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PDA Letter

May 2004

A Monthly Communication for the Members of PDA—
An International Association for Pharmaceutical and
Biopharmaceutical Science and Technology

PDA Comments on Two FDA Draft Guides and a WHO Paper, pages 17, 18 and 19

Strong Science Program at 2004 PDA Annual Meeting

The 2004 PDA SciTech Summit™ and Annual Meeting in Orlando, March 8–12, represented one of PDA's best science agendas in years!

Word is out that the planning committee for the 2004 PDA SciTech Summit and Annual Meeting put together one of the strongest science-based conferences PDA has held in years.

Naturally, the scientific discussions in the meeting rooms included a number of presentations on one of PDA's core areas of competence—aseptic processing. Speakers addressed a variety of topics in this area, including new pre-sterilized closed-vial filling technologies, blow-fill-seal technologies, isolators and the latest news from FDA regarding the aseptic processing guidance.

The SciTech Summit program also covered topics like process analytical technology, new product development and delivery systems, innovative techniques for contamination control, disposable manufacturing systems and more.

Over the next several months, the *PDA Letter* will include articles covering many of the presentations

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PDA Interviews USP's Roger Williams

Roger Williams, USP

Earlier this year, PDA's Senior Editor Walter Morris met with USP CEO and Executive Vice President Roger Williams to discuss his first four years at USP. Dr. Williams reviewed the accomplishments made by USP during the most recent quinquennial cycle, set to close in March 2005. He also addressed the pharmacopeia's initiative to align its nomenclature more closely with that established by the International Conference on Harmonisation and other programs at USP meant to better serve its stakeholders.

Dr. Williams is the steward of the world's oldest and only independent (non-government) pharmacopeia. Before the U.S. FDA existed, Americans trusted products that adhered to USP standards. While many things have changed at USP since it was founded in 1820, one thing has not: USP still maintains a leadership role as the primary source of product standards and analytical method instruction for the pharmaceutical and biopharmaceutical industries in the United States and many countries across the globe. USP's independence and reliance on sound science has lent credibility to an industry that at times has faced serious credibility issues with consumers.

With the industry going through what is perhaps the most comprehensive change ever in terms of manufacturing and control capabilities and the therapies being offered, USP must work very hard to remain a key source of standards for the pharmaceutical industry. The biggest question is: How can USP continue to provide monographs and reference standards in an industry that is relying more and more on biological and genetically-based materials and private standards?

Dr. Williams answered this and other important questions. This is Part 1 of that interview:

Walter Morris: Roger, you joined USP at the beginning of the 2000–2004 quinquennial cycle. With that cycle winding down, what can you say has been the pharmacopeia's biggest accomplishments?

Dr. Williams: First of all, USP contracted with a

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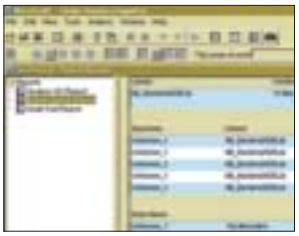

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PDA Letter

Important Dates...

- **June 1**—EMEA xenogeneic cell therapy medicinal products "points to consider" document becomes effective
- **June 8**—FDA E-Labeling Rule becomes effective
- **June 11**—FDA public meeting on Part 11
- **July 1**—EMEA Note for Guidance on Minimising Risk of TSE becomes applicable
- **July 5**—Deadline for public comment on FDA CDER Draft Guidance on CMC submissions for drug substances

Advertising Deadline: 1st of each month prior to issue date. Contact Nahid Kiani at kiani@pda.org or +1 (301) 656-5900 ext. 128.

IN THIS ISSUE...

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Neal G. Koller
PDA President

President's Message

Leverage Your Membership for Excellence

PDA continuously challenges itself to provide valuable education and resources to our members. Often this column serves to inform you of all the latest developments. This month, however, I'd like to address how each of us in PDA—every member, task force member, chapter officer, interest group member, board member—can challenge ourselves to use our relationship with PDA to achieve excellence and advance our careers.

As professionals in a very demanding community, PDA members are constantly challenged to expand our knowledge base in order to improve our products, processes, compliance, etc., and to ensure that our careers advance as our job skill requirements change. The body of knowledge required to fulfill our professional duties grows daily: Every hour, every day there are new technologies, new products and new regulatory requirements to learn and to put into practice. The challenge is to find time to take advantage of all the career-long professional development opportunities within PDA to learn, to grow and to stay ahead of the curve.

PDA's professional career development opportunities are recognized for excellence and come in a number of forms. They can be summarized into four basic areas:

1. Participation
2. Knowledge
3. Education & Training
4. Networking

As we explore each area, challenge yourself to take advantage of these opportunities to improve your skills and enhance your career.

Participation: Participation is perhaps the most beneficial career development opportunity within PDA. Through participation, you can attain valuable new leadership skills. If you participate as a Chapter Officer, a Chapter Regulatory Guidance Task Force Leader, a SAB or RAQC Task Force Leader, a Program Committee Planning Chair or any of the other many leadership positions in PDA, the experience and skill sets you develop will be extremely valuable throughout your career.

Join the Science Advisory Board (SAB) or an SAB Task Force or an Interest Group to become experienced at high level scientific collaborations with other experts in your field. Become involved in PDA's processes for characterizing and assessing the value of new science and technology and develop new skills by participating in the scientific peer review process. Join a team of experts and learn how to author a Technical Report on new technologies and methods.

Take advantage of the unique PDA professional development opportunities to learn the details, the scientific and regulator's rationale and the impact of new regulations by participating in the Regulatory Affairs and Quality Committee (RAQC), an RAQC Task Force or a Chapter Regulatory Guidance Task Force. Participation provides a special opportunity to understand the regulatory process and contribute to the improvement of regulations, significantly helping your company and advancing your career.

Submit scientific studies to the *PDA Journal of Pharmaceutical Science and Technology*, case studies to the *PDA Letter* and text books to the PDA Technical Book Advisory Committee. The process of research, writing and publication of original work provides you a valuable education and exposure to new colleagues and fresh ideas—all of which will help you perform better on the job.

Speak at conferences, teach through the PDA Training and Research Institute (TRI), volunteer to assist at conferences and courses (volunteers also receive a discount) and work on program committees—each provides unique professional development opportunities and leadership experiences valuable to your career and company.

Each of these PDA participation opportunities provides a unique organizational and personal leadership skill set for professional development at every stage of your career.

Knowledge: Use your PDA membership to learn. The development and communication of relevant scientific information is a mainstay of PDA and a great career advancement benefit for members. PDA provides knowledge via scientific publications (the Journal, the Letter, Technical Reports, text books, regulatory guidance comments and more). The *PDA Letter* and the PDA Web site present timely scientific developments and regulatory news. The challenge is to expand your knowledge base: Visit www.pda.org two or more times each week to learn "What's New," or read the current and past editions of the Letter. Access the PDA Sci-Tech Discussion Forum on the PDA Web site (www.pda.org/science) to get answers to important career-related questions or participate in a science discussion. Go to the E-store at www.pda.org/estore to find the technical books, multimedia educational tools, videos, journal articles and other resources that help us do our jobs better, enhancing career development.

Education & Training: With the right information at hand, it is easier to make a good decision, achieve success and advance your career. The challenge is to take advantage of your

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PDA's First 2004 Audio Conference a Success

PDA is receiving positive responses for its first audio conference of the year. On March 30, 2004, more than 275 participants from more than 40 companies dialed into hear "Applying Risk Assessment Tools to Computer System Compliance" presented by Keith Benze, Vice President of Compliance, SEC Associates, Inc.

The audio conference explored a "thought process" for conducting risk assessments for computer system compliance. Four key questions on this topic were answered during the presentation:

1. Do I have to validate my computer systems?
2. If so, how much work is necessary?
3. Which systems are in scope of Part 11?
4. What controls do I need for those systems?

Following the event, participants were able to understand how systems are used as part of the overall process; what records, if any, are being processed and used; do the appropriate level of work to assure systems function as expected and apply the controls necessary to assure complete and accurate records.

Participants rated the conference very highly. While not all felt the conference matched their exact needs, most felt it was very valuable. The following quotes come directly from course evaluation forms:

- "It was a good review of information as well as new information;"
- "The questions and thought process associated with risk assessment were useful;"
- "I will be applying this information to our search for a more robust training tracking software program."

If you missed this audio conference, you can purchase the conference CD and transcript, including the question and answer session, speaker handout materials and a full written transcript. Visit pda.org/audio/future.html and click on the "Audio Conferences" link. ■

New Faces at PDA

PDA welcomes five new staff members, all joining the PDA Global Headquarters in Bethesda, Maryland: **Shelbah Adams**, **John Johnson**, **Deborah Stokes**, **Jason Brown** and **Sheritha Wright**. All five are here to help ensure that PDA brings the best possible service to our members!

Shelbah is a welcomed addition as PDA's newest Executive Assistant to the President. She holds an Associate Degree in Business Administration from Danville Community College and has extensive experience in business administration, with over 25 years in the mortgage banking/real estate investment industries and in State government. Shelbah is charged with ensuring that PDA President Neal Koller knows where and when his next appointments are, arranging his travel itinerary, and most importantly, reminding him about his wedding anniversary, his children's birthdays and to go home in general! She also provides much needed support to the PDA Board of Directors.

John joins the PDA Market Services department as Marketing Manager will he will help ensure timely dissemination of information regarding PDA events, courses, publications and other services. He has extensive marketing and communications experience, having worked previously as a corporate communications specialist for Allegheny Energy, an editor for the Children's National Medical Center and a public affairs programmer for Giant Food Inc. He graduated from the University of Maryland with a BA in English Language and Literature.

Deborah and Jason are the newest additions to the PDA Programs and Meetings department. Deborah Stokes is a Certified Meeting Professional with experience working for the National Society of Black Engineers, where she rose quickly through the ranks to become the manager of their convention and meeting services division. She graduated from the University of California, Davis, BA in Psychology. Jason graduated from Morgan State University in 2002 with a BS in Telecommunications. Prior to joining PDA as our new Meetings Coordinator, he worked for MAMSI Health Insurance and served as a substitute teacher for the Montgomery County Maryland public schools.

As PDA's newest Data entry and Customer Service Coordinator, Sheritha will help find answers for member inquiries, process new memberships and renewals and handle other data entry projects. This May, Sheritha will receive her BA in Marketing and Management from the University of Maryland. ■

President's Message, from page 6

PDA membership to get that education and training so valuable to career growth—a conference, a TRI course, an interactive PDA audio conference—and learn from the expert presenters, the course instructors and the regulators. Ask questions, get answers and challenge assumptions. PDA provides the highest possible level of science and technology content, education and training programs, creating environments and activities conducive to formal and informal learning and providing a solid educational foundation for your career development.

Networking: Make connections with peers, regulators and esteemed experts in the pharmaceutical and biopharmaceutical communities and advance your career by developing the most valuable resource possible—a network of relationships from around the world to help you solve problems. There is a tremendous fundamental value in attending an event where people can engage in fact-to-face communication about their profession and learn to do their jobs better. There is no substitute for the personal connection and interaction that takes place. Whether you intend to network with colleagues, garner best practices or absorb as much information as possible, the end result of networking at a PDA event will be value. The challenge is to use your time at every PDA event to develop new contacts, new resources, new friends.

A challenge shared by all PDA members is reach out to colleagues in the pharmaceutical and biopharmaceutical communities to engage them in PDA. Teaching colleagues new to PDA about the value of the Association in the community at large will help them begin the process of using PDA membership for career advancement while assuring that new ideas are infused into the important scientific and regulatory work being advanced by current members.

PDA opportunities teach invaluable skills, including leadership, responsibility and teamwork. These and other professional development opportunities offered by PDA will help prepare you and your colleagues—junior and senior alike—for career advancement. ■

Missed the 2004 PDA Annual Meeting?

Mark your calendars now for the 2005 Annual Meeting **next April**!

SciTech Summit, from cover

made at the SciTech Summit to ensure that all PDA members benefit from this valuable conference. This month, the *PDA Letter* includes summaries of four Interest Group discussions that took place during the 2004 PDA SciTech Summit and Annual Meeting (starting on page 9).

A major highlight of the 2004 PDA SciTech Summit and Annual Meeting was the introduction of PDA's New, Innovative Technologies™ (NIT) Exhibition Program. The NIT™ Exhibition Program represents PDA's most recent science and technology initiative that utilizes the PDA peer review system to bring the recently introduced and soon-to-be introduced technical innovations to the membership. It is designed to help PDA members and their companies stay ahead by exposing them to the latest ('latest' meaning introduced either 12 months prior to or 12 months after the conference) technologies relevant to the industry. When new, innovative technologies and services are first to market, PDA members will be the first to know.

A major highlight of the 2004 PDA SciTech Summit and Annual Meeting was the introduction of PDA's New, Innovative Technologies™ (NIT) Exhibition Program.

The PDA NIT Exhibition Program utilizes a two-pronged PDA peer-review system: **the NIT Exhibition Board** and **Industry Expert peer-review group**. The system works to assure products submitted for participation in the NIT™ Program are new and valuable to PDA members.

Five new technologies were cleared by the peer-review system and were on display at the 2004 Annual Meeting:

- **EXTERM™** by ClorDiSys: A broad spectrum disinfecting tablet that gently and effectively allows companies to eliminate contamination.
- **VISTA™** by Lighthouse Instruments and develop with funding from FDA: An in-line, non-destructive, leak detection system.
- **CACTUS-OS** by Opulus Ltd.: Provides seamless computing and open standards to competency training.
- **Liquid Particle Explorer** by Sci-Tec, Inc.: Combines image analysis and Raman spectroscopy for the measurement of the size, shape and chemical composition of particulate contaminants in parenterals and other high purity liquids.
- **High Precision, Automatic Head Space Gas Analysis Machines**, by Wilco AG: In-line lead detection machine.

More information on these products and the NIT Exhibitions Program is available at www.pda.org/exhibits/NIT.html. ■

[**Editor's Note:** Please see pages 29–30 and page 37 for photo highlights from SciTech Summit.]

Interest Group Meeting Reports From the 2004 PDA SciTech Summit and Annual Meeting

At the 2004 PDA SciTech Summit and Annual Meeting most of PDA's Interest Groups assembled to review current issues and/or report their progress. Over the next several months, their reports will be published in the *PDA Letter*. The following groups have submitted reviews of their discussions for this edition:

Quality Assurance/Quality Control—U.S. Branch

Leader: **Don Elinski, Validation Manager PWC, Eli Lilly and Company**
E-mail: **elinski@aol.com**

The QA/QC Interest Group provides members an opportunity to network on topics of mutual interest at the PDA Annual and PDA/FDA Meetings. In addition the Interest Group sponsors a forum on the PDA Website where members can ask questions and dialogue with other Industry experts. Topics of note from the last year were taken from the QA/QC forum by IG leader Don Elinski and presented to the Group as potential topics for discussion.

Richard Friedman, Team Leader: FDA Guidance and Policy, CDER Office of Compliance, U.S. FDA, along with many industry representatives, participated in the meeting at the 2004 PDA Annual Meeting and SciTech Summit. Topics of discussion are summarized below.

Shipping Validation: Recent 483's indicate the FDA is concerned about the impact of excursions. This continues to be a topic of interest in the industry and the subject of several PDA specific meeting segments.

Isolators: FDA is finalizing its guidance on aseptic processing. It takes 18–24 months to install either an isolator or a conventional filling room. Isolators are favored for sterility assurance, but they need to be designed to accommodate highly automated reliable processes.

Quality Agreements: Outsourcing makes the FDA nervous. The relationships are not clearly delineated in the cGMP's. Quality agreements can help in defining responsibilities and quality concepts between the supplier and the drug product owner. Device GMP's clearly call for appropriate quality systems, agreements, structures and design controls. These are good concepts that can be applied to the drug world.

1996 cGMP rewrite: FDA is still working on these. If the industry would like to see them finalized it should write to FDA, via the PDA, requesting their expedition. Since 1996, much of the content has been either clarified or has become part of cGMP.

Bulk Holding Times: Generally two weeks. Thirty days is recommended in the U.S. FDA stability guidance. Contributing factors to consider in solids are settlement, conglomeration and vibration. Liquids, of course, are subject to concern over possible microbial growth.

Requalification of Equipment: Should be based upon a review of change controls, deviations and PM records. One company uses an interval of five years for process re-validation based on cumulative change control risk.

Annex 1 vs. cGMP: PQRI worked with FDA on most of the issues with the aseptic processing guidance. Alignment with the EU's Annex 1 still leaves some issues. Both sides are looking at changes. The FDA has used the ISO classifications in their document. They also switched to the metric system in air sample nomenclature. The FDA aseptic processing guideline will, however, specify a "suitable sample" dependent on the collection efficiency, but will not require a full cubic meter to be sampled.

Risk-Based Compliance: Failure Mode and Effect Analysis and Hazard Analysis and Critical Control Point are good methods. Many companies are using Six Sigma methodology. FDA is not specifying how to do risk analysis at this point, but feels it should be based on good science. Supplier certification is a risk area industry should look to for defect reduction.

FDA Inspection of Research Facilities: FDA is not doing much here. cGMPs here really should be risk based and dependent on stage of clinical product.

In all, discussions were good and open. The QA/QC Interest Group—U.S. Branch will meet again at the PDA/FDA meeting. Of course, PDA members from all over the world are encouraged to attend. A panel discussion on "Health Hazard Analysis" and its relationship to complaint management is planned.

Filtration Interest Group—U.S. Branch

Leader: **Jack Cole, Jack Cole and Associates** (not present)
E-mail: **jvcole@aol.com**
Presiding Chair for Meeting: **Jerry Martin, Senior VP, Pall Corporation**
Minutes: **Montgomery Carlisle, Product Specialist, W. L. Gore & Associates**

The IG discussion opened with Task Force reports:

Sterilizing Gas Filtration Task Force: Document is almost complete. It will detail best practices, validation by filter manufacturer. Final draft to be submitted to PDA Science Advisory Board (SAB) and the PDA Board shortly.

Depth Filtration Task Force: Committee formed and first meeting scheduled for March 10,

continues on page 10

Didn't get a chance to attend an IG at the 2004 PDA Annual Meeting?

You'll have another chance at the 2004 PDA/FDA Joint Regulatory Conference.

Go to www.pda.org for more details!

Interest Group Updates, from page 9

at the 2004 PDA Annual Meeting and SciTech Summit. George Quigley, Vice President, Ertel/Alsop was named task force leader.

Virus Filtration Nomenclature Task Force: Meeting scheduled March 11, at the 2004 PDA Annual Meeting and SciTech Summit to review working draft. Gail Sofer, Director, Regulatory Services, BioReliance, is the task force leader.

Open Discussion topics:

Steam in Place: Damage from SIP is the most common cause of filter failure.

One end user reported that he sees bulging (ballooning) in cartridges after steaming. Details of his application:

- 10" or 20" filter cartridge
- Filter is integrity tested alcohol wet and then dried with nitrogen prior to steaming.
- Steam in reverse direction with 20–25 psi steam

There was a lot of discussion about this problem. Possibilities were that the filter was not adequately dried prior to steam introduction or possibly became blocked with condensate droplets. Another possibility was that incoming pressure was too high such that steam delta P exceeded design criteria. Most filter manufacturers recommend steaming with 3–5 psi pressure drop across the filter in either direction, and steaming in the forward direction since the cartridge is stronger in that direction and better able to handle excursions without damage.

It was noted that if steam was added later to this system, the system may not be engineered appropriately (steam traps, condensate drains, etc.) for SIP. Inadequate drainage of condensate would cause bulging.

Polypropylene softens and approaches its melting point at ~140–145°C. Another suggestion was that the steam was too hot and it was softening polypropylene in cartridge.

It was noted that sterilizing with super-heated steam is not better than sterilizing with saturated steam. The heat of vaporization is the primary source of energy for sterilization. Super-saturated steam is also not advisable since water droplets in the super-saturated steam could impact the membrane in the cartridge and cause blockage and excessive delta P.

Proposal from users/PDA to develop standardized rating systems for 0.1 and 0.2 micron sterilizing filters: A review of the history of 0.2 micron sterilizing filter challenges was presented by Jerry Martin:

- The FDA discovered in the mid '60's that a 0.45 micron filter challenged with $>10^7/cm^2$ of B.
- Diminuta (ATCC 19146) would not ensure sterility, while a 0.22 micron filter challenged at that level could provide a sterile effluent. This lead to the recommendation of 0.22 (or 0.2) micron filters as "Sterilizing Grade."
- ASTM Standard F838 established a best practice for performing the B. diminuta
- Challenge to classify membrane filters as "sterilizing". This standard is still supported by ASTM, but is classified as "withdrawn" because its parent committee disbanded and has not put it through ASTM's required 5 year renewal cycle. This document is referenced in PDA Technical Report #26 and by many sterilizing filter manufacturers.

There is no standard test for distinguishing a 0.2 micron from a 0.1 micron filter. For 0.1 micron challenges, every filter manufacturer uses a different strain of microplasma. So, filters that have the same nominal rating can have different retention performance. A Scope Statement for a sterilizing filter standard test was drafted by the PDA SAB but has not yet been widely distributed. The general feeling of participants was that this standard would not provide a benefit to the end user because:

- There are no published studies to determine the most penetrative
- Mycoplasma and limited studies on whether a "diminutive" bacteria would be a better challenge (diminuta is not the smallest bacteria).
- This standard will not tell end user how filter will work in their application.
- The end user would still have to validate the selected filter in their drug and operation (Bioburden process specific validation).
- A standard might force a variety of filter options out of the market.
- Proposed topic for next meeting of the Filtration Interest Group discussion: extractables.

Lyophilization Interest Group—U.S. Branch

Leader: **Edward Trappler, President, Lyophilization Technology**
E-mail: **frzdry@lyo-t.com**

The interest group session opened with the typical introduction, description of the format, request for participants to contribute topics and their comments to the discussion.

Participants were surveyed for preferences in the objectives, goals, and structure of the interest group sessions. The unanimous consensus was for an informal forum with the participants identifying topics for discussion. The benefits to participants was the open exchange of information, exploration of current topics and issues, as well as the opportunity for someone new in the field as a learning experience, gaining insights into the technology.

Topics introduced at the SciTech Summit were:

- Critical Process Parameters
- Application of PAT
- Process Validation
- Use of Isolators
- Equipment Qualification

The group also wanted to discuss some of the topics covered during the 2003 Annual Meeting in

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PDA
An International Association For Pharmaceutical Science And Technology

The *New* PDA Publications E-store is here!

PDA is pleased to announce that its Publications E-store is now available online at https://www.pda.org/pubs. The fully-interactive E-store is a one-stop shop of the largest selection of scientific, technical, and regulatory resources PDA has offered in its 57-year history.

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or

✓ Browse the **"Table of Contents"** by publication type (for PDA Technical Reports, PDA Proceedings, Training Videos, and more) much like you would a hard-copy of the PDA Publications Catalog.

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Recent Sci-Tech Discussions

"Bioburden of active ingredients and products" & "Dye leak testing of ampoules"

The following, unedited remarks are taken from the Pharmaceutical Sci-Tech Discussion Group, a PDA-sponsored Online Forum at www.pda.org. PDA Online Forums are free of charge and open to the public. They serve as a platform for exchanging practical and sometimes theoretical, ideas within the context of some of the most challenging issues confronting the pharmaceutical industry. If you are not currently a member of a discussion group, we encourage you to visit our Web site and join.

This month's posting...

Question 1

The European Pharmacopoeia states that "certain active ingredients and products that cannot be terminally sterilized may be subjected to a sterile filtration procedure…Solutions are passed through a bacteria-retentive membrane with a nominal pore size of 0.22 μm or less …

Due to the potential additional risks of the filtration method as compared with other sterilization processes, a pre-filtration through a bacteria-retentive filter may be advisable in cases where a low bio burden cannot be insured by other means."

My question is: At which levels is a bio-burden to be considered as "low" (10cfu/ml, 100cfu/ml…)?

Are there any references where limit for a low bio burden is given?

Response 1

Depending on the material, a bioburden in the excipient or active ingredient will normally be accepted at 100 cfu per gram or per ml provided that the likely contamination level in the pre-sterilized bulk product is not likely to exceed the safety margin for the filter type to be used. The exception to this is water. For manufacture of aseptically filtered products water should have a bioburden of 1 cfu per 100 ml.

Bulk solutions should have a bioburden of 10 cfu per 100 ml prior to being passed through a sterilizing grade filter. If the bulk solution has a higher bioburden it should be passed through an initial filter to reduce the bioburden to that level.

Response 2

If you want a reference for what constitutes a low bioburden in the EU, take a look at the CPMP/QWP/486/95 "Note for Guidance on Manufacture of the Finished Dosage Form" (EMEA). In there it specifically states that "in most situations" a bioburden of NMT 10cfu/100ml would be acceptable when submitting your regulatory application. This means that if you register a higher bioburden level, they will ask your to justify it. The guidance continues and states that if this "requirement" (i.e. 10cfu/100ml) is not met, it is necessary to use a pre-filter to obtain a sufficiently low bioburden. There is no U.S. guidance that I know of that states a level as do the Europeans. I personally think it a bit over the top to be expected to start with a WFI grade product when we filter through a validated system that has been proven to remove at least a 10E7/cmE2 challenge. This is the reality though.

Response 3

One must achieve a low bioburden since prefiltration as a means to reduce high bioburden is not acceptable due to possible pyrogen problems. Have you thought about the bioburden steam sterilization method where one titrates a sterilization cycle based on bioburden and microbial resistance. Overkill is not the only way to go. One can't look at bioburden alone as one needs to be concerned with the total challenge to the filter which is result of bioburden and volume filtered.

Question 2

Is anyone aware of a way to validate the dye leak test for filled sealed ampoules?

Response 1

Ampoules are immersed in a dye solution under pressure. This is a physical method to evaluating container/closure leakage.

Response 2

I recommend using Leak Test in Autoclave under pressure, a more representative test, as mentioned in Tech. Monograph of Parenteral Society - England. Ampoules are not correctly sealed, are broken under pressure, enough.

Response 3

You can get excellent ideas on Test Validation from The Parenteral Society's Tech. Monograph No. 1 "The prevention and Detection of leaks in Glass Ampoules."

I've validated in past this Test according some ideas on it document.

Response 4

You can use alternative methods as Blotting Paper, High Frequency Spark Test or Dye bath; all methods apply for suitable conditions, advantages and disadvantages, as all.

For thermo labile products in ampoules, I think and remember, as which specifically, for example Vitamins. We remember too that ampoule products require final sterilization in autoclave if it's possible, if not, at temperatures of 121° C, other temperatures are required, as usual 112–116° C, We need to use Fo calculations at this temperatures for lethality, then use leak test alternative methods, include Dye Bath, as mentioned.

Response 5

Ampoules are immersed in a dye solution, such as 1% methylene blue, and applying at least 64 cm of vacuum for a minimum of 15 min. The vacuum on the tank is then released as rapidly as possible to put maximum stress on weak seal. Next, the ampoules are washed. Defective ampoules will contain blue solution.

Response 6

Please notice that Dye Bath Test has, between others, next disadvantages, unsuited for highly colored solutions, contamination by undetected dye, and as has been mentioned, ampoules need subsequent cleaning.

I you need the test for QC purposes, well, if not, consider other alternatives.

Response 7

I understand the test. I'm just not sure how to validate it. It seems to me you would need some sort of positive control to show that if you did have a cracked ampoule, the dye test would detect it. I'm not aware of anywhere you could purchase or obtain positive control glass ampoules though. Any ideas?

Response 8

There are specially made autoclaves with arrangement for loading the entire batch of say 50,000–100,000 filled ampoules or even more, with provision for spraying dye solution. The entire chamber is filled with dye solution & pressure/vacuum is applied for some time. The ampoules are washed with fresh water. This entire system (Dye solution and water) is in recirculation so that you can reuse the dye solution and water after due treatments (filtration etc to reduce bioload).

I think application of vacuum is better since broken ampoule and liquid tend to collapse under vacuum than under pressure where the fine particles can spread.

If the product undergoes terminal sterilization the process should be done after sterilization so that weaker ampoules/v slightly cracked ampoules are also detected.

As per my knowledge this is the way in which filled ampoule batches are checked for leakage. ■

Interest Group Updates, *from page 10*

Atlanta last November:

- Product monitoring
- OQ/Shelf mapping
- Condenser performance
- Unique experiences
- PAT
- Inspection

Not to imply any significance of the importance of any one subject, the topics will be presented here generally following the order they were introduced during the session, reflected in the listing above.

Critical process parameters of shelf temperature, chamber pressure and time were highlighted. The term "shelf temperature" is actually measured as the heat transfer fluid going to the shelves. Another method has been measuring the temperature using thermocouples mounted on the shelves, calculating the average, discarding the highest and lowest temperatures, recalculating the average, and using a recalculated average as the input for shelf temperature control. This control logic is uncommon, quite involved and considered antiquated technology. Measuring the shelf outlet at fluid discharged from the shelf manifold was also mentioned, as well as the differential between the inlet and outlet, particularly during freezing. These techniques were of interest in monitoring and considered antiquated and uncommon for process control.

Discussions on chamber pressure as a critical process parameter began with **methods of measurement**. The accuracy and precision is greater when using the electronic manometer as compared to the Pirani gauge. Different approaches to pressure control during the process included the most common method of introduction of sterile filtered nitrogen into the chamber, termed nitrogen bleed. Stifling the vacuum pump by introducing air into the suction inlet of the vacuum pump and modulating the valve between the chamber and condenser are alternate methods, although not considered to be a contemporary technique.

Time for each process step, the third critical process parameter, along with changes in the shelf temperature, was, in some aspects, also associated with product temperature. A soak, being a fixed time at a target shelf temperature setpoint, was agreeably straightforward, with a few permutations in methods that have been used. These are mostly associated with product temperature, as indicated in Table 1 below.

Table 1: Processing conditions where variable time is incorporated.

Freezing: Combination of specified product temperature, **add** time if necessary
Primary Drying: combination of specified product temperature, **add** time if necessary
Primary Drying: combination of specified product temperature, **and** time
Secondary Drying: Combination of specified product temperature, **a range** for time

A ramp, reflecting a rate of change from one shelf temperature to another, needs to be well controlled. Left uncontrolled, the actual rate achieved will be strongly influenced by the equipment performance and batch size. With even the simplest control automation, such ramp rate control is easily accomplished.

continues on page 14

Interest Group Updates, from page 13

Discussions on product temperature were lively. Separately, participants referred to product temperature monitoring as providing both "good and bad data." Thermocouples are the preferred method of product temperature measurement. It was recognized that the size of the thermocouple wire used in manufacturing is not conducive to accurate placement in the product container and often moves when placing the probed container onto the shelf. Positioning the container on the shelf also was reported to be a significant challenge. Most often, the containers are placed at the front of selected shelves. One participant indicated they placed the container approximately six inches from the front, verifying suitable aseptic technique for the procedure by including the task as part of conducting media fills. The benefits of product temperature measurements identified in the discussions are listed in Table 2.

Table 2: Considerations in product temperature monitoring.

Can only be used with manual loading.
Provides a "fingerprint of the process".
Useful in assuring process consistency.
A PAT tool.
Critical in development, scale-up and first three validation batches
Need for greater monitoring and control of the lyophilizer and process.

Alternate methods for evaluating the progression of the process and product temperature were also introduced into the discussions. These included use of a pressure rise and a comparison between a thermoconductivity gauge and electronic manometer, as well as a manometric measurement that estimates product temperature during sublimation in primary drying based on the vapor pressure of ice corresponding to the product temperature.

The condenser temperature, like product temperature, was indicated to be a dependent and non-critical process parameter. The condenser temperature should be monitored and alarmed, with temperature lower than -40° to -50°C expected. Performance of the condenser was described to be dependent upon pressure and vapor stream composition.

The session in March was just over two hours with lively discussions that also included considerations for **equipment qualification**. Choosing performance parameters and setting acceptance criteria were the major points in the discussions. This was coupled with the concern of how to handle "vintage" equipment. Shelf mapping was the major topic, with approaches of monitoring to include the inlet and outlet of each shelf as a minimum, with five locations consisting of each corner and the center of each shelf. Temperature uniformity criteria of ±1° across each shelf, ±2°C across all shelves, and shelf temperature control of ±1°C are preferred. Evaluation of the control and uniformity should also include the control point of shelf inlet in the acceptance criteria. Discussions also included the need to specify the criteria in the user requirements or user design specifications and whether such a test may need to be included as part of a requalification study.

As is usual, discussions focused on the topics of greatest interest to the group of participants. Once again, the discussions were informative and insightful. A reflection on the contemporary concerns and challenges, along with gaining an awareness of what others in the industry are doing, are the benefits to participants in this interest group meeting.

Production and Engineering Interest Group—U.S. Branch

Leader: **Frank Bing, Consultant, Abbott Laboratories**
E-mail: **frank.bing@abbott.com**

The Production and Engineering Interest group met on Tuesday morning at the SciTech Summit. The guest speaker was Mr. James E. Alexander of DuPont Dow Elastomers. Mr. Alexander provided a very thorough and enlightening presentation on the factors that effect the performance of elastomeric seals used in pharmaceutical processes. He began by explaining the differences in polymer architecture that dictate the desired performance characteristics of any elastomeric compound.

One of the key factors in assuring a thermoplastic's expected performance is knowing and controlling the constituents of any given compound. Since the polymer's supply chain may be lengthy, including the base elastomer supplier, a rubber compounder, a part molder, a distributor and a final supplier, the exact identity of a part may often be difficult to determine.

Mr. Alexander suggests that this be controlled with thorough purchase specifications. A properly written specification for thermoplastic seal should include identification of the base elastomer by manufacturer and grade, identification of all fillers and additives, the expected performance in key characteristics such as temperature, durometer, fluid resistance, toxicity, etc., and approved part suppliers or manufacturers.

This excellent presentation will be posted on the P&E IG section of the PDA Web site. ■

PDA Interest Groups & Leaders

The following is a list of PDA Interest Groups (IGs). Starting in 2004, PDA began establishing "Branches" of each IG in the various regions of the world that we serve. The list below includes the names of the Leaders for each Branch of the IG, the Leader's affiliation and their e-mail address. More detailed information on PDA's Interest Groups and contact information is available on the PDA Web site at: www.pda.org/science/IGs.html.

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VP's Message

Dedrick

Reflections toward the Future

Reflecting back, my first three months at PDA have brought me many insights into the Association, its members and their needs. It has been a time of rapid assimilation and learning about PDA and its culture. I have had the opportunity to meet with many members at conference and chapter meetings both internationally and domestically to discuss what the important issues are for PDA members, what they are looking for from the Association and how PDA can best serve the membership moving forward.

It is very clear that PDA members not only need, but want to look to the future and embrace new technologies, opportunities and challenges facing their individual companies and the pharmaceutical and biopharmaceutical communities as a whole. In discussions with members, I've learned that PDA must continue advancing good science and its application in assessing product quality and in deriving the regulation of new innovations in the industry. Innovation is essential for the future, and PDA and its growing global membership are poised for this challenge.

To provide the best service to our members, the scope of PDA is rapidly evolving from its ever present competence in parenteral drug manufacturing and microbiology to include biotechnology, bio-nanotechnology and combination products. The challenges we face in delivering valuable information in these areas parallel those being addressed by regulatory agencies around the globe to advance product development in an efficient manner, to reduce the cost of making and consuming medicines, and to produce products that are safe and more effective.

Looking specifically at combination products (i.e., drug-device, drug-biologic, and device-biologic products), our members both in industry and the regulatory agencies are trying to answer difficult regulatory and scientific questions. These products are blurring the boundaries established by the regulatory bodies for product types, causing, in some cases, confusion as to how to handle the product registration process and post-approval cGMP compliance. Seeing the need to formalize its handling of combination products, the U.S. FDA established the Office of Combination Products last year.

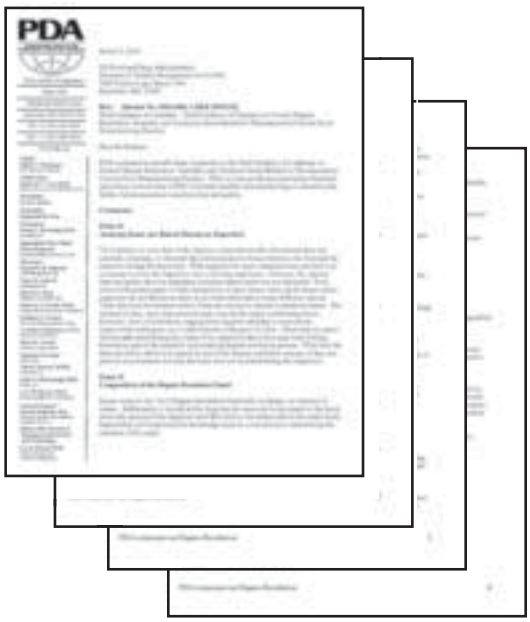
FDA also recognized, rightly, that the trend in industry will be for the creation of even more combination products in the future. Increasingly, these types of products incorporate cutting edge, novel technologies that hold great promise for advancing patient care. For example, innovative drug delivery devices have the potential to make treatments safer, more effective and more convenient to patients. Drug-eluting cardiovascular stents have the potential to reduce the need for surgery by preventing the restenosis that often occurs following stent implantation. Drugs and biologics can be used in combination to potentially enhance the safety and/or effectiveness of either product used alone. Biologics are being incorporated into novel orthopedic implants to help facilitate the regeneration of bone required to permanently stabilize the implants.

Industry, too, predicts that significantly more combination products will be submitted for review as technological advances continue to merge therapeutic products and blur the historical lines of separation between drug, biologic and device medical products. Since combination products involve components that would normally be regulated under different types of regulatory authorities, and frequently by different centers, they also raise challenging regulatory, policy, and review management issues. Helping industry to establish a sound scientifically supported path for regulatory advancement through this uncharted territory represents an enormous opportunity for PDA's members.

Another regulatory development driven by the transforming industry is FDA's transfer of therapeutic products from CBER to CDER, including monoclonal antibodies for in-vivo use, cytokines, growth factors, enzymes, immunomodulators, thrombolytics, proteins intended for therapeutic use, and other non-vaccine therapeutic immunotherapies. This consolidation provides great opportunities for PDA to further contribute to the development and coordination of sound scientific methodology in support of good regulation. This will lead to a more efficient, effective, consistent and less burdensome regulatory program for human drugs and biologics and reduced time-frames and costs to industry. In response, PDA has activated its Biotechnology Advisory Board (BioAB) that will be responding to global initiatives in this area. **[Editor's Note:** Look for more information on the BioAB in the next edition of the *PDA Letter*.]

Looking forward from these reflections I am very excited to be a new part of PDA and look forward to having the opportunity to participate in shaping the future of the pharmaceutical and biopharmaceutical industry. The better our science, the fewer our failures and the greater our successes. ■

PDA RAQC Comments on FDA Dispute Guide: "Lack of Consistency in Timeframes"



March 5, 2004

US Food and Drug Administration
Division of Dockets Management (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Ref.: [Docket No. 03D-0386, CDER 2003131]
Draft Guidance for Industry – Draft Guidance for Industry on Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical Current Good Manufacturing Practice.

Dear Sir/Madam:

PDA is pleased to provide these comments on the Draft Guidance for Industry on Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical Current Good Manufacturing Practice. PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical manufacturing and quality.

Comments:

Point #1
Assuring Issues Are Raised During an Inspection

The Guidance is very clear in the Agency's expectations that this process does not preclude, eliminate, or diminish the communication of issues between the firm and the inspector during the inspection. PDA supports the open communication and sees it as necessary to move the inspection into a learning experience. However, the Agency must recognize there are legitimate instances where issues are not discussed. Even where both parties agree to daily discussions of open issues, there can be issues where inspectors do not discuss an issue as an observation due to many different reasons. There also may be instances where firms are reticent to discuss contentious issues. The element of time, more than personal style, may be the major contributing factor. However, fears of retribution, ranging from negative attitudes to more severe inspectional techniques, are a valid concern on the part of a firm. There may be issues that are not raised during the course of an inspection that a firm may want to bring forward as part of the scientific and technical dispute resolution process. PDA feels the firms should be allowed to appeal as part of the dispute resolution process, if they can provide sound reasons for why this issue was not reviewed during the inspection.

Point #2
Composition of the Dispute Resolution Panel

Issues raised to the Tier 2 Dispute Resolution Panel will, by design, be technical in nature. Additionally, it should not be forgotten the issues are being raised, to this level, above the opinion of the inspector and ORA (both at the district and at the center level). Impartiality and broad scientific knowledge must be a cornerstone in determining the selection of the panel.

PDA feels strongly that the Dispute Resolution Panel must include panel members outside of the Agency. Impartial expertise can be provided by other knowledgeable experts outside of the agency. Professional organizations, such as the PDA, can compile a list of pre-qualified experts in the spectrum of technologies involved who can be available for participation on the Dispute Resolution Panel.

Point #3
Disclosure of Information

As part of a response to an inspectional observation in the existing process, companies have provided information which is redacted upon public disclosure. Companies, through the benefit of time and experience, are "calibrated" to know how much and which information to provide and through the benefit of a development of trust, know how the Agency will disseminate the information.

Raising an issue as part of the Tier 1 technical dispute process will, in all likelihood, require more information than normally contained within a response to an inspectional observation submitted to the Agency. Additionally, the Agency will face a difficult decision: how much information to release to sufficiently explain the issue and the decision from the dispute balanced against the need to maintain the confidentiality of the proprietary information.

continues on page 21

PDA Blend Uniformity Task Force Comments on FDA BU Draft: "Guidance Avoids Term 'Validation'"

April 2, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, RM 1061
Rockville, MD 20852

Ref: [Docket No. : 2003D – 0493]

Draft Guidance for Industry on "Powder Blends and Finished Dosage Units-Stratified In-Process Dosage Unit Sampling and Assessment"

PDA is pleased to provide these comments on the FDA Draft Guidance for Industry on "Powder Blends and Finished Dosage Units-Stratified In-Process Dosage Unit Sampling and Assessment".

PDA is an international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical science, manufacturing and quality. Our comments were prepared by a committee of experts in the field. These stakeholders are ready to work with FDA via PDA to further develop and refine the guidance for Powder Blends and Finished Dosage Units-Stratified In-Process Dosage Unit Sampling and Assessment that would ensure quality products in the market place, which is the ultimate goal of both FDA and industry. PDA was instrumental in initiating blend uniformity analysis evaluations in Technical Report No. 25. This report provided the foundation for PQRI activities.

We are pleased to offer our comments in order to further improve the document. We trust that our comments will be received as they were intended; that is, to strengthen the utility of the guidance that will be used by people with very diverse needs: ORA, Compliance, OPS, and the regulated industry.

Of particular note are the following recommendations:

1) The PQRI report to the FDA recommended the exclusion from the requirements of the guideline those products where the determination of dosage-form uniformity by weight variation is allowed. The former draft BU guidance for ANDA products also excluded these products. If they are not excluded, it is recommended that the Agency reassess the economic impact to the industry of the additional burden of now running both potency and weight variation analysis on these products.
2) The guidance avoids the term "Validation" and uses less descriptive titles like "verification of manufacturing criteria." PDA feels that the reluctance to use the term "Validation" creates a disconnect with the PQRI proposal making the Guidance more difficult to interpret. The term "Validation" is well defined by the Industry and the FDA and the term should be utilized to denote those activities in this guidance that clearly fall under its purview.

PDA would like to praise the cooperative effort between Industry and the FDA via PQRI that has resulted in the utilization of good science and logic to bring resolution to an area of some controversy and disagreement. The resultant benefactor of this Guidance will be the consumer, who now can be assured of the efficacy of their medication.

PDA would be pleased to offer our expertise to assist in the clarification of our comments, and the continued evolution of this important guidance. We look forward to working with FDA, industry and other professional associations to develop a world-class guidance document.

Acknowledgements:

PDA thanks the members of the Blend Uniformity Task Force for their input in developing these comments.

Name	Company
James Bergum	Bristol-Myers Squibb Company
Jim Carron	Pharmaceutical Services Corporation
Bob Dana	Elkhorn Associates
Don Elinski	Eli Lilly and Company
Garnet Peck	Purdue University
Laura Foust	Eli Lilly and Company
Daniel H. Gold, Ph.D.	D. H. Gold and Associates, Inc.

continues on page 21

PDA Distribution Task Force Comments on WHO Working Document: Repackaging & Relabelling Out of Scope

March 31, 2004

Dr. S. Kopp
Quality Assurance and Safety: Medicines
Essential Drugs and Medicines Policy
World Health Organization
1211 Geneva 27, Switzerland

Ref: WHO Working Document QAS/04.068: Good Distribution Practices (GDP) For Pharmaceutical Products

Dear Dr. Kopp:

PDA is pleased to provide these comments on the WHO Working Document QAS/04.068: Good Distribution Practices (GDP) for Pharmaceutical Products. PDA is an international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical and biopharmaceutical science, manufacturing and quality. Our comments were prepared by a committee of experts in the field.

PDA understands the value that clear and concise documentation on Good Distribution Practices can provide for both regulatory bodies and regulated industry. As such, we are pleased to provide WHO with our comments on Working document QAS/04.068, Good Distribution Practices (GDP) for Pharmaceutical Products. The key points we would like to make are:

- In the scope and elsewhere, the document discusses appropriate activities related to repackaging and relabeling. We believe the references to repackaging and relabelling should be deleted as these activities are clearly covered by Good Manufacturing Practice regulations and guidelines, and are not normally considered distribution activities.
- Wherever possible, definitions should match industry standard definitions. Creating new definitions or modifying existing definitions can lead to unnecessary confusion and misunderstanding. The definitions we have recommended are from Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2002 and its Annex 18.
- Section 6.11 is highlighted as a specific concern as it requires work outside of the scope of GMP that would be difficult if not impossible to implement. We contend that stability studies by the manufacturer should define the storage conditions, including shipments; to ensure products meets its quality characteristics throughout its shelf life.
- The various sections on vehicles and equipment refer to cleaning validation, e.g., 8.3. We agree that bulk liquid transport vehicles may require cleaning validation. Some sections could be interpreted to mean that transport vehicles carrying bulk containers and/or finished goods also require cleaning validation and we believe that in such cases, cleaning validation is not necessary. Cleaning should be appropriate to ensure that no mix-ups or contamination can take place.

PDA has reviewed the document in detail and our comments are attached. For ease of review, we have listed our comments by line number and section/paragraph. We have included a copy of the document with line numbering.

PDA would be pleased to offer our expertise to assist in the clarification of our comments, and the continued evolution of this important guidance. We look forward to working with WHO, industry and other professional associations to develop a world-class guidance document.

Acknowledgements:

PDA thanks the members of the PDA Good Distribution Practices (GDP) for Pharmaceutical Products Task Force for their input in developing these comments.

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Joyce Ramsbotham	Solvay Pharmaceuticals
Mark Staples	PDA New England Chapter
Dan Linehan	PDA West Coast Chapter
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continues on page 21

21st Century Initiative

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PDA An International Association For Pharmaceutical Science And Technology

FDA

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To register, get more information or to reserve exhibit space, visit
www.pda.org/PDAFDA2004
Tel: +1 (301) 656-5900 • E-mail: *info@pda.org*

Dispute Resolution Letter, *from page 17*

For an issue to be elevated into the Tier 2 Dispute Resolution Panel, even more detailed information will need to be forwarded by the company to the Agency. Any correspondence between the Agency and the firm will also be subject to disclosure. The confidentiality measures to be employed must be of the highest order and should be discussed between the Agency and the firm. At a minimum, the Agency must afford the company an opportunity to review and first comment regarding what the agency intends to disclose.

Point #4
Pending Regulatory Action during Interim Periods

It seems inappropriate to take regulatory action while the dispute resolution process is underway. However, it is understandable there may be rare cases, in the interest of public health, where prompt regulatory action is necessary. While there is a pending dispute resolution, the Guidance should clarify the conditions under which the Agency will forestall regulatory action and clarify the conditions under which the Agency will proceed with further regulatory action.

Point #5
Timing

There is a lack of consistency in time frames as specified in the Guidance. The Agency has stated it has "generally thirty days" to respond the firm if the Agency disagrees with the firm's request at the Tier 1 level. Further, the Agency can delay a response, albeit with a communication to the firm, without defining a time frame for completion of the request. PDA anticipates that responses from the Agency will be completed in the given thirty days and suggests that in the rare circumstances where additional time is required, a maximum time of sixty days be set as the limit.

As an issue progresses into the Tier 2 Process with the need for convening a Dispute Resolution Panel, time frames are not clearly stipulated. Once a determination has been made that an issue warrants review at this level, it will be reviewed at the next meeting for which there is sufficient time on the agenda. While PDA commends the Agency for assuring each issue is given the proper attention and time it deserves, there is concern of the potential for substantial delays in the process. Related to this concern, is how the Agency will proceed with further regulatory actions as a result of the inspectional observations (see discussion on Point #4 above).

Point #6
The Dispute Resolution Process as a Learning Tool for both the Agency and Industry

The Agency's position on whether the decisions reached by this process will set a precedent for other similar situations should be made clear. PDA would like to suggest there be a procedure for circulating the information within the Agency as training on the issues and the scientific decisions. Included in this process would be clarification if these decisions effect in practice a change of rules. This can in fact, lead to consistency in the interpretation of regulations by inspectors in the field.

After appropriate redaction, the information from these disputes is invaluable as a learning tool for industry as well.

Go to www.pda.org for complete letter.

Powder Blends Letter, *from page 18*

David Long	Eli Lilly and Company
Russell E. Madsen	The Williamsburg Group, LLC
Jerome Planchard	Patheon
Richard Poska	Abbott Laboratories
George Robertson	PDA
Paul Vogel	Lachman Consultants
David Whiteman	Aventis Pharmaceuticals

PDA thanks you again for the opportunity to comment on this draft guidance. If you require further information, please feel free to contact me via the information below.

Sincerely,

Victoria Ann Dedrick
PDA
Vice President, Quality and Regulatory Affairs
Phone: 301-656-5900; Ext. 147
email: dedrick@pda.org
Web site: www.pda.org

Attachment: Comment Grid

WHO Working Document Letter, *from page 19*

PDA again thanks WHO for the opportunity to comment on this draft guidance. If you require further information, please feel free to contact me via the information below.

Sincerely,

Victoria Ann Dedrick
PDA
Vice President, Quality and Regulatory Affairs
Phone: 301-656-5900; Ext. 147
email: dedrick@pda.org
Web site: www.pda.org

Attachment: Comment Grid

Go to www.pda.org for comment grids to both letters.

***Williams Interview**, from cover*

business consulting firm. Interaction with this consulting firm basically started what I would call a **vigorous reengineering process**. Their advice was for us to pay attention to our core business. Ever since that time there has been tremendous change in the organization to do that.

The reengineering cycle will go on and on. USP is moving at warp speed and I don't necessarily see an end to the reengineering. Every organization has to continually reinvent themselves to take into account changing times. The world is certainly not staying stable and if anything it is accelerating in terms of the change. I would say, overall from a strategic standpoint, I am proud of the way USP has dealt with this transformational activity because it is a customer-centric activity. We want to pay attention to our core customers and, via our standard-setting activity, give them products and services that they are going to need.

Walt: Can you point specifically to some accomplishments that have resulted from the agenda established at the 2000 USP Convention? Or can you identify projects that are incomplete and will spill into the next cycle?

Dr. Williams: The core of USP is of course the *USP-National Formulary* [USP-NF]. We are trying to meet the need of customers—pharmaceutical manufacturers, some dietary supplement manufacturers and compounding professionals. USP speaks broadly not only to the United States; many companies throughout the world rely on USP. USP-NF has to be a very comprehensive document and speak to many different stakeholders. In so doing, we service the ultimate customers—practitioners and patients.

USP-NF has undergone many changes since I've been here. It has a completely new set of introductory material. It comes out annually with two supplements as opposed to every five years with ten supplements. The rationale for that is that it is much easier for manufacturers to leaf through two supplements and then the book to find out what is going on rather than reaching back through ten supplements.

Walt: How have the stakeholders responded to this change?

Dr. Williams: People seem to like it. Furthermore, we have completely transformed the way we present it to the world. It is available as a site-license on the Web and as a CD-ROM and in print. I don't think we can go much further. I think the sales of the books are vigorous and it is doing well.

Everything revolves on content of the USP-NF. There are two major aspects of the book related to content. One is the monograph—and of course monographs are the core of the core—and then the general chapters. And we now have a very good understanding how the general chapters relate to the monographs or don't relate to the monographs as the case may be. That is the "above 1000 vs. below 1000" debate that you sometimes hear. Our general counsel has given us very good wording that clearly delineates what it means to be a chapter above 1000. ***(Editor's note:** The next installment of this interview contains more discussion of "general chapters" and their role.)*

Transformation of the monograph itself is another area we are concentrating on. The truth is the old USP monograph, if I can call it that, didn't take into account the changes that arise as a result of the International Conference on Harmonisation (ICH) and the impact of ICH on regulatory agencies. A specific manifestation of that is impurities.

In the past USP had a complicated way of looking at impurities and controlling them. We now have a new guideline on the topic. We worked with industry, our staff, and the Council of Experts to think about impurities and other aspects of the monographs in terms of ICH terminology and approaches.

You'll remember that ICH talks about characterization and setting specifications in the ICH "Q6A" and "Q6B" documents [specifications

Did you know?

Dr. Williams spoke at the 2004 PDA SciTech Summit and Annual Meeting. He addressed ICH nomenclature and other issues of interest to PDA.

for new drugs and specifications for new biopharmaceuticals]. I'm delighted to say that Eric Sheinin [USP Vice President, Information and Standards Development] is here, and he was the rapporteur for Q6A. We were perfectly positioned with Eric to make that transition.

The monograph now will contain what ICH calls **"universal tests" and "specific tests."** The universal tests are description, identification, assay and impurity so that every ingredient or dosage form should have those tests. Then there are some specific tests depending on the ingredient or the dosage form. Dissolution is a specific test, but it is obviously not universal. Then there are procedures connected with the test. So when you are looking at the performance test for the oral solid dosage form, for example, it can be either disintegration or dissolution. And then a lot of the general chapters speak to techniques. Techniques can be picked up and be part of a procedure in a monograph. We have a very clear understanding now of how all this fits together, and not only a clear understanding, but a solid nomenclature for it, as well as a solid understanding of what a new monograph needs to be.

Based on work from many individuals, when we talk about a new monograph for a small molecule, we are thinking about it being a **"flexible monograph"** to take into account different routes of synthesis. In other words, we are going to move away from the concept of one-size-fits-all which sometimes leads to endless debates in the PF [USP *Pharmacopeial Forum*] and go more to a flexible monograph which may have a different impurity test procedure depending on the impurities arising in different routes of synthesis. The new monograph of the future may be what I would call a "composite monograph" where we have to get information from different manufacturers depending on how the material is characterized, how the specification is set and what the specification is.

Walt: Is this task of changing the monograph and implementing ICH language a project you brought with you when you joined USP or a project you identified after you were on board?

Dr. Williams: A lot of things came together and a lot of it was fortuitous. For example, we have a very talented volunteer on the Council of Experts named Judy Boehlert, who Chairs the Noncomplex Actives and Excipients Expert Committee. She served as the rapporteur for "Q3A" for ICH—that is impurities for small molecule ingredients. So between Eric and Judy, we were perfectly positioned to bring in this transformation of the USP monograph. I have been very lucky because, first of all, the staff here is terrific, and second of all, we have a terrific group of volunteers.

Another thing that we started doing in this cycle is building **stakeholder forums and project teams**. These are advisory bodies that we set up so that we can gain customer input. We have four of

continues on page 25

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Williams Interview, *from page 23*

them now. The most vigorous one is the Prescription/Nonprescription Stakeholder Forum which focuses on manufacturers of general prescription and OTC products. They—USP staff and the Council of Experts members—have figured out maybe 20 hot topics that are of interest. The stakeholder forums and project teams are very much like the ICH model or the PQRI model where you have a steering committee and working groups that focus on topics.

The stakeholder forums and project teams in this cycle are definitely advisory. We want to make sure that we don't usurp, if you will, the standard setting responsibilities of the Council of Experts.

Walt: Did you lead the effort to establish these advisory bodies?

Dr. Williams: It actually came from my predecessor Jerry Halpern [former USP Executive Director]. Just a gleam in his eye. We actually made it a reality and it has turned into a vigorous activity.

You know, USP is very interesting. If you think about FDA and its guidances they talk about information that people need to supply to the regulatory agency, but they don't tell you the review decision. A manufacturer gets all the information together but it is up to the reviewer to reach the conclusion. A USP monograph is a similar concept but it also gives you **the final decision**. A monograph actually tells you what the specification is. It is complete unto itself. I call it a safe harbor. The monograph gives you the requirement.

Walt: I can see how that runs into difficulty when things change; when ICH establishes new criteria for things like impurity and you go back to the monograph and it doesn't match.

Dr. Williams: We were out of tune with ICH but now we are aligned. My hope is that we stay aligned.

Walt: Right. It takes effort. What is USP putting in place to ensure that these standards stay current?

Dr. Williams: We'll continually modify the guideline as necessary to take into account modifications to ICH. But an example of what you are talking about is the comparability protocol. The comparability protocol for biotech moves over into large molecules.

Walt: Later, I have some questions on that and I think that is an important area for PDA members. Turning back for a minute—and I understand that all of this is ongoing—but if you could identify projects that really need to be accelerated in the next cycle?

Dr. Williams: One area is dosage forms. One of the most important dosage form tests is the performance test. The performance test right now for oral solid dosage forms is satisfied by either disintegration, less often, or dissolution, more often.

Like all USP procedures, the dissolution performance test continually merits improvement to make it better. USP has two project teams working on that with the idea that they will come to a better understanding of what we are doing in testing the dosage form for dissolution. If you think about ICH lingo, dissolution is a procedure with acceptance criteria, and if you look at the dissolution procedure it is actually a study with stages of acceptance. If you do your study and stage one is okay, you can stop, or go to stage two or stage three if it isn't. You have these little branch points that tell you that you either pass or fail. This is a study design that tests a hypothesis. We are also looking at how to set the acceptance criteria.

Another initiative during this cycle, and this one might be of great interest to PDA: Dissolution just speaks to one type of dosage form, but we have worked out a taxonomy such that we can talk now about dosage forms by route of administration. There are five routes of administration: parenteral, mucosal, oral, topical and inhalation.

Now each one of those routes of administration can be connected with a dosage form that might need a different performance test. So we have performance tests for inhalation products. An interesting one for your membership is that we don't have a **performance test for parenteral products**. New parenteral dosage forms include lipids, liposomes, microspheres, and implants. We didn't need to think about parenterals so much because they were all solutions. But thanks to the creativity of the industry, now we have to be thinking about new approaches here.

Walt: Because of dissolution—every oral solid manufacturer running the same performance test with similar acceptance criteria—the Biopharmaceutical Classification System evolved, opening the door for regulatory relief, particularly for generic manufacturers and post-approval changes. Can USP help identify a standard performance test for other dosage forms that can serve as a trigger for more regulatory relief?

Dr. Williams: Well I see you are getting to something that is important although it may be early. If you had a good performance test say for a liposome, would the agency allow you to make a post approval change based on that performance test if you showed the performance in vitro was not going to change? Why not? Right now they do that with dissolution for certain oral dosage forms.

Without these techniques and procedures a manufacturer would have to do a lot of characterization and maybe another bioequivalence study, which for these dosage forms is sometimes very difficult. ■

Part 2 of this interview will appear in the June edition.

Dr. Williams talks about biologics, revision of Chapter <111> and the role of General Chapters above 1,000.

Regulatory Briefs

Important Dates

June	**1**	**EMEA** xenogeneic cell therapy medicinal products "points to consider" document becomes effective.
June	**8**	**FDA** E-Labeling Rule becomes effective.
June	**11**	**FDA** public meeting on Part 11.
July	**1**	**EMEA** Note for Guidance on Minimising Risk of TSE becomes applicable.
July	**5**	Deadline for public comment on FDA **CDER** Draft Guidance on CMC submissions for drug substances.
August	**31**	**EMEA** API Master File guideline becomes effective

U.S. FDA

CDER Amends 21 CFR 314.70 and... In the April 8 *Federal Register*, the U.S. FDA announced that its regulations on supplements and other changes to an approved application will be amended to reflect the manufacturing changes provision of the FDA Modernization Act of 1997. The final rule requires manufacturers to assess the effects of manufacturing changes on the identity, strength, quality, purity, and potency of a drug or biological product as those factors relate to the safety or effectiveness of the product. The final rule sets forth requirements for changes requiring supplement submission and approval before the distribution of the product made using the change, changes requiring supplement submission at least 30 days prior to the distribution of the product, changes requiring supplement submission at the time of distribution, and changes to be described in an annual report. The amended rule becomes effective on June 22, 2004. A link to the April 8 *Federal Register* notice is included at www.pda.org/regulatory/RegNewsArchive.html.

...Revises "Changes" Guidance FDA simultaneously published a revised version of its guidance on "Changes to an Approved NDA or ANDA." The revisions were made to reflect newly amended 314.70. The guidance is intended to assist applicants in determining how they should report changes to an approved new drug application (NDA) or an abbreviated new drug application (ANDA). Links to the April 8 Federal Register notice and to the guidance are available at www.pda.org/regulatory/RegNewsArchive.html.

Public's Part 11 Opinions Sought June 11 FDA is holding a public meeting to discuss various topics concerning its regulations on electronic records and electronic signatures in 21 CFR Part 11. As an element of its drug quality initiative for the 21st Century, FDA has been re-examining Part 11 as it applies to pharmaceuticals and all FDA-regulated products. FDA will consider the input from the public meeting and comments on the topics presented in this document as we evaluate potential changes to Part 11. The public meeting will be held at the National Transportation Safety Board Boardroom and Conference Center, 429 L'Enfant Plaza, SW., Washington, DC 20594, +1 (202) 314-6421. More information on this meeting is available in the April 8 *Federal Register*. A link to the notice is available at www.pda.org/regulatory/RegNewsArchive.html.

Validation CPG Eases Criteria for Technology Effective March 12, 2004, FDA revised its Compliance Policy Guide (CPG) on process validation and renamed the document to accurately reflect its breadth of coverage. The whereas the CPG previously included only "drug product" in the title, the document is now called: "Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval." The most far reaching change in the revised CPG—which is an internal document that establishes the enforcement approach to a particular regulatory area—is that it eases the number of process validation runs required prior to approval for drugs produced using "advanced engineering principles and control technologies." Also of note, the document deletes the previous reference to "three" validation (or conformance) batches at commercial scale as adequate minimum proof of process validity—a number is no longer suggested. In addition, the revised version recognizes the International Conference on Harmonisation Q7A guidance on cGMPs for APIs, already adopted by FDA.

In announcing the revised CPG, FDA stated, "This is an important first step in the Agency's plan to address the area of process validation. The next step will be to update the 1987 guideline on process validation to reflect modern manufacturing principles, technology, and science. The final step of this process will be a revisiting of the proposed revisions of the cGMPs, the *Federal Register* dated May 3,1996. This effort is being taken in concert with FDA's initiative on the regulation of pharmaceutical quality known as "Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach."

A link to the revised CPG is available at www.pda.org/regulatory/RegNewsArchive.html.

FDA Exploring "Critical Path" to Medical Product Approval On March 16, FDA released a report called "Innovation or Stagnation? – Challenge and Opportunity on the Critical Path to New Medical Products." The report examines the development path for all types of medical products—drugs, biologics and medical devices—to identify what problems exist and what steps need to be taken to bring the critical path into the 21 st Century. The report particularly focuses on the

continues on page 28

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Anthony Mire-Sluis, Ph.D., Senior Chemist, FDA, CDER
Daniel G. Schultz, M.D., Director, Office of Device Evaluation, FDA, CDRH

Regulatory Briefs, *from page 26*

unique opportunities for FDA to collaborate with academic researchers, product developers, patient groups, and other stakeholders to make the critical path much faster, predictable, and less costly.

The report was prepared under the direction of Janet Woodcock, M.D., Director, Cross Center Initiatives Taskforce, with the involvement of CDRH Director Dr. David Feigal, CBER Director Dr. Jesse Goodman and Acting CDER Director Dr. Steven Galson, as well as key FDA staff. It carefully examines the current state of the critical path between medical innovation and medical product development and found disturbing trends indicating systemic problems.

The report notes that despite notable advances in innovative fields of biomedical research as genomics, proteomics and nanotechnology, there has been a downward trend in recent years in the number of innovative medical product applications to FDA and its counterpart agencies throughout the world. While the number of new product applications and approvals was modestly higher in 2003, the fact remains that most of these new scientific fields are not yet having a fundamental impact on patient care. Although these and other problems are attributable to a variety of factors, FDA's report focuses on one important cause—that new science is not being adequately harnessed to guide the technology development process in the same way that it is accelerating the discovery process.

A link to this report is available at www.pda.org/regulatory/RegNewsArchive.html.

Vincent Lee, Ph.D., Joins CDER Office of Pharmaceutical Science Vincent Lee, Ph.D., joins the CDER Office of Pharmaceutical Science (OPS) as a Senior Pharmacist and will advise OPS senior management. Prior to joining the FDA, Dr. Lee held several academic positions, most recently as Adjunct Professor of Pharmaceutical Sciences, School of Pharmacy, University of Southern California. Simultaneously, he served as Vice President, Biological, Formulation, and Material Sciences, ALZA. Dr. Lee received a Ph.D. in pharmaceutics from the University of Wisconsin. He also served on FDA's Advisory Committee for Pharmaceutical Science. Dr. Lee will be involved in OPS activities related to the regulation of new and complex pharmaceutical products and to the development of strategies that will increase our scientific understanding of new technologies and methodologies and help us determine the effect of these technologies on pharmaceutical quality. In addition, Dr. Lee will apply his academic background to establish internal training programs on pharmaceutical concepts, particularly concerning the interrelationship between processes and products.

Mansoor Khan, Ph.D., Joins CDER Office of Testing and Research Mansoor Khan, Ph.D., is the CDER Office of Testing and Research's new Director for the Division of Product Quality Research. Dr. Khan's research expertise is in the design and evaluation of novel controlled drug delivery systems—including nano-drug delivery systems, mechanisms of oral delivery of proteins, statistical evaluation of critical processes and formulation variables, application of artificial neural networks for product and process optimization, and physical, chemical, biopharmaceutics characterization of dosage forms. Dr. Khan will develop DPQR research programs to support CDER and FDA initiatives and provide support for regulatory policy development in the areas of CMC and Biopharmaceutics and risk-based CGMP's.

Dr. Khan was a Professor of Pharmaceutics and Founding Director of the Graduate Program in the School of Pharmacy at Texas Tech University Health Sciences Center. He is recognized leader in pharmaceutical sciences through his extensive publications and professional activities. He received a Ph.D. in Industrial Pharmacy from St. John's University at New York.

NIH and FDA Launch New Human Gene Transfer Research Data System In March, the National Institutes of Health and FDA launched a new Genetic Modification Clinical Research Information System (GeMCRIS)—a Web-accessible database on human gene transfer. GeMCRIS, developed collaboratively by the two agencies, is a unique public information resource as well as an important new electronic tool to facilitate the reporting and analysis of adverse events on these trials. The new system will provide information to the public directly and will improve the government's ability to monitor adverse events in gene therapy research. Acting FDA Commissioner Lester M. Crawford, D.V.M., Ph.D., emphasized that "the development of GeMCRIS illustrates the government's commitment to addressing public and patient concerns about safety while advancing gene therapy. Providing accurate and complete information about ongoing gene therapy studies is the best way to achieve this goal."

EMEA

API DMF Procedure for Europe Outlined in Guideline In late February, the EMEA's Committee for Proprietary Medicinal Products and the Committee for Veterinary Medicinal Products adopted a final guidance on its new active substance master file procedure (also called European drug master file procedure). Master files for active ingredients will only be accepted when they support a Marketing Authorisation Application or Marketing Authorisation Variation. The guideline becomes effective August 31, 2004. A link to the guideline is available at www.pda.org/regulatory/RegNewsArchive.html. ■

Photos from the 2004 PDA SciTech Summit and Annual Meeting

PDA's Executive Committee: Georg Roessling, Stephanie Gray, Floyd Benjamin, Nikki Mehringer and Neal Koller.

Robert Mello strategizes with members of the Pharmaceutical BFS International Operators Association.

Maik Jornitz and Theodore Meltzer display the new PDA Editor/Author awards.

David Stack, Millipore, wins New Ride!

The PDA booth: KiKi Coffman greets Suzanne Levesque, Phillipe Gomez, Ted Meltzer, Maik Jornitz and Lisa Skeens.

Photos from the 2004 PDA SciTech Summit
(continued)

SciTech participant meets PDA author Jeanne Moldenhauer

Merck's Greg Guyer discusses risk management.

Eli Lilly Career Development Workshop.

PDA's Strategic Planning Committee.

George Robertson talks shop with Russ Madsen, Mary Lou Madsen and Berit Reinmüller.

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Enhancing Your Membership through PDA Interest Groups

Membership in PDA provides more member benefits than discounts on conference registrations and collecting publications through the mail. One of the best ways members can make the most of their memberships is to become involved with PDA Interest Groups. Interest Groups are free and open to all PDA members and there is no limit to the number of Interest Groups in which a member can participate.

Interest Groups bring together members with common scientific and professional interests to interact with one another, exchange information, network and advance specific scientific issues. They are the foundation upon which most of PDA's science and technology initiatives are built. Interest Groups also help provide relevant program topics for PDA meetings and can provide a source of experts to serve on RAQC or SAB task forces. The pharmaceutical and biopharmaceutical communities greatly benefit from the new science, technical reports, points-to-consider and surveys that grow out of Interest Groups. Currently, 21 Interest Groups are active and a complete list of Interest Groups and their leaders may be found on page 15 and on the PDA Web site at: www.pda.org/science/IGs.html.

Joining an Interest Group is as easy as contacting its leader. Interest Groups generally meet during PDA events, like the upcoming PDA/FDA Joint Regulatory Conference, Courses and Tabletop Exhibits in September. Some groups remain active throughout the year by meeting at Chapter events, teleconferencing, and posting updates on the PDA Web site. Any PDA member can attend an Interest Group meeting. PDA members can suggest the creation of a new Interest Group at any time.

For questions related to Interest Groups or suggestions for new ones, contact George Robertson, Ph.D., VP, Science and Technology, at +1 (301) 656-5900, ext. 139 or Robertson@pda.org, or Sopita Lapsomphop, Coordinator, Science and Technology Department, at +1 (301) 656-5900, ext. 153 or Lapsomphop@pda.org. ■

by KiKi Coffman, Chapter Coordinator

Chapter Focus: Capital Area Chapter

In the fall of 1993, a phone call from a recently relocated PDA member to then-PDA President Edmund Fry initiated the formation of the Capital Area Chapter. The Chapter was approved in 1994 and has been adding local benefits to the PDA membership in the area ever since.

Twelve years later, the Chapter has consistently held successful meetings, usually three to four each year, with its most recent meeting in April titled, "Designing a Cleaning and Disinfection Program in GMP Controlled Environments," presented by Art Vellutato, Jr., VP Technical Support Operations, Veltech Associates, Inc.

The Chapter also recently spearheaded a movement to create the official PDA Chapter Scholarship Guidelines under the direction of Capital Area Chapter president, Dr. Barry Friedman, Director for Quality Control at Cambrex.

"This award, the first of its kind for PDA, is made possible by the vendors that sponsor our Chapter dinners," Dr. Friedman stated. "We thank these vendors for their continuing sponsorship."

The program guidelines were updated to be consistent with the dollar levels specified in the Chapter Financial Policies and based on a proposed scholarship description sent to PDA by Friedman. The Capital Area Chapter of PDA announced its initial awarding of a one year scholarship for US$5,000 to an individual entering his or her senior college year.

This award, presented to University of Maryland, Baltimore County (UMBC), is in recognition of the students that UMBC has placed within Biotechnology in the greater Baltimore/Washington, D.C., community. The guidelines are currently posted under "Chapter Leader Resources" in the "Members Only" section of www.pda.org. In the future, PDA will prominently cover the PDA Chapter Scholarship Program and recipients in the *PDA Letter* and will work to generate interest in each participating PDA Chapter's geographic region.

For more information about the Capital Area Chapter, contact Barry A. Friedman, Ph.D., Director, Quality Control, Cambrex Bio Science Baltimore, Inc., at barry.friedman@cambrex.com or PDA Chapter Coordinator KiKi Coffman at coffman@pda.org. ■

by KiKi Coffman, Chapter Coordinator

New member contact information is forwarded to Chapters on an ongoing basis. For immediate notification of Chapter events, please contact your local representative and ask to be placed on the Chapter mailing list.

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PDA Membership Application

M

LTR 05/04

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- ❑ Government Regulatory Agency
- ❑ Industry Supplier
- ❑ Medical Device Manufacturing
- ❑ Pharmaceutical Manufacturing
- ❑ Pharmacy
- ❑ Recruiter
- ❑ Other

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- ❑ Aerosols
- ❑ Analytical Chemistry
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- ❑ Biotechnology
- ❑ Computers
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- ❑ Manufacturing/Production
- ❑ Microbiology
- ❑ Ointments
- ❑ Ophthalmics
- ❑ Packaging
- ❑ Parenterals
- ❑ Quality Assurance/Quality Control
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- ❑ Sterilization/Aseptic Processing
- ❑ Training
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Chapter Events Calendar

May

21: **Mountain States Chapter**, Golf Social, Longmont, Colorado
24: **Italy Chapter**, EuroForum on Biotech, Florence

June

7: **Italy Chapter**, Aseptic Processing – European and U.S. Perspective: A round table to be held during "Pharmintech" week (June 8–11), Bologna
9: **Delaware Valley Chapter**, Water Systems, Malvern, Pennsylvania
9: **Metro Chapter**, "Disinfection/ Sanitization," Clark, New Jersey
21–22: **Central Europe Chapter**, EuroForum on "Common Technical Document – Learning by Doing" Basel, Switzerland
TBD: **Taiwan Chapter**, Annual Meeting, Taipei

September

6–8: **Central Europe Chapter**, "Aseptic Processing Course," Basel, Switzerland
22: **Delaware Valley**, Aseptic Processing, Malvern, Pennsylvania
27: **Central Europe Chapter**, EuroForum on Biosafety, Basel, Switzerland

October

4–5: **Central Europe Chapter**, Course on Visual Inspection, Berlin, Germany

November

8–9: **Central Europe Chapter**, World NanoBiotechnology Forum, Basel, Switzerland
11: **Delaware Valley Chapter**, Environmental Monitoring, Malvern, Pennsylvania
19: **Metro Chapter**, "Current Compliance Trends," Clark, New Jersey
29–30: **France Chapter**, Two-Day Summit, Brussels, Belgium
TBD: **Japan Chapter**, Annual Meeting, Tokyo, Japan

December

TBD: **Central Europe Chapter**, EuroForum on Pharma Economics

VP's Message

"White Noise or Headsets"

Mello

Once again I am on the road, or rather, in the air, this time en route to Puerto Rico. Yes, I know what you are thinking—it *sounds* great (sun, sand, etc.), but many of you with manufacturing sites on the island and offices elsewhere know better. In reality it's a long commute. In my case, 1500+ miles. My editor must be glad I'm flying because this month's column is due and he thinks I write better at 35,000 feet. This time he will be thrilled because, according to our pilot, we are cruising at 41,000 feet. That extra 6,000 feet of inspiration means he can have my column ahead of deadline. If everyone followed this logic, I could single-handedly turn the airline industry back to profitability!

Actually, it is not the altitude that matters for my creativity, it's the solitude. I currently have a minimum of three hours with the "white noise" of the engines and ventilation system in the background. For me, "white noise" is any sort of background sound that I need not pay attention to. Of course there is the fact that there are no telephones, cell phones, pagers, emails, staff emergencies or other interruptions. It seems that "white noise," or quiet, works best for me. However, I have seen others demonstrate their own creative abilities with music blasting through their headsets. To each his own, I suppose.

Creativity can be expressed both within and outside of the workplace. In the workplace it leads to new products, new ideas or new solutions to seemingly impossible problems. Creativity draws from our experiences, from our knowledge base, from what we have learned and what we continue to learn. Training, be it on the job, at a conference or at a PDA Training and Research Institute course, expands both your knowledge base and your potential. For example, in mid-June, the Institute is offering ten courses covering core areas of manufacturing (both for active pharmaceutical ingredients—APIs—and aseptic processing), quality assurance, validation, and information technology/network infrastructure qualification. The full brochure and registration information can be found on the PDA Web site at: www.pda.org/calendar/course-calendar.html.

Education and training of this kind gives you the tools to be creative. It allows you to *see* that "box" that everyone tells you to "think outside of." Creativity is important if businesses are to grow and prosper—a message PDA members were energetically reminded of at the 2004 PDA Annual Meeting and SciTech Summit in Orlando, Florida, this past March. Those who were there for the conference and the Institute courses certainly will not forget Joel Strack (Business Programs Facilitator, the Disney Institute) challenging the pharmaceutical industry to be more opened minded to creativity and change—a timely message considering the new emphasis being placed on improved quality systems by regulatory agencies around the world!

At the Institute we offer a broad range of laboratory and lecture-based programs to expand your professional knowledge. It is up to you to find the trigger to the creativity that crystallizes and focuses your knowledge. That's when you start to notice that you are meeting your objectives or that your tasks and assignments are being completed on or ahead of schedule. So go out and get the knowledge base. We can help with that. Finding that creative trigger is up to you. Sometimes it is a very unlikely spot, like the seat of a commercial airplane 41,000 above sea level.

That's enough "white noise" for me now. Maybe I'll switch to some music. I just spotted the headset in the seatback in front of me. ■

Views from the Orlando Course Series at the 2004 PDA SciTech Summit/ Annual Meeting

Sandra Lowery demonstrates proper gowning in her course on Aseptic Processing and Contamination Control lecture.

Robert Mello takes a moment to learn.

Anne Marie Dixon makes a point in her course on Compliance Auditing of Cleanrooms and Controlled Environments.

2004 Aseptic Processing Training

The 2004 dates for the PDA Training and Research Institute laboratory course on Aseptic Processing have been established. Due to the intensive hands-on nature of this course, class registration must be limited to 20 students per session. In response to the overwhelming registration requests for the four session dates in 2003, PDA Training and Research Institute has added a fifth session for 2004. This extremely popular two-week course sells out rapidly, so we urge you to register early. The registration information is now available on our Web site, www.pda.org/PDF/TRI-Courses/TRI-04-Aseptic-RegForm.pdf.

The remaining 2004 dates are as follows:

Session III
Week 1 May 24–28
Week 2 June 14–18

Session IV
Week 1 August 16–20
Week 2 September 13–17

Session V
Week 1 October 4–8
Week 2 November 1–5

$7,800 members/$9,300 nonmembers; *Faculty:* John Lindsay and David Matsuhiro ■

For Hotel Information, go to www.pda.org

Upcoming PDA Training and Research Institute Education Courses

Course No.	Title/Topic	Dates
142	**Designing, Operating and Controlling High-Purity Water Systems for Regulatory Compliance**	October 25–27, 2004
230	**Environmental Mycology Identification Workshop**	December 2–3, 2004
NEW	**Pharmaceutical Microbiology Workshop**	July 27–30, 2004
NEW	**Developing a Moist Heat Sterilization Program Within FDA Requirements**	August 9–11, 2004
NEW	**Advanced Environmental Mycology Workshop**	September 1–3, 2004
301	**Fundamentals of D, F and z Value Analysis**	October 14–15, 2004
NEW	**Rapid Microbiological Methods**	October 18–22, 2004
NEW 319	**What You Need to Know to Select Adequate Thermal Validation Equipment**	November 22–23, 2004
NEW	**Developing and Validating Cleaning and Disinfection Programs**	November 18–19, 2004
400	**Cleaning Validation**	November 15–17, 2004
NEW	**Remediation of Existing Computer Systems**	November 18-19, 2004

These courses will be held at the PDA Training and Research Institute in Baltimore, Maryland, unless otherwise noted. **For course content information,** call the PDA Training and Research Institute directly at +1 (410) 455-5800. For registration information, call PDA's world headquarters in Bethesda, Maryland at +1 (301) 656-5900.

PDA Training and Research Institute Registration Form

R
LTR 05/04

1. **Please type or print your name, address and affiliation.**

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2.

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TOTAL _____

Deadline: Enrollment is limited for the benefit of all attendees; this necessitates early registration. Paid registrations must be received one week prior to the event. **Confirmation:** Written confirmation will be sent to you once payment is received. You must have this written confirmation to be considered enrolled in a PDA event. Please allow one week for receipt of confirmation letter. **Substitutions:** If a registrant is unable to attend, substitutions are welcome and can be made at any time, even on-site up to the time of the course. If you are pre-registering as a substitute attendee, indicate this on the registration form. **Refunds:** Refund requests must be in writing. If received one month prior to the start of an event (course series, conference, etc.), a full refund, minus a $55 handling fee, will be made. If received two weeks prior to the event, one-half of the registration fee will be refunded. After that time, no refunds will be made. **Event Cancellation:** PDA reserves the right to modify the material or instructors without notice or to cancel an event. If an event must be canceled, registrants will be notified as soon as possible and will receive a full refund of fees paid. PDA will not be responsible for discount airfare penalties or other costs incurred due to a cancellation. **For more details, call PDA at (301) 656-5900.**

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"Cleanroom Clothing Systems: People as a Contamination Source"

by Bengt Ljungqvist & Berit Reinmueller

Increasing cleanliness demands in a variety of industries require an in depth knowledge of the performance of modern cleanroom clothing systems. This superb set of observations from case studies performed in a dispersal chamber or "body box" will help manufacturers determine the effectiveness of the clothing systems of their choice.

The prime function of cleanroom clothing is to serve as a filter protecting both the product and process from airborne contamination. Clothing systems should be designed to envelop a person and not allow significant amounts of contaminants to be dispersed into the Cleanroom. Properties of the fabrics used can be assessed by measurements of air permeability, particle retention, and pore size. The fabric itself should disperse the minimum of particles and be resistant to breakdown and tearing. However, the effectiveness of cleanroom clothing will deteriorate due to factors such as aging, wear, washing, drying, and sterilization. The system used tested the combined filtration efficacy of fabric, construction, and design of clothing and evaluated these factors. Contents include Testing Methods, Test Series, Source Strength, Test Results, Discussion of the Results, and Guidelines for Pharmaceutical Production From the EU, USA, and ISO.

Item No. 17206

US$135 member/US$169 nonmember

Table of contents:

- Observations From Case Studies
- Methods
- Test Series 1
- Test Series 2
- Source Strength – New Clothing Systems
- Test Series 3
- Discussion of Test Results
- Guidelines For Pharmaceutical Production
- Some Calculations
- References
- Symbols and Abbreviations
- Appendix: Clothing Systems Evaluated
- Test Series 1
- Test Series 2
- Test Series 3
- Supplier's Specifications
- Photos of Evaluated Fabrics

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PDA-DHI Press Books

Item No.	Title	Author/Editor	Price (All US$) Member	Nonmember	Government
17173	Practical Change Control for Healthcare Manufacturers	Angie Jamison	$120	$149	$ 50
17174	Understanding GMP: A Practical Guide	Martyn Becker	$170	$209	$ 70
17175	Microbial Risk Assessment in Pharmaceutical Clean Rooms	Bengt Ljungquist/ Berit Reinmuller	$ 75	$ 90	$ 30
17176	Quality Control Systems for the Microbiology Laboratory: The Key to Successful Inspections	Lucia Clontz	$170	$209	$ 70
17177	Electronic Records and Electronic Signatures Compliance Assessment	Chris Reid/ Barbara Mullendore	$ 90	$109	$ 40
17179	The Internal Quality Audit	Monica Grimaldi/ Janet Gough	$120	$149	$ 50
17180	The External Quality Audit	Monica Grimaldi/ Janet Gough	$120	$149	$ 50
17181	Media Fill Validation Environmental Monitoring During Aseptic Processing	Michael Jahnke	$ 90	$109	$ 40
17182	Introduction to Environmental Monitoring in Pharmaceutical Areas	Michael Jahnke	$ 90	$109	$ 40
17183	Steam Sterilization: A Practitioner's Guide	Jeanne Moldenhauer	$215	$269	$175
17184	Rapid Analytical Microbiology: The Chemistry and Physics of Microbial Identification	Wayne P. Olson	$195	$239	$130
17185	Microbiology In Pharmaceutical Manufacturing	Richard Prince	$240	$299	$160
17188	Understanding Active Pharmaceutical Ingredients	Siegfried Schmitt	$ 80	$109	$ 35
17189	Change Control	Soren Schwartze	$ 75	$ 90	$ 30
17199	GMP in Practice: Regulatory Expectations For The Pharmaceutical Industry Third Edition	James Vesper	$105	$129	$ 75
17192	Hosting a Compliance Inspection	Janet Gough	$120	$149	$ 50
17193	Microbiological Monitoring of Pharmaceutical Process Water	Michael Jahnke	$ 90	$109	$ 65
17194	Sorting Out the Critical Variables: A Worked Example for the Non-Statistician	Alfred Wachter	$ 90	$109	$ 40
17195	Validation Master Plan, The Streetwise Downtown Guide	Trevor Deeks	$ 80	$109	$ 60
17196	Laboratory Systems Validation Testing and Practice	Paul Coombes	$120	$149	$ 50
17197	Filtration Handbook: Integrity Testing	Maik W. Jornitz/ Theodore H. Meltzer	$185	$229	$ 75
17198	Quality and Safety of Gene Medicines: A Practical Guide	Anthony Meager	$155	$189	$ 65
17200	Commercial Off-The Shelf Software Validation for 21 CFR Part 11 Compliance	David Nettleton/ Janet Gouch	$185	$229	$ 75
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17204	Supply of Chemicals in the Pharmaceutical Industry: Regulatory Guidelines and Rulings	Mark Selby	$185	$229	$ 75
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PDA Technical Reports

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PDA Technical Monograph No. 1: Validation of Steam Sterilization Cycles [1978] 36 pp. $75 member/$550 nonmember **Item No. 01001**

TR3: Validation of Dry Heat Processes Used for Sterilization and Depyrogenation [1981] 55 pp. $75 member/$550 nonmember **Item No. 01003**

TR4: Design Concepts for the Validation of a Water-For-Injection System [1983] 12 pp. $75 member/$550 nonmember **Item No. 01004**

TR5: Sterile Pharmaceutical Packaging: Compatibility and Stability [1984] 137 pp. $75 member/)$550 nonmember **Item No. 01005**

TR7: Depyrogenation [1985] 116 pp. $75 member/$550 nonmember **Item No. 01007**

TR9: Review of Commercially Available Particulate Measurement Systems [1988] 30 pp. $75 member/$550 nonmember **Item No. 01009**

TR10: Parenteral Formulations of Proteins and Peptides: Stability and Stabilizers [1988] 26 pp. $75 member/$550 nonmember **Item No. 01010**

TR11: Sterilization of Parenterals by Gamma Radiation [1988] 10 pp. $75 member/$550 nonmember **Item No. 01011**

TR12: Siliconization of Parenteral Drug Packaging Components [1988] 14 pp. $75 member/$550 nonmember **Item No. 01012**

TR13: Revised: Fundamentals of an Environmental Monitoring Program [2001] 37 pp. $75 member/$550 nonmember **Item No. 01013**

TR14: Industry Perspective on the Validation of Column-Based Separation Processes for the Purification of Proteins [1992] 11 pp. $75 member/$550 nonmember **Item No. 01014**

TR15: Industrial Perspective on Validation of Tangential Flow Filtration in Bio-pharmaceutical Application [1992] 13 pp. $75 member/$550 nonmember **Item No. 01015**

TR16: Effect of Gamma Irradiation on Elastomeric Closures [1992] 12 pp. $75 member/$550 nonmember **Item No. 01016**

TR17: Current Practices in the Validation of Aseptic Processing—1992 [1993] 21 pp. $75 member/$550 nonmember **Item No. 01017**

TR18: PDA Report on the Validation of Computer-Related Systems [1995] 17 pp. $75 member/$550 nonmember **Item No. 01018**

TR19: Rapid/Automated ID Methods Survey [1990] 7 pp. $75 member/$550 nonmember **Item No. 01019**

TR20: Report on Survey of Current Industry Gowning Practices [1990] 5 pp. $75 member/$550 nonmember **Item No. 01020**

TR21: Bioburden Recovery Validation [1990] 8 pp. $75 member/$550 nonmember **Item No. 01021**

TR22: Process Simulation Testing for Aseptically Filled Products [1996] 16 pp. $75 member/$550 nonmember **Item No. 01022**

TR23: Industry Survey on Current Sterile Filtration Practices [1997] 13 pp. $75 member/$550 nonmember **Item No. 01023**

TR24: Current Practices in the Validation of Aseptic Processing [1997] 23 pp. $75 member/$550 nonmember **Item No. 01024**

TR25: Blend Uniformity Analysis: Validation and In-Process Testing [1997] 99 pp. $75 member/$550 nonmember **Item No. 01025**

TR26: Sterilizing Filtration of Liquids [1998] 31 pp. $75 member/$550 nonmember **Item No. 01026**

TR27: Pharmaceutical Package Integrity [1998] 48 pp. $75 member/$550 nonmember **Item No. 01027**

TR28: Process Simulation Testing for Sterile Bulk Pharmaceutical Chemicals [1998] 15 pp. $75 member/$550 nonmember **Item No. 01028**

TR29: Points to Consider for Cleaning Validation [1998] 23 pp. $75 member/$550 nonmember **Item No. 01029**

TR30: Parametric Release of Pharmaceuticals Terminally Sterilized by Moist Heat [1999] 6 pp. $75 member/$550 nonmember **Item No. 01030**

TR31: Validation and Qualification of Computerized Laboratory Data Acquisition Systems [1999] 12 pp. $75 member/$550 nonmember **Item No. 01031**

TR32: Auditing of Suppliers Providing Computer Products and Services for Regulated Pharmaceutical Operations [1999] 277 pp.
Print: $100 member/$575 nonmember **Item No. 01032**
CD-ROM: $75 member/$550 nonmember **Item No. 01132**

TR33: Evaluation, Validation and Implementation of New Microbiological Testing Methods [2000] 37 pp. $75 member/$550 nonmember **Item No. 01033**

TR34: Design and Validation of Isolator Systems for the Manufacturing and Testing of Health Care Products [2001] 25 pp. $75 member/$550 nonmember **Item No. 01034**

TR35: A Proposed Training Model for the Microbiological Function in the Pharmaceutical Industry [2001] 24 pp. $75 member/$550 nonmember **Item No. 01035**

TR36: Current Practices in the Validation of Aseptic Processing-2001 [2001] 34 pp. $75 member/$550 nonmember **Item No. 01036**

Points to Consider for Aseptic Processing, Volume 57 Number 2 Supplement [2003]. $75 member/$550 nonmember **Item No. 03004**

PDA Technical Resource Order Form

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LTR 05/04

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Company, Colleague & Product Announcements

Millipore introduces its new Millistak+ and Millistak+ HC 316L stainless steel filter housings. The new housings join Millipore's Millistak+ HC filters, which compress multiple stages of mammalian cell culture clarification into one efficient, cost saving step.

The Millistak+ housings further streamline the clarification process. A unique compression mechanism (patent pending) ensures consistent sealing pressure and fast, trouble-free operation. By eliminating the conventional threaded post and nut, change out can be executed in minutes. In addition, the wide range of accessories and CIP systems enable users to configure a complete housing system.

Millistak+ HC filters combine charged depth media and membrane separation technologies to enhance filter capacity and retention. By removing larger particles through sieving action and small ones through adsorption, this advanced technology reduces equipment, expendables, maintenance labor costs and WFI usage. The full range of Millistak+ media is available in a variety of formats including disposable Millistak+ Mini and Opticap™ capsules.

Available in a variety of sizes, the Millistak+ housings accommodate the Millistak+ HC and Millistak+ lenticular filters. The housings meet the European and U.S. manufacturing requirements and support process development through pilot and full-scale manufacturing. For more information on Millistak+ filters and housings, visit www.millipore.com/millistakhousings.

Eli Lilly bestows a US$6 mil. gift to the Oklahoma Medical Research Foundation in April for the creation of two endowed faculty chairs, to be called the Eli Lilly Chairs in Biomedical Research. Lilly and the Foundation have jointly researched blood and cardiovascular diseases for two decades. The collaboration focused on finding a cure for sepsis, a life-threatening blood disease that claims 1,400 lives every day. In 2001, Lilly's drug Xigris became the first and only FDA-approved treatment for adult severe sepsis patients who are at a high risk of death.

"Lilly's collaboration with OMRF has yielded many important discoveriesduring the more than 20 years we have worked together," said J. Anthony Ware, MD, Lilly's Vice President for Cardiovascular Research and Clinical Investigation. "This gift salutes our teamwork, and we are confident it will help find treatments and cures for some of today's most challenging medical problems."

Genentech promotes Todd Pierce to Vice President, Corporate Information Technology (CIT), in late March. In this role, Pierce will continue to manage Genentech's CIT group, including information technology (IT) strategy, planning, application development, operations and networking. In addition, he will chair the company's IT Strategy Council.

Novartis, Aventis to merge? Over the last few months, Novartis and Aventis have been going back and forth over a possible merger. The new company would become the world's second largest pharmaceutical company behind Pfizer. Due to possible opposition of the French Government, which may not look too kindly at a Swiss company buying a French firm, Novartis has asserted that it will only enter into a negotiation phase if formally invited by the Aventis Supervisory Board and if the French Government assumed a neutral position.

Pfizer joins Dow 30. The Dow Jones & Co. wasn't fooling around April 1 when it added a third pharmaceutical company to its Dow Jones Industrial Average (the Dow 30). Pfizer joins Merck & Co. and Johnson & Johnson. Since 1990, Pfizer has surpassed all its rivals in the pharmaceutical industry to become the world's largest manufacturer of drug products.

"As the world's largest company devoted to healthcare, the addition of Pfizer to the Dow Jones Industrial Average appropriately reflects the importance of this sector to investors, patients and the global healthcare community," said Pfizer Chairman and Chief Executive Officer Hank McKinnell.

Cardinal Health, promotes Frank Harmon to Senior Vice President, Manufacturing Operations for Sterile Fill Finish. In his new position, Harmon will oversee all manufacturing operations including, engineering, production, maintenance, metrology, validations, materials management, human resources, finance and information technology for locations in Albuquerque, New Mexico, Raleigh, North Carolina and Humacao, Puerto Rico. ■

—information taken from company releases

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***Calendar of Events**, from back cover*

Maximizing SOPs – An Untapped Resource of Training Solutions

Everything You Wanted to Know About Environmental Monitoring but Were Afraid to Ask

Qualification and Validation of API Manufacturing Operations

Achieving cGMP Compliance During Development of a Biotechnology Product

Annual Product Reviews: How to Comply with FDA & ICH Requirements

18–22 **PDA Training and Research Institute Laboratory Course *Rapid Microbiological Methods*** (PDA Training and Research Institute, Baltimore, MD)

25–27 **PDA Training and Research Institute Laboratory Course *Designing, Operating, and Controlling High Purity Water Systems for Regulatory Compliance*** (PDA Training and Research Institute, Baltimore, MD)

November

1–5 **PDA Training and Research Institute Laboratory Course *Aseptic Processing Training Program*—**Week 2 (PDA Training and Research Institute, Baltimore, MD)

11–12 **PDA Training and Research Institute Laboratory Course *Developing and Validating Cleaning and Disinfection Programs for Controlled Environments*** (PDA Training and Research Institute, Baltimore, MD)

15–17 **PDA Training and Research Institute Laboratory Course *Cleaning Validation*** (PDA Training and Research Institute, Baltimore, MD)

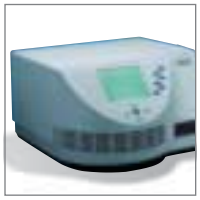
18–19 **PDA Training and Research Institute Laboratory Course *Remediation of Existing Computer Systems*** (PDA Training and Research Institute, Baltimore, MD)

December

2–3 **PDA Training and Research Institute Laboratory Course *Environmental Mycology Identification Workshop*** (PDA Training and Research Institute, Baltimore, MD)

6–7 **PDA Training and Research Institute Lecture Course *Computer Products Supplier Auditing Process Model: Auditor Training*** (PDA Training and Research Institute, Baltimore, MD)

6–7 **PDA Training and Research Institute Laboratory Course *What You Need to Know to Select Adequate Thermal Validation Equipment*** (PDA Training and Research Institute, Baltimore, MD)



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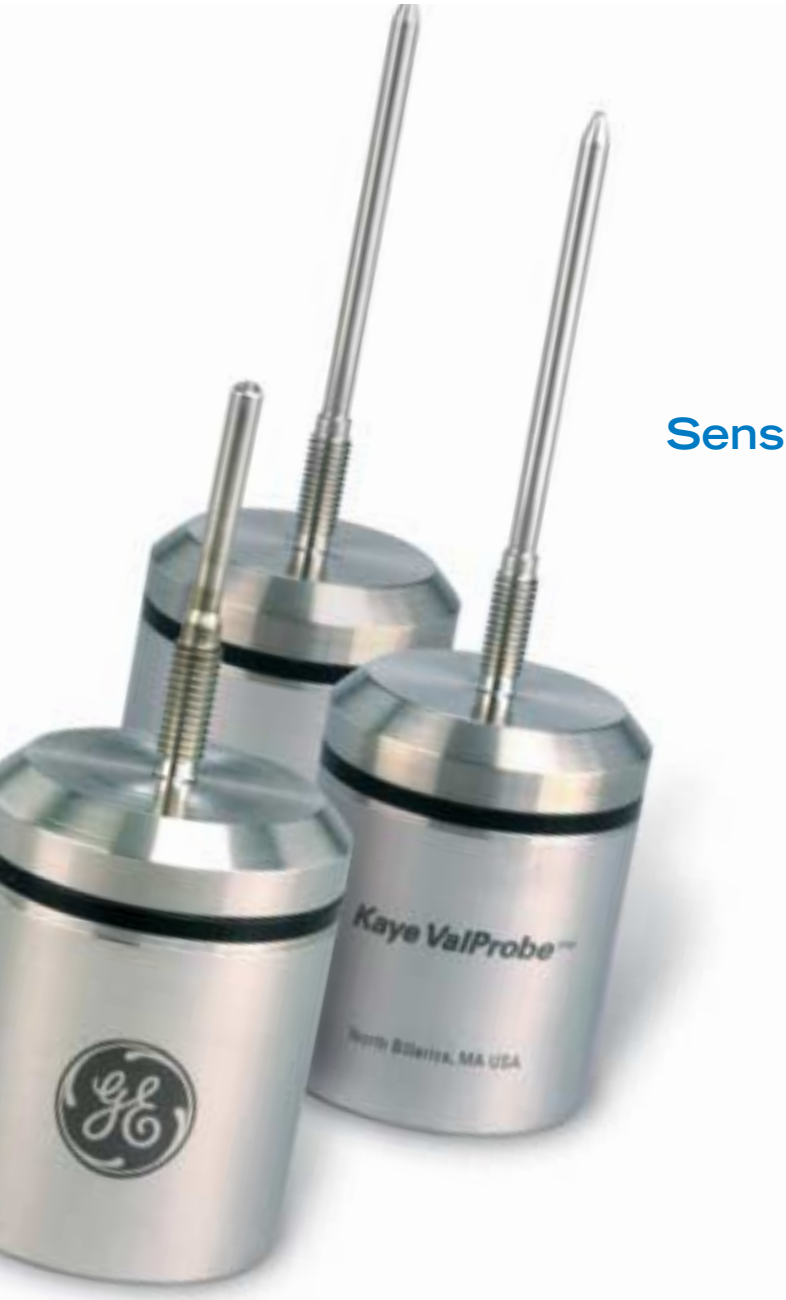
GE Infrastructure - Sensing



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Be sure to see us at:
PDA SciTech Summit, Booth 501, and
INTERPHEX, Booth 1421

Calendar of Events

2004

June

3–4 **PDA Training and Research Institute Lecture Course *Computer Products Supplier Auditing Process Model: Auditor Training*** (PDA Training and Research Institute, Baltimore, MD)

7–8 **2004 PDA/R3Nordic Conference** in collaboration with KTH ***Scientific, Industrial and Regulatory Aspects of Clean Products and Devices*** (Hilton Stockholm Slussen, Stockholm, Sweden)

14–18 **PDA Training and Research Institute Laboratory Course *Aseptic Processing Training Program***—Week 2 (PDA Training and Research Institute, Baltimore, MD)

15–17 **PDA Training and Research Institute** ***Toronto Course Series*** (The Westin Harbour Castle, Toronto, Canada)
Sterile Manufacturing with Blow/Fill/Seal Technology
Basic Concepts in Cleaning and Cleaning Validation
Cleanroom Management
Computer and Network Infrastructure (CNI) Qualification Using C3Q™
Preparing for an FDA Pre-Approval Inspection
Qualification and Validation of API Manufacturing Operations
Analytical Problem Solving for CAPA Systems
GMP Fundamentals
How to Develop Validation Protocols
Radiation Dosimetry and Calibration

August

9–11 **PDA Training and Research Institute Laboratory Course *Developing a Moist Heat Sterilization Program Within FDA Requirements*** (PDA Training and Research Institute, Baltimore, MD

16–20 **PDA Training and Research Institute Laboratory Course *Aseptic Processing Training Program***—Week 1 (PDA Training and Research Institute, Baltimore, MD)

23–27 **PDA Training and Research Institute Lecture Course *CGMP Trainer's Qualification Program*** (PDA Training and Research Institute, Baltimore, MD)

30-9/1 **PDA Training and Research Institute *Chicago Course Series*** (The Drake Hotel – Chicago, Chicago, IL)

September

1-3 **PDA Training and Research Institute Laboratory Course *Advanced Environmental Mycology Identification Workshop*** (PDA Training and Research Institute, Baltimore, MD)

6–8 **Pan European PDA Training and Research Institute Lecture Course *Fundamentals of Aseptic Processing*** (UBS Ausbildungs-und Konferenzzentrum, Basel, Switzerland)

7–8 **PDA-BFS Joint Workshop on Blow/Fill/Seal Processing** (Holopack Verpackungstechnick GmbH, Germany)

13–17 **PDA Training and Research Institute Laboratory Course *Aseptic Processing Training Program***—Week 2 (PDA Training and Research Institute, Baltimore, MD)

20–24 **2004 PDA/FDA Joint Regulatory Conference, Courses and Tabletop Exhibits** (Omni Shoreham Hotel, Washington, DC)
PDA Training and Research Institute Lecture Courses:
Change Control & Documentation
Auditing Pharmaceutical Microbiology Laboratories
Basic Concepts in Cleaning & Cleaning Validation
Compliance Auditing of Cleanrooms and Controlled Environments
Qualification and Validation of API Manufacturing Operations
Auditing Techniques for CGMP Compliance

October

4–5 **PDA Training and Research Institute Lecture Course *Visual Inspection*** (Berlin, Germany)

4–8 **PDA Training and Research Institute Laboratory Course *Aseptic Processing Training Program***—Week 1 (PDA Training and Research Institute, Baltimore, MD)

14–15 **PDA Training and Research Institute Laboratory Course *Fundamentals of D, F, and z Value Analysis*** (PDA Training and Research Institute, Baltimore, MD)

18–20 **PDA Training and Research Institute *Boston Course Series*** (Hyatt Regency Boston, Boston, MA)
PDA Training and Research Institute Lecture Courses:
Analytical Problem Solving for CAPA Systems
Design and Validation of a Cleaning and Disinfection Program
Introduction to Writing and Auditing CGMP Documentation
CGMPs for Bioprocesses
Pharmaceutical Water Systems Design and Validation

For the most up to date information on all PDA meetings and conferences go to **www.pda.org**

Coming in June
New and improved department-specific calendars.

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