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PMF NEWSLETTER

A Publication of the Pharmaceutical Microbiology Forum
DISTRIBUTED INTERNATIONALLY

Volume 12, Number 6 June, 2006

The PMF gratefully acknowledges the contributions of :
- Vectech Pharmaceutical Consultants, Inc, (http://www.vectech.com)
- High Peaks Associates, Inc. (http://www.highpeaks.us)

to the continued success of the *PMF Newsletter*

International Concerns

Scott Sutton, Ph.D.
Editor, PMF Newsletter

This issue of the newsletter features a commentary of a recently issued risk assessment model for aseptic processing. The Author, a member of the newsletter's editorial board, provides a personal commentary on the implementation and utility of the recently issued technical monograph describing the risk assessment model.

In the third in a series of essays on the harmonized microbial limits tests, we take a look at the difference between "objectionable" and "specified" microorganisms and why it matters. Next month we will conclude, in the fourth of this three-part series, with an additional article presented by request on a method of determining if a particular organism is "objectionable."

Important Links:

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

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

The contrary group "Microbiologists for Common Sense and Reason" have submitted another essay. In this essay, a representative under the pseudonym of Dr. A. Nonymous describes the need for the management of a Microbiology lab function to know something about the technical subject matter.

There is finally an alert to look out for 7 new USP chapters that are published in Supplement 2 of USP 2006 (see page 7). 4 of these have an effective date of Aug. 1, 2006, the other three (the harmonized microbial limits chapters) are effective August 1, 2007 (to allow time for product test revalidation). Our thanks to Tony Cundell for the alert on the PMFList.

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Review of The Parenteral Society and The Scottish Society for Contamination Control's *Risk Management of Contamination (RMC) During Manufacturing Operations in Clean rooms* (Technical Monograph No. 14)

Eric Strauss
Teva Pharmaceuticals, Israel

One of the favorite buzz phrases in our industry over the last few years has been "Risk Management". The process of identifying risks, assessing their potential impact and acting to reduce them is not new at all. In fact it can be said it is these very activities that have occupied a good percentage of our time for many years, although we may not have codified them using "risk" terminology.

We in the pharmaceutical microbiologist community are not immune to risk initiatives and often are called upon to support and guide the QA and manufacturing sectors when designing and executing risk activities. Unfortunately, the risk model systems that are widely available are not necessarily compatible to the risk situations we face in manufacturing of sterile/clean pharmaceuticals. The large and small biological systems (e.g. operators and microbes) that occupy our manufacturing sites tend to make the potential contamination risks hard to predict. There is a void of published guidance giving practical advice on how to perform risk models targeting the arduous discipline of manufacturing in cleanroom environments.

Whyte and Eaton have attempted to fill this void by creating a technical monograph that describes a risk management system especially designed for cleanroom operations.

This monograph is mainly a compilation of four previously published articles. It is intended to present an overall Risk Management System geared at contamination in pharmaceutical clean room manufacture.

About the Author: Eric Strauss Eric was born, raised and educated in the USA and has worked in the pharmaceutical industry since moving to Israel 20 years ago.
He holds a masters degree in biology and has been accredited as a Specialist Microbiologist by the NRM since 1996.
Coming up through the microbiology laboratory, Eric has held positions in QA and currently is the Associate Director of Regulatory Compliance, Sterile Manufacture for Teva Pharmaceuticals Global Pharmaceutical Operations.

The monograph is organized as follows:

Preface 1: Availability and Choice of Risk Management Systems for Contamination Control in Cleanrooms
Preface 2: Derivation of Equations that Determine Contamination, and Models for Use in **Risk Assessment**
Application of the RMC System:

1. Identification of Sources and Routes of Contamination
2. Risk Assessment and Methods of Reducing Risk
3. Establish and Effective Monitoring Programme
4. Verification of the System
5. Documentation
6. Staff Training
7. Assessing Microbial Risk to Patients from Aseptically Manufactured Products

Appendix A: Information on the Frequency of Sampling, Upper Contamination Limits, and Physical Requirements

It is clear from the outset that the authors are highly knowledgeable of cleanroom manufacture and risk management systems in general. All potential sources of contamination are addressed.

Never the less, as I reviewed the monograph with an eye to the learning a (simple?) risk management system, I found the monograph to be very confusing as it tended to rely heavily on the theoretical. I will try accent the more positive points where we may be able to use the methodology.

It starts out with two prefaces. The first very briefly goes over the existence of ready-made risk management systems in use (*e.g.* HACCP) coming to the conflicting conclusion that overall HACCP is the most closely related to our industry, but the Risk Assessment tools of FMEA are more suitable for adoption in the system to be presented in the monograph.

The authors state that a major component of risk management is "risk assessment". They continue to say that although the HACCP system contains a risk assessment method, the most suitable method for assessing the microbial risk in cleanrooms is the FMECA method. No com-

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Microbial Limits Tests
The Difference Between "Absence of Objectionable Microorganisms" and "Absence of Specified Microorganisms"

Scott Sutton, Ph.D.
Vectech Pharmaceutical Consultants

We have to note from the outset that USP and FDA frequently are interested in the same thing. From the vantage point of USP, there is a need to have a test for sterility, for antimicrobial efficacy, for Antibiotic/ Vitamin Potency, for Bacterial Endotoxin, for Microbial Limits etc. The need for these tests is not driven by any concern over "Good Manufacturing Process" (GMP). It is governed by the USP monographs found in the *National Formulary* (NF). If there is a monograph that requires a test for antimicrobial efficacy, then chapter <51> Antimicrobial Effectiveness Test" is the referee test used to demonstrate that characteristic.

FDA has similar, but separate concerns. Where the requirements are identical, the referee chapters in USP (those numbered under <1000>) are enforced. However, there are situations where the FDA's concerns are not covered by a USP referee test method. One such situation is with the CFR requirement that medicines be "free of objectionable microorganisms." 21CFR 211.113 under the section "Control of microbiological contamination. (a)" states "Appropriate written procedures, designed to prevent objectionable microorganisms on drug products not required to be sterile, shall be established and followed." This is reinforced by 21 CFR 211.165 which states "Testing and release for distribution... (b) There shall be appropriate laboratory testing, as necessary, of each batch of drug product required to be free of objectionable microorganisms."

About the Author: Dr. Sutton earned his Masters and PhD in Microbiology from the University of Rochester (NY). He has over 20 years experience in the pharmaceutical industry as a microbiologist. He has worked with the USP Microbiology Committee of Experts since 1993, serving as vice-chair since 2000. Dr. Sutton also operates an information source on the internet, The Microbiology Network) which provides services to microbiology-related user's groups and supports the PMFList, a microbiology Email list and the PSDGList (pharmaceutical stability topics). He also serves as editor for the PMF Newsletter and as a reviewer for several print publications.

So, here we have a problem. The USP monograph for a product (as provided in the current *National Formulary*) may require "Absence of *Pseudomonas aeruginosa*." There is a test in the Microbial Limits chapter to demonstrate the absence of *Pseudomonas aeruginosa*. However, although this test may be required to demonstrate compliance with the monograph requires as laid out in *NF* it does not meet the FDA concern that any organism in the final product be acceptable to the product and the target population (*i.e.* are not "objectionable").

The FDA Concern

FDA will enforce the GMP requirement that if your product approval to market submission contained a statement that you would test the finished product by the *Microbial Limits Tests* that in fact you must do that. This is purely a GMP concern. However, the Agency has been absolutely clear on the concern over *objectionable* microorganisms in the product, and that fact that testing to the USP chapter might be necessary, but it is not sufficient to demonstrate microbial quality. In fact, in the 1993 instructional guide for inspections of QC Microbiology Labs (1) the FDA states:

> "For a variety of reasons, we have seen a number of problems associated with the microbiological contamination of topical drug products, nasal solutions and inhalation
> products. The USP Microbiological Attributes Chapter <1111> provides little specific guidance other than "The significance of microorganisms in non-sterile pharmaceutical products should be evaluated in terms of the use of the product, the nature of the product, and the potential hazard to the user." The USP recommends that certain categories be routinely tested for total counts and specified indicator microbial contaminants. For example natural plant, animal and some mineral products for Salmonella, oral liquids for E. Coli [*sic*], topicals for P. aeruginosa and S. Aureus [*sic*], and articles intended for rectal, urethral, or vaginal administration for yeasts and molds. A number of specific monographs also include de-

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Who is in Charge of the Micro Lab?

From the Poison Pen of Dr. A. Nonymous
Member – *Microbiologists for Common sense and Reason*

The GMPs as well as a number of other laws and regulations require that a pharmaceutical manufacturer produce and sell a safe product suitable for its intended purposes. It is well understood that safety has a cost both in money and resources. Regardless of the efforts made and good intentions, there will always be a chance for adverse reactions in any given population. The number and severity of such adverse reactions that would constitute an un-safe product has been the subject of much debate and varies considerably with the individual circumstances (1, 2, 3). Those issues surrounding the potential adverse effects of a product containing viable microorganisms are particularly vexing. In such instances, the manufacturer must make the determination as to what is or is not safe. There are various regulations, guidelines and recommendations concerning microbial content and how it should be assessed (USP, Pharm Eur and JP). However, following these will not guarantee a "no risk" result. Not following them can and will result in adverse regulatory action as well as increased vulnerability to potential civil liability. The regulatory agencies expect that such decisions be made by microbiologists trained in the specific sub-disciplines which allow them to possess the basic background and knowledge to support the decision process (4, 5).
The current regulatory climate and initiatives are directing manufacturers to substitute scientific based judgments for proscriptive regulation and guidance (6). This approach is causing confusion and vexation in many parts of the pharmaceutical industry. Historically, microbiologists have not achieved the proportion of policy making positions seemingly reserved for chemists and engineers. This statement is not designed to produce animosity but to simply state a fact. Neither chemists nor engineers are routinely trained in biological systems, pathological mechanisms and microbial pathogenicity. What they are trained in are definitive results and predictability which are not terms used to describe living systems. Consequently, many manufacturers have established a system (intentional or not) where decisions are made by individuals not specifically trained in all relevant areas. Compounding this is the assumption that there is an extra word in the qualification portion of the cGMPs:
"a) Each person engaged in the manufacture, processing, packing, or holding of a drug product shall have education, training, and experience, [**POSITION**] or any combination thereof, to enable that person to perform the assigned functions. CFR 21-211.25 Personnel qualifications"

This assumption that assigned position within the organization is a suitable substitute for relevant educational training and experience has the potential to cloud judgment and to substitute the individual's education and experience base for facts that do not exist. While it is true that a good manager is a valuable asset, not all good managers are equal. This is a critical issue in a technical department where decisions on technical matters are an integral part of the manager's job, technical matters he may not be competent to understand. This causes a problem at times, for example when faced with a difficult decision of a technical nature. When faced with several options, a natural response is to find a third party arbitrator. The writers of the various regulations and guidelines addressing microbiological issues have provided such third party information. Inadvertently or not, this information is not designed to educate but is designed to provide guidance for the trained and experienced microbiologist. Unfortunately, also included in this literature are paradigms and assumptions that scientifically are not supportable. The law of unintended consequences has resulted in a situation affecting many manufacturers where microbiological decisions are made by non-microbiologists, based upon guidance meant to be applied in a completely different situation. It is not uncommon to have a corporate culture where managers assume (through mis-reading and mis-understanding) regulatory and guidance document support (for practices they would like to do; and prohibitions against practices they are disinclined to support) that does not exist.

The microbiological issues that most clearly illustrate the above are two.

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About the Author: Dr. A. Nonymous is a Ph.D. microbiologist currently employed in the pharmaceutical industry within a large company. He/she has over two decades of microbiology experience in the industry.

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1. Total count
2. Microbial identification i.e. objectionable organisms

The concept of total count is very simple until the variables are considered. The most significant variable is that counts are reported as colony forming units (CFU). In reality, it is virtually impossible to determine the number of individual organisms that correspond to a CFU as a colony on a plate my have arisen from a single cell or thousands of cells. However, specifications are written that assume a CFU is a discreet unit reproducible and unchanging for any given sample. Microbial contamination is not necessarily uniformly distributed nor should it be expected to stay at a uniform level. The USP (7) states that when an acceptance criterion for microbiological quality is prescribed it is interpreted as follows: {because of the inherent error potential of the method}

- 10 cfu: the maximum acceptable count = 20
- 100 cfu: the maximum acceptable count = 200
- 1000 cfu: the maximum acceptable count = 2000 and so forth

The basis of most risk assessment programs for non-sterile products is the identity of any microbial contaminants. With the identity known, then there is a large amount of literature on which to base an assessment of the organism's potential to cause harm. One common compendial test is the USP limits test (USP <61>) which is commonly referred to as a pathogen screen. In reality, USP <61> is not a pathogen screen and never was (editor's note – see article by Sutton in current issue). It is an absence test for certain specific organisms originally developed in the food industry to indicate the potential presence of other food pathogens. Many well known problem organisms commonly found in pharmaceuticals would not be detected by this method yet this USP method is commonly mis-used as a pathogen screen because naive and insufficiently trained individuals believe that it is. The USP and FDA guidance documents clearly state that all recovered organisms need to be evaluated for significance and determined to be or not to be objectionable. –Many companies seem to think that this determination can be made without doing even a minimum identification or even a Gram stain! A review of product recalls for microbial contamination will show that the majority of such recalls, where specific organism are mentioned, are not the compendial organisms specified to be absent in USP <61>. This should be considered a warning that there are more than 4 potentially objectionable organisms. Even when an organism is identified by an automated system (chemical or genetic), it cannot be reliably assumed that other systems will confirm that identification nor that the organisms referenced in the literature would , in fact, be the same organism identified.

Another paradigm that has the potential for significant adverse consequences is that compendial requirements are the only requirements. Again, in reality, compendial requirements are, at best, absolute minimums and should not be assumed or relied upon to be all that is required. Compendial informational chapters should not be relegated to the realm of the assumed to be unenforceable as they do represent standard industry practices.

Rationalizations based on paradigms and assumptions around microbiological issues have a great potential to cause harm and to establish an environment where questioning the utility of an established microbiological control program is not condoned. The current regulatory expectations that microbiological excursions be fully investigated and a root cause identified (RCA) along with corrective and preventative actions (CAPA) illustrates these points. Part of such investigations should be to evaluate method capabilities, sampling plans, etc. and to test theories not just assure that the relevant SOPS were followed-- which is an Out of Specification (OOS) exercise. It is very frustrating for many microbiologists to be hand cuffed and not allowed to perform a real investigation which may uncover system weaknesses of which the powers that be would prefer to be ignorant.

To summarize this diatribe, the ignorance (lack of relevant education and experience) about pharmaceutical microbiological control among non-microbiologist and some microbiologists is considerable. This only underscores the need for trained, experienced and appropriately educated microbiologists in supervisory positions, as called for in the draft USP chapter <1117> (8). Many times the result is to belittle or dismiss such concerns until some event such as a regulatory inspection, product re-call or other adverse happening forces the issue. The concept of systemic problems around microbiological control requires a detailed knowledge of microbiology not common in many management structures. The predictable response is the quick fix and recidivism. The regulatory concepts around adequate microbiological control no longer condone such approaches. Once this fact is understood, then it is up to the authors of the regulations and guidelines to

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parison or supportive reasoning is given.

Without clear explanation, the monograph uses multiple "risk" phrases that are confusing due to their similarity. For instance I understand that **Risk Systems** include multiple stages, the most important one is **Risk Assessment** (a.k.a. **Risk Analysis**). To perform a true risk assessment, you need correct **Risk Models.** The risk models need specific equations per circumstance (e.g. airborne contamination versus contact contamination).

The second preface is concerned with deriving a great deal of equations to model risk.
The authors place an ominous NOTE on the first page of the preface stating:

> "*An understanding of the derivation of the equations and choice of models described in this section is not essential to the application of the RMC system. It is therefore possible to move on to the next sections of this monograph and return to this preface if it is necessary to obtain the reasons and scientific proof of the methods used*."

I should have taken the hint!

Equation #1 is an intuitive summary of "Contamination deposited on a product". All the factors that could affect this are included and it is indeed a good starting point. What follows though is a multitude of subsequent equations with some being slight adjustments to the original, but slanted to the model under review. While this sounds very plausible, it turns out sometimes just to be theoretical. In Equation 2, the authors have to admit the irrelevance of the equation, "Unfortunately, most of the information required to solve Equation 2 is seldom available and it is necessary to use descriptors as surrogates for the numerical values required." Another example of the theoretical slant of some of the equations is in Equation 4. "To solve Equation 4 it is necessary to know the deposition velocity of the microbe carrying particles in the air surrounding the product. This is generally unknown, although values of the average size of microbe carrying particles are available in the research literature and from these a settling velocity can be calculated".

Equation 7 is an equation defining Risk mathematically for the actual risk assessment. It states:
Risk = criticality of the occurrence x frequency of occurrence.

Equation 8 goes on to use a FMEA definition of risk:
Risk (priority number) = Probability x Severity x Likelihood of Detection.

The authors, having brought up Equation 8, state that as the Likelihood of detection for microbial contamination is not directly relevant, so Equation 7 should be the basis for future use.

Now that we have a bag full of risk model equations to use when we get to the assessment step, the monograph goes into the seven steps comprising the risk system.

Step one - Identification of Sources and Routes of Contamination.
This section is a good review of the basic microbial contamination sources of a clean room and surroundings.

Step two - Risk Assessment and Methods of Reducing Risk
Please note that this is considered a first level assessment, to rate the identified risks from step one. Equation 9 is brought forth, which is the original Equation 1 (remember him) using general descriptors in place of numerical data which is normally not available.
Equation 9:
Risk from microbial contamination (risk rating) = A x B x C x D
A = microbial contamination on, or in source
B = ease of dispersion and transfer of contamination
C = proximity if contamination source from critical area
D = effectiveness of contamination control method

This is a good overall way to rank risk as it is intuitive and does not require complicated equations. The mono-

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Internet Address	Description
http://www.fda.gov/ora/inspect_ref/igs/iglist.html	FDA's collection of inspection guides. One of particular interest here is the 1993 "Guide to Inspections of Microbiological Pharmaceutical Quality Control Laboratories" (http://www.fda.gov/ora/inspect_ref/igs/micro.html)
http://www.epa.gov/nerlcwww/	The EPA Microbiology Home Page. The purpose of this site is to provide access to microbiology related information that has been developed or managed by the Agency. EPA methods related to bacteria, viruses and protozoans can be found at this site.
If you have found an Internet site that contains information of relevance to pharmaceutical microbiology, please let us know.	

Upcoming Events

June

- 5th - 6th **PMF Microbiology GMP Conference**
  Location: Philadelphia, PA
  Web Site: http://www.highpeaks.us/2006/GMP/

- 26th - 29th **Aseptic Processes and Sterile Processes**
  Location: Amsterdam, The Netherlands
  Web Site: http://www.ivthome.com/shop/Scripts/prodList.asp?idcategory=2&sortField=STARTDATE

Offering In-House Courses on Microbiology/ Aseptic Processing:

- The Microbiology Network/High Peaks Associates http://www.highpeaks.us/in-house.htm

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

USP Corner

Any questions concerning USP documents should be sent to Radhakrishna (Radha) Tirumalai, Ph.D. 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.

Supplement 2 to USP 2006

- *Harmonized* <61>, <62> and <1111> (effective August 1, 2007)
  - <61> Microbiological Examination of Non-sterile products: Microbial Enumeration Tests p. 3757
  - <62> Microbiological Examination of Non-sterile products: Test for Specified microorganisms p. 3761
  - <1111> Microbiological Quality of Non-Sterile Pharmaceutical Products p. 3801
- <1072> Disinfectants and Antiseptics (new; effect. Aug. 1, 2006) p. 3792
- <1112> Application of Water Activity Determination to Nonsterile Pharmaceutical Products (new; effect. Aug. 1, 2006) p. 3802
- <1117> Microbiological Best Laboratory Practices (new; effect. Aug. 1, 2006) p. 3804
- <1223> Validation of Alternative Microbiological Methods (new; effect. Aug. 1, 2006) p. 3807

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make such clear and unequivocal to avoid the concept that there is an "out" around compliance.

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7. USP. 2003. <1111> Microbiological Quality of Nonsterile Pharmaceutical Products Harmonization. *Pharm Forum* 29(5):1733-1735
8. USP. 2004. <1117> Microbiological Best Laboratory Practices. *Pharm Forum* 30(5):1713-1721

Discussion List Update

PMFList:
Number of Subscribers: 1,579
Number of Countries: 62
Number of Messages Last Month: 151

PSDGList (Pharma Stability Discussion Group):
Number of Subscribers: 800
Number of Countries: 19

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

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graph goes on to suggest a risk assessment committees from various disciplines determine the risk scores to be used when assigning risks. Examples are given. Although the manner in which the committee would decide on the scores of each risk is reminiscent of what we do daily without calling it "risk assessment", I think it is a good way to codify a first stage simple risk assessment exercise.

What follows in the monograph is a second level, higher risk area assessment once the first run-through has been completed. Here the authors state the obvious "Generally speaking, the higher risks are likely to occur in the production area where the product is open to potential contamination."

The high "risk" production stages now need to be broken down into individual activities and each activity's risk assessed, with the total risk of the activities added together to get the risk for the whole stage. The higher risk activities can then be targeted for correction, to reduce the overall risk. Got that?

How to perform the risk described above is explained with more equations. More complication is put in by the author's suggestion to assign weighting coefficients to correct imbalances in different activities (i.e. some activities are more risky than others and therefore need a weighting correction).

A second level of assessment, even without the need to add in weighting coefficients would bring us down to the more practical evaluation of the risk activity, and may be worthy to perform.

Steps three through seven are more QA orientated (documentation, training, re-assessment etc...) and not specific to risk management methodology.

Overall, I think the most simplistic risk assessment model put forth in the monograph may be helpful to use as a learning tool, but the monograph in total falls short of teaching us a practical risk management system that we can put into use easily.

Akers & Agalloco have recently published their own risk assessment method *in Risk Analysis for Aseptic Processing: The Akers-Agalloco Method* (5), They themselves discuss Whyte/Eaton's method in order to contrast it to their own.

Whereas Whyte/Eaton base their risk assessment method on the principal of modeling theoretical microbial deposition onto the exposed product , Akers/Agalloco focus their method on risks directly related to human interventions during the aseptic process. Simply put, they take the accepted idea of that where more human interventions are required; risk will be higher, and develop a risk assessment model around this.

Both Whyte/Eaton and Akers/Agalloco take into consideration technical aspects such container opening size and time of exposure, Akers/Agalloco also emphasize facility design, level of automation and working environment technology . Both models give examples of risk contribution scores that although are admittedly arbitrary, are formulated from the author's experience. Akers/Agalloco's tables depicting the various scores are more simplified and easier to follow.

Both methods, whether using Whyte/Eaton's more theoretical parameters as part of the risk assessment calculations, or Akers/Agalloco's simplified, self-evident scheme, are intended to help identify and sort risk activities. They are not ends onto themselves.

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finitive microbial limits.

As a general guide for acceptable levels and types of microbiological contamination in products, Dr. Dunnigan of the Bureau of Medicine of the FDA commented on the health hazard. In 1970, he said that topical preparations contaminated with gram negative organisms are a probable moderate to serious health hazard. Through the literature and through our investigations, it has been shown that a variety of infections have been traced to the gram negative contamination of topical products. The classical example being the Pseudomonas cepacia contamination of Povidone Iodine products reported by a hospital in Massachusetts several years ago.

Therefore, each company is expected to develop microbial specifications for their nonsterile products. Likewise, the USP Microbial Limits Chapter <61> provides
methodology for selected indicator organisms, but not all objectionable organisms. For example, it is widely recognized that Pseudomonas cepacia is objectionable if found in a topical product or nasal solution in high numbers; yet, there are no test methods provided in the USP that will enable the identification of the presence of this microorganism.

A relevant example of this problem is the recall of Metaproterenol Sulfate Inhalation Solution. The USP XXII monograph requires no microbial testing for this product. The agency classified this as a Class I recall because the product was contaminated with Pseudomonas gladioli/cepacia. The health hazard evaluation commented that the risk of pulmonary infection is especially serious and potentially life-threatening to patients with chronic obstructive airway disease, cystic fibrosis, and immuno-compromised patients. Additionally, these organisms would not have been identified by testing procedures delineated in the general Microbial Limits section of the Compendia. . . .

Microbiological testing may include an identification of colonies found during the Total Aerobic Plate Count test. Again, the identification should not merely be limited to the USP indicator organisms.

The importance of identifying all isolates from either or both Total Plate Count testing and enrichment testing will depend upon the product and its intended use. Obviously, if an oral solid dosage form such as a tablet is tested, it may be acceptable to identify isolates when testing shows high levels. However, for other products such as topicals, inhalants or nasal solutions where there is a major concern for microbiological contamination, isolates from plate counts, as well as enrichment testing, should be identified."

Why is this a concern? To understand this we have to go back to the 1970's. USP had a test for the "Bacteriological Examination of Gelatin" as early as 1942 (2). However, most non-sterile medications in the US were not required to assay for microbiological quality attributes until the introduction of the Microbial Limits Tests in 1970 (3). In the late 1960's several outbreaks of disease were traced back to pathogen-contaminated medications, and this prompted increased attention to the microbial content of non-sterile drugs (4). Later in the 1980's there was a series of articles appearing in the literature describing contamination by *P. cepacia* (currently *Burkholderia cepacia*) (5, 6) and its survival in disinfectants(7 – 11). This lead to the addition of requirements in the 21 CFR to ensure that there are not *objectionable* organisms in product released to market (see above). Add to this the knowledge that the USP "Absence of *Pseudomonas aeruginosa*" assay will not identify presence of *B. cepacia* (as discussed).

The USP Concern

The USP is on record as early as 1982 verifying that the demonstration of "absence of *objectionable* microorganisms*"* is not the intent of the chapter. In a one page *Stimuli to the Revision Process* the microbiology committee of the time states:

"The tests described in the *Microbial Limits Tests* <61> were not designed to be all-inclusive, *i.e.*, to detect all potential pathogens. To accomplish this, an extensive text on laboratory detection of microorganisms would be required. The procedures in USP were designed to detect the presence of specific

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"index" or "indicator" organisms. Nevertheless, the present chapter does not preclude the detection of *Ps. Cepacia* – the organism requires subsequent differentiation. The chapter does not provide specific methods for this, nor does it provide procedures for detecting thousands of other potentially pathogenic organisms. Individual monographs include requirements for limits on total aerobic counts and/or absence of one or more of the four selected "indicator" organisms. The chapter on *Microbial Limits Tests* provides methods to assure that one may test for those microbial requirements in the individual monographs...

In conclusion, the *Microbial Attributes* and *Microbial Limit Tests* chapters accomplish their intent. If a manufacturer needs particular tests for any specific organisms that are potential problems in a process or a final product, the quality control microbiologist can provide specific detection procedures. Many such procedures are published in several laboratory texts on microbiology."

Conclusions

On the question of the microbial quality of non-sterile pharmaceuticals, the USP and the FDA are in agreement – the product must be safe for use. The *NF* monograph requirements for absence of specific organisms is a minimal requirement, and should not be taken as proof that the product is suitable for sale from a microbiological perspective.

The manufacturer is responsible for the quality and safety of the product marketed, and it is the clear expectation of FDA (as described in CFR) that this will include a determination of the microbial safety – *i.e.* the "absence of *objectionable* microorganisms" from the product. These positions have been publicly stated for decades and should not come as a surprise to anyone. The harmonized microbial limits tests only address the "absence of *specified* microorganisms" and leave the determination of the "absence of *objectionable* microorganisms" in the capable hands of each company's appropriately educated and well-trained microbiology group.

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