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PMF NEWSLETTER

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Water Activity

One of the recently released new chapters from USP is chapter <1112> Application of Water Activity Determination to Nonsterile Pharmaceutical Products." This chapter provides some opportunities to manufacturers of non-sterile dosage forms that did not earlier exist. Anthony Fontana provides a detailed review of the chapter, the theory and the opportunities in this area.

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

This month will see the Fall Forum take place in Rochester, NY. This year we have a large number of researchers presenting data and interpretation on a variety of topics that have been identified by the membership as of interest. This is sure to be a great conference. Next on the calendar for PMF is an open conference. This format was used extensively in the past by USP to solicit input on chapters under development. The format consists of a preliminary set of presentations, and then facilitated discussion groups led by regulatory authorities designed to encourage communication among the participants (regulatory experts and attendees alike). This conference is the only one of its type planned for 2007.

We seem to have struck a nerve with the discussion of "counting colonies." Among the responses was a call from an FDA Lab Head who felt the discussion had not been exactly accurate and wanted clarification. After discussion we decided his point was important enough to warrant a follow-up article, which appears on page 9.

Finally, Karen McCullough *et al* put on another excellent conference on the Bacterial Endotoxin Test in San Francisco. This conference has become the premier event of its type and the PMF is very proud to present it to the pharmaceutical community.

Scott Sutton, Ph.D. scott.sutton@microbiol.org

Understanding Water Activity for Reduced Microbial Testing Using USP Method <1112>

Anthony J Fontana Jr. Ph.D.,
Senior Research Scientist, Decagon Devices, Inc.

Abstract
Water is recognized as being very important, if not critical, to the chemical, physical, and microbiological stability of most pharmaceuticals. Controlling the water within a product, by chemically or structurally binding it or else through some method of drying has long been used in the pharmaceutical industry. Water activity is a measure of the energy status of water in a product and is reduced through chemical binding or drying. It's not the amount of water, but rather the water activity that plays a critical role in the microbiological, chemical, and physical stability of pharmaceutical dosage formulations and ingredients. Knowledge of the water activity of pharmaceuticals is essential to obtain a dosage formulation with optimal shelf life properties.

Introduction
Water activity is defined as the ratio of the vapor pressure of water in a material (p) to the vapor pressure of pure water (p_o) at the same temperature. Relative humidity of air is defined as the ratio of the vapor pressure of air to its saturation vapor pressure. When vapor and temperature equilibrium are obtained, the water activity of the sample is equal to the relative humidity of air surrounding the sample in a sealed measurement chamber. Multiplication of water activity by 100 gives the equilibrium relative humidity (ERH) in percent.

$$a_w = p/p_o = ERH\ (\%) / 100$$

As described by the above equation, water activity is a ratio of vapor pressures and thus has no units. It ranges from $0.0a_w$ (bone dry) to $1.0a_w$ (pure water). There are several factors (osmotic, matrix, and capillary) that control water activity in a system. It is a combination of these factors in a product that reduces the energy of the water and thus reduces the vapor pressure above the sample as compared to pure water. Water activity is a measure of how tightly water is "bound" and related to the work required to remove water from the system. Due to varying degrees of osmotic and matrix interactions, water activity describes the continuum of energy states of the water in a system rather than a static "boundness." Water that is "bound" should not be thought of as totally immobilized.

Microbial and chemical processes are related to water's "bound" energy status in a fundamental way. Since moisture content only provides information about the amount of water and not the availability or "boundness" of water, it is unreliable for determining susceptibility to microbial growth. Because water is present in varying energy states, analytical methods that attempt to measure total moisture in samples don't always agree or relate to safety and quality. For example, a product may contain a relatively large percentage of moisture, but if the water is chemically "bound" with the addition of humectants or solutes, such as salts, sugars, or polyols, the water is biologically unusable for the microbial growth processes. The water activity concept has served microbiologists and food technologists for decades and is the most commonly used criterion for food safety and quality, however water activity has not been widely adopted in the pharmaceutical industry. Some key papers describing water activity, its measurement, and pharmaceutical applications are listed in Table 1.

Now there is a published USP (United States Pharmacopeial) Method <1112> that utilizes water activity. USP Method <1112> Microbiological Attributes of Non-sterile Pharmaceutical Products – Application of Water Activity

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Determination provides guidance on the influence of water activity as it pertains to the susceptibility of a product formulation to microbial contamination. Knowledge of the behavior of microorganisms in pharmaceutical products at different a_w levels is essential to effectively utilize USP method <1112>. The chapter discusses the potential for improving product preservation by maintaining low water activity. The determination of the water activity of non-sterile pharmaceutical dosage forms aids in the following:

- Optimizing product formulations to improve antimicrobial effectiveness of preservative systems
- Reducing the degradation of active pharmaceutical ingredients within product formulations susceptible to chemical hydrolysis
- Reducing the susceptibility of formulations (especially liquids, ointments, lotions, and creams) to microbial contamination
- Providing a tool for the rationale for reducing the frequency of microbial limit testing and screening for objectionable microorganisms for product release and stability testing using methods contained in the general test chapter Microbial Limit Tests <61>

Materials and Methods

Minimum water activity values for growth were obtained from a survey of literature values. AquaLab Series 3TE (Decagon Devices, Inc., Pullman WA) was used for all testing of pharmaceutical and over-the-counter (OTC) drug products.

Results

Table 2 lists the minimum water activity level for growth of USP-specified and objectionable microorganisms for pharmaceutical products. The lowest a_w at which the vast majority of pathogenic bacteria will grow is about 0.91. The only exception to this is *Staphylococcus aureus*, which will grow at a water activity of 0.86 under aerobic conditions. The minimum water activity level for growth of molds and yeast is 0.70 and is lower than that for bacteria. The lowest level for any microbial growth is 0.61.

Microorganisms require a certain amount of "free" water to support growth (Table 2). Control of the water activity in a pharmaceutical product can be used to inhibit microbial growth. Water activity controls all aspects of microbial growth. Table 2 lists the minimum water activity level for growth of different microorganisms. At water activity levels above minimal growth limits, water activity lengthens the lag phase, lowers the log growth phase, and reduces the stationary phase number of organisms. If the microorganism produces a toxin, then the toxin production will stop at a higher water activity level than growth inhibition. Low water activity also prevents spore germination if spores are present in the product. Water activity is not a kill step. Some organisms can survive for a period of time at lower water activity levels. These organisms are not actively growing, but are waiting for conditions to change (i.e. increased a_w). Microorganisms do die at slow rates at the lower water activity levels. Thus, it is important to know or control the water activity level of pharmaceuticals.

Reduced water activity will greatly assist in the prevention of microbial contamination of pharmaceutical products, and the formulation, manufacturing, and test-

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Table 1. Key water activity papers for pharmaceuticals

Author	Year	Title	Citation
USP	2006	<1112> Application of water activity determination to nonsterile pharmaceutical products.	United States Pharmacopeia-National Formulary (USP 29 –NF 24, 2nd Supplement), Washington, D.C. p. 3802-3803.
Fontana, A.J.	2005	Sample preparation for water activity analysis.	Pharmaceutical Formulation and Quality 7(4):66-68.
Fontana, A.J. and J. Mumford	2005	Incorrect water measurements costly; water activity is key to pharmaceutical safety and quality.	Pharmaceutical Formulation and Quality 7(6):63-66.
Grant, W.D.	2004	Life at low water activity.	Philosophical Transactions of the Royal Society, London, B 359:1249-1267.
Scott, V.N., R.S. Clavero, and J.A. Troller.	2001	Measurement of water activity (a_w), acidity, and brix.	*In* F.P. Downes, and K. Ito (ed.) Compendium of Methods for the Microbiological Examination of Foods. American Public Health Association, Washington, D.C. p. 649-651.
Enigl, D.C.	2001	Pharmaceutical stability testing using water activity.	European Pharmaceutical Review 6:46-49.
Werner, D.	2000	Water activity an underestimated parameter in pharmaceutical quality control.	Pharmeuropa 12:373-375.
Enigl, D.C.	1999	Creating 'Natural' preservative systems by controlling water activity.	Pharmaceutical Formulation & Quality 3 (5):29-34.
Friedel, R.R.	1999	The application of water activity measurement to microbiological attributes testing of raw materials used in the manufacture of nonsterile pharmaceutical products.	Pharmacopeial Forum 25(5):8974-8981.
Friedel, R.R. and A.M. Cundell.	1998	The application of water activity measurement to the microbiological attributes testing of nonsterile over-the-counter drug products.	Pharmacopeial Forum 24(2):6087-6090.
Enigl, D.C. and K.M. Sorrels.	1997	Water Activity and Self-Preserving Formulas.	*In* J.J.Kabara, and D.S.Orth (ed.) Preservative-Free and Self-Preserving Cosmetics and Drugs: Principles and Practice. Marcel Dekker, p. 45-73.

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ing of non-sterile dosage forms should reflect this parameter. When formulating drug products, the water activity should be evaluated so that the product may be self-preserving.

To lower water activity of a product, one can remove water, add ingredients, or lower the temperature. Adding ingredients such as salt, sugars, glycols, glycerin or amino acids will result in a formulation with a lower water activity that discourages the proliferation of microorganisms in the product. These added ingredients cause some of the "free" water to be "bound" and thus unavailable to the microorganisms for growth. However, there is a limit to how many of these additives one can add before it effects the taste and texture of the product.

Since different products will have different concentrations of water activity reducing ingredients and different amounts of water, each product type will have a unique water activity. Table 3 lists the water activity values or ranges of common pharmaceutical and OTC drug products.

Conclusion

Table 3 can be used to establish a microbial limit testing strategies for typical pharmaceutical and OTC drug products based on water activity. Pharmaceutical drug products with water activities well below 0.75, i.e., direct compression tablets, liquid-filled capsules, nonaqueous liquid products, ointments, and other listed in Table 3, would be excellent candidates for reduced microbial limit testing. This is especially true when pharmaceutical products are made from ingredients of good microbial quality, in manufacturing environments that do not foster microbial contamination, by processes that inherently reduce the microbial content, and in manufacturing sites that have an established testing history of low bioburden associated with their products.

References:

1. Decagon Devices in-house testing, Pullman Washington. a_w values were obtained using Decagon AquaLab Water Activity Meters Series 3TE (chilled mirror).
2. Labuza TP. 1993. Water activity: theory, management, and applications. AACC Water Activity Course. February 16-19, 1993, St Paul, MN.
3. Friedel RR and Cundell AM. 1998. The application of water activity measurement to the microbiological attributes testing of non-sterile over-the-counter drug products. *Pharmacopeial Forum* 24:6087-6090.

The paper is adapted from a poster presented at the PDA's 2006 Annual Meeting from April 24 - 28, 2006 in Anaheim, California.

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Internet Address	Description
http://jpdb.nihs.go.jp/jp14e/	English Version of the Japanese Pharmacopoeia, Fourteenth Edition. When and if any discrepancy arises between the Japanese original and its English translation, the former is authentic.
http://www.pheur.org/site/page_601.php	Complete list of slides and presentations from the conference "New Microbiology Chapters of the European Pharmacopoeia" held October 2-3, 2006 in Strasbourg, France
If you have found an Internet site that contains information of relevance to pharmaceutical microbiology, please let us know.	

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Table 2. Minimum Water Activity Level for Growth

Microorganism	Minimum A_w for Growth
Pseudomonas aeruginosa *Clostridium botulinum,* Type E	0.97
Bacillus cereus *Clostridium botulinum,* Type A, B *Escherichia coli* *Salmonella spp.* *Clostridium perfringens* *Burkholderia cepacia* *Klebsiella* *Lactobacillus viridescens* *Pseudomonas aeruginosa*	0.95
Enterobacter aerogenes *Pseudomonas fluorescens*	0.94
Micrococcus lysodekticus *Rhyzopus nigricans*	0.93
Listeria monocytogenes *Mucor plumbeus* *Rhodotorula mucilaninosa*	0.92
Serratia marcesens *Plesiomonas shigelloides* *Shigella spp.* *Vibrio chlorea; V. parahaemolyticus* *Yersina enterocolitica; Y. pseudotuberculosis* *Aeromonas caviae; A. hydrophilia; A. sobria*	0.91
Bacillus subtilis *Staphylococcus aureus* (anaerobic) *Saccharomyces cerevisiae*	0.90
Candida spp	0.88
Staphylococcus aureus (aerobic)	0.87
Paecilomyces variotti	0.84
Penicillium chrysogenum	0.83
Aspergillus fumigatus	0.82
Penicillium glabrum	0.81
Aspergillus flavus	0.78
Aspergillus niger	0.77
Halobacterium halobium (halophilic bacterium)	0.75
Zygosachharomyces rouxii (osmophilic yeast)	0.62
Xeromyces bisporus (xerophilic fungi)	0.61
No Microbial Proliferation	<0.60

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Table 3. Water Activity Values of Typical Pharmaceutical and OTC Drug Products

MAIN CATEGORY, Subcategory, Item	**a_w Value or Range**	**Source**
CONSUMER PRODUCTS		
Hair Products		
Hair gel	0.982	1
Shampoo	0.982-0.987	1
Lotions		
Body Cream	0.972-0.983	1
Deodorant gel bar	0.984	1
Lip Balm, topical/oral	0.360	3
Sun blocker	0.940-0.981	1
Soap		
Soap, Creamed	0.567	1
Soap, Regular	0.740-0.757	1
Soap, with glycerin	0.659-0.759	1
Soap, with glycerin and lanolin	0.856	1
Toothpaste		
Toothpaste	0.585-0.984	1

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Open Conference on Compendial Issues
February, 2007

The PMF is hosting an "Open Conference on Compendial Issues" this winter for the membership. The format and purpose of this meeting is somewhat unique.

The compendia play a large role in the activities of the QC laboratory, and our input into their discussions is of enormous benefit to both their deliberations and the quality of the documents that result. In addition to the opportunity to write to the compendia to offer comments, PMF is providing an opportunity for the membership to meet in small groups with representatives from international regulatory agencies to discuss issues relating to laboratory operations (GMP) and the microbiological quality of finished products.

The conference will start with a half-day Plenary session providing background information, and then the attendees will break into smaller groups to participate in discussion format sessions of interaction with the regulatory experts. At the end of the conference, each topic session will be summarized. All attendees will receive a transcript of the proceedings.

This will be the best opportunity you will have to provide input into the new chapters of the compendia, and to help direct further activity and regulatory thinking. Next month the *PMF Newsletter* will provide detail on the conference speakers, organization and registration method.

This Open Conference format compendial meeting has not been offered since 2002, and this is the only conference of its type planned for 2007. The purpose of the meeting is to make your concerns and issues known to those responsible for the standards. Attendance at this conference is estimated to be very large, and will be capped at the capacity of the meeting facility.

Don't Miss this Singular Opportunity!

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Table 3. Water Activity Values of Typical Products (cont)

MAIN CATEGORY, Sub-category, Item	**a_w Value or Range**	**Source**
PHARMACEUTICALS		
Analgesic	0.401	1
Analgesic (gelatin capsules) Liquid	0.530	1
Analgesic (gelatin capsules) Gelatin	0.533	1
Anti-allergic	0.443	1
Antibiotic Pills (cefacilin)	0.441	1
Anti-migraine, Pills	0.386	1
Anti-inflammatory Cream	0.852	1
Anti-inflammatory Ointment	0.975	1
Anti-inflammatory Suspension	0.870	2
Antimicotic Cream	0.950	1
Anti-micotic Powder	0.537	1
Aspirin	0.440	1
Citrobioflavonoide and vitamin C syrup	0.801	1
Cough Drop, Liquid Center	0.400	3
Cough Suppressant	0.890	3
Cough Syrup	0.912-0.965	1
Decongestant/Antihistamine (liquid-filled capsule)	0.450	3
Epileptic Syrup	0.835	1
Lactulose Syrup (laxative)	0.823	1
Laxative	0.927	1
Menstrual Pain, Pills	0.459	1
Mucolitic Elixir	0.904	1
Neurotonic Syrup	0.935	1
Potassium Gluconate, Elixir	0.926	1
Rectal Suppositories	0.290	3
Tonic Syrup	0.950	1
Vaginal Suppositories	0.300	3
Vitamin C Tablets	0.330	1
Vitamin, Multivitamin Tablet	0.300	3

A Conversation with FDA About BAM and "Counting Colonies"

Scott Sutton

Well, the "Counting Colonies" essay drew some response! Thank you all for the encouragement. It is gratifying to find a topic that meets so many needs and is viewed positively. With that sentiment in mind, I want to share a phone call I got from an FDA Laboratory Head.

The Lab Head started off with many compliments about the article. I, of course, became very worried at this point. Once the compliments were completed, he moved to the point of the phone call which was my discussion of the way FDA's Bacterial Analytical Manual (BAM) handled colony counts above the upper limit. I think I wrote that the BAM method might not be superior to guessing (see box). He wanted to discuss the point with me. (oh boy!)

He reminded me that this method (found at http://www.cfsan.fda.gov/~ebam/bam-3.html#-International) was specifically for foods, not for pharmaceutical microbiology, medical device microbiology, or personal products microbiology. I replied that this argument was a bit esoteric and that most practitioners use the best science they can find – much of it from food microbiology. Acknowledging the point, he went on to inform me that I had taken the passage out of context and so had presented it incorrectly.

The Lab Head explained that the BAM Chapter 3 "Aerobic Plate Count" is a complete chapter included to complement and clarify later chapters in the manual. In subsequent chapters the BAM describes the analysis for the testing of bioburden in food and cosmetic products. Routinely the product under test in an FDA field laboratory is serially diluted from 10^{-1} to 10^{-6} because of the anticipated high bioburden levels. This dilution series was critical, in his opinion. If the 10^{-6} plates have more than 250 colonies each on them, then an estimate of the counts is sufficient. He repeated his point - an estimate of the count is sufficient to determine how badly the product (food) is overly-contaminated at this 10^{-6} dilution. By discussing only the plate count estimation mechanism without noting the need to perform an adequate range of product dilutions, I had incorrectly created the impression that the BAM was supportive of doing inadequate dilutions (i.e. 10^{-1}, 10^{-2}), then estimating the number at lower product dilutions. That is not the case and should not be tolerated in industry laboratories if pharmaceutical components or finished products with potentially high bioburden are not diluted adequately. He went on to state that under normal conditions, failure to adequately dilute the sample in order to provide colony numbers in the countable range was sufficient reason to invalidate that portion of a test due to lab error. Accurate counts from bioburden assays are important data for the evaluation of potential source of contamination on those products and helpful during the risk assessment process to determine potential harm to the product/patient. Accurate bioburden counts give insights for the level of indigenous microbial challenge against sterilization processes that are based on microbial levels found in the pre sterilization material. And last, an accurate bioburden count aids in the assessment of the effectiveness of the sanitization/disinfection process used in the manufacturing of those drugs. An underestimation of the true bioburden count can come back and bite you during an FDA inspection. The minimal time and cost of not performing the extra product dilution is not worth the regulatory grief.

I agree with the FDA Lab Head that my presentation of the method was incomplete as I did not present it in context of the required dilution series for the referenced test. This error was inadvertent and I hope that this notice corrects any misunderstanding that I may have created. My current understanding is that if this BAM method is referenced, the dilution series *must* extend to at least a 10^{-4} dilution before the estimation mechanism can be invoked. As always, the SOP should have a solid justification for have a solid justification for this practice.

Excerpt from last month's article:

"Upper Limit

The upper limit of plate counts is dependent on a number of factors. . .

TNTC can be reported out several ways. ASTM (7) recommends reporting this out as >"upper limit". For example, a 1:10 dilution with more than 200 CFU on a spread plate would be reported as '>2,000 CFU/mL (or gram)'. FDA's BAM recommends counting the colonies from the dilution with plates giving counts closest to 250, counting a portion of the plate, estimating the total number and then using that number as the Estimated Aerobic Count. It is not clear to the author how this is greatly superior to guessing. In my opinion this is an invalid plating and needs to be done correctly at a later date (note I am strenuously avoiding the use of the word *retest*. This result invalidates the plating and therefore the test was not performed correctly.) I know this is a hardship to the lab, who were trying to reduce the plating load initially by not plating out sufficient dilutions. However, making a mistake initially is not a reasonable excuse to avoid doing it correctly after the mistake is recognized. If the lab wishes to use this 'estimated count' it should, at a minimum, have it clearly described in their 'counting CFU' SOP with a rationale as to when the plate counts are not critical and can be estimated in this fashion. . ."

Upcoming Events

October

- 12th - 13th **PMF Fall Forum**
  Location: Rochester, NY
  Website: http://www.highpeaks.us/2006/PMF.Fall.Forum/
- 25th CTFA Microbiology Seminar
  Location: Newark, NJ
  Website: www.ctfa.org
- 27th - 28th **PDA Microbiology Meeting**
  Location: Bethesda, MD
  Website: http://www.pda.org/microbiology2006/

November

- November 29th - 30th **15th Annual PharMIG Meeting**
  Location: Nottingham Belfry Hotel
  Contact: Maxine Moorey (maxine@pharmig.org.uk)
- November 29th - 30th **Cleanroom Design, Construction, Validation, Maintenance, Monitoring** (Microrite)
  Location: Crowne Plaza, Burlingame
  Website: **Brochure**

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. 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: 1,753
Number of Countries: 63
Number of Messages Last Month: 209

PSDGList (Pharma Stability Discussion Group):
Number of Subscribers: 859
Number of Countries: 21

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

The 2006 PMF Bacterial Endotoxin Summit – San Francisco

The 2006 PMF Bacterial Endotoxin Summit (BES) was enthusiastically received by everyone in attendance. Conference materials that included a complete copy of the presentations as well as a copy of the book "Endotoxins: Pyrogens, LAL Testing, and Depyrogenation (Drugs and Pharmaceutical Science, Vol. 111)" by Kevin L. Williams (ed) Marcel Dekker Publ. (2001) for future review.

Moderator Karen McCullough did a fantastic job of putting together an outstanding faculty for this event. Having received numerous requests to run the conference again this year (PMF's first BES was held in Philadelphia in February) we were able to bring nearly all of our original presenters together to San Francisco, and presented a well-rounded update on the bacterial endotoxin test.

Karen McCullough of Roche Molecular Systems moderated the conference, providing commentary and perspective from her years of experience both from a corporate setting and as a consultant.

Michael Dawson of Associates of Cape Cod gave an industry perspective on compliance documents and on setting specifications for finished products and raw materials.

Ronald Berzofsky, Ph.D. of GeneChoice provided context to the discussion with a strong overview of the science underlying the BET and depyrogenation considerations.

Alan Baines of Cambrex Bio Science Walkersville, Inc. provided a background on the gel clot method and discussed methods of determining inhibition and enhancement.

We would like to thank John Dubczak of Charles River Laboratories for filling in at the last minute for Foster Jordan who was unable to attend. John described methods for setting endotoxin limits and determining MVD and MVC.

Robert Mello, Ph.D. of FDA provided a perspective on regulatory and compliance initiatives under consideration.

Speakers (L-R): Michael Dawson, Alain Baines, Ron Berzofsky, John Dubzak, Karen McCullough, Robert Mello

All speakers provided commentary throughout the conference (frequently on each other's topics!) and were accessible at breaks and during the reception for further conversation. The meeting ended with each speaker providing a glimpse of what was new in the industry from their perspective. One of the strengths of the small conference format favored by the PMF is the opportunity for discussion throughout the course of the day, not only among the presenters but with the attendees as well.

The reception was also a big hit. A fine social gathering, it provided an opportunity for the attendees to spend some quality time with the vendor-exhibitors, and it was just a fun evening and a great networking and shop-talk time for everyone.

Comments received on the event:

- "Great balance between lecture and group activities. I was pleased that exhibitors were given time to present…"
- "Really enjoyed - informative, interesting, relaxed and pleasant…"
- "Overall I enjoyed the conference. The speakers were good and accessible…"
- "Please include the regulations with seminar packet. Great Job!"
- "HPA staff is very professional. They were willing to go out of their way to assist me."
- "Truly enjoyed and was very informative. Please keep the PMFList going!"
- "This was a strong seminar. Presentations were, of course, different in style but of excellent quality."

Continuous improvement is a hallmark of the group. Comments from earlier conferences were incorporated into this one - "break out" sessions to work on GMP problems and a Day 1 Round Table are examples of these improvements. Suggestions for improvement from this conference included:

- "Would like to see new products earlier in the two day summit"
- "A practical session would also be a good idea"
- " Food-reception-great! Too bad local folks went home, It was a nice way to interact with everyone."

Clearly this conference was a strong addition to the year, and one that PMF was glad to be able to bring it to the industry. We would like to thank the organizers – High Peaks Associates (http://www.highpeaks.us) for the fantastic job they did again "behind the scenes" both in the preparation and execution of the conference leaving the scientists able to concentrate on the content, rather than the machinery, of the conference.

PMF is planning to schedule another BES conference in 2007 – stay tuned!