* free to all subscribers to *USP*. This might solve the problem in terms of having more copies of *PF* available. Whether the *PF* would be available to all parties potentially affected by proposed revisions is another matter. Therefore, a variation on the free bundling proposal involves providing *PF* for free as an online service to subscribers of *USP*. This approach certainly runs the risk for USP of having to absorb a financial loss. Remember that although USP is a non-profit organization that does not mean it is a charitable organization. It has a highly trained staff necessary to maintain the "book," along with a laboratory staff necessary to support the testing and packaging of chemical reference standards.

Are there other potential solutions? I think so. Here is one based upon the understanding that the *USP* is actually your (as in the "public's") compendium. Your input to the process is critical. Without it, your compendium can require you to ensure that your product can pass a required test which in fact it cannot. Your input is essential in part to ensure that the proposed methods are suitable robust and rugged. Because this compendium is your compendium, it seems appropriate to ask that you share some of the expense associated with the *PF* process. Perhaps the USP could bundle the *PF* for all subscribers to the *USP*. This would occur automatically, whether you choose hard copies or electronic copies. The price for the *USP* would therefore rise to cover the additional expense of the *PF* portion. Yes this would result in a higher annual expense for the *USP*, but it would not take many disasters similar to those described above for chapters <231> and <62> for the additional expense to be more than compensated for.

Can you think of other approaches? I'm sure the USP would be glad to hear them. Please remember though that the USP needs to make enough money to sustain itself, and it may therefore be unreasonable to ask the USP to absorb the monetary loss associated with providing the *PF* for free. Remembering that the *USP* is your compendium, and thinking back, as many of you can, to the angst brought about by official chapters and monographs that put your company and its products in potential risk of being noncompliant, it seems reasonable that your alternative approaches involve an incremental expense for access to both the *USP* and *PF*.

Who is a Microbiologist?

"We become just by doing just acts, temperate by doing temperate acts, brave by doing brave acts." *Aristotle*

Scott Sutton, Ph.D.

Who is a microbiologist? This was a question recently posed on the PMFList (1). The answers on the list were entertaining, but not really instructive. Let me take a few minutes of your time to try to explore this.

The question is growing in prominence from a cGMP perspective. In the United States the FDA, for example, has been know to issue 483 observations that cite the laboratory management's inability to recognize absurd data (dilution series inverted, the isolation of obligate anaerobes from surface samples, *etc.*) or to competently recognize and interpret the significance of pathogenic organisms in non-sterile medicines. The concern is clearly that in certain facilities the microbiology functions are being led by persons who are not competent in the field.

In addition to the FDA interest there is the recently released USP chapter <1117> Microbiological Best Laboratory Practices" (2) which states:

> "The demands of microbiological testing require that the core educational background of the staff, supervisors, and managers be in microbiology or a closely related biological science. They should be assigned responsibilities in keeping with their level of skill and experience."

This chapter goes on to describe supervisory educational expectations:

> "Microbiologists with supervisory or managerial responsibilities should have appropriate education and in-house training in supervisory skills, laboratory safety, scheduling, laboratory investigations, technical report writing, relevant SOPs, and other critical aspects of the company's processes as suggested in their role of directing a laboratory function."

The talk about "appropriate" education is not particularly clear. Going to Wikipedia.com, the definition of "microbiologist" reads (3):

> "A **microbiologist** is a biologist that studies the field of microbiology. They typically hold a Bachelor of Science degree majoring in microbiology. Microbiologists can be known under different names depending on the field of microbiology they specialize in:

- **Bacteriologists** - work in the field of bacteriology and study bacteria.
- **Environmental Microbiologists** - work in the field of environmental science and study microbial processes in the environment.
- **Food Microbiologists** - work in the food industry and study microorganisms that cause foodborne illness and spoilage.
- **Industrial Microbiologists** - generally work in field of biotechnology and study microorganisms that produce useful products.
- **Medical Microbiologists** - medical practitioners

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(doctors) who have chosen to specialize in the diagnosis and treatment of microbial diseases in patients.

- **Mycologists** - work in the field of mycology and study fungi.
- **Protozoologists** - work in the field of protozoology and study protists."

We have a definition of a microbiologist as a scientist who studies microbiology. This probably is helpful in some situations, but in all honesty I don't find it really useful in this discussion (I would go to a traditional dictionary for more scholarly acceptable definition, but a quick check shows most definitions as circular as the one from Wikipedia). Perhaps the best way to approach this question is operationally. A microbiologist can be defined by what she does well. Aristotle taught

> "We become just by doing just acts, temperate by doing temperate acts, brave by doing brave acts."

Perhaps we can become microbiologists by doing microbiology acts. The PDA addressed the range of "microbiology acts" in a technical report devoted to training (4). What follows is a synopsis of these competencies that make up a microbiologist:

1. General expertise
   - Microbiological Concepts
     - Microbial taxonomy & ecology
     - Aseptic practices
     - Clean room classification and monitoring regimes
     - Validation
     - Contamination sources & controls
   - Theoretical considerations
     - The vital macromolecules that support biological and microbiological processes
     - The central dogma of molecular biology
     - Cell wall influence on microbial staining
     - Biofilms and biofouling
     - Strategies for detecting microbial growth
     - Contamination controls to mitigate against adventitious contamination of manufacturing, sampling, and testing processes
     - Epidemiological and clinical significance of microorganisms
     - Validation
     - Range of microorganisms
     - Purpose of controls
     - Microbial growth
     - Safety measures
     - Environmental influence on microbial growth
     - Meaning of sterility
     - Microbial inactivation and prevention approaches
2. Equipment and instrument use
3. Monitoring of defined process hazard points
4. Aseptic practices
5. Laboratory math skills
6. Microbiological testing and support programs
7. Product classifications
8. Specifications
9. Quality systems and CGMPs
10. Microbial enumeration
11. Microbial classifications and identifications
12. Microbiological-based process testing tools
13. Sterile (or non-sterile, as appropriate) processing knowledge
14. Processing facility (area) assessment

That is quite a list. Colleges don't teach that stuff it seems – where is a pharmaceutical microbiologist to learn these skills? The obvious answer is the lab director or supervisor. The only realistic opportunity to learn the details of pharmaceutical QC microbiology is by exposure to a competent leader. This need for competent leadership is reinforced when consideration of biosafety concerns is added to the equation. The United States Centers for Disease Control (CDC) offers a guidance document on precautions for handling Biosafety Level 2 organisms (5):

> "**Biosafety Level 2** builds upon BSL-1. BSL-2 is suitable for work involving agents that pose moderate hazards to personnel and the environment. It differs from BSL- 1 in that 1) laboratory personnel have specific training in handling pathogenic agents and are *supervised by scientists competent in handling infectious agents and associated procedures [italics added by author]*; 2) access to the laboratory is restricted when work is being conducted; and 3) all procedures in which infectious aerosols or splashes may be created are conducted

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Upcoming Events

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
  Contact Steven Paul (stp@usp.org) for information on the course "Fundamentals of Microbiological Testing"

New Guidance Documents

"Guidance for Industry and FDA Staff : **In Vitro Diagnostic Devices to Detect Influenza A Viruses**: Labeling and Regulatory Path." This document was issued on: May 1, 2007 at http://www.fda.gov/cdrh/oivd/guidance/1594.pdf. It is intended to provide guidance on steps to ensure the safe and effective use of in vitro diagnostic (IVD) devices intended for use in the detection of influenza A (or A/B) viruses directly from human specimens.

European Medicines Agency launches **EudraGMP** – the Community GMP database . This document was issued on May 1, 2007 at http://www.emea.europa.eu/pdfs/general/direct/pr/19364007en.pdf. EudraGMP is a new database designed to facilitate the exchange of information on compliance with good manufacturing practice (GMP) within the European medicines network.

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: 2,378
Number of Countries: 64
Number of Messages Last Month: 270

PSDGList (Pharma Stability Discussion Group):
Number of Subscribers: 955
Number of Countries: 23

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

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in BSCs or other physical containment equipment."

Beyond the responsibility of supervising (and training) new microbiologists, the lab director has significant responsibilities in terms of biosafety for the lab as described by CDC:

- "Laboratory directors are compelled to evaluate and ensure the effectiveness of their biosafety programs, the proficiency of their workers, as well as the capability of equipment, facilities, and management practices to provide containment and security of microbiological agents."
- "The laboratory director is responsible for selecting additional safety practices, which must be in keeping with the hazards associated with the agent or procedure."
- "The laboratory director or principal investigator should also ensure that the necessary safety equipment is available and operating properly."
- "Laboratory directors are responsible for providing facilities commensurate with the laboratory's function and the recommended biosafety level for the agents being manipulated."
- "The laboratory director is specifically and primarily responsible for assessing the risks and applying the appropriate biosafety levels."
- "The laboratory director is specifically and primarily responsible for the safe operation of the laboratory. His/her knowledge and judgment are critical in assessing risks and appropriately applying these recommendations."
- "Laboratory directors should also conduct independent risk assessments before beginning work with an agent or procedure new to the laboratory, even though an agent summary statement is available."

CDC and Training:

- "The laboratory director or principal investigator should ensure that laboratory workers have acquired the technical proficiency in the use of microbiological practices and safety equipment required for the safe handling of the agent, and have developed good habits that sustain excellence in the performance of those practices."
- "Laboratory directors or principal investigators should train and retrain new staff to the point where aseptic techniques and safety precautions become second nature."
- "The director or person in charge of the laboratory is responsible for providing or arranging the appropriate training of personnel."
- "Laboratory directors and principal investigators should use risk assessment to alert their staffs to the hazards of working with infectious agents and to the need for developing proficiency in the use of selected safe practices and containment equipment."

It seems clear that most of the laboratory's policy decisions, where it is critical to understand the science of microbiology, are the responsibility of the supervisor. As described in the USP chapter <1117> the supervisor is critical to the success of the lab. However, the supervisors are not only responsible for a great deal in the lab, but they must also serve as Subject Matter Experts (SME) for the company. This responsibility can be in sterility assurance, product safety (particularly in the determination of "absence of objectionable organisms" for non-sterile products), and in many other aspects of product quality (see the PDA's list above).

In addition to the laboratory work, the microbiology SME is responsible for bringing new technologies into the QC laboratory. Denoya, *et al* (6) have described the difficulties faced by many QC microbiology laboratories in this task and the need for a new training curriculum to meet this need.

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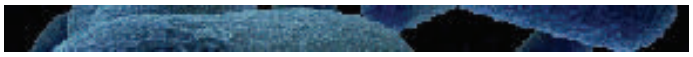

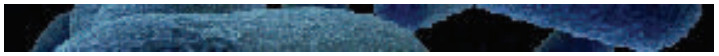

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So, who is a microbiologist? The answer will be different depending upon the level of the tasks being performed. A strong microbiology lab will have bench technicians with appropriate educational background in microbiology or a related field, and/or who have experience training under a strong microbiologist. They can become microbiologists by performing microbiology acts over several years under the tutelage of a competent scientist who explains the "why" of the microbiology acts being performed.

The supervisor or director level microbiologist must know the "whys" of acts in several key microbiologist roles:

1. Chief technical resource and trainer
2. Responsible party for biosafety issues in the lab
3. SME for the company
4. Technology bloodhound

Knowing the "whys" brings us back to the FDA and the CDC concern about competency. While it is possible to find people without academic credentials in microbiology who can fulfill this role (usually through extensive experience and self-education) it is not an easy matter. One path to self-improvement and accreditation is through the American Society of Microbiology (ASM) which maintains the National Registry of Microbiologists (7, 8). This is an international registry of microbiologists who have demonstrated technical knowledge through testing, and continued improvement through training as evidenced by training and accumulated Continuing Education Units (CEU).

It is also difficult to find a recent college graduate (even one with a very impressive new Ph.D.) who has the necessary temperament, experience and outlook to serve as trainer and SME for the company. The key role as "head microbiologist" is one that demands a combination of scientific competence and leadership skills.

Who is a microbiologist? Who has the knowledge, skills, proficiencies and experience to function as a responsible steward of the company's resources and products? Both the bench technician (skilled in the acts, and comprehending the "whys") and the supervisor who can teach the "whys" are microbiologists.

We return to Aristotle, although performing the "acts" is not sufficient in a technical discipline. The microbiologist performs microbiology acts, and in addition she knows the reasons for the manner the acts are performed as well as their value to the patient and the company.

References

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Cleaning Validation: Practical Compliance Solutions for Pharmaceutical Manufacturing by Destin A. LeBlanc

Reviewing this book is a departure of sorts for the *PMF Newsletter*. Cleaning Validation: Practical Compliance Solutions for Pharmaceutical Manufacturing is not a book about microbiology (of the 49 short chapters in this compact book, only one deals with microbial studies and one with bacterial endotoxin studies). So why present this discussion?

There are a lot of myths, folk lore, "common practices" (call them what you will) in the pharmaceutical industry. Microbiology is full of them. In those areas where microbiology and chemistry overlap, these practices multiply. Cleaning validation is one such area where a great deal of confusion leads to questionable practices. The microbiology unit will (should) play a major role in the design of cleaning validation studies for Manufacturing, both in sterile and in non-sterile processing. However, the microbiology unit is concerned primarily with the reduction of viable contaminants, the cleaning validation must also demonstrate elimination of chemical contaminants, either from components of previously manufactured batches or from the cleaning agents used to remove them. It is important that the microbiologist on the project have an understanding and appreciation for these issues.

Cleaning Validation is a great place to start for a reference source on this information. Earlier in this newsletter we mentioned that much of pharmaceutical microbiology is not taught in a university, that you learn it on the job ("Who is a Microbiologist?"). Most of us learn cleaning validation that same way. However, we all have to be on guard against the tendency to ascribe "the XXXX way" (fill in the blank with any company name) with veracity merely because this is the way we have always done it. Repeating a mistake 100 times does not make it less of a mistake. This text can serve as an excellent "sanity check" for comprehension of specific topics, and as a start for examination of our own practices. The book is short (228 pages, excluding index) and very readable. However it is not designed to be read cover-to-cover.

Destin LeBlanc presents monthly *Cleaning Memos* on his web site http://www.cleaningvalidation.com. This book is a collection of these *Cleaning Memos* from 2000 to 2004, updated and revised to improve clarity. Each of the short chapters (2-4 pages) was originally a different *Cleaning Memo*, with the book having the chapters organized into sections with similar themes:

- General Topics
- Special Situations
- Residue Limits
- Analytical Methods
- Sampling
- Sampling Recovery
- Protocol Issues
- Grouping Strategies
- Regulatory Issues
- Microbial Issues (2 chapters)
- Visually Clean Issues
- Validation Maintenance

In addition, the book boasts a modest index, but with such short chapters and such descriptive chapter headings the index is almost superfluous. As examples, chapter titles include:

- "What's a contaminant?"
- "Why TOC Is Acceptable"
- "Selecting Swab Sampling Sites"
- "Cleaned Equipment Hold Times"
- "Understanding and Applying 'Visually Clean'"

This book is not designed to provide educational instruction to someone new to the topic of cleaning validation. It does not follow the traditional method of starting with basic concepts and building to the complex. Rather, it is a great resource if you have a question about something you heard in a meeting that doesn't sound quite right and you need to check it. In addition, each chapter provides references to allow the reader to do some research on the topic himself.

I recommend Cleaning Validation: Practical Compliance Solutions for Pharmaceutical Manufacturing by Destin LeBlanc to the QC microbiologist's library. While it does not deal with microbiology as its primary topic, we find ourselves involved in cleaning validation discussions as part of cross-functional teams and need to understand the other aspects of the task. This treatment of the subject is clear, readable and level-headed.

Scott Sutton, Ph.D.