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PDA Letter

Volume XLI • Issue #7

July/August 2005

In This Issue...

FDA's Aseptic Guidance: Training and Implementation One Year Later

As the one-year anniversary of the final U.S. FDA aseptic processing guidance approaches, implementation and training by the agency and manufacturers are well underway.

A discussion with key industry leaders reveals that the guidance is meeting industry needs, implementation is at an advanced stage and the document contains few surprises, thanks largely to the extensive and unprecedented public outreach leading up to the final guidance. In talking with FDA, it is clear that the agency is planning a comprehensive program for investigator training, and that the guidance and the extensive public outreach have produced a notable decline in the number of industry queries about aseptic processing and has contributed to the recent fall in the number of recalls attributed to the lack of the assurance of sterility. All agree that the guidance might be the most successful regulatory document produced to date.

Contributing to Part 1 of this article (beginning page 14) were **Richard Johnson,** Director, Quality Center of Excellence - Drugs, Abbott Laboratories, and **Martin Van Trieste,** VP, Worldwide Quality, Bayer - Biologicals. The two experts made substantial contributions to the development of the aseptic guidance, serving on both the PDA Task Force that drafted the 2002 PDA "Points to Consider on Aseptic Processing" and the Product Quality Research Institute working group that produced a lengthy commentary to the FDA aseptic processing "concept paper." Their contributions continued following the publication of the guidance as participants on the program planning committee that developed PDA's aseptic processing guidance training workshops.

In Part 2 (beginning page 18), **Rick Friedman,** Team Leader - Guidance and Policy, Office of Compliance, FDA Center for Drug Evaluation and Research, talks about the agency's training efforts, international harmonization of aseptic processing standards and the next important document his policy development team is tackling.

Part 3 (beginning page 22) includes excerpts from a recent PDA audio conference on the aseptic guidance.

continued on page 14

PDA Parenteral Drug Association

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PDA
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2005 PDA Visual Inspection Forum

Overview

Visual inspection continues to be an important element of the manufacturing process and the quality assurance of injectable products. This two-day interactive forum will closely examine:

- ✓ New developments in the field of visual inspection, including contributions to a basic understanding of the sampling and inspection process
- ✓ Preparation and use of inspection standards
- ✓ Practical aspects of manual and automated methods and the regulatory and compendial requirements that govern them

The forum will also provide a unique opportunity to discuss your inspection challenges with the experts.

Who Should Attend

This conference will be of value to mid- and senior-level professionals with specific interest in visual inspection in the areas of:

- ✓ **Manufacturing**
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- ✓ **Parenteral Development**

What You Will Learn

PDA has organized this forum to provide the most current information for you to use immediately in your plant by enabling you to:

- Understand particulate inspection methods and equipment
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- Learn about compendial requirements and regulatory trends
- Examine techniques to validate visual inspection methods
- Find out how to identify and control foreign material

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For more information and to register online visit:

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Coming Next Month...
Viral & TSE Safety

July & August's Top 10 Bestsellers

From the PDA Publications Store

Technology Transfer: An International Good Practice Guide for Pharmaceutical and Allied Industries

This publication serves as a comprehensive overview and guide to the technology transfer process for pharmaceutical drug substance and products and the corresponding analytical methods and tests from R&D to production.

Item No. 17218

Check out these titles and more from the PDA Publications Store.

1. **Technology Transfer: An International Good Practice Guide for Pharmaceutical and Allied Industries, by Mark Gibson**
   Item No. 17218, PDA Member: $200; Nonmember: $249
2. **Filtration Handbook: Liquids, by Maik W. Jornitz and Theodore H. Meltzer**
   Item No. 17208, PDA Member: $185; Nonmember: $229
3. **Validation of Steam Sterilization Cycles, PDA Technical Report No. 1**
   Item No. 01001, PDA Member: $75; Nonmember: $270
4. **Good Practice and Compliance for Electronic Records and Signatures – Part 3: Models for Systems Implementation and Evolution**
   Item No. 13003, PDA Member: $95; Nonmember: $190
5. **Laboratory Validation: A Practitioner's Guide, edited by Jeanne Moldenhauer**
   Item No. 17201, PDA Member: $250; Nonmember: $309
6. **Good Practice and Compliance for Electronic Records and Signatures – Part 2: Complying with 21 CFR Part 11**
   Item No. 19002, PDA Member: $95; Nonmember: $190
7. **Filtration Handbook: Air and Gas, by Maik W. Jornitz and Theodore H. Meltzer**
   Item No. 17209, PDA Member: $185; Nonmember: $229
8. **Microbiology in Pharmaceutical Manufacturing, by Richard Prince**
   Item No. 17185, PDA Member: $240; Nonmember: $299
9. **Validation of Dry Heat Processes Used for Sterilization and Depyrogenation, PDA Technical Report No. 3**
   Item No. 01003, PDA Member: $75; Nonmember $270
10. **Steam Sterilization: A Practitioner's Guide, by Jeanne Moldenhauer**
    Item No. 17183, PDA Member: $215; Nonmember: $269

Featured Titles

Quality Assurance: A Practitioner's Guide
Item No. 17212

Pharmaceutical Quality
Edited by Richard Prince
Item No. 17207

PDA Archive on CD-ROM
Item No. 01101

2004 Update
Item No. 01002

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PDA Embraces Roots as *Parenteral Drug Association*

In 1946, Arthur D. Herrick, a New York attorney specializing in drug-related affairs recognized that the emerging field of injectable (parenteral) drug dosage forms needed new, unique and distinctive technology for manufacturing and quality control. His vision was shared by many of his industry colleagues, and so the Parenteral Drug Association (PDA) was formed.

With PDA's 60th anniversary on the horizon, the Strategic Planning Committee has undertaken the initiative of reassessing the Association's name and logo—the cornerstones of our identity.

As a result, the committee has recommended and received board approval to:

1) Emphasize name "Parenteral Drug Association," and promote the association's identity as such ("PDA" for short)
2) Revise the logo to include "Parenteral Drug Association"

Over the past few years PDA has avoided using its formal name, "Parenteral Drug Association," because the Association has broadened its reach and expertise beyond parenteral drug dosage forms alone. Parenterals are the heart and soul of PDA. The focus on the science, technology and regulations affecting the manufacture and QC of parenteral drugs has relevance to the manufacture of many other dosage forms.

Even when our membership's interests take us to new areas of science and technology in the future, we remain an organization with a foundation based on the science of sterile production and QC, and we will continue to take pride in our name, the "Parenteral Drug Association."

To further emphasize our name, the committee has also proposed that the text within the PDA logo be changed to "Parenteral Drug Association." The revision more clearly proclaims our identity and our roots. As you will see on the front cover, the new logo seems as if it has been with us all along.

Six decades since PDA's formation, the Association and the professional community in which it operates are dramatically different than they were in the beginning. Many distinguished scientists have followed Mr. Herrick and have added to the reputation of our organization. PDA has grown and remained relevant because of its dedicated membership and its leadership, including such past chairs and honorary members as: **Kirsch, Avis, Carleton** and **Personeous** in the '60s and '70s; **Cole, Lachman, Pflug** and **Kieffer** in the '80s; and **Kemper** and **Korczynski** in the 90s. (Of course many others deserve formal recognition, but space does not permit.)

Our central purpose remains unchanged from1946—*Connecting People, Science and Regulation* as the Parenteral Drug Association.

Member Volunteer Opportunities

The PDA Audit Committee.

PDA's Board of Directors is seeking new members to serve on the Audit/Finance Committee to ensure that PDA maintains the highest level of integrity in its financial governance and provides proper oversight to ensure the security of its financial reserves. Though associations are not subject to the requirements of the Sarbanes-Oxley Act, PDA has chosen to proactively conform with good audit oversight practices in anticipation of future regulation affecting not-for-profit organizations.

To comply with such practices, the Audit Committee is seeking PDA members who have significant accounting or related financial management experience. This requirement can be met by someone who has past experience in finance or accounting with or other comparable experience or background which would result in financial acumen. The best candidate will have had experience as a CEO, CFO or senior officer of a corporation or operating division with profit and loss responsibilities.

For additional information or to express your interest in this volunteer opportunity, please contact Lance Hoboy, VP, Finance & Strategic Planning at +1 (301) 656-5900 (ext. 114) or hoboy@pda.org.

Establishing a Meaningful Environmental Monitoring Program

Jeanne Moldenhauer, PhD, Vectech Pharmaceutical Consultants, and Editor, *Environmental Monitoring*

An appropriate microbiological monitoring program should be established and used in production and laboratory facilities for both sterile and non-sterile products. The complexity and frequency of testing may vary depending upon the type of product, the type of sterilization process, e.g., terminal sterilization versus aseptic filling, and even within processes, e.g., overkill sterilization cycles versus combined biological indicator bioburden-based cycles and absolute bioburden-based cycles. Aseptic processing is the most stringent application of these principles.

The established monitoring program should include definition of many characteristics, including, for example:

- Frequency of monitoring
- Type of monitoring
- Sites monitored
- Alert and action level requirements
- Precise descriptions of the actions to be taken when alert and action levels are exceeded.

Once a program is established, it should be followed. Defining a program that cannot be maintained is inappropriate. The established program should be *meaningful, manageable and defendable.*

What is a Meaningful Monitoring Program?

Collecting environmental monitoring data is easy. There are a large number of vendors who will provide systems that collect data. Generating copious amounts of data printed out in a tabular format, not separated by sample site or sample method, provides little useful information unless the raw data is "translated" or "formatted" into a form that makes it easy to interpret. For example, in a Grade A/ISO 8/Class 100 room, where the Action levels are 1 cfu (normal count is zero), it is difficult to graphically represent the data. However, it may be meaningful to determine the incident frequency rate (i.e., how many days of zero counts are typically seen before having a count of one). It is important that the data collected be reported in a way that is useful and conveys what is happening in the program.

Jeanne Moldenhauer signs a book for a fan

One can also collect data from monitoring sites that may not be representative of the process monitored, e.g., numerous ceiling samples, but no samples from the actual work area. It is important to ensure that the sampling sites used in the program are scientifically based, reflect the current regulatory requirements and represent the actual process being monitored.

Another component of a meaningful environmental control program is ensuring that the program can identify what is known about the environment, eliminates those things that have never occurred, incorporates the capabilities of the system, and ensures that the laboratory testing simulates what is actually occurring in the production environment.

What is a Manageable Environmental Monitoring Program?

Establishing a program that requires 18,000 samples/month may be really great, but if it takes four months to trend the data, it probably is not a manageable system since by the time the data is available for review, so much has changed that the data is worthless. Another difficult situation is to collect a lot of data from sites that don't provide useful information.

If a company has 300 sample sites that are tested daily, the amount of information required for identification of each site could make it difficult to really analyze the data if all of the data is trended manually.

The ideal situation is to have data that can be collected within the staffing, laboratory and cost constraints of the facility, and have reporting and review structures to obtain the data in a timely fashion that allows for appropriate corrective action, if necessary.

Defendable

The program established and implemented must be defendable. That means that the procedures used are scientifically sound and justified, it meets the applicable regulatory requirements, and is appropriate to produce a product that is safe for the end-user.

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Recent Sci-Tech Discussions: Storage of Cartridge Filters, Bioburden Limits

The following unedited remarks are taken from PDA's Pharmaceutical Sci-Tech Discussion Group, an online forum that serves as a platform for exchanging practical, and sometimes theoretical, ideas within the context of some of the most challenging issues confronting the pharmaceutical industry. Join at www.pharmweb.net/pwmirror/pwq/pharmwebq2.html.

Storage of cartridge filters

We use 5 & 10 inch cartridge filters for our products. We use each cartridge four times. Can you suggest some method acceptable to regulatory authorities, for the storage of cartridge filter before reusing it?

Respondent 1

The first question which comes into my mind what is the filter used for? I believe that will be critical to gain any regulatory acceptance of the re-use of filters.

In respect to storage, I have seen most of the people, when reusing filters, which is very rare, that the filter is extensively flushed and then autoclaved with an autoclave wrap and appropriately package. Certainly chemical treatment is also possible, for example the storage in a solvent/water mix. In any case whatever method is utilized it needs to be fully validated. First, the flush has to show that no product residue remains in the filter, the flush after the autoclaving cycle should show no elevated endotoxin levels, the storage itself has to show that it is not compromised over a long term. To summarize, the validation efforts hopefully are justified by sufficient savings of reusing the filter.

Respondent 2

There is insufficient data to answer your question as some of it depends on whether your filter is targeting Sterile filtration or otherwise.

A simplistic answer to this is: Flush with 'sufficient quantity' of WFI, drain completely, Wrap in a sterilization pouch, autoclave at 121°C for 30 minutes. Store in Clean area ready for use.

I can almost see the rest of the forum sit up: How do you know the filter is used on Water soluble medium, can you guarantee moisture free sterilized product to ensure endotoxin not forming. Where are you going to store it, what validated pattern this will fit into, what is the hold time permissible after sterilization, what is the particulate flush position...the list of questions can be endless.

I suggest you contact you filter manufacturer and down size the cartridge to a capsule if flow rate is not an issue and discard after every use. If cost is a major constraint, even consider going back to the traditional disk filters (192 mm) if differential pressures are not too great.

Avoid walking down this path of "reuse" especially in aseptic process.

Bioburden limits

We have validated our bioburden limits before and after sterile filtration of our liquid injection. Our bioburden limits before filtration is 1 cfu/10 ml. Though it never happened but if our bioburden limits before filtration exceeds the limit of 1 cfu/10 ml than what steps we should take before proceeding for sterile filtration and filling. Please clarify according to regulatory requirement .

Respondent 1

The European guidance on bioburden includes the following:

- raw materials other than water: up to 100 cfu/g or ml (although exceptions might be argued for strong acids and alkalis)
- water: 1 cfu/100 ml
- prefiltration solutions: 10 cfu/100 ml.

You need to have adequate data to validate the capacity of the sterilization filter(s)—it is expected that there will be two such filters in series.

The validation studies usually employ a challenge of 107 cfu per cm^2 of filter area. Consideration needs to be given to the challenge organism and the menstruum in which it is placed (which should be as close as possible to the product being filtered, but without any antibacterial agents). ➤

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You will know the volume of product that you will pass through the filter. Your will know the bioburden (and the type of organisms present). You need to calculate the safety factor in removal of bioburden. It might be necessary to negotiate on an acceptable safety margin.

Respondent 2

When you establish limits of CFU before and after sterile filtration we take few things into consideration:

- CIP validation
- SIP validation
- Area cleaning procedures
- Environmental conditions (EMP) validation
- Procedure of sterile filtration and its validation

Based on the data from above mentioned sources and its engineering we land up with some upper limit and Lower limit, however in the present case you have established 1 cfu/10 ml. My suggestion to you is please see if you can fix upper and lower limits secondly if cfu increase you must Investigate the above mentioned points.

Respondent 3

The CPMP guideline (CPMP-QWP-486-95) quotes a maximum of 10 cfu/100 ml. If this maximum is exceeded, one has to utilize a prefilter to reduce the bioburden level, preferably another 0.2 micron rated filter. Even when one considers that this guideline does not make sense whatsoever, one has to fulfill the regulatory requirement, if one distributes within Europe. The good news is one does not necessarily need to utilize redundant 0.2 micron filtration, but could use a filter with a coarser retention rating, which allows for higher flow rates and sufficient protection. Nevertheless, this prefiltration step requires to be validated as the final filtration step.

One has to create the evidence that the filters work with the process environment, with the product contact under process conditions. These are routine tests and need to be performed for any sterilizing filtration step.

The guideline though quotes that when two 0.2 micron filters are used, validation will be reduce. That is not true, as one has to show that filter one does its job as well as filter two. When two 0.2 micron filters are used, the question of integrity testing becomes complex, when to integrity test, how without compromising the filtrate side of filter 1 and what happens when one filter fails. Additionally there have been studies which showed that a second 0.2 micron filter does not enhance the safety, as when filter 1 is penetrated, filter 2 will also be penetrated. Redundant filtration is rather an insurance level than a safety enhancement. Process validation is the key for both, insurance and safety.

I enclosed a paper published discussing the controversial guideline Mentioned: "Considerations in Sterile Filtration. Part II: The Sterilizing Filter and Its Organism Challenge: A Critique of Regulatory Standards," M.W. Jornitz, J.E. Akers, J.P. Agalloco, R.E. Madsen and T.H. Meltzer, *PDA Journal of Pharmaceutical Science and Technology*, Vol. 57, No. 2.

Establishing a Meaningful Environmental Monitoring Program, continued from page 7

Applicability

Environmental monitoring programs are appropriate for manufacturing of sterile products and non-sterile products. The most stringent application of these procedures is for sterile products manufactured by aseptic processing, while less stringent procedures may be appropriately employed for terminally sterilized products, and even less stringent procedures for non-sterile products.

The Book

The chapters in ***Environmental Monitoring*** have been written by a variety of authors with extensive experience and should provide practical guidance on how to establish and maintain a system that will be meaningful, manageable and defendable.

Jeanne Moldenhauer, PhD, is a consultant with Vectech Pharmaceutical Consultants, Inc. She has over 25 years of experience in sterile process validation, regulatory affairs and microbiology. She is the leader of PDA's Microbiology and Environmental Monitoring Interest Group and a member of PDA's Scientific Advisory Board. She also chairs the Rapid Microbiology User's Group.

USP Analytical Microbiology Expert Committee Ramps Up Efforts

The U.S. Pharmacopeia's Analytical Microbiology Committee of Experts had a very productive five-year revision cycle, 2000-2005.

Several revised USP Chapters (less than 1000), Information Chapters (1000-1999) and chapters devoted to nutritional supplements (2000+) were revised or established during the five-year cycle. In addition, a number of Stimuli Articles were published in the USP *Pharmacopeial Forum*.

The group's efforts are well-documented in an article in the May-June 2005 *PDA Journal for Pharmaceutical Science and Technology* (vol. 59, no. 3) by Scott Sutton, Joseph Knapp and David Porter.

All of the members of USP's AMC Expert Committee are also PDA members.

Below are two tables included in the article that outline the USP Chapters and Stimuli Articles the group worked on during the 2000-2004 cycle.

Table I. Summary of Activity

	Pharmacopeial Preview	In-Process Revision	Finalized	Total
<51> Antimicrobial Preservatives – Effectiveness			1	1
<55> Biological Indicators – Resistance Performance Tests		2		2
<61> Microbial Enumeration Tests		2		2
<62> Microbial Procedures for Absence of Objectionable Microorganisms		1		1
<71> Sterility Tests		1	1	2
<85> Bacterial Endotoxins Tests			1	1
<1035> Biological Indicators for Sterilization		1	1	2
<1072> Disinfectants and Antiseptics	1	2		3
<1111> Microbiological Attributes of Nonsterile Pharmacopeial Articles		2		2
<1112> Application of Water Activity Determination to Nonsterile Pharmaceutical Products	1	1		2
<1116> Microbiological Evaluation of Clean Rooms and Other Controlled Environments		1		1
<1117> Microbiological Best Laboratory Practices	1	1		2
<1207> Sterile Product Packaging – Integrity Evaluation		1	1	2
<1208> Sterility Testing – Validation of Isolator Systems		2		2
<1209> Sterilization - Chemical and Physicochemical Indicators and Integrators		1	1	2
<1211> Sterilization and Sterility Assurance of Compendial Articles		1		1
<1222> Terminally Sterilized Pharmaceutical Products - Parametric Release		2	1	3
<1223> Validation of Alternative Microbiological Methods	1	1		2
<1227> Validation of Microbial Recovery from Pharmacopeial Articles				0
<2021> Microbial Enumeration Tests – Nutritional and Dietary Articles		1		1
<2022> Microbiological Procedures for Absence of Specified Microorganisms in Nutritional and Dietary Supplements		1	1	1
<2023> Microbiological Attributes of Nonsterile Nutritional and Dietary Articles		1	1	2

Table II. Stimuli Articles Published

Stimuli Article	Reference
The FDA Process Analytical Technology (PAT) Initiative – an Alternative Pharmaceutical Manufacturing Practice (APMP) USP Project Team 18 – Process Analytical Technology	**30** (6):2254-2264 Nov-Dec 2004
The USP Perspective to Minimize the Potential Risk of TSE Infectivity in Bovine-Derived Articles Used in the Manufacture of Medical Products. Deveau, I, et al	**30** (5):1911-1921 Sept-Oct 2004
Sterilizing Filtration with Microporous Membranes. Jornitz, MW and TH Meltzer	**30** (5):1903-1910 Sept-Oct 2004
Microbial Identification in the Pharmaceutical Industry. Sutton, SVW and AM Cundell	**30** (5):1884-1894 Sept-Oct 2004
Significant Digits and Rounding Torbeck, L	**30** (3):1090-1095 May-June 2004
The Role of Rapid Microbiological Methods Within the Process Analytical Technology Initiative. Singer, DC and AM Cundell	**29** (6):2109-2113. Nov-Dec 2003
Review of the Media Section and Incubation Conditions for the Compendial Sterility and Microbial Limit Tests. Cundell, AM	**28** (6):2034-2041 Nov-Dec 2002
Comparison of Microbiological Testing Practices In Clinical, Food, Water and Pharmaceutical Microbiology In Relation to the Microbiological Attributes of Nutritional and Dietary Supplements. Cundell, AM	**28** (3):964-985 May-Jun 2002
An Alternative Methodology for the General Test Chapter Microbial Limit Tests <61>. Casey, W et al	**27** (1):2046-2050 Jan-Feb 2001
The Effects Of Antimicrobial Preservatives On Organisms Derived From Fresh Versus Frozen Cultures. H. Muth, and W. Casey	**26** (2):519 Mar-Apr 2000

Key to Tables I and II

In Table I, the authors indicate the number of times a chapter was published in the ***Pharmaceutical Forum*** (PF), either as a Pharmaceutical Preview, an In-Process Revision or a finalized chapter between 2000 and 2005. For example, Microbial Enumeration Tests, <61>, was published twice as an In-Process Revision. The article in the PDA Journal gives a complete explanation for each chapter.

In Table II, the authors list Stimuli Articles published in the 2000-2005 revision cycle related to their work with references to the PF.

USP Analytical Microbiology Expert Committee

James Akers, PhD, Kennedy and Associates

Anthony Cundell, PhD, Consultant

Edward Fitzgerald, PhD, Fitzgerald Consulting

Dennis Guilfoyle, PhD, U.S. FDA

Joseph Knapp, PhD, University of Pittsburgh School of Pharmacy [Expert Committee Chair]

Michael Korczynski, PhD, Mikkor Enterprises

Robert Lamm, PhD, Savient Pharmaceuticals

Terry Munson, PAREXEL Consulting

David Porter, PhD, USP

Donald Singer, GlaxoSmithKline

Scott Sutton, PhD, Vectech Pharmaceutical Consultants

EDQM Holds First OMCL Information Day

At the invitation of the European Directorate for the Quality of Medicines (EDQM), 300 representatives from 33 countries assisted in the first information day dedicated to the activities of the European Official Control Laboratories of Medicines (OMCL) network. The meeting took place at the University La Sapienza, Rome, May 27, 2005.

The birth of the OMCL network in Strasbourg, France dates back to 1994, under the aegis of the Council of Europe, with the goal to coordinate the administrative, scientific and technical activities of the national control laboratories in all member countries of the European Pharmacopoeia.

Under the extremely complex regulation of medicines, the control of safety, quality and efficacy of medicines is the responsibility of the national authorities of the country that has granted the marketing authorisation application. On the other hand, the responsibility for the organization of the control is collective if it is the European Union who has granted the marketing authorisation for the European market of its member states.

It was the aim of all OMCLs to closely collaborate as laid down by the legislation in the relevant regulations, directives and guidelines. The Network was born with the help of a group of very dedicated and enthusiastic experts. They strongly believed in their project and wanted to make it a daily, routinely based operational centre for the control of medicines in Europe, independent from the manufacturers and based on mutual confidence and work sharing.

Whilst control is important especially for the patients, the OMCL Network is also contributing importantly to the entire system of development, assessment, control and enforcement as it is not a stand alone body, but interacts in close and efficient collaboration with all authorities involved in licensing, supervision, inspection and pharmacovigilance.

The creation of the OMCL network has permitted for the first time a common and harmonised approach with regard to post-marketing surveillance:

- By facilitating the exchanges of know-how between the different national authorities
- By working with national control laboratories from the same quality control assurance base and same level of performance

To ensure the validity of the data and results delivered the OMCL network has developed:

- A Quality Management System of its own based on the ISO standard 17025 for testing laboratories, complemented with their own specific guidelines and has set up a system of Quality Audits and assistance to implement and maintain a high level of QA throughout the Network.
- Regular measurement of technical competence with an intense programme of PTS which is in place for both biological and physico-chemical/pharmaceutical methodologies, indeed 26 biological and 45 physico-chemical have been carried out so far.

Specific activities, such as the Official Control Authority Batch Release for human biologicals, Centrally Authorised Products sampling and testing were installed, based on harmonised and structured procedures. Indeed more than 170 drug products were tested between 1999 and 2004 and in addition 27 different drug substances were included in the programme within the same time period. Other activities are under development for mutually recognized products and immunobiological veterinary medicinal products.

General control activities such as Market Surveillance Study based on screening of the quality available on the European market have also been set up especially for generics and herbal products. To date 25 MSS have been carried out.

The General European OMCL Network (GEON) comprises 85 members (OMCLs) from 32 European countries and associated members such as Australia, Canada and Morocco.

[From an EDQM press release.]

FDA's Aseptic Guidance Part 1: PDA Outreach Aims to Assist Small Firms

It doesn't take a long conversation with Richard Johnson and Martin Van Trieste to learn that participation in the development process for regulatory guidances provides a great opportunity for firms to prepare for policy changes. You also learn that the success of the aseptic guidance is directly linked to the unprecedented public outreach FDA pursued prior to finalizing the document.

PDA: As you know this is an important subject for our membership. The development of this guidance was a real focus of PDA and its members for several years, and a lot of our members were involved with you in the creation of this guidance. We appreciate your willingness to share your thoughts nearly a year after the final guidance published. Can you tell us how far along you are in your implementation efforts for the guidance?

Johnson: Abbott has proactively been evaluating most of the changes based on the draft. Our participation in the process through PDA gave us a good insight into what the final document might look like, so we didn't have to wait for the final document.

Van Trieste: The guidance did not change Bayer's view of cGMPs related to aseptic practices. The basic principles have been well understood, and our procedures were established in accordance with them. The guidance clarified several vague points that were interpreted differently by some in the industry and at FDA. This guidance, however, still allows for interpretation so that solutions can be tailored to a specific situation or to advance technology. On the other hand, in the areas that were contentions in the past, where different interpretations were causing difficulty between some members of industry and the agency, the guidance does a good job of clarifying these areas.

As far as implementation, I think the programs that we had in place at Bayer prior to the new guidance document coming into place were in-line with the spirit and intent of the guidance document.

PDA: We are not really surprised to hear that large companies like yours are already current as far as implementation goes.

Johnson: You know, in these training meetings that we've been having, we have done surveys of the participants. Martin and I are working on an article to publish those results. Apparently, most companies fall into that category [already implementing most of the changes], which surprises me. It tells you that most people were probably reacting to the draft guidance.

Van Trieste: Richard and I, in particular, have been working on this guidance very closely since the mid-1990s. So we were attuned to all of the issues, and we were adjusting our processes and procedures as we were going.

PDA: So the lengthy public outreach period not only contributed to a good guidance, but helped facilitate early implementation among those firms paying attention. What about those who elected to wait for the final guidance?

Van Trieste: That is where the PDA outreach came in to play. PDA did a series of training sessions to try to reach as many companies as we could. That is why we went to Europe. That is why we conducted training in various locations in the United States, especially San Francisco to help a lot of the small biotech companies that needed to be compliant.

PDA: Can you identify any procedures or SOPs that were changed as a result of the guidance?

Johnson: Our media fill procedures have probably been the ones that have seen the most changes.

Van Trieste: The changes we made to our procedures involved wording our documents in a way that is similar to what is in the guidance document. In the past, we had the same intent, and we were doing the same kind of things ultimately requested by the guidance document, but of course, our words were different because we couldn't anticipate the exact language in the final guidance document. We do this because when an investigator comes in, they have a limited amount of time and resources to do their job, and they don't need to learn a different language, a different ➤

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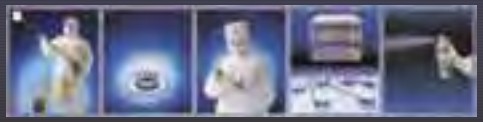

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vocabulary. There is a guidance document that creates a common dictionary for us to use, and it behooves everybody to use those common terms.

But not only that, we added to our documented procedures our logic and rationale for why we do things (what I would call the organizational knowledge). For example, the guidance document might say pick a temperature between 20 and 35 degrees to incubate your media fills, as long as what you pick as your set point stays within ±2.5°. So we have, of course, picked a temperature, but what we did was actually put the rationale for why we picked that particular temperature into our documented procedure. So now an investigator and our employees can see the rationale.

This explicit documentation can streamline and facilitate the inspection process, but it also ensures consistency on our behalf by not relying on individual's intrinsic knowledge. When we communicate our procedures, we do it consistently because we have them in writing.

PDA: Were there any surprises in the final version compared with the draft?

Johnson: I don't know that there were any surprises. I know there were several important clarifications of the agency's current interpretation, and that should help promote investigator consistency. That was one of the big issues that industry in general, and PDA specifically had been addressing.

Van Trieste: I don't think there were surprises. One thing I want to make sure comes out really loud and clear, from my perspective, is that I believe this is one of the best guidance documents ever issued by the FDA. I think that the extensive public outreach that the FDA participated in, that PDA was very active in, created a very good guidance document, because it took a lot of the industry's scientific knowledge and perspective and incorporated that with the compliance and regulatory pieces—and the scientific knowledge—from FDA. So when the final document issued, it was a very scientifically sound document that addressed both industry's concerns and FDA's concerns. Therefore, I wasn't shocked with anything that came out at the end of the day.

PDA: While FDA won't say this is the best guidance ever, they acknowledge that the unprecedented public outreach was very beneficial.

Van Trieste: I think it is a good guidance. It is very comprehensive. It has a good balance between allowing companies to implement what is best for the operations because it is not too prescriptive, but in certain areas where very prescriptive language is necessary, it provides that level of detail so smaller companies who read the document can say, "Oh good, that is what they mean. That is enough detail for what I need to do." I think it strikes a very good balance of being prescriptive when necessary, but allowing companies to implement the best solution.

PDA: Industry wanted the original 1987 guidance updated for a long time. Now that it has happened, does it address all the important issues?

Johnson: There are several important clarifications. Obviously, it is more detailed. Things have evolved. So it was important to get an updated document. I wouldn't say that everything has been addressed, but the major issues have.

Van Trieste: Absolutely.

PDA: The guidance makes a strong statement that sterile drugs which can be terminally sterilized should be terminally sterilized. Why do companies choose not to sterilize products that can be sterilized in the end?

Johnson: This has been an issue that has been discussed at least for the last 15 years. There are several reasons why a company might elect to aseptically process a product where the formulation might be compatible. For example, they might have a special package that offers some benefit to the patient, like a prefilled syringe. The package may not be compatible with terminal sterilization but the formulation might be. From a risk-standpoint, if you have a prefilled syringe, that is one less aseptic transfer that the health care provider has to do. So what offers a better benefit?

There is also a question of stability. If you add some level of heat there may be some increase in impurities. So you have to make a judgment. Is the effect on stability less of a risk of than the risk of contamination through aseptic processing.

This is nothing new. It is the first time that it is in an official document from FDA. They have talked about it. It has been a practice. It is explicitly in the European requirements, but it is the first time that it is in a final document from FDA. But it is not a big surprise to our industry. I think most reputable manufacturers have been following this advice.

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FDA's Aseptic Guidance Part 2: FDA Uses Rapid Communication Mechanism to Train Staff

When talking with CDER's Rick Friedman, one understands the enormity of the challenge FDA faces in training its compliance staff and its large field staff to the new aseptic processing guidance. While training for the CDER compliance staff already has occurred, a comprehensive program for field drug investigators is in development. Training on the aseptic guidance has partly fallen under the broader education effort for the cGMPs for the 21st century initiative.

PDA: Where is FDA with respect to the training of field investigators on the guidance?

Friedman: We have made significant progress but still have some work to do. Over the last year , we have trained our compliance officers at the Center, and we have begun to train investigators through the industrial sterilization course, which just took place in June. This is not a new course, but ORA has incorporated updated concepts found in the aseptic processing guidance. So what remains to be completed is a training session to discuss details with the entire field and to clarify any subtleties.

And there is actually a new mechanism that we have just began to routinely use to communicate policy evolutions. We are working with ORA to create an ongoing series of videoconferences for the field which will ensure better integration between the center and the field as we implement the 21st century initiative. In order to ensure implementation of a program, you need to train those effected by it—those who are the implementers—from the grass roots all the way up through management in the specifics of the program and the why, or philosophies, behind the program. So we have embarked on this series of "Pharmaceutical cGMPs for the 21st Century" interactive training sessions. We started with the basics, and the first video conference was held on June 2. It featured key officials from OC (David Horowitz, Joe Famulare), OPS (Jon Clark) and ORA (Susan Setterburg and Doug Ellsworth), who shared with the field the reasons why we've changed our policies in the last two years as part of the 21st century initiative.

PDA: So this video on June 2 wasn't specific to aseptic processing?

Friedman: No. Our next step is to begin drilling down to specifics of the initiative during future sessions, and one of the specific topics that we plan to cover is aseptic processing.

PDA: Why has FDA elected to use videoconferencing as opposed to the more traditional classroom-based lectures?

Friedman: Keep in mind that ORA's DHRD [Division of Human Resource Development] already administers a comprehensive training program for FDA investigators —the videoconference is additional. And when you have fast-moving program changes, like we do right now, in order to keep up you sometimes need to use correspondingly rapid communication mechanisms. The videoconference is one very effective way to do things at this time to supplement our routine training.

PDA: Will there be some kind of aseptic GMP certification like FDA offers with other training, i.e., PAT? Will there be testing? In other words, how do you know the investigators are learning the details?

Friedman: The ORA folks have a formal procedure for certification, and aseptic processing is part of the technical training. Videoconferences provide important and informative updates. Courses like industrial sterilization and others include testing. So it depends on what your aim is for the particular communication mode. In the case of videoconferences, we want to articulate major policy changes to our organization, and it has a Q&A aspect to it. Participants can fax in, call or e-mail questions—which they did during the first videoconference on June 2. In the case of investigator courses in more of the traditional classroom setting as our industrial sterilization course, we want to teach and then test comprehension.

This is all about fully disseminating policy evolutions. There is this great paper from Wharton School of Business. It says that any CAPA [corrective and preventative action], or any other improvement plan, whether it is at FDA or a company, is best implemented by fully communicating the policy modification and making clear management's absolute and ➤

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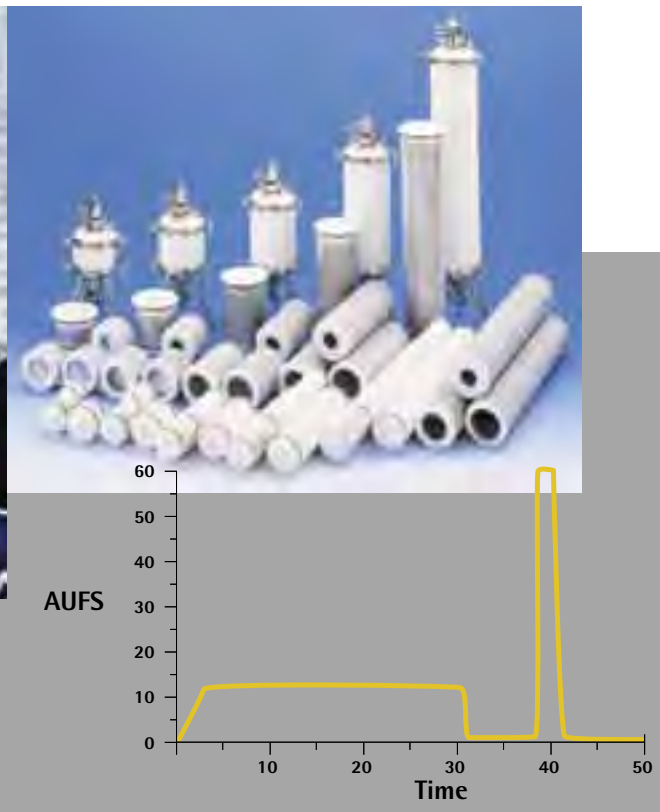

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unambiguous support for it. It sounds intangible, but it is really imperative. You can change an SOP, but until you train people in that SOP, they might not adequately understand how the organization intends to implement it, unless it is a rather basic one.

PDA: And the changes in the guidance aren't so basic?

Friedman: No, while the guidance is often self-explanatory, it is also useful to flesh out its underlying philosophies and discuss its practical application, including highlighting some of the rationales found in PQRI's recommendation (www.pqri.org). And what we are doing is something we've never consistently done before. While we frequently conduct outreach to industry, we are realizing that we also need to identify areas where we can more proactively communicate with our field colleagues in a way that exceeds what we have traditionally done. So this is one of the mechanisms that we use. It is an opportunity for an informative discussion which generally involves district management, compliance branches, and all drug investigators.

PDA: You can imagine why we spent so much time on communication and training. One of the biggest concerns of industry when a new guidance, especially one of this magnitude, rolls out is that enforcement might not be consistent.

Friedman: There is good reason to not be concerned about that because the way FDA is constituted, there are checks and balances that are even more strengthened by the 21st century initiative which require review of any enforcement recommendation, and that now includes all warning letters. Centralized review at CDER promotes more uniform policy interpretation and enforcement decisions by the FDA.

PDA: And has this been working?

Friedman: Personally, I think it has provided substantially more confidence on the part of industry and FDA in our regulatory decision making—similar to our experience with preapproval inspections over the years.

We reminded ourselves through the 21st century initiative that by acting together in making many of our daily decisions, we can enhance the quality of those decisions. For example, for evaluating post-approval manufacturing changes, we are seeing the great value of participation by Center product and technical specialists in inspections.

PDA: The important thing is you are all working in concert now. Are the rules of engagement, so to speak, between the branches better defined?

Friedman: I think there were some organizational disconnects that needed to be procedurally improved. We've made great strides. It is not as if we didn't collaborate regularly, but the means of integration of the three organizational pieces was not always well defined. We are further clarifying the procedures that we use to integrate.

PDA: You participated in PDA's aseptic processing training. Were there any questions about any areas of the guidance that surprised you? In other words, did industry have trouble understanding certain portions which you thought were slam dunks?

Friedman: I would say that there have been very few questions about the clarity of any particular passage in the guidance. I think we are reaping the benefits of the extensive input by the public and our equally extensive collaboration internally in the years leading to the final document. This last year of relative silence—which is music to our ears—is indicative of all the hard work that went into the guidance to create clear, feasible, and valuable standards for aseptic processing.

PDA: So there haven't been questions on areas of the guidance leaving you scratching your head saying, "I thought they'd get this?"

Friedman: No. People occasionally have sought more detail on HEPA filtration and the crimping environment. But the marked decline in questions on aseptic processing over the last year has really been a pleasant surprise.

PDA: We have heard through the surveys conducted at our training workshops that a lot of companies felt that they are either completely or close to completely finished with their implementation. Does that surprise you?

Friedman: Not too much. Over the last several years during which we collaborated both internally and externally to develop this guidance, I was very pleased to see that the industry was often proactively updating their SOPs to incorporate concepts and philosophies found in the concept paper and in the draft guidance. So because of those proactive actions by the industry, I think there was less of a need for many firms to update their procedures. In other cases there were companies waiting for the guidance to be finalized, and in those cases, some

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FDA's Aseptic Guidance Part 3: Essential Information on Buildings and Facilities

PDA is the top source of quality educational information for the sterile drug industry, thus our decision to return to our roots as the Parenteral Drug Association. Our talented and committed members are the driving force behind our various offerings.

In May, PDA presented an audio conference titled "FDA's Revised Guideline on Aseptic Processing: Essential Information on Buildings and Facilities." Richard Johnson, Director of the Quality Center of Excellence, Abbott Laboratories, started the conference with some background information. Next, John Grazal, Senior Director, Global Compliance Management Group, AstraZeneca gave the talk, "Essential Information on Buildings and Facilities."

Below is excerpt from the audio conference.

FDA's Revised Guideline on Aseptic Processing: Essential Information on Buildings and Facilities—May 19, 2005

Richard Johnson: PDA is a leader in aseptic processing. If you're not familiar, I would refer you to [PDA] Technical Reports No. 22, which covers process simulation, TR#26, which covers sterilizing filtration, and TR#34, which deals with isolation technologies. All of these topics are dealt with in the FDA guidance. There also is the "Points to Consider Document," the PQRI representation and numerous conferences since the "Concept Paper" and informal and formal comments offered at every stage. So in summary, PDA has been very actively engaged, since 2001, to influence this FDA guidance….

PDA's "Points to Consider Document" included a number of topics. Thirty-seven of the topics that are covered in the FDA Guidance are in agreement with the PDA position. Five of the topics, FDA is in partial agreement with the PDA position. There is one topic that they are not in agreement, and six topics that were not addressed at all. More importantly, all 18 PQRI recommendations were adopted and are directly included in the Aseptic Guidance. PDA made 100 comments on the draft of the FDA Guidance. Thirty-nine of those were adopted, 19 alternate proposals were adopted and 52 of the comments were not accepted in this version of the document for one reason or another. So I think, in summary, PDA has been very effective at influencing the FDA Guidance….

John Grazal: High Efficiency Particulate Air filters—HEPA filters—what are some of the requirements that FDA is—recommendations, I should say, is FDA discussing in the guideline? HEPA filtered air should be supplied in critical areas at a velocity sufficient to sweep away from the filling closing and maintain unidirectional airflow during operations. You'll notice throughout the Guideline that the term "laminar" has been replaced by "unidirectional"—a recognition that we cannot laminar airflow in the kind of conditions that we have—so unidirectional airflow rather than laminar….

The velocity parameters—in talking about HEPA filtered air—the velocity parameters established should be justified and appropriate to maintain unidirectional airflow and air quality under dynamic conditions within the critical area. So we're talking here now about HEPA filtered air within the critical area, within the Class 100 (ISO 5) areas, and the expectation that there be unidirectional airflow and an appropriate velocity to maintain that unidirectional airflow and sweeping motion under dynamic conditions. In other words, under conditions where we're actually performing processing in the area.

...Referring back to the .45 meters per second and 90 feet per minute plus or minus 20 percent. That has now been reduced to a footnote in the Guideline. There was heavy discussion about whether we really needed to have that in there at all. But the FDA did come back and determine that while it does not remain in the body of the document, it is a footnote and it is only a recommendation, kind of a starting point to think about velocity.

The velocity and…the sweeping away of particles in the critical area is a very important control aspect in our buildings and facilities. Clearly, the FDA has an expectation that airflow velocity should be determined, that we document that, and then we monitor that velocity. A kind of a stepwise process for looking at that would be to take a process activity in a critical area and look at optimizing that process activity—looking at any interventions and optimizing those interventions in terms of the way they're performed, in terms of the way the equipment is oriented in the Class 100 area, etc. And then doing some airflow pattern testing using smoke or some other visual assessment of the airflow in the critical area to show that the equipment placement, to show that the interventions into the zone are appropriate and are optimized in terms of airflow qualities. You know, to use that airflow pattern work to again further try to optimize—tweak, if you will—the kinds of interventions that are being performed to make sure that we don't get bounced back and get the proper kind of airflow in the area.

An important aspect that's sometimes overlooked, but one which FDA emphasizes and has emphasized in many inspections and does mention in the guideline, is not only to look at the airflow within the critical area, but be very mindful of the threshold between the critical area and the background area, between the ISO 5 zone, where exposed, and the ISO 7, the immediate background area. Are we getting the proper sweep? Is there any possibility of airflow from the lesser controlled area into the critical area? That's a very important point and it's one that we want to take into account when we're looking at the proper velocity.

Once we've optimized that, and we've looked at the thresholds, and we're happy that we've got a good, solid airflow and that is visualized…now what is the velocity measurement? So we're correlating the proper airflow with a nice, easy thing that we can do, and that is velocity measurements. And that gives us an ability to go back over time and show, as part of an investigation or as part of routine monitoring, that we have the proper airflow that we qualify in.

The guideline, I think in the Appendix, also references a little bit more of a comprehensive approach to looking at airflow and visualization. And they reference what is commonly known as the LR method—Ljungqvist and Reinmuller method for demonstrating proper airflows, and that's a method that's discussed in a 1993 article in the *PDA Journal*….

Clean area separation—it is vital for rooms of higher cleanliness to have a substantial positive pressure differential relative to adjacent rooms of lower cleanliness. For example—again, this is a direct quote from the guideline: "A pressure differential of at least 10 to 15 Pascals should be maintained between adjacent rooms of different classification with the doors closed." That's an important proviso….

We need to maintain the pressure differential. It is a critical control parameter in our facility. It's a critical means by which we maintain control in the facility and is given

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PDA Aseptic Processing Facts

Richard Johnson, Abbott Laboratories
Richard Johnson co-chairs the program committee for the PDA Aseptic Processing Guidance training workshops in 2004 and 2005. An additional workshop has been added this year. It will be held in Las Vegas, November 3-4, 2005. Richard also co-chairs PDA's Science Advisory Board and is the leader of the PDA Aseptic Processing Interest Group.

The LR Method
The "LR Method" referred to by John Grazal is presented in a paper by Bengt Lungqvist, PhD, and Berit Reinmuller, PhD, entitled, "Interaction Between Air Movements and the Dispersion of Contaminants: Clean Zones with Unidirectional Air Flow," published in the *PDA Journal of Pharmaceutical Science and Technology*, Vol. 47, No. 2. Journal articles can be purchased at the PDA Archives, which can be accessed at www.pda.org.

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Washington, DC

September 15, 2005
Mycoplasma Contamination by Plant Peptones
Washington, DC

October 20-21, 2005
2005 PDA Visual Inspection Forum
Bethesda, Maryland

November 3-4, 2005
Aseptic Processing Guidance
Las Vegas, Nevada

April 24-28, 2006
PDA Annual Meeting

May 8-10, 2006
2006 Training Conference
New Orleans, Louisiana

Training

Lab and Lecture calendar events are held at PDA-TRI Baltimore, MD unless otherwise indicated.

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August 22-26, 2005
Aseptic Processing Training Program (Week 1)

September 7-9, 2005
Advanced Environmental Mycology

September 19-23, 2005
Aseptic Processing Training Program (Week 2)

October 6-7, 2005
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August 9, 2005
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September 8, 2005
PDA Mountain States Chapter
Vendor Show

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September 22, 2005
PDA West Coast Chapter
Dinner Meeting

September 28, 2005
PDA Southeast Chapter
Vendor Show
Durham, North Carolina

September 28, 2005
PDA Capital Area Chapter
Rapid Microbiology and Contemporary Idenfification Systems in Support of Manufacturing
Gaithersburg, Maryland

October 4, 2005
PDA Southern California Chapter
Combination Products and USP Update
Irvine, California

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September 20, 2005
PDA and the PDA Italy Chapter
Rapid Micro TM 33
Milan Italy

September 21-22, 2005
PDA Training & Research Institute
Career-long Learning™
Basel, Switzerland

October 24-25, 2005
The Universe of Pre-filled Syringes - 2005
Munich, Germany

November 10, 2005
PDA and PDA Europe
PDA Nanotechnology Conference 2005
London, England

November 15, 2005
PDA and the PDA Prague Chapter
PDA EuroForum
PAT - Industry, Regulator and Academic
Budapest, Hungary

November 24, 2005
PDA and the PDA Central Europe Chapter
PDA EuroForum
Pharmaceutical Product Labeling
Vienna, Austria

November 30-December 2, 2005
PDA Training & Research Institute Laboratory Course
Practical Aspects of Aseptic Processing
Basel, Switzerland

December 6-7, 2005
PDA and the PDA France Chapter
Biosimilars/Extractables & Leachables
Paris, France

INDIA

October 7, 2005
PDA IndiaForum
PDA and the PDA India Chapter
Microbiology for Pharmaceuticals and Cleanrooms
Mumbai, India

ASIA/PACIFIC

August 2005
PDA Korea Chapter
TBD

September 8, 2005
PDA Australia Chapter
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November 24, 2005
PDA Australia Chapter
Annual Meeting and Holiday Dinner

November 2005
PDA Japan Chapter
Annual Meeting
Tokyo, Japan

December 2005
PDA Korea Chapter
TBD

FDA's Aseptic Guidance Part 3: Essential Information on Buildings and Facilities, continued from page 23

some good discussion in the Guideline and certainly gets a lot of attention during inspections.

When the doors are open, outward airflow should be sufficient to minimize the ingressive contamination and it is critical that the time a door can remain ajar be strictly controlled. So what the Agency is telling us here is, 1) you know, you have to maintain a pressure differential that you've qualified, and then 2) in terms of your monitoring program, you need to have good control over opening of doors between different cleanliness levels or different classifications. The time that a door can remain ajar be strictly controlled—that, to me, says you need to have some sort of a time limit that allows you to move in and out of areas but, you know, uses an alarm condition or some other means to alert people in the area that a door has been left open and a critical parameter (differential pressure) could be negatively impacted. The key thing here, of course, is that we want to make sure our system gives us advanced warning the way we set up our alert levels or alarm levels. We definitely don't want to be going into a reversal condition. We don't want to get into a situation where lesser quality air is moving into higher classified areas, and it's important to set up our alarms and our time limits on opening of doors to make sure that situation doesn't exist….

Talking about air now but in a different context. In terms of membrane filtration, compressed gas should be of appropriate purity. That is, it should be free from oil and it's microbiological and particle quality after filtration should be equal to or better than the air in the environment into which the gas is produced. The italicized note there draws your attention to a new —almost a brand new PDA Technical Report that has been published and issued on the filtration of gases and would really recommend to have a look at that report for basically the state-of-the-state in terms of membrane filtration of compressed gases….

Talking about membrane filtration of gas in our aseptic area and particularly in the context of sterility maintenance. The use of sterile membrane filters is recommended in three areas specifically in the Guideline. So do you have a sterile membrane filter, i.e., defined at this point as a nominal 0.2 micron filter? Do you have those filters installed for autoclave air lines for introducing air into the autoclave chamber, for the lyophilizer vacuum break and also for any tanks which contain sterilized materials (three specific areas that the FDA has chosen to mention in the Guideline for the use of 0.2 micron or better membrane filters)?

Q & A:

Mary: Yes, please, we have a question regarding supporting clean areas. In the case where you're terminally sterilizing and then, of course, you go into supporting assembly areas, what is the requirement for the environmental monitoring at that point?

Grazal: Okay, yeah, the question revolves around environmental monitoring for supporting clean areas, particularly in the case of a terminally sterilized product or device. I mean the starting point for determining the level of monitoring would be to look to the classification of the area in which the activity is taking place. The FDA does recognize at several places in the Guideline that the use of or the application of a terminal sterilization process means that you can take another look, perhaps at the frequency and extent of monitoring in terms of comparing that to what you would do for aseptic processing. So the FDA is not too specific about the frequency of monitoring in any area. You know, we talked about that earlier in terms of regular monitoring or monitoring, you know, to cover each shift. But they do recognize that there is some discretion there if a product is terminally sterilized. So we would look to, for example, some of the historical and kind of well-known values that are out there and kind of key off of that.

Mary: It would then be within your discretion based on your history and trends to develop and rationalize your frequency?

Grazal: Exactly, using again, those common kind of values that are out there—industry kind of norms generally in the context of aseptic processing, using that as a starting point.

Johnson: I would maybe add, John, that although this Guidance, this FDA Guidance really focused on aseptic processing and not terminal sterilization, I do believe that the EU Annex I does have some requirements included in there that deal specifically with production of terminally sterilized product. So I would urge you, if you are making product that is also sold in the European Union, to look at Annex I and see if there are any requirements there that you need to consider.

Mary: Thanks.

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FDA's Aseptic Guidance Part 1: PDA Outreach Aims to Assist Small Firms, continued from 17

Van Trieste: I'm a strong supporter of this statement. Not everybody in industry would agree with me. This was how I was taught growing up in the business: If you can terminally sterilize, you should do it. It reduces the potential for contamination. I think there are some companies where the addition of sterilizers suitable for sterilizing final product would require a major capital investment. For example, a company who has a large aseptic operation and is running products that need to be aseptically produced. If they develop a new product that can be terminally sterilized, they might have to add an autoclave, or multiple autoclaves. That can be a significant capital investment. And sterilizers take a long time to design, purchase, install and validate. You are looking at, from start to finish, a three to five year process. Also, you need to have specialized skills to operate and maintain the sterilizer.

PDA: Is a business reason for foregoing the autoclave now acceptable?

Van Trieste: I don't believe business reasons are going to be satisfactory.

PDA: Do you see this guidance, in the context of FDA's broader 21st century GMP initiative, opening the door for your company to consider using/expanding the use of isolator and other barrier systems? Rapid micro methods?

Johnson: This document did get grouped into the 21st century initiative, but in a sense it is a stand-alone subject; it has been in progress for a long time. I think that more guidance on how you use risk evaluation/risk management for aseptic processing would be good. I'm hopeful that this prospective PQRI task force on post-approval changes for sterile products can advance those ideas.

My personal perspective is that I don't know if this document is going to change anybody's position on isolators and other technologies. I know that we did not get that kind of response in the survey from the participants at the PDA meetings. Is this document going to encourage you to adopt isolation technology, most of the people responded, "no," as I recall. That doesn't mean that they are not going to adopt it. It just means that this document hasn't influenced the decision. I don't think it hurts. At least it does address the fact that there are these newer technologies.

Van Trieste: I don't think the guidance document in itself will encourage people to adopt new technologies. But on the other hand, I don't see the guidance document hindering people. That is really important. A lot of people in our industry stopped working on computerized systems to improve manufacturing processes because of all the uncertainty with 21 CFR Part 11. I don't see that happening here. I see the guidance as neutral to the technology that you use. It doesn't promote one, but it doesn't hinder you from advancing either. That is important. About 30% of the respondents to the PDA workshop survey said that the guidance document would help in making the decision to utilize isolators.

PDA: If you have been inspected since the guidance published, how do you feel the application of the guidance has been by inspectors?

Johnson: We have not had an aseptic inspection since the final guidance. Yet, as with any guidance, training is a very important issue. This one is a very dense document. There is a lot of stuff in there. You know, there are always going to be opportunities for interpretation.

PDA: You co-chaired the committee that developed the PDA Aseptic Processing Guidance Training courses. What is your assessment of them so far and how important was FDA's participation?

Van Trieste: I think the FDA being there was generally well received by the participants. I think it really depended on the individual and then what the audience wanted to hear. Our members really wanted to hear the FDA's point of view.

I think if you look at who attended the training conferences, you are going to see a fairly large representation by smaller companies. I was at all five meetings and when I looked at the attendee list from each of them, there were many companies that I had never heard of.

PDA: A fourth Aseptic Processing Guidance training workshop has been added for 2005. Will the program change at all?

Johnson: We are looking at some changes. Specifically, we want to add some discussion of international guidance. We want to have an update from the PDA Task Force on risk analysis. We are looking at how we can apply risk analysis to aseptic processing. We are going to have that group provide an update.

PDA: Will it be a better program?

Van Trieste: Of course it is going to be better. If Annex 1 comes out in time, we will be addressing the similarities and the differences between the FDA document and what is in the new Annex 1. That

will be a big difference. I think we will spend a little more time on some case studies than we did in the first set. Based on the feedback we received, we will be tweaking it.

PDA: Since it is in Las Vegas, will there be time for gambling?

Van Trieste: Absolutely. The gambling starts at nine at night and ends at five in the morning!

PDA: Eli Lilly's Glenn Wright—a former PDA board member and a member you worked closely with on aseptic processing—is now involved with the PQRI effort to develop a post-approval changes guidance for sterile products. How important to you and your company is this initiative?

Johnson: We've been waiting for post approval guidance for sterile products for a long time. Obviously, it would be an excellent opportunity to move forward.

Van Trieste: I think it would be a very valuable tool. To have clear guidance about when something is required to be submitted as a prior-approval supplement, as a changes-being-effected supplement or as an annual report—we have great debates in Bayer about this. We spend, I think, wasted effort making those decisions. And therefore, if we had clear guidance, it would make us more efficient as an organization, it would decrease the chance of making a mistake and putting something in the wrong category. We typically—and I think most of the industry—err on the conservative side. More definitive and more prescriptive guidance would be welcomed.

PDA: Where is Europe with Annex 1? There has been some controversy with this, and PDA had a workshop in 2003?

Johnson: I can tell you what we understand is that they are planning to do a revision of Annex 1. We are hoping that it will be released for comment prior to the November aseptic processing guidance meeting. In anticipation of that we are planning to discuss it. We are also expecting a new Japanese guidance document, and we plan to discuss it as well.

PDA: Will you talk about the compliance tool that was developed for PDA?

Van Trieste: People are actively using it. I receive phone calls from people who say they like the tool and that it has been very helpful to them. The compliance tool does three things. First, it allows you to create a road map of your procedures back to the guidance document, and to make sure that you address all of the issues that are discussed in the guidance. So it prepares you for an FDA inspection. Second, it helps you identify any gaps that you may have so you can fill them. Last, most importantly I think, it allows you to train everybody in your organization who needs to be trained on the guidance in a very methodical way, going step by step through the document—this is what it says, this is what our procedures say, and this is why we comply with the guidance document.

Interestingly, FDA has called and asked for permission to use that tool in various training sessions that they conduct.

FDA's Aseptic Guidance Part 2: FDA Uses Rapid Communication Mechanism to Train Staff, continued from 20

companies may now be considered behind in evaluating their standards to see if they are consistent with current GMP thinking.

PDA: Is that characteristic of good regulatory guidance, when it doesn't have a lot of surprises and force unanticipated movement by the industry?

Friedman: It certainly signifies extensive efforts toward consensus building. I think when you look at what we've done—and this has been mentioned many times—the outreach afforded to the revision of the aseptic guidance was unprecedented, and it included the primarily industry-populated PQRI aseptic processing work group. Because of the numerous consensus building activities, I think there were very few surprises, and that was a great example of industry and FDA working together to develop good, practical standards.

PDA: If the new aseptic guidance reflects current good manufacturing practices, how long will it be a good standard? In other words, what is its shelf-life?

Friedman: I think that question requires some capacity for soothsaying. I would only estimate that the major policy statements made in the guidance will likely live for a significant period prior to necessitating revision. There are certainly lessons that we will learn as science and technology evolve that will compel us to revisit and update our current thinking at some point. Revisions of the more minor variety could be ➤

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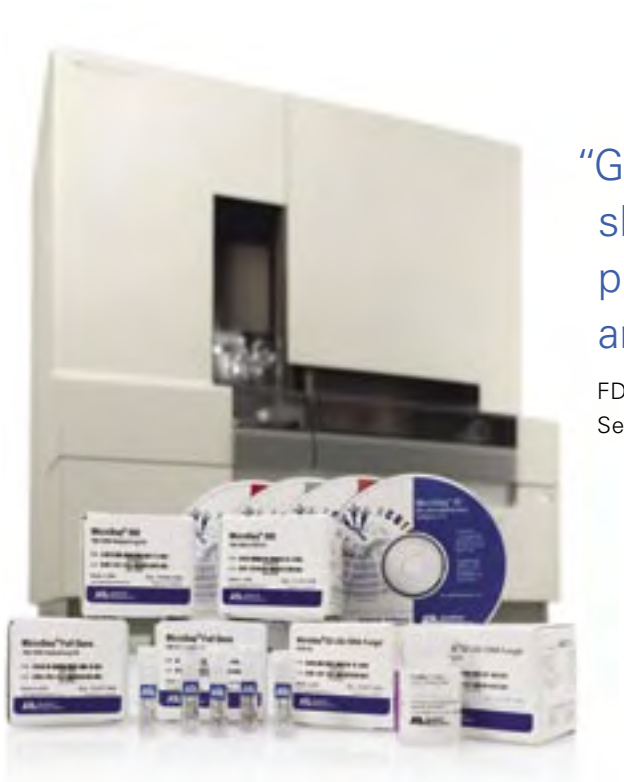

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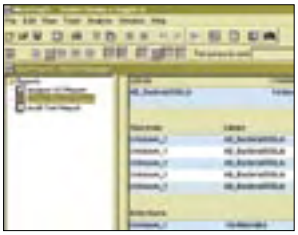

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undertaken every few years, perhaps prior to any need for a major overhaul again.

PDA: Would minor revisions be done through the Q&A?

Friedman: Yes, exactly. The Q&A postings replace the old human drug cGMP notes. In accord with good guidance practices, we provide further clarity on aspects of existing policies, such as the aseptic guidance, on the CDER Web site.

PDA: You know as well as anyone that recalls due to the lack of assurance of sterility have been common in the recall data over the last five to six years, but they have been down in the last year and a half. Would you say that the guidance has had an impact?

Friedman: I think any effort to sensitize people to the basic principles of aseptic processing is worthwhile because, perhaps more than any other manufacturing method used by the pharmaceutical industry, aseptic manufacturing requires an operational vigilance that when breached can lead to a serious product failure. Both the new revised aseptic processing guidance and the process that we have all followed to get there might be yielding significant benefits such as preventing defects. Although, I still think we can improve our recall numbers in that area.

PDA: Is any work needed to harmonize FDA's aseptic processing GMPs with the EU's?

Friedman: Thanks to the input from companies and industry organizations through public comments as well as PQRI's efforts, we consider ourselves to be substantially harmonized. It is also important to note that Table 1 of the FDA guidance, which includes air cleanliness classifications and recommended microbial levels, is now harmonized between the European Union and the United States, thanks to the PQRI work group.

PDA: Do you believe that more harmonization can be accomplished?

Friedman: I think we could iron out one or two more issues, although I believe that the EC group that is responsible for the maintenance for Annex 1 is already looking at these issues right now.

PDA: Could you give an example of what remains to be harmonized?

Friedman: Media fill acceptance criteria.

PDA: Now on to some new "news." Your team is involved with FDA's effort to revise its validation guidance for industry. Do you envision having the considerable amount of public outreach for this document as there was for aseptic?

Friedman: Consistent with our other recent efforts on cGMP manufacturing guidance, we have been participating in multiple forums, including PQRI's Process Robustness work group and various industry meetings, that have been very useful as we have been revising the validation guidance and we will continue this outreach until we finalize it.

PDA: Do you see this as challenging a document as Aseptic was?

Friedman: We've already addressed the fact that three conformance batches is not a magic number, discussed the life-cycle, and stressed the value of continuous verification of key processing attributes in our compliance policy guide on validation. So that was a major step forward. We are now working on updating the understanding of validation and qualification in the 21st century, and we are incorporating basic and well-accepted tenets such as good experimental design, and review and interpretations of data, and continuous improvement throughout the life cycle are included in the guidance. These are concepts that industry and FDA are in general agreement on. The draft guidance mechanism that we use and which has worked well for FDA and the public for so many years will provide an important opportunity for comment and discussion prior to finalization. As always, we will review and evaluate all comments that come in on the guidance. In addition to that, we will be sure to listen carefully during our outreach efforts.

PDA: How about the timing?

Friedman: Our tentative goal is end of calendar year 2005 for the draft.

PDA thanks Richard Johnson, Martin Van Trieste and Richard Friedman, as well as their respective organizations, for contributing to this article. The interviews were conducted by PDA Senior Editor Walter Morris.

PDA Queries EMEA on Stability Testing in EU

Gautam Maitra, PDA

European health officials informed PDA Regulatory Affairs and Quality Committee (RAQC) members Stephen Bellis, Ivax UK, and Gautam Maitra, PDA, that stability testing does not need to be conducted in an EU member state at the EMEA GMP Interested Parties Meeting, May 12, 2005, in London.

PDA representatives have attended the EMEA GMP Interested Parties Meeting since the EMEA took the unique step of initiating the dialogue in 2004.

This year's meeting was attended by inspectors from each EU Member States. Representing the EMEA were Emer Cooke, Head of Sector, Inspections, EMEA, David Cockburn, Scientific Administrative Support, Inspections Sector, EMEA, and Katrin Nodop, PhD, Principal Administrator (Scientific), Inspections Sector, EMEA. The European Commission was represented by Sabine Atzor.

At the GMP Interested Parties Meeting, invited industry participants are asked to present a "problem statement" and a "position statement" pertaining to a specific GMP issue.

PDA's problem statement for the 2005 meeting involves a pharmaceutical manufacturer in the European Union which was advised by a member of their competent authority that, upon implementation of the addition to Chapter 6 of the EU *Guide to Good Manufacturing Practice: On-going Stability*, stability testing will have to be performed in a Member State of the European Union. The stability testing requirement would apply to all products, whether they were manufactured in a Member State or a third country.

PDA's position statement argues that the official's interpretation of the EU's stability requirement is not scientifically justified. This position is supported by the large number of companies successfully performing stability testing in non-EU countries. The companies performing stability testing in non-EU countries are subject to inspection by the competent authorities of the EU. A laboratory performing stability testing in support of product in the European market shall be appropriately qualified to perform the tests required of it. PDA does not believe the Addition to Chapter 6 was written with the intention of requiring all stability testing to be performed within a Member State of the EU.

PDA asked the Ad Hoc Inspectors Group to clarify the issue.

Responding for the GMP Inspectors Group, John Lynch, an inspector from Ireland, explained that this aspect of stability testing in GMP was quite new. The EU inspectors believe that this stability testing can be carried out outside of the EU, but reminded the group the work is to be performed under GMP, the laboratories are subject to inspection, the QP is to receive periodic data/reports and the QP is to be knowledgeable of the lab performing the work.

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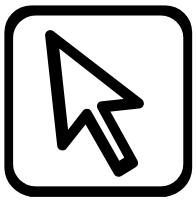

July 28
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Speaker: Tracy TreDenick, BioTechLogic, Inc.

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PDA Volunteers Taking Action and Leading the Way

Vicki Dedrick, PDA

The heart of PDA is its volunteers. The many men and women just like you who give freely of their energy, time and expertise to enhance and grow our professional community. PDA volunteers come from industry, academia and regulatory agencies, all working together to advance our discipline through the utilization of good science and technology.

PDA volunteers are hard at work in a number of significant areas to support the growth and development of members through the use of good science and technology. 2005 is proving to be one of the most active years for PDA volunteer initiatives. If you are not yet volunteering at PDA, now is the time to put your expertise to work and get involved. The Regulatory Affairs and Quality Committee (RAQC), the Science Advisory Board (SAB) and the Biotechnology Advisory Board all have numerous activities ongoing and can always use your help.

This article is intended to provide you with some insight into recent and current PDA initiatives. If a topic interests you and you have expertise in that area, please contact PDA via the "Member Opportunities" link on the PDA home page, www.pda.org, to get involved.

The RAQC, lead by Amy Scott Billman, Executive Director, Vaccines, U.S. Regulatory Affairs, GlaxoSmithKline, is very proactive in leading PDA in the development of comments and original initiatives. The RAQC is adding new activities to their work program all the time. Some of its 2005 activities include:

- Submission of comments to FDA and ICH on the ICH Q8 Step 2 document on "Pharmaceutical Development"
- Formation of a new task force to comment on the ICH Q9, Quality Risk Management and a group to provide input to ICH Q10, Quality Systems, currently in development
- Collaboration with the newly formed Product Quality Research Institute (PQRI) Working Group for a Guidance on Post-Approval Changes – Sterile Products. The RAQC will be working closely with PDA members in this Working Group to ensure that PDA's substantial expertise in this important area of manufacturing is included
- Development of comments on the EMEA Parametric Release Concept Paper, as well as a Draft Guidance on Exploratory Investigational New Drugs
- Creation of an original PDA Pocket Guide on FDA 483 and Warning Letter issues for members

In 2004, the PDA RAQC commented on 14 regulatory documents/guidances coming from FDA, EMEA and WHO. In addition, RAQC generated a White Paper on Post-Approval Changes – Chromatography for submission to the FDA docket for consideration. This document will publish later this year as a PDA Technical Report.

As PDA's most active group, the SAB offers members plenty of opportunities to get involved. Lead by Richard Johnson, Director, Quality Center of Excellence – Drugs, Abbott Laboratories, and Martin Van Trieste, VP Quality, Bayer, the SAB has a staggering work program for 2005. Managing and moving these activities forward requires a lot of volunteers. The following list of on-going projects may give you some ideas of where to get involved:

- Risk Management: a Task Force has been formed to develop a PDA Technical Report and a computerized compliance tool.
- Aseptic Processing: Revision of PDA Technical Reports (TR) impacted by the FDA Aseptic Processing Guidance. Task Forces are being formed to revise the following TRs:
  - TR #22, *Process Simulation Testing for Aseptically Filled Products*
  - TR #26, *Sterilizing Filtration of Liquids*
  - TR #13, *Fundamentals of an Environmental Monitoring Program*
- New PDA Technical Reports in production: *Selection and Use of Bio-Indicators for Monitoring Sterilization Processes; Microbial Data Deviations (OOS); Process and Finished Product Extractables; Validation of Aseptic Processing for Manual Procedures; Glass Defects; Glass Handling Practices; Visual Inspection of Parenterals;* and *Lyophilization*.

SAB can hang its hat on the fact that two Technical Reports have been published already in 2005: TR #40, *Sterilizing Filtration of Gases*, and TR #41, *Virus Filtration*. Later this year, PDA will publish TR #39, *Cold Chain Management*; TR #28 (revised) *Process Simulation Testing for Sterile Bulk Pharmaceutical Chemicals*; and

TR #42, *Validation of Protein Manufacture*.

The Biotechnology Advisory Board, PDA's newest, had its first official meeting in April at the PDA Annual Meeting. This committee, co-chaired by **John Geigert**, PhD, President, BioPharmaceutical Quality Solutions, and **Gail Sofer**, Director, Regulatory, GE Healthcare, has already developed an aggressive work program that includes:

- Development of a *Workshop on Mycoplasma in Plant-Based Raw Materials* scheduled to take place in September 2005
- Development of a new Technical Report on *Biopharmaceutical Reprocessing*
- Development of a new Technical Report on *Viral Clearance Requirements for Clinical Trial Materials*
- Development of a new Technical Report on *Virus Spike Preparation Standardization*
- Development of a new Technical Report on *Nomenclature for Small Virus Filtration*
- Development of a Biosymposium meeting for 2006 in the San Francisco area.

For more information on participating in any of the activities listed above, contact PDA by filling out a volunteer form at www.pda.org/volunteer/index.html, or e-mail Robert Dana at dana@pda.org.

In addition to all of the scientific, technical and regulatory projects, PDA has numerous opportunities for you to get involved in program committees for meetings, conferences and workshops. Share your expertise through the presentation of an audio conference or work with the PDA Training and Research Institute to develop a training or laboratory course. Joining a PDA Interest Group is another way to provide input and gain knowledge through discussion of the latest issues affecting our industry today.

No matter what your level of experience, there is an opportunity for you to be actively involved at PDA. Being involved gives you the opportunity to interact with your peers, grow, develop new skills and contribute to your professional community.

Chapter Contacts

The following is a list of the PDA Chapters, organized by the regions of the world in which they are located. Included are the Chapter name, the area(s) served, the Chapter contact person and his or her e-mail address. Where applicable, the Chapter's Web site is listed. More information on PDA Chapters is available at www.pda.org/chapters/index.html.

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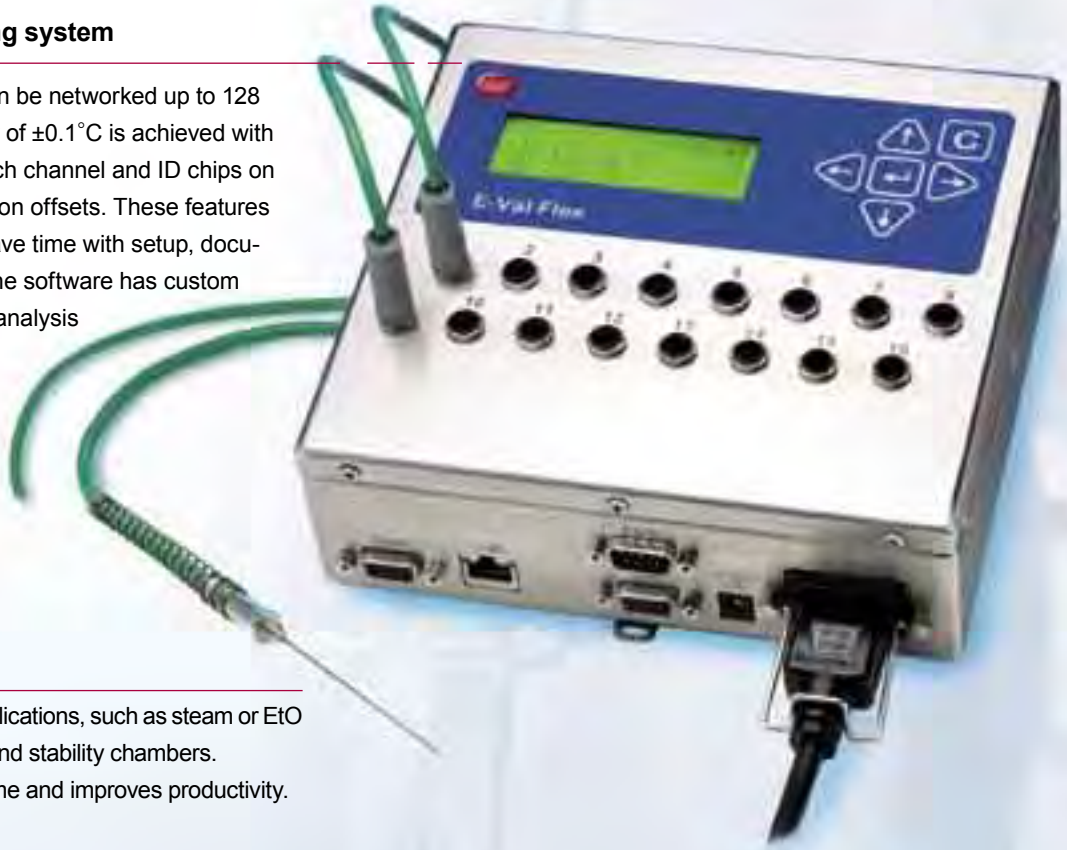
E-Val Flex
Thermocouple monitoring system

The PC controlled system can be networked up to 128 channels. A system accuracy of ±0.1°C is achieved with the cold junction built into each channel and ID chips on thermocouples store calibration offsets. These features plus automated calibration save time with setup, documentation and traceability. The software has custom validation reports; validation analysis features and is compliant to 21 CFR, part 11.



TrackSense Pro

Ideal for thermal validation applications, such as steam or EtO sterilization, mapping rooms and stability chambers. Dramatically reduces setup time and improves productivity.

TrackView

Network data acquisition software designed for plant wide data acquisition and alarming.

Calibration Baths & Temperature Standards

The bath and temperature standard can be integrated into the software for automated multi-point calibration.

Thermal Validation Solutions

ellab
Building Confidence

Photo Highlights from the 2005 PDA Annual Meeting

The 2005 PDA Annual Meeting was in Chicago, Ill., April 4-8.

Conference attendees visit exhibit booths (top) and the Poster Sessions (middle, bottom)

Nikki Mehringer presents certificates at the first PDA Annual Graduate Research Symposium

PDA Immediate Past Chair Floyd Benjamin (left) presents the PDA Distinguished Service Award to Ronald Tetzlaff

Theodore Meltzer (left), Vicki Dedrick and Julius Knapp

PDA Chair Nikki Mehringer presents her Eli Lilly colleague, Glenn Wright, the PDA Frederick J. Carleton Award for his distinguished service as a past PDA Board member

DHI's Amy Davis chats with authors Bengt Lungqvist and Berit Reinmuller

2006 PDA Annual Meeting–

Pharmaceutical Manufacturing Science in the 21st Century: From Innovation to Implementation

What better place than California for industry, regulators and academia to pull together to find solutions to the many challenges facing the pharmaceutical industry. As Program Committee Chair for the 2006 Annual Meeting, it is my pleasure to invite you to join your friends and colleagues in Anaheim for this not-to-be-missed event April 24-26, 2006.

Building on the success of previous PDA Annual Meetings, our association will continue to offer a rich technical and scientific program designed to stimulate interaction and provoke discussion. While our meeting is some months away, there are two things that you can do now to make it a success: (1) respond to the "Call for Papers" ***(see p. 46)*** and contribute to the discussion and (2) place the meeting on your 2006 calendar.

I look forward to seeing you in Anaheim!

John Geigert
Program Committee Chair

bioMerieux presents a new automated microbial identification system

The winners of the 2004 PDA Honor Awards

Mike Jornitz (left) and Ted Meltzer (right) sign a book

Nikki Mehringer welcomes PDA members to the 2005 PDA Annual Meeting (top) and poses with key-note speaker, Jeffrey Macher (right)

PDA Directors and new members at the New Member Breakfast

Michael VanDerWerf (left), Cindy Rockel (top center), Zena Kaufman (top right) and Marie Breen discuss "The Move to Risk-Based Quality Systems"

Photo Highlights from PDA's May Meetings

The 2005 PDA Viral & TSE Safety Conference and the 2005 PDA Extractables/Leachables Forum were in Bethesda, Md., this past May

The "New Technology" Panel at the Viral & TSE Safety Conference

The 2005 PDA Viral & TSE Safety Conference Program Planning Committee poses with PDA Acting President, Bob Myers (left)

PDA staff ready to assist participants at the Extractables/Leachables Forum

Nobel Laureate Stanley Prusiner (left) poses with members of the Viral & TSE Safety planning committee

The Extractables/Leachables Forum drew a big audience

Q&A session at the Viral & TSE Safety Conference

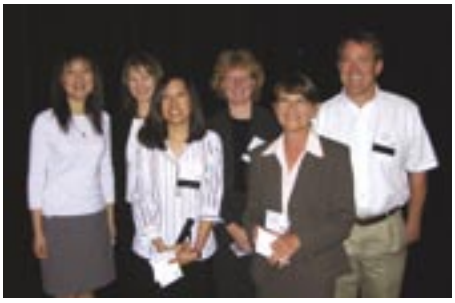
CDER's Moheb Nasr, addresses PDA's Extractables/Leachables Forum

Networking during a break at the Extractables/ Leachables Forums

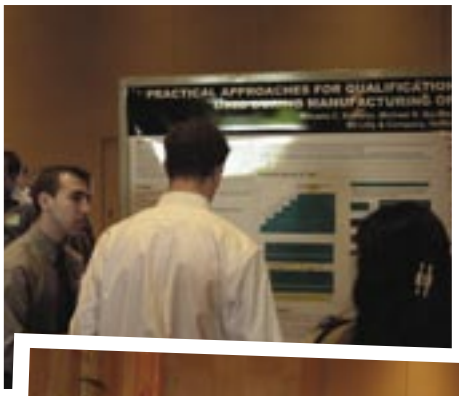
The Viral & TSE Safety Conference takes a break for lunch; beef was not on the menu!

Cheese, crackers, grapes and posters at the Extractables/Leachables Forum

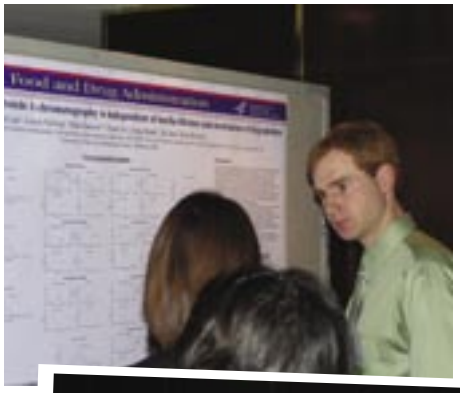
The "TSE: Current Developments and Safety Approaches" Panel at the Viral & TSE Safety Conference



Yuan Xu, Dorothy Lister, Lenore Norling, Jeri Ann Boose, Hannelore Willkommen and Mark Baily



The exhibits and the posters were well-attended at PDA's Extractables/Leachables meeting



Posters were a popular attraction at the Viral & TSE Safety Conference

Vice President's Message

Gail Sherman, VP, Education

Learning While Teaching at PDA

August 9 marks my first anniversary with PDA and the Training and Research Institute. The past year has been a true learning experience for me as I transitioned from 34 years of employment with the U.S. Federal Government to the private sector.

At the time, my colleagues thought I had lost my mind and any intelligence that might have gone with it when I decided to take only a one-day break between leaving the U.S. FDA and joining TRI. But in my own defense, I am a "Type A personality," and I was truly looking forward to yet one more challenge before I really retired to knit booties for my now grandnieces and nephews!

TRI hosts visitors from Russian medical technology group, TEMPO: (top photo, from left) Natalia Popova, Nikki Mehringer, Bob Myers, Gail Sherman, Bob Dana, Zoryana Grishina, Maria Douglass (U.S. Dept. of State), Yuri Remnev and Matt Clark; (bottom photo) James Wamsley shows the TEMPO visitors TRI's cleanroom

The first lesson I experienced was "commuting 101," since TRI is located about 45 miles from my home near Washington. Never during my 34 years in Federal service had I traveled more than ten miles to get to work—I guess I was lucky. This new experience—the long and slow trek up and down I-95 to Baltimore in heavy traffic each day—almost drove me to an early retirement. Fortunately, I now work a few days a week nearer to home at PDA's Global Headquarters.

My second lesson was on how TRI conducts its very successful laboratory courses. My first week at TRI just happened to coincide with Mike Korzynski's (TRI's first Director) laboratory course, "Developing a Moist Heat Sterilization Program Within FDA Requirements." TRI's renowned Aseptic Processing Training Program was on the schedule for my second week. With multiple instructors, labs, lectures and students going in every direction, I quickly began to wonder what was I doing here? One of my instructors (and I have claimed them all as "mine") told me three months later that he didn't expect to see me again after those first two, crazy weeks! But persistence rules, and if nothing else, I am persistent!

Since we were nearing the end of the year, my next challenge was the budget, and like students taking a TRI lab course, I received hands-on training! I had done budgets many times at FDA, but I soon learned that the government budget and the private budget are very different; for the latter, spending actually had to be reconciled! How many nights did I sleep at my computer trying to make those numbers work? Too many to count, but I learned budgeting! It was a lesson well-learned, with the 2006 planning experience, thus far, being ever so much easier. But will I ever learn what a forecast is?

And then there was the challenge of sorting out who does what, when and why at TRI, a challenge all new managers face no matter what the organization. Forgive me for taking a moment for touting the great work of my Laboratory Education Manager. If not for James Wamsley, I don't think we could have gotten through the remainder of 2004 and the first part of 2005. We did, and our laboratory courses have been very successful so far this year, with participation exceeding 2004. A feather in James' cap is the Aseptic Processing laboratory course we are offering in Basel. After six years of building a strong reputation in our Baltimore facility, TRI is finally taking its aseptic processing laboratory course to Europe to benefit our members there ***(see story, p. 45)***.

With our lecture courses, we've managed to have one success after another. Our PDA/FDA training course series in 2004 drew double the participants than originally planned, which was very encouraging because it took place in my first six weeks (bragging rights probably are not mine)! In the

beginning of 2005, I was off to Rome, where I had an opportunity not only to provide education in Europe, but to be educated on fine dining the Roman way—epicurean experiences to be sure. But back to reality. We trained in San Francisco, then in Chicago for the PDA Annual Meeting and next in Princeton, New Jersey.

My longest-learned lesson so far has been on the frantic pace of life outside of FDA, not that FDA life wasn't frantic—its just that we found an occasional "un"busy day or two. I'm not sure that exists at PDA TRI, and so when I ask "where is the downtime?" James glibly responds, "there is none!"

We continue on the fast track at TRI. In the remainder of 2005, we still have course series in Denver, New Orleans, Basel and at 2005 PDA/FDA Joint Regulatory Conference. Plus, we are offering lectures at TRI in Baltimore in August and September, and at least ten more lab courses at the facility, including two more Aseptic Processing Training Programs! For 2006, we are planning courses in: Lake Tahoe, Raleigh, St. Louis, Missouri, New Orleans, Anaheim, Boston, Tokyo, Washington, London and, of course, in Baltimore at our own facility. And we continue to look for new opportunities every day.

I find that interest in TRI is rising. We are receiving many calls and inquiries that hopefully will become training opportunities for us. We met with a Russian delegation in June, and are very much looking forward to possible collaborations with them. We also met with representatives of the Jordanian government, have had conversations with the Chinese Pharmaceutical Manufacturers Association and have spoken with USP about possible collaborations in India and the Middle East. In addition, our instructors are always proposing new and updated courses, symbolic of their true commitment to TRI.

And new this year was the establishment of the TRI Advisory Board. The members are actually developing the training courses for the PDA Biennial Training Conference, and I think having fun doing so. We have subcommittees currently meeting regularly to discuss e-learning, certification and standardization. I am pleased to be working with a group of dedicated folks who are interested and excited about what they are doing for PDA!

So as I look toward my first anniversary with PDA, I look back to all the lessons I've learned by joining the private sector. I never imagined these challenges could be so rewarding. I've had the opportunity to interact with so many wonderful and dedicated people during this past year in so many different settings, in very different ways, and that has been a gift that many people never have the opportunity to experience. There is so much more to do to move this organization forward—our motto at TRI has become "moving forward." Onward and upward we go, and the booties, well, they'll have to wait a little longer.

The TRIAB meets at TRI: (clockwise from front center) Gregg Sherman, Barbara Van der Schalie, George Grigonis, Bob Myers, Eddie Ballance, Gregory Meyer, Gail Sherman, Lina Divitt and Surat Baloda

James Wamsley talks shop with visitors at TRI's Open House

TRI faculty member, John Lindsay, works with Center for Drug Evaluation and Research staff during training

A First For Me; a Second for TRI

James Wamsley, PDA TRI

While most of America was relaxing with family and friends on their porches, in their backyards and around their barbecues to celebrate Memorial Day weekend, I was at a local restaurant with one of TRI's faculty members eating lunch and hashing out the final details for one of our new courses, Practical Aspects of Aseptic Processing. This local restaurant, however, was in Basel, Switzerland. And while I was slightly disappointed to miss a holiday with my family, I was excited to be chewing the fat (literally, one of the orders was an entire plate of lightly smoked bacon) in Switzerland during my first official visit to Europe!

This was TRI's second laboratory training in Europe. PDA has built a strong reputation for our laboratory training in Baltimore during our first six years, which has led to strong demand to provide hands-on aseptic processing training closer to our membership around the world. In 2004, we chose Europe and the centrally-located Basel with its Industrial Pharmacy Lab as our first "off-shore" destination.

We also decided to develop a unique three-day course, called Practical Aspects of Aseptic Processing, which provides participants with the knowledge needed to evaluate, improve or implement an aseptic processing program. Some key topics covered include: cleanroom standards, requirements and regulations; ISO requirements for airflow in your APA; airflow studies; and proper gowning requirements. The expert faculty was led by John Lindsay, Aseptic Solutions, Inc., who also leads the faculty of the ten-day program in Baltimore. John was joined by Maureen Mueller, Quality Systems Consulting, Veronique Von Buynder, Genzyme, and Peter Koger, VAI.

While the new Basel course shares some key components of the ten-day Aseptic Processing Training Program offered in our Baltimore lab, it should not be confused as a condensed version or as a replacement for this training course. The Basel course, unlike the Baltimore course, focuses primarily on pre-production issues. There are several hands-on segments for the students to put into practice what the faculty is teaching.

Although this was only the second time we had run the course, everything came together beautifully—thanks in part to the staff at the Industrial Pharmacy Lab. The students were very responsive and interactive with the faculty members. They were excited to participate in the hands-on laboratory exercises that supplemented the lectures. The feedback received from the students was overwhelmingly positive with respect to the material presented and faculty's qualifications.

You can participate in one more offering of Practical Aspects of Aseptic Processing in Basel once more this year—November 30-December 2. I am looking forward to once again participating in this most valuable training experience for our European members, even if it means trading in American barbecue for Swiss smoked bacon!

Aseptic Processing Training at PDA TRI

Amanda Olsen, PDA

What is it that distinguishes PDA Training and Research Institute's Aseptic Processing Training Program?

PDA TRI's ten-day comprehensive Aseptic Processing Training Program provides the perfect balance of hands-on laboratory and lecture training. Attendees have the opportunity to learn from a faculty comprised of more than 20 industry professionals with diverse backgrounds and a range of real-world expertise, equipping you with tools and actual experience you can bring home and apply immediately on the job.

"I feel so much more qualified and confident to do my job; great mix of theory and hands-on techniques," said one recent course attendee and PDA member.

Two five-day sessions allow for an in-depth look into an expanse of specific topic areas. These two sections are scheduled four weeks apart, allowing for intense, comprehensive learning with minimal impact on your job/organization.

Week one provides a review of the fundamentals and principles associated with aseptic processing. Topics such as filtration and liquid filter integrity testing, sanitization techniques, sterilization validation and good aseptic processing techniques are learned through a combination of lectures and laboratory exercises using equipment at TRI's state-of-the-art facility.

The second week builds on what was learned in the first week, concentrating on all elements of producing a sterile, aseptically filled product and focusing on the importance of good documentation practices. Participants will gain direct experience in root cause analysis and failure investigations. Attendees gain hands-on experience in the Aseptic Processing Area, Methods Development and Process Engineering Laboratories.

TRI's Aseptic Processing Training Program includes approximately 47 hours of hands-on laboratory training and group project work, in addition to extensive coverage of topics during the lecture sessions. The culmination of the ten-day course is the formulation, filling and release of product.

Another recent attendee commented, "This was the most practical training I've received to date."

Registration is limited to assure active involvement and meaningful interaction with other students and our expert faculty. Space is still available for our last 2005 session: October 17-21 (Week 1) and November 14-18 (Week 2).

2006 PDA Annual Meeting

Pharmaceutical Manufacturing Science in the 21st Century
From Innovation to Implementation

Anaheim, California
April 24 – 26, 2006

Call for Papers

Dear Friends and Colleagues:

Have you or someone you know in the pharmaceutical and biopharmaceutical community done something special in the past year, something that would be of particular interest to the rest of the world? Such as:

- Solved an unusually difficult technical problem
- Validated a difficult process or an unusual dosage form
- Submitted an MAA, BLA or an NDA which includes some of the "new" things we are hearing about: risk-based decisions, PAT, nanotechnology, etc
- Expanded upon ideas about what "risk-based" means and how it can be implemented
- Developed a new sterilization process or method

Why not let the world know about it? We encourage you to submit a scientific abstract for presentation at the **2006 PDA Annual Meeting**, which will be held April 24-26, in Anaheim, California.

Abstracts must be non commercial in nature, describe new developments or work and significantly contribute to the body of knowledge relating to pharmaceutical manufacturing, quality management and technology. Industry case studies demonstrating advanced technologies, manufacturing efficiencies or solutions to regulatory compliance issues are preferable and will receive the highest consideration. All abstracts will be reviewed by the Program Planning Committee for inclusion in the meeting or in poster sessions.

ABSTRACTS MUST BE RECEIVED BY September 30, 2005 FOR CONSIDERATION.

PDA is seeking presentations 30 minutes in length, that present major challenges and practical approaches to resolution in the following areas:

- Aseptic processing of medicinal products
- International regulatory and harmonization initiatives
- Industry manufacturing/product trends
- Combination products
- Risk management and risk-based GMP
- Supplier quality management
- Use of disposables in manufacturing
- Packaging, labeling and anti-counterfeiting measures
- Glass defects and AQL
- Innovative biotech upstream and downstream processing
- Contract manufacturing issues and quality agreements
- Design and management of multi-product facilities
- Blend uniformity and solid dose manufacturing
- Validation of pharmaceutical and biotech processes
- Viral safety evaluation
- Process analytical technologies (PAT)
- Quality management systems for pharmaceuticals and biopharmaceuticals
- Industry case studies—compliance and quality issues
- Microbiology initiatives and trends
- Rapid microbiological methods
- Barrier isolation technology
- Sterilization
- Environmental Monitoring

Commercial abstracts featuring promotion of products and services will not be considered

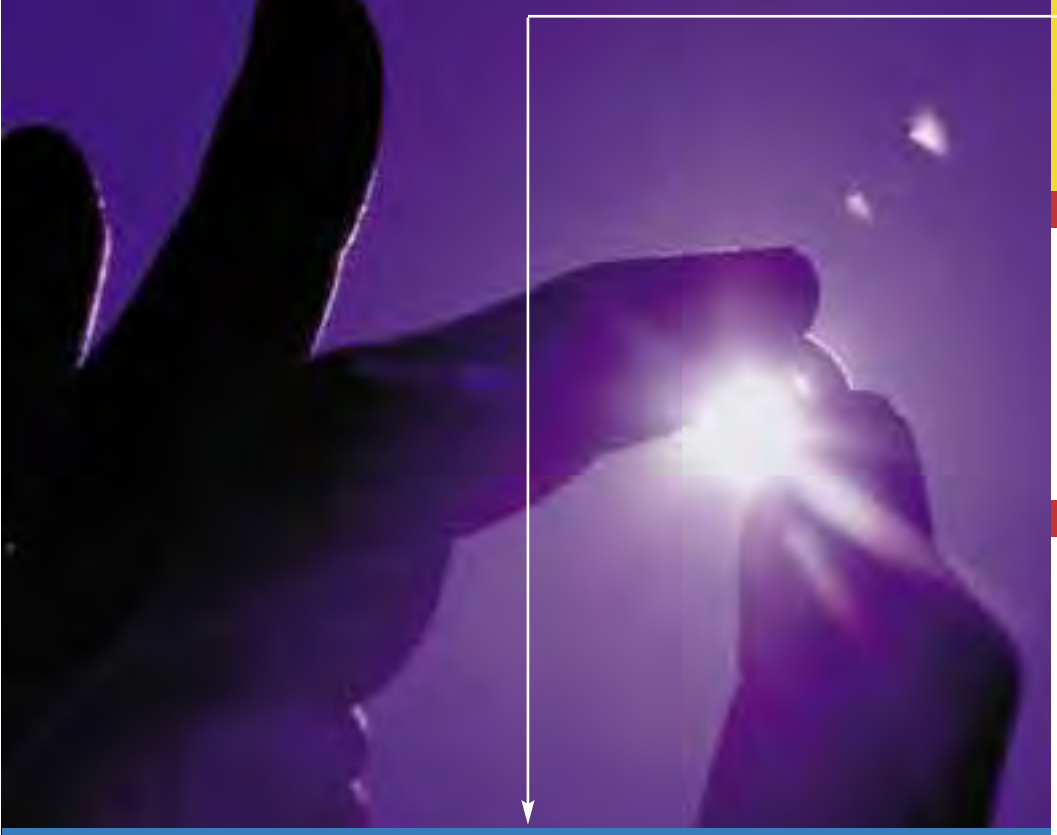
Please include the following information. Submissions received without full information will not be considered:

- ✓ Title
- ✓ Presenter's biography
- ✓ Additional authors
- ✓ Full mailing address
- ✓ Phone number
- ✓ Fax number
- ✓ E-mail address of the presenter
- ✓ 2-3 paragraph abstract, summarizing your topic
- ✓ The type of forum in which you can present your topic (traditional, case study, discussion/debate, panel)
- ✓ Target audience (by job title or department)
- ✓ Explanation of specific take-home benefits your target audience can use immediately on-the-job
- ✓ Key objectives of your topic and what new information you will present that has not been presented elsewhere

PDA also reaches a broad market with their signature audio conferences. If you are interested in submitting your abstract as a possible audio conference 1-2 months after the conference, please submit as well.

Upon review by the program committee, each submitter will be advised in writing of the status of his or her abstract after September 30, 2005. PDA will provide one complimentary meeting registration per presentation. Additional presenters will be required to pay appropriate conference registration fees. With the exception of health authority speakers, all presenters are responsible for their own travel and lodgings.

Visit us at the 2005 PDA/FDA Joint Regulatory Conference in Washington, DC, September 11-14, 2005 at Table #57



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