Science • Technology • Quality • Regulatory • Community

PDA Letter

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November/December 2004

In This Issue...

PDA Recognized for "Instrumental" Role in Aseptic Guidance

FDA CDER Office of Compliance official Richard Friedman thanked the PDA membership for their "instrumental" role in the development of the final guidance on cGMPs in aseptic processing of sterile drugs at the 2004 PDA/FDA Joint Regulatory Conference, Washington, D.C., September 20-22.

After several years of hard work to update FDA's original 1987 guideline on the topic—including the publication of a "concept paper" in 2002, a Product Quality Research Institute working group study, and the release of a draft guidance in 2003—the final aseptic processing guidance finally published a week after the PDA event.

Addressing the final plenary session, Friedman discussed the soon-to-be-released document in general terms. Joining him on the podium were Richard Johnson, Director, Quality Center of Excellence – Drugs, Abbott Laboratories, and session moderator John Lindsay, President, Aseptic Solutions. The importance of the document to PDA was evident by the large number of conference attendees who stayed for the final session to hear the presentations.

Acknowledging the effort of "many people in FDA and industry," Friedman took a moment to credit PDA for its strong contribution. "Perhaps no organization has been more instrumental in the publication of pragmatic aseptic guidance than PDA. I would like to take this opportunity to acknowledge PDA and its members' many recommendations—both informally and formally—over these last several years," he stated.

The document also reflects the "strong partnership" between FDA's Office of Regulatory Affairs (ORA), CBER and CDER, remarked Friedman.

The end result, he said, is a guidance on aseptic processing "that provides clarity and consensus in interpreting many difficult technical aspects of GMP, incorporates a risk-based mind set throughout, and explicitly encourages the use of technological advancements in the manufacture of sterile pharmaceuticals."

Additional Work To Be Done

Release of the final guidance does not mean mission accomplished for FDA or PDA. Friedman outlined additional work to be done, including the revision of CDER's sterile process inspection compliance program, 7356.002A, to

Continued on page 16

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9. Evaluation, Validation and Implementation of New Microbiological Testing Methods, Technical Report no. 33
   (Item No. 01033, US$ 75/member, US$ 270/nonmember).

10. Validation of Dry Heat Processes Used for Sterilization and Depyrogenation, Technical Report No. 3
    (Item No. 01003, US$ 75/member, US$ 270/nonmember).

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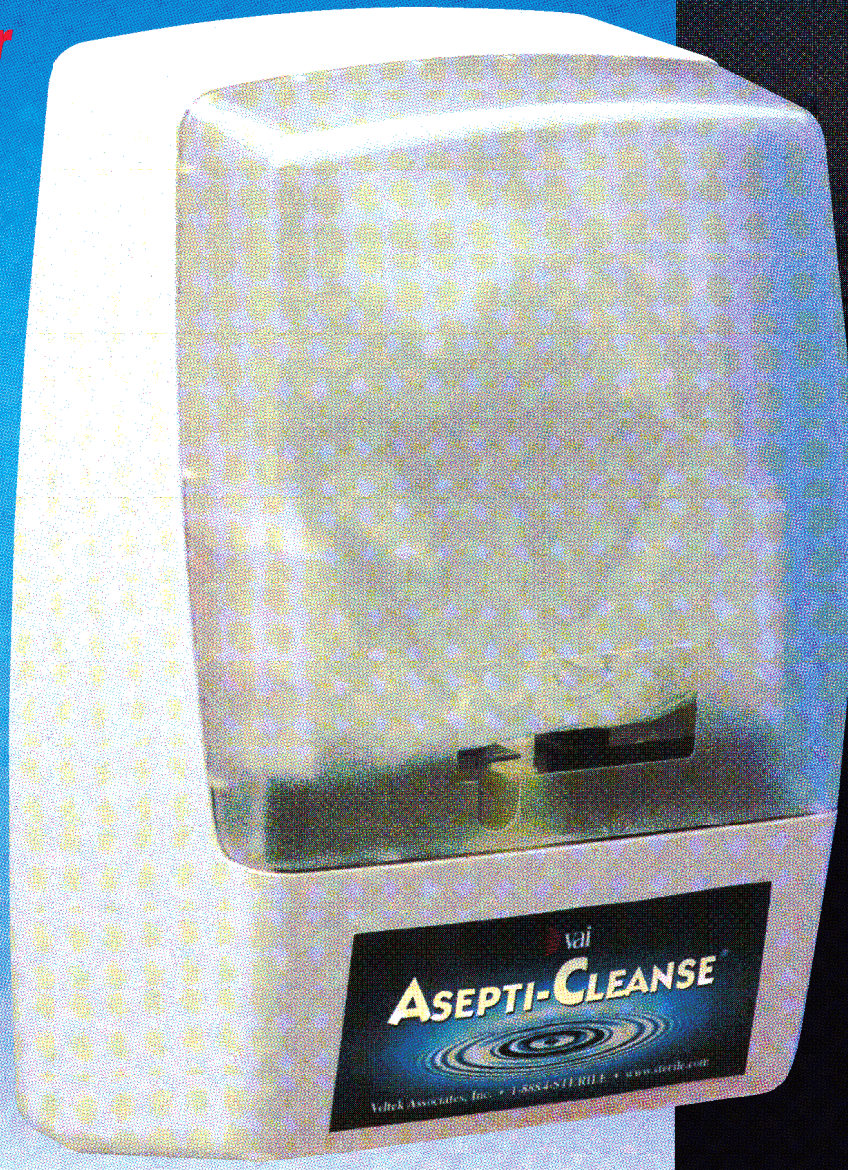

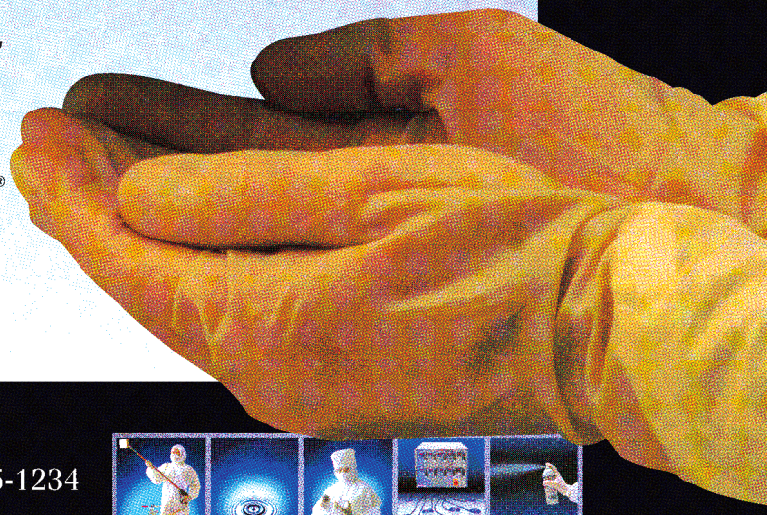

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Neal G. Koller
PDA President

President's Message

PDA Science and Technology: An Active and Productive 2004

This has been an active and productive year for PDA's science programs thanks to the strong leadership provided by the PDA Science Advisory Board (SAB).

On behalf of everyone at PDA, I want to thank all the member volunteers serving on the SAB for their hard work, particularly SAB co-chairs James Fernandez (Fernandez and Associates) and Martin Van Trieste (Bayer). Without the dedication of the SAB volunteers, PDA could not fulfill our Mission: "to advance pharmaceutical and biopharmaceutical science and technology internationally by promoting scientifically sound and practical technical information and education for industry and regulatory agencies."

One of the best ways we accomplish our Mission and a cornerstone of our science offerings is the technical report program. PDA is on track to publish a number of new or revised technical reports in the coming months.

Mailed with the Sep./Oct. issue of the *PDA Journal of Pharmaceutical Science and Technology*, was the revised TR#32—PDA's industry-standard auditing process for computer products and service providers. PDA Science and Technology Vice President George Robertson, PhD, discussed the availability of this document and highlighted all of the new material included in his column in the September issue of the *PDA Letter*. Spinning off of the revision effort, the PDA Industry Advisory Board is currently searching for volunteers to serve on a new task force to expand the scope of the revised TR#32 to additional services and products commonly used in our manufacturing communities.

Also, PDA is close to publishing a number of new technical reports on chromatography post-approval changes, sterile filtration of gases, biotechnology process validation, and viral filtration. Technical Report projects nearing completion include microbial data deviations and chemical out of specifications. To learn more about these upcoming publications and the PDA volunteer members who are authoring them, please turn to Dr. Robertson's column on page 8.

If you would like to participate in any of these projects or initiate a new technical report task force, please contact Dr. Robertson or go to the new PDA Web page established for our volunteers: www.pda.org/volunteer.

An exciting new initiative is underway to restructure the PDA Interest Groups (IGs), which are often the point of origin for PDA science and technology reports. On behalf of PDA, I want to thank PDA Board of Directors member Kathleen Greene (Novartis) for leading this effort, which will ultimately help PDA better support members by enhancing their ability to communicate through the IGs on important scientific and technical issues.

Under the initiative, the PDA IGs will be grouped together into five "sections" according to relevance. The five sections are: Quality Systems and Regulatory Affairs, Laboratory and Microbiological Sciences, Pharmaceutical Development, Biopharmaceutical Sciences, and Manufacturing Sciences.

Each IG section will have a steering committee made up of the IG leaders and a liaison from the PDA Regulatory Affairs and Quality Committee (RAQC) and/or SAB. The section steering committees will be chaired by a "coordinating head." The goal is to have section-specific Web sites available to support the IGs by providing a forum for communication outside of formal PDA meetings.

Over the years, Interest Groups have served as a great forum for expert and practical subject-specific information and as an important avenue for PDA members to meet and discuss topics of interest and/or concern. Under this exciting new structure, PDA members all over the world will have greater access to these groups. More information on this initiative will be published in the *PDA Letter* and on the PDA Web

site in the coming months.

Biopharmaceutical sciences continue to be an area of importance to PDA members. Reflecting this was the large number of people who took time to attend the PDA Biotechnology Interest Group meeting following the conclusion of the 2004 PDA/FDA Joint Regulatory Conference. Among other things, the group discussed the progress of the aforementioned technical report on biotechnology process validation. PDA also is forming a Biopharmaceutical Advisory Board to establish the strategic perspective and provide oversight for PDA's scientific, technical and regulatory activities in the biopharmaceutical community. This group will help PDA plan and produce guidance, technical reports and monographs, and help steer our activities with regulatory authorities.

If you would like to participate in the biotech IG or the new biopharmaceutical advisory board, please contact Dr. Robertson or go to the new PDA Web page for volunteering opportunities: www.pda.org/volunteer.

Looking ahead, I want to draw your attention to all the exciting new science-based events PDA has scheduled for 2005. In Rome, March 1-4, the PDA International Congress will feature several first-time presentations on new technologies for aseptic processing and biopharmaceutical manufacturing plus many more truly terrific scientific talks. The 2005 PDA Annual Meeting in Chicago the following month will place the spotlight on a host of scientific and technological advances in the pharmaceutical sciences. The conference features a track on manufacturing science and a track on the latest developments in academia and R&D. In May, the PDA Viral & TSE Safety Conference and the PDA Extractables/Leachables Forum will bring focus to the latest trends in these two challenging and important areas. These represent just a few of the many science-based events and training courses PDA will bring to the community over the next 12 months.

As one can see, it has been an active and productive year for PDA's science and technology programs. The publication of several new technical reports reflects years of hard work by PDA's member volunteers. And with many technical report projects moving rapidly forward, new organization for the PDA Interest Groups, the new Biopharmaceutical Advisory Board, and exciting science-based events on the horizon, PDA is setting the stage for an even better 2005. Stay tuned!

Just in! Election Results for the 2005 PDA Board of Directors

Eric Sheinen and **Laura Thoma** are newly elected. **Kathleen Greene** and **Tim Marten** are re-elected. More details next issue. The 2005 PDA Board of Directors:

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Laura Thoma, PharmD
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New Faces

Kelly Coates
PDA Membership & Chapters Manager

PDA is pleased to announce the appointment of Kelly Coates to the position of Manager, Membership & Chapters. In this role, Kelly will develop and manage all efforts supporting PDA's membership and Chapter development. As the new leader of membership initiatives worldwide, Kelly will serve as the primary link between PDA's Chapter leadership and PDA Headquarters in Bethesda, Md.

Previously, Kelly managed membership services and program development for the American Society of Civil Engineers.

Kelly earned her MBA from the Robert H. Smith School of Business at the University of Maryland. She also earned a BA in Chemistry with honors from the University of Virginia.

Kelly's e-mail address is coates@pda.org, and she can be reached by telephone at +1 (301) 656-5900, ext. 149.

George A. Robertson
Vice President, Science and Technology

Vice President's Message

The Unsung Heroes

I wanted to use my column this month to thank many of the people who have contributed to the resurgence of technical documents moving through the Science Advisory Board. We can claim success in the publication of the revised PDA Technical Report #32, *Auditing of Suppliers Providing Computer Products and Services for Regulated Pharmaceutical Operations* and the publication of the PDA Book, *Good Practice and Compliance for Electronic Records and Signatures, Part 3: Models for Systems Implementation and Evolution (GERM 3)*. With those contributions distributed or available for purchase, I thought you might be interested to preview several Technical Reports underway at this time. They are in no particular order:

Microbial Data Deviations (aka "Microbial Out of Specifications") is being led by PDA stalwart Jeanne Moldenhauer, PhD (Vectech Pharm. Consultants). This PDA Technical Report will address such items as investigation templates, ideas for corrective action, and suggestions on how to write a deviation report.

Process Validation of Protein Manufacturing is a contribution from many of our members on the West (left) coast. Bob Seely (Amgen) and Chris Bussineau (Chiron) are two of the major players in this effort. A comprehensive work, it will particularly focus on the aspects of process validation as they apply to biotech products. Most interesting are the two detailed examples of a cell culture process description and a downstream purification process flow.

Frank Bing (Abbott) and Srikanth Sundaram (Schering-Plough) co-chaired the new report on *Sterilizing Filtration of Gases*. Included in this volume will be such subjects as, how filters work, filter selection and system design criteria, specific applications and user responsibilities for validation of critical applications.

Lynn Torbeck (Torbeck & Associates) has been shepherding the chemical out-of-specifications Technical Report through its development. You'd think that with the importance of the Barr Decision over a decade ago, the issue of chemical OOS would have been addressed in a comprehensive way. It appears that PDA will, once again, be leading the field in developing detailed guidance in this area.

Gail Sofer, PhD (GE Healthcare), a huge contributor to many PDA activities, as well as Kurt Brorson, PhD (U.S. FDA) have been leading a Task Force working on a multi-pronged approach to virus filtration. I have had the privilege of working with Gail and Kurt on editing the Technical Report the group has drafted . Although the concept of using filters to remove viruses from biological products is not new, this Technical Report, like Technical Report #26, *Sterilizing Filtration of Liquids,* provides focused information on a very specific topic. Truly a "practitioner's handbook."

Last, but not least, I would like to recognize the contributions of Jim Agalloco (Agalloco & Associates) and Russ Madsen (The Williamsburg Group) who have been leading a team in a major revision and expansion of Technical Monograph #1, *Validation of Steam Sterilization Cycles.* It is now rechristened as Technical Report #1, *Industrial Moist Heat Sterilization in Autoclaves.* Among other things, it expands the size of the document from 36 to over 180 pages! Obviously, this expansive effort has not been without numerous revisions. This multi-year project has been through almost 20 versions. This is a HUGE amount of dedication by many, many people, and wonderfully represents what makes PDA the fantastic organization it is.

As I mentioned before, the reports and people cited here are not intended to be comprehensive, nor are the credits for those involved. Just be prepared in 2005 for a bumper crop of PDA technical excellence.

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Pfizer's PAT Strategy Sheds Light on Manufacturing Future

"Processability" of raw materials scrutinized on Pfizer loading docks

Walter Morris, PDA

At the 2004 PDA/fDA Joint Regulatory Conference, participants gained valuable insights into how process analytical technology (PAT) could change the way manufacturers control their manufacturing operations, improve product quality and eliminate costly and time-consuming errors.

Speaking for Pfizer, Joep Timmermans, PhD, Senior Manager, Process Analytical Support Group, outlined the various unit operations for which the company is applying different PAT tools. Addressing an attentive and large audience, Dr. Timmermans presentation contained several concrete examples of PAT application and plenty of supporting data.

Dr. Timmermans referred to PAT in the plural to emphasize the various technologies that can be applied on-, in- or at-line. He defined PAT as: "A process analytical technology provides (near) real-time, (semi-) continuous data about a process monitoring, control, and/or automation, or can be converted into process knowledge." He stressed the complexity of the technology and the data collected.

PAT vs. Traditional Methods

Besides the timing and location of the analytical exercise, the differences between PAT and traditional, laboratory-based methods includes the focus, with PAT analyzing "processability" and lab methods measuring a product or component's attributes.

Further contrasting PAT with traditional testing, Dr. Timmermans described product testing as "a policing function because we are checking what we did, we actually did correctly."

PAT, on the other hand, involves becoming more proactive. "We are not policing. We are actually continuously verifying that our processes are heading in the right direction even before we get to the end of the process. We are doing extensive characterization of our raw materials, we are doing extensive characterization of our various unit operations that we executed in our manufacturing process. And by making sure that we are continuously within certain limits in each of these steps, we thereby can assure that the finished product is of acceptable quality because that is how we designed our processes."

> ***"Unlike some other organizations where people may be looking at reducing end-product testing as one of the goals for implementing PATs, we see that ultimately as a long- term benefit, but we don't consider that to be our primary goal for putting our measurements online or on the production floor."***

Pfizer has a number of justifications for using PAT. First, the company views the technologies as a set of tools which can be applied to achieve the elimination of variation in its processes and achieve "right first time" (RFT) manufacturing. Once achieved, RFT manufacturing would mean "no investigations, no reworks, no rejects and no waste," explained Dr. Timmermans.

Pfizer's goals with PAT do not include eliminating finished product testing. "Unlike some other organizations where people may be looking at reducing end-product testing as one of the goals for implementing PATs, we see that ultimately as a long-term benefit, but we don't consider that to be our primary goal for putting our measurements online or on the production floor."

PAT Advantages

Dr. Timmermans next discussed some of the advantages of using PAT, including better process understanding and the identification of critical to quality factors. The company hopes to reduce or eliminate deviations and reduce cycle times, inventory levels and costs, while at the same time, improve capacity utilization, compliance and quality assurance.

Many of the advantages outlined by the Pfizer executive are well-known to those following FDA's PAT initiative. Several are cited in the agency's PAT guidance, which was published in final form with the multiple documents released at the end of September as part of the 21st Century drug quality initiative. *PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance* addresses the technological framework for the various technologies that can be utilized under a PAT program and outlines a generalized regulatory approach. A link to the PAT guidance and other initiative documents is available on the PDA Web site.

Dr. Timmermans showed a graphic that identified the PAT tools Pfizer is using to monitor specific unit operations in a generic direct manufacturing process. The unit operations involve raw material testing and dispensing followed by dry compaction, wet granulation, or fluid bed dryer milling, blending, compression or capsule fill-

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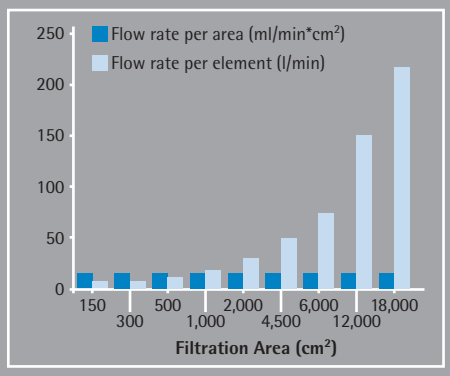

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ing, coating, and concluding with blister packaging or bottle filling. The box on page 12 outlines the information Dr. Timmermans presented.

Following this review of PAT principles and applications, Dr. Timmermans discussed specifically how Pfizer is utilizing some of the technologies.

Implementation involves "root cause analysis group," said Dr. Timmermans. The group "supports the sites with atypical investigations when they get an atypical dissolution result [for example] for a particular batch. They use very new, novel technologies… to better understand what is different about that particular batch."

Should Pfizer eventually achieve RTF manufacturing, "this group in the long term will get reduced in size very significantly, if not be eliminated." However, "right now they play a vital role in providing us with insights into our drug product and the performance and how it correlates with some of the performance measures."

Determining "Processability"

Some of the most interesting work Pfizer is doing with PAT involves the determination of the "processability" of raw materials, e.g., excipients, with near-infrared (NIR) analyzers. The technology provides the firm with a more accurate correlation between the physical characteristics of a raw material and product attributes like tablet performance or process performance like capsule filling.

Over time, Pfizer has established "conformance libraries" for several excipients and raw materials which are used to compare all incoming materials. These libraries of characterization data have become more important in Pfizer's decisions on whether to use certain incoming materials than the standard compendial testing.

Pfizer can "more easily build a correlation to tablet performance, capsule filling, etc., etc."

Citing work the firm has done with magnesium stearate (typically used to lubricate products for compression), Dr. Timmermans explained how the process works: "If we use a certain batch of magnesium stearate…and we notice that the manufacturing process of a product using that particular batch is giving us problems, then we put a flag next to that batch of material and we see if we can use those libraries that we are building up…to give us an idea of what material works well in our processes and what does not work well."

One Pfizer plant has become "very advanced in implementing" this system, Dr. Timmermans declared. Personnel at the plant "really can now decide on the loading dock whether the materials that they are receiving are appropriate for the manufacturing processes."

The plant now has agreements with vendors whereby they ship back material that does not conform "even if they meet the regular compendial specifications," stated Dr. Timmermans.

Dr. Timmermans pointed out that the typical compendial testing of magnesium stearate focuses solely on identification and purity. "Processability" and physical parameters, on the other hand, "are often ignored or not well characterized."

When samples of magnesium stearate are sent to the laboratory, Pfizer tests for fatty acid composition (identification test) and total water content. By contrast, the firm can assess the material's hydration state, the degree of crytallinity and the surface area (particle size and shape) at the loading dock using NIR. With all this additional data, Dr. Timmermans asserted, Pfizer can "more easily build a correlation to tablet performance, capsule filling, etc., etc." He noted that "surface area really is an indicator of how effectively it can coat the material that it is supposed to lubricate."

Continuing with the magnesium stearate example, Dr. Timmermans revealed an interesting finding. The conformance libraries were able to tell Pfizer precisely why magnesium stearate from one supplier works well in a specific process and while the same excipient from a different supplier does not.

Performing a vision-based particle size analysis of the excipient from two different sources, a supplier in Brazil and one in Japan, Pfizer found "dramatically different" particle size distri-

PATs Use Per Unit Operations

Raw Material Testing
Vision Particle Analyzer (lab based)
NIR Conformance testing (lab based)

Dispensing
NIR Material I.D.

Dry Compaction/Wet Granulation/FBD Milling
Power consumption granulation end point
Acoustic granulation end point
On-line vision particle size analysis
NIR Loss on Drying
On-line UV cleaning

Compression/Capsule Filling
NIR Core Potency
NIR Chemical Imaging (lab-based)

Coating
NIR Coating Thickness

Blister Packaging/Bottle Filling
Imaging of Blisters

butions. The particle size differences were "amplified," Dr. Timmermans remarked, when the data was converted to surface area. It showed that the Japanese material had twice the surface area of the Brazilian material.

"Both of these passed our compendial tests; there was nothing wrong with these materials," asserted Dr. Timmermans. "But they had vastly different performance in our manufacturing process."

PAT's API Applications

Moving on to the next unit operation, API production, Dr. Timmermans discussed the performance of reaction monitoring using probes inserted into a recirculation loop. The probes take fingerprints of the chemical reaction as it occurs. The data collected allows Pfizer to extrapolate the reaction time of the synthesis and can identify the precise point in time to stop the synthesis, or the point at which "there is actually a detrimental affect of degradation occurring if you continue to process," said Dr. Timmermans. This tool allows companies to "optimize and maximize" their processes by knowing when to turn off their reactors "as opposed to letting something react for a number of hours or a preset amount of time."

Next, Dr. Timmermans demonstrated the results of a vision-based particle size analysis tool in the discharge chute from the mill. The tool is essentially a camera mounted on one side of the chute and a fluorescent diffuser on the other to illuminate the particles flowing through the tube.

"Our analysis time, now, for ensuring the quality of the product is about 15 minutes. So as the product is being filled and being packaged and shipped to the distribution centers we actually have our results already. So we can make this a continuous manufacturing facility for this particular product."

Using advanced software to analyze the pictures, Dr. Timmermans pointed out that Pfizer "only count particles that are in focus, because if they are not in focus they can be blurred and then we can actually have artificial particle size. But because there is so much product flowing through this particular tube, even just focusing on those particles that are in focus gives us a very high count and a very good reliable distribution analysis for what the particle size distribution looks like."

Dr. Timmermans also discussed an online laser-based system used to measure particle size. This tool is employed, he noted, to handle denser particle streams for which the vision-based particle size analysis is not effective.

The next example provided by the Pfizer executive involved the use of gas chromatography (GC) online to monitor a continuous liquid manufacturing process. This tool is employed to monitor multiple components of the finished product.

One of the biggest benefits of using GC online, according to Dr. Timmermans, is a significant reduction in processing time. "GC takes a number of hours," he explained. "By putting online GC analyzers at various critical points in the processes, we are continually monitoring the process. Our analysis time, now, for ensuring the quality of the product is about 15 minutes. So as the product is being filled and being packaged and shipped to the distribution centers we actually have our results already. So we can make this a continuous manufacturing facility for this particular product."

Another example discussed by Dr. Timmermans involved the use of NIR and mid-infrared and other probes to verify cleaning procedures. The probes monitor the removal of APIs and detergents from process equipment. He stated that some facilities have replaced the typical swab test for cleaning verification in favor of these advanced tools.

Timmermans went on to discuss several more examples of how Pfizer has employed PAT tools. Other unit operations where PAT has been applied so far at Pfizer include blending, granulation and tableting.

Based on Dr. Timmerman's examples, it is apparent that the utilization of PAT holds great advantages with truly remarkable possibilities.

PDA BIOTECHNOLOGY INTEREST GROUP UPDATE

Frank Matarrese, GxP Consulting

Over 60 PDA members extended their stay in Washington, D.C., to participate in the PDA Biotechnology Interest Group following the conclusion of the 2004 PDA/FDA Joint Regulatory Conference (September 20-22).

The IG discussed the progress of the PDA Process Validation for Protein and Peptide Manufacturing Task Force, which is working on a draft PDA Technical Report, and to receive a preview of the Association's new cleaning and disinfection initiative.

PDA Scientific Advisory Board (SAB) Chair, James Fernandez (Fernandez and Associates), introduced two Task Force members who provided an overview of the project's progress. Robert Seely, PhD, Associate Director, Process Development, Amgen, and Stephen Notarnicola, PhD, Principal Scientist, Biogen Idec, outlined the draft Technical Report. They stressed that the document will cover process validation of protein and peptide manufacturing only to the point of the bulk drug substance; formulation, filling, and finishing processes will not be covered.

Dr. Seely noted that the draft report is the culmination of the efforts of the sixteen member Task Force, which has been working for nearly two years. The technical report relies on a science-based approach and attempts to avoid the pitfalls of addressing opinion-based validation issues that have arisen during regulatory review or inspections in recent years. The draft report is meant to be a comprehensive source of information with extensive references to existing technical standards, reports and guidance documents. The contents of the report were reviewed in detail by Dr. Notarnicola, including validation prerequisites, the elements of process validation at the manufacturing stages leading up to the bulk drug substance, documentation and other quality and compliance requirements.

The PDA Biotechnology IG meeting drew many participants

The draft report is targeted to go through the PDA peer review process, which includes consideration by SAB and the PDA Board, prior to being issued as a final report in spring 2005.

The PDA Initiative on Cleaning and Disinfection was outlined by Arthur Vellutato, PhD, Vice President, Veltek Associates. Topics covered by the initiative include cleaning and disinfection of cleanroom structural surfaces, process equipment surfaces, components introduced to controlled environments and product contact surfaces. Examples of specific challenges for each topic area were presented for the IG's consideration and comment. The proposed timing for the initiative included December 2004 for finalizing Task Force membership and January 2005 for the group's first meeting. An outline of the topics is tentatively due in June 2005, with the draft of the first section targeted for November 2005. Dr. Vellutato extended an invitation to PDA members to participate in this initiative.

These presentations were given as part of the PDA Biotechnology IG's mission of providing a forum for scientific, regulatory and educational discussions for PDA membership in order to meet the challenges facing the biotechnology sector of the industry. Copies of these presentations are available on the PDA Web site. Additionally, interest in participation, ideas and requests for topics at future Biotechnology IG sessions may be addressed to IG Leader Frank Matarrese, frank_matarrese@alamedanet.net, Robert Seely, PhD, or (Amgen) rseely@amgen.com.

Robert Seely, Stephen Notarnicola and Genevieve Lovitt

PDA Interest Groups & Leaders

The following is a list of PDA Interest Groups (IGs). The list below includes the IG's name and contact information for each IG's leader, including the leader's affiliation and his or her 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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PDA Recognized for "Instrumental" Role in Aseptic Guidance, from cover

reflect the systems-based approach and risk concepts incorporated into the guidance. In addition, FDA is planning investigator training and continued communication and outreach to industry.

PDA and its members are playing a key role in facilitating training and outreach on the new aseptic guidance. The PDA forums, *Aseptic Processing: The New Guidance,* held Oct. 29 in Washington, D.C., and Nov. 16 in Frankfurt, Germany, represent the initial *Career-long Learning*™ events PDA is planning to help inform and train industry and agency personnel on the guidance. FDA participated in the two autumn forums and will have an expanded role in the 2005 training workshops. Of course, PDA has a long history of providing state-of-the-art aseptic processing training at its Training and Research Institute. [*Turn to p. 19 for more information on PDA's 2005 Training Courses and Events related to aseptic processing.*]

Friedman also alluded to possible future "adjustments" to the aseptic processing guidance necessitated by the evolving 21st Century cGMP initiative.

Implementation, training and future updates to the guidance should be more efficient, if not easier, than the effort to revise the 1987 document, according to Friedman. "Our collective hard work over the last several years clarifying standards will make the next steps easier for all of us. In short, our collective future looks promising in terms of better comprehension of regulatory interpretations in this area."

A Harmonized Guidance

The FDA microbiologist took the opportunity to highlight a number of key areas in the guidance and aspects that were heavily influenced by PDA, the PQRI committee and other public commentators.

"Our collective hard work over the last several years clarifying standards," maintained Friedman, "will make the next steps easier for all of us. In short, our collective future looks promising in terms of better comprehension of regulatory interpretations in this area."

One of the key concerns expressed by various commentators on the draft document was the lack of harmonization with the European Union, particularly in the area of cleanroom air quality designations. Friedman called it one of the most "persistent complaints heard" from industry throughout the development of the document.

In response, FDA has tailored the final document so that it applies the cleanroom classifications found in the International Organization on Standardization (ISO) document 14644, *Cleanrooms and Associated Controlled Environments.* Further, the microbial values for air quality is harmonized with those in the EU Annex on sterile drug products.

More harmonization is apparent in the "Buildings and Facilities" section of the document, subsection "design and control." The recommended pressure differential was changed in the final document to 10-15 Pa, the same value in the EU Annex.

Once again, harmonization was the concern when FDA decided to change the minimum room classification recommendation in Appendix 2, "Blow-Fill-Seal Technology." The final document allows for an ISO 8, or Class 100,000, room when BFS technology is in use. ISO 5, or Class 100, is expected in the critical areas.

PDA and the PQRI working group were not the only expert bodies that influenced revisions to the draft. Friedman credited the CDER Advisory Committee for Pharmaceutical Science (ACPS) for a few additions to the final document.

For example, Friedman credited ACPS discussions for the addition of language on material flow in the "design" portion of the guidance's "Building and Facilities" section. The new language stresses that *it is critical to adequately control material (e.g., in process supplies, equipment, utensils) as it transfers from lesser to higher classified clean areas to prevent the influx of contaminants.* Regarding this portion of the guidance, Friedman commented, "I think this is really a critical part of the addition to the design section. The advisory committee was instrumental to getting it in the guidance."

The closing plenary session of the 2005 PDA/FDA Joint Regulatory Conference drew a large audience

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FREE *PROFESSIONAL REFERENCE GUIDE*

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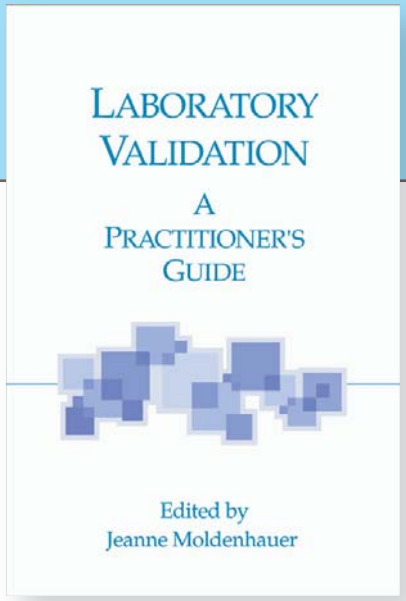
The following booklets have been selected from the chapters of

Laboratory Validation: A Practitioner's Guide

Editor: *Jeanne Moldenhauer*

(2003, Item No. 17201 Price: US$ 250 Member/US$ 309 Nonmember)

These booklets offer a complete overview of a specific topic and provide practical advice for anyone interested in current aspects of laboratory validation.



Special Regulatory Issues for Microbiology Laboratories and Validation of Microbiological Methods

Author: *Jeanne Moldenhauer*

This booklet provides an overview of investigational observations, as identified in warning letters and FD-483's issued by FDA and discusses the procedures used for microbiological method validation.

24 Pages, ISBN: 1-930114-70-2
Item No. 17223
Member: US$ 35
Nonmember: US$ 45
Government: US$ 15

Validation of Rapid Methods And Systems and Validation of Sterility Test Suites And Isolators

Author: *Jeanne Moldenhauer*

This booklet provides guidance on the validation of equipment, software and methods and discusses the methods used to validate the sterility testing area.

33 Pages, ISBN: 1-930114-71-0
Item No. 17224
Member: US$ 35
Nonmember: US$ 45
Government: US$ 15

Validation of Microbial Identification Systems

Author: *Jeanne Moldenhauer*

This booklet discusses the general principles for validating different systems and provides examples of protocols for one type of available technology.

86 Pages, ISBN: 1-930114-72-9
Item No. 17225
Member: US$ 90
Nonmember: US$ 115
Government: US$ 40

Validation Procedures For The Bacterial Endotoxins Test

Authors: *James F. Cooper and Cheryl Moses*

This booklet describes the two types of LAL-test procedures that are used to validate applications of Bacterial Endotoxins Test (BET) in the parenteral industry.

28 Pages, ISBN: 1-930114-73-7
Item No. 17226
Member: US$ 35
Nonmember: US$ 45
Government: US$ 15

Validation Of Environmental Monitoring Methods

Author: *Dawn McIver*

This booklet is intended to begin the thought process and help the reader to design a validation plan that is appropriate for the facility being monitored and the methods being used.

23 Pages, ISBN: 1-930114-74-5
Item No. 17227
Member: US$ 35
Nonmember: US$ 45
Government: US$ 15

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The ACPS and other public commentators persuaded FDA to include and "adjust" language on "alternative test methods," declared Friedman. In the final document, the "Laboratory Controls" section contains a subsection on alternative methods which states: "Other suitable microbiological test methods (e.g., rapid test methods) can be considered for environmental monitoring, in-process control testing, and finished product release testing after it is demonstrated that the methods are equivalent or better than traditional methods (e.g., USP).

Valuable Additions

The new document addresses "the biggest weakness" of the original 1987 guideline on aseptic processing—personnel—Friedman remarked. The section emphasizes the importance of aseptic technique, maintaining proper gown control, as well as training, qualification and monitoring.

According to Friedman, a "very valuable addition" to the guidance is Appendix 3, "Processing Prior to Filling and Sealing Operations." The appendix supplements the information contained in the guidance "with information on products…that are subject to aseptic processing at points early in the manufacturing process, or that require aseptic processing through the entire manufacturing process because it is impossible to sterile filter the final drug product."

PDA's Comments

Prior to Friedman's remarks, Abbott's Richard Johnson discussed the comments that PDA submitted to the agency regarding the draft aseptic guidance. Without the benefit of having the final guidance, Johnson reviewed several of the key concerns raised in PDA's comments on the draft guidance released in 2003. He also expressed PDA's position that the draft contained multiple improvements over the initial "concept paper" published by FDA in late 2002.

PDA's general comments regarding the draft aseptic processing guidance were:

- There is a need for clear expectations during inspections.
- There is need for FDA 483s based on appropriate technology, science and best practices.
- Some items in the draft guidance are better covered elsewhere (for example, product application commitments should take precedence to the guidance).
- Terminally sterilized products should not be covered by the guidance.
- Detection of microbial contamination on a critical site should not necessarily result in batch rejection.
- Single point excursions do not warrant the rejection or placement on hold of product.
- Actions should be taken only if results exceed norm over a sampling period.
- Investigations on single point excursions not clear.

Walter Morris, PDA

Nikki Mehringer and Kathleen Greene (standing)
Richard Johnson, Rick Friedman and John Lindsay

2005 PDA TRI Aseptic Processing Training Program

The PDA Training and Research Institute will hold its Aseptic Processing training course five times in 2005. The interactive training will include actual examples and methods for complying with each section of FDA's *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*. Below is a list of when the five two-week courses will be held.

#1

February 7-11 & March 14-18

#2

April 18-22 & May 16-20

#3

June 13- 17 & July 11-15

#4

August 22-26 & September 19-23

#5

October 17-21& November 14-18

PDA Training on FDA's New Aseptic Processing Guidance

With the publication of FDA's final guidance on aseptic processing, PDA has designed a workshop to help industry implement the document. The Asptic Processing Training Workshop will be held four times in 2005:

San Francisco, California
February 14-15, 2005

Washington, D.C.
March 2005

Chicago, Illinois
April 2005

London
May 3-4, 2005

Victoria Ann Dedrick
Vice President, Quality and Regulatory Affairs

Vice President's Message

The New Regime – Changes to the European Regulatory Environment

2004 was a year of transformation for the European regulatory environment for pharmaceutical and other health care products.

First and foremost among the changes was the accession of 10 new Member States to the European Union (EU) on May 1, 2004. The addition of these new Member States presents many regulatory challenges—and opportunities—to the centralized regulatory structure and the industry at large.

The preceding day, four important new pieces of legislation changing the legal framework for medicinal products in Europe were published. These were:

1. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency
2. Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use (*more on this below*)
3. Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use
4. Directive 2004/28/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/82/EC on the Community code relating to veterinary medicinal products in parallel to Directive 2004/27/EC

Following tough and extensive lobbying the revision to the EU pharmaceutical legislation is substantial. More than 200 individual changes to the existing rules were made to clarify definitions, add administrative and procedural provisions including critical changes in the approval process for generics and in the regulatory powers of the Competent Authorities at the Member State level.

The revised rules provide for more active and centralized surveillance of the market and industry's performance and practices. It puts into place a centralized decision-making process around older products which were previously handled at the national level. There are also provisions for financial penalties for companies involved in regulatory infringements.

Competent Authorities will benefit from enlarged discretion due to increased flexibility of standards for suspension, revocation of license or changes to approvals. The new process calls for much more transparency toward both patients and industry, including approval conditions, pharmacovigilance information and reasons for license revocation.

The changes also brought with it a new nomenclature: EMEA now becomes the European Medicines Agency, but the acronym stays the same. The Committee for Medicinal Products for Human Use (CHMP) replaces the CPMP, and there is also the new HMPC, the Herbal Medicinal Products Committee.

Most provisions take effect during the last quarter of 2005, but some take effect now. The new data exclusivity rules related to generics will not have real impact until 2014.

Regarding revisions to the Community code on medicinal products for human use (2004/27/EC), the following summarizes the major changes:

- New rules for generic products
  - "Eight plus two years" of data exclusivity
  - Definition of a generic product
  - Same quantitative and qualitative composition in the active substance
  - Same pharmaceutical form
  - Bioequivalence
  - Broader flexibility to allow "hybrid" applications
  - Generic copies of centrally approved properties
  - Generic approval in a Member State without a reference product
  - New indications for a well established product

  Bolar amendment concerning patent infringement
- Specific rules for Follow-on Biologics or Biosimilars – applies specifically to products that do not meet all the rules necessary to be considered a generic.
- The scope of the centralised procedure now covers:
  - All biotechnology products,
  - All NCEs (new chemical entities) for the treatment of AIDS, cancer, neurodegenerative disorders or diabetes,
  - Orphan products, and
  - From May 2008 any new active substance for the treatment of auto-immune diseases, immune dysfunction and viral diseases.
- Legal standards for marketing authorizations – there is a new definition of risk and a risk/benefit rational requirement. All authorizations are solely based on quality, safety and efficacy.
- Patient information – pilot program to disseminate information, use of the internet, discussions of risk/benefit – looking to provide good quality, objective, reliable and non-promotional information on medicinal products.
- Accelerated approval process – 150 days versus 210 days
- Enhanced pharmacovigilance – intensive and stricter post-market surveillance with coordination and verification.
- Marketing authorisation validity – still 5 years, but on renewal will essential be valid forever
- Increased transparency – reasons for withdrawals, refusals to grant authorizations, the pharmacovigilance database and national assessment reports.
- Supply obligations – a type of protection against drug shortages requiring market authorization holders to ensure appropriate and continued supply of medicinal products to meet patient needs.
- Compassionate use – powers rest with the Member State
- Member State specific authorizations – utilization of this provision remains unclear
- Support of Small to Medium Size Enterprises (SMEs)

This brief overview provides you with some insight into some of the changes that are taking place in the European medical products arena. For more detailed information on the changing European regulatory environment, you can purchase the CD and transcript from the November 30 PDA audio conference in which I will be discussing the topic in depth, including a brief overview of the new medicinal herbal products legislation, updates to changes to the medical devices directives and more.

PDA Calendar of Events for North America

Please visit www.pda.org for the most up-to-date event information, lodging and registration.

Conferences

February 14-15, 2005
Aseptic Processing Training Workshop
San Francisco, California

March 2005
Aseptic Processing Training Workshop
Washington, DC

April 2005
Aseptic Processing Training Workshop
Chicago, Illinois

April 4-8, 2005
2005 PDA Annual Meeting
Chicago, Illinois

May 16-18, 2005
PDA Viral & TSE Safety Conference
Bethesda, Maryland

May 23-25, 2005
PDA Extractables/Leachables Forum
Bethesda, Maryland

September 11-14, 2005
PDA/FDA Joint Regulatory Conference, Courses and Exhibition
Washington, DC

Training

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

LAB

January 25-28, 2005
Pharmaceutical and Biopharmaceutical Microbiology 101

February 7-11, 2005
Aseptic Processing Training Program (Week 1)
Week 1: February 7-11
Week 2: March 14-18

February 17-18, 2005
Computer Products Supplier Auditing Process Model: Auditor Qualification

February 24-25, 2005
Environmental Mycology Identification Workshop

March 3-4, 2005
Developing and Validating Cleaning and Disinfection Programs for Controlled Environments

March 7-9, 2005
Biopharmaceutical Course Series
San Francisco, California

March 22-23, 2005
Validating a Steam Sterilizer

April 18-22, 2005
Aseptic Processing Training Program (Week 1)
Week 1: April 18-22
Week 2: May 16-20

May 2-4, 2005
Pharmaceutical Course Series
Princeton, New Jersey

May 25-27, 2005
Cleaning Validation

June 2-3, 2005
Environmental Mycology Identification Workshop

June 13-14, 2005
Computer Products Supplier Auditing Process Model: Auditor Qualification

AUGUST 10-12, 2005
Developing a Moist Heat Sterilization Program Within FDA Requirements

AUGUST 22-26, 2005
Aseptic Processing Training Prgm (Week 1)
Week 1: August 22-26
Week 2: September 19-23

LECTURE

JUNE 13-17, 2005
Aseptic Processing Training Program (Week 1)
Week 1: June 13-17
Week 2: July 11-15

JULY 11-15, 2005
Aseptic Processing Training Program (Week 2)
Week 1: June 13-17
Week 2: July 11-15

Chapters

April 11, 2005
PDA Canada Chapter Annual Meeting
Toronto, Ontario, Canada

PDA Calendar of Events for Europe/Asia Pacific/Middle East/India

Please visit www.pda.org for the most up-to-date event information, lodging and registration.

EUROPE

January 24, 2005
PDA EuroForum Prague, Czechoslovakia

January 31, 2005
PDA EuroForum Basel, Switzerland

February 2, 2005
PDA together with the PDA UK/Ireland Chapter
Biotechnology Conference: Risk, Regulation & Resource
Oxford, United Kingdom

March 1-4, 2005
2005 PDA International Congress,Courses and Exhibition
Rome, Italy

May 3-4, 2005
Aseptic Processing Training Workshop
London, England

May 12, 2005
PDA EuroForum
London, England

June 2, 2005
PDA EuroForum
Budapest, Hungary

June 13, 2005
PDA EuroForum
Barcelona, Spain

June 20, 2005
PDA EuroForum
Milan, Italy

October 10-11, 2005
Taormina Conference
Sicily, Italy

November 3, 2005
PDA EuroForum
Lisbon, Portugal

November 24, 2005
PDA EuroForum
Paris, France

December 5, 2005
PDA EuroForum
Vienna, Austria

Date TBD
PDA EuroForum
London, England

INDIA

January 21-22
PDA IndiaForum

March 18-19
PDA IndiaForum

May 20-21
PDA IndiaForum

September 16-17
PDA IndiaForum

November 22-23
PDA IndiaForum

FDA's New Mantra: Science and Partnering

Victoria Dedrick, PDA

Along with the 21st Century Initiative on cGMPs, FDA has been working hard to re-engineer itself into a friendlier, more human-faced organization. Anyone who has worked with FDA over the years is bound to see the changes taking place. The movement from enforcer to partner is apparent in many areas along with a more logical division of labor.

A commitment to strong and sound science will mean CDER scientists stay on the cutting edge of new technologies. The center's mission depends, more than ever, on a solid cadre of experienced physicians, toxicologists, chemists, statisticians, mathematicians, project managers and other highly qualified and dedicated professionals. This influx of strong scientists utilizing a risk-based approach to evaluation makes it easier for industry to clearly justify its products and processes based on good science.

At present, the quickening pace of scientific discoveries is propelling the development of a tidal wave of novel, extremely complex products and processes that will soon put the FDA to a crucial test. They include genomics- and proteomics-assisted drug development and disease detection and diagnosis; robotics; nanotechnology; minimally invasive surgery and medical imaging; xenotransplantation and organ replacements; stem cell-derived products and assisted reproduction; biosensors and new drug delivery systems; individualized drug therapy; and transgenics.

The FDA will have to acquire expertise in new informatics, artificial intelligence, and new knowledge management; develop better tools for quantitative risk assessment, modeling, clinical trial design and analysis; design better predictive tests involving transgenics, biomarkers, alternatives to test animals, and computational science; and find better methods for rapid product testing, and for easier identification of foodborne, waterborne and other natural toxins, allergens, and transmissible spongiform encephalopathies.

FDA is calling for a new focus on modernizing the tools that researchers and product developers use to assess the safety and effectiveness of potential new products and to mass produce high-quality therapies.

As if that were not sufficiently challenging, the FDA will have to accomplish these tasks at a time when our rapidly aging population will increase the need and expectations for the FDA's public health services. To meet this historic test, and to expedite the availability of new medical marvels to the public, the FDA cannot wait until the products emerge according to the standard pace of today's R&D pipelines. The agency must achieve the critical mass of scientific, medical and financial resources-without delay.

As the gatekeeper for these products and technologies, the FDA will have a decisive impact on their safety, effectiveness and the speed of their availability to the public.

FDA is calling for a new focus on modernizing the tools that researchers and product developers use to assess the safety and effectiveness of potential new products and to mass produce high-quality therapies. New scientific and technical tools--including assays (tests), standards, computer modeling techniques, biomarkers, and clinical evaluation techniques--will improve predictability and efficiency of products along the development path, raising the success rate of finding new safe and effective therapies.

For example, FDA is developing an ECG research database and toolkit to improve its ability to evaluate drugs for cardiac safety and to enhance efficiency of ECG data collection and submission. The goal is to better enable sponsors to predict success and failure in earlier stages of product development, lowering the overall costs of new product development.

FDA also developed and implemented a more flexible and innovative approach to the clinical trials needed to evaluate medical screening devices. This new trial design allows small companies, which often cannot afford the normally required large-scale trials, to use common protocols so that their data can be pooled for analysis. The design currently allows manufacturers to test the effectiveness of digital mammography for screening use.

Such success stories can only be accomplished through a concerted and joint effort by industry, academia, patient groups and the FDA. Key to this effort will be the development of a "Critical Path Opportunities List" that will identify and prioritize the most pressing development problems and the areas that provide the greatest opportunities for rapid improvement and public health benefits.

FDA has consulted and solicited suggestions from all interested parties to identify and address specific defined critical path opportunities to make

product development more efficient and predictable. Besides holding several workshops on the critical path, the agency established a docket for public comment. Out of all the numerous comments vetted by the agency, two stand out as overriding concerns: clinical trials and biomarkers and endpoints.

In addition, the FDA intends to refocus its own activities and take on new partnerships, as needed, to fulfill these priority opportunities. These actions promise not only to bring medical breakthroughs to patients more quickly, but also to do so in ways that ensure greater understanding of how to maximize patient benefits with a minimum of risk.

PDA has and must continue to play a strong role as one of FDA's key partners for the future. As FDA moves toward risk-based science to drive its decisions, PDA's expertise and long time excellence in science and technology make us their ideal partner.

PDA Comments on New European GMP Requirements: Product Quality Review & On-Going Stability

James Lyda, PAREXEL Consulting

Last December the European Commission announced amendments to the EU Guide to Good Manufacturing Practice for two areas (1) On going stability, Chapter 6, and (2) Product Quality Review, Chapter 1. A PDA task force of members from Europe and the US reviewed the proposed changes and prepared consensus comments that were submitted to the EC by June 30, 2004.

The proposed GMP changes address areas in which guidance was lacking or limited in the European GMP Guide, but are more articulated in the US GMPs. Following long standing PDA practice, the committee adopted as their underlying rationale that additions to the European requirements should be harmonized with the U.S. requirements, and should have technical merit. Both letters are reproduced in this issue of the *PDA Letter*.

A sincere 'Thank You' is in order for the following PDA members who either prepared, reviewed or offered suggestions on the comments:

Anita Beate Albrechtsen, Ferring Pharmaceuticals, Denmark

- Steve Bellis, AstraZeneca, UK
- Clive Blatchford, Aventis Pasteur, France
- Marco Budini, Chiron Vaccines, Italy
- Garrett Egan. Wyeth Medica Ireland
- Don Elinski, Eli Lilly, USA
- Ed Fry, Ivax Pharmaceuticals, USA
- Bob Dana, Elkhorn Associates, USA
- Anne-Marie Gallo, Aventis Pharma, France
- Norbert Hentschel, Boerhinger Ingleheim, Germany
- Miroslav Janousek, Leciva, Czech Republic
- James Lyda, PAREXEL Consulting, Switzerland (Chair)
- Brian Matthews, Alcon Laboratories, UK
- Claudia Nardini, Kedrion SpA, Italy
- Stephan Roenninger, F. Hoffman LaRoche, Switzerland
- Trudy Schots, ZLB Bioplasma, Switzerland
- Ian Symonds, Glaxo SmithKline, UK
- Fernando Tazon Alvarez, Almirall Prodesfarma, Spain
- Anders Vinther, CMC Biopharmaceuticals, Denmark

PDA's Regulatory Affairs and Quality Committee (RAQC) submitted several written comments to health authorities around the world in 2004 in response to draft and final guidances and to communicate PDA positions on particular issues. Below is a list of the regulatory guidances for which RAQC provided comments during the year. The chair(s) of the RAQC Task Force is indicated in parentheses.

FDA Draft Guidance for Industry –Draft Guidance for Industry on Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical Current Good Manufacturing Practice (Zena Kaufman, Pfizer Inc.)

FDA Draft Guidance for Industry on "Powder Blends and Finished Dosage Units –Stratified In-Process Dosage Unit Sampling and Assessment (Don Elinski, Eli Lilly and Company)

WHO Working Document QAS/04.068: Good Distribution Practices (GDP) for Pharmaceutical Products (Steven Bellis, IVAX Pharmaceuticals)

WHO Guideline for Sampling of Pharmaceuticals and Related Materials, Working Document QAS/03.066/Rev. 2 (Don Elinski, Eli Lilly and Company)

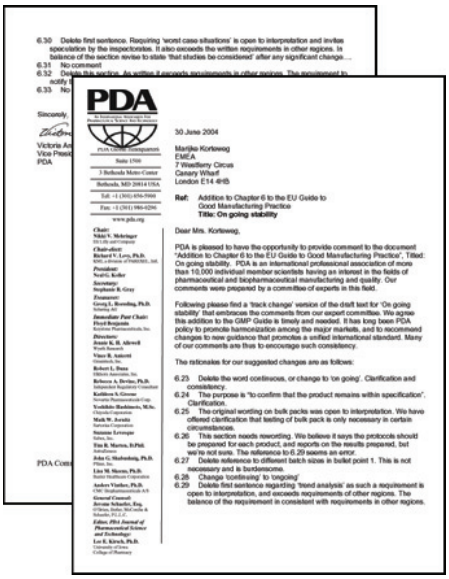
Addition to Chapter 1 to the EU Guide to Good Manufacturing Practice, Titled: Product Quality Review (James Lyda, PAREXEL Consulting)

Addition to Chapter 6 to the EU Guide to Good Manufacturing Practice (James Lyda, PAREXEL Consulting)

AS/04.066/Rev. 3, *WHO Guidelines for Sampling of Pharmaceuticals and Related Materials: Risk Assessment with Respect to the n, r, p Plans* (Don Elinski, Eli Lilly and Company)

Draft Guidance for Industry and FDA: Good Manufacturing Practices for Combination Products (Michael A. Gross, QLT, Inc.)

Draft Guidance for Industry: Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations (Michael Van Der Werf, Pfizer, Inc., and Zena G. Kaufman, Pfizer, Inc.)



30 June 2004

Marijke Korteweg
EMEA
7 Westferry Circus
Canary Wharf
London E14 4HB

Ref: Addition to Chapter 6 to the EU Guide to Good Manufacturing Practice

Title: On going stability

Dear Mrs. Korteweg,

PDA is pleased to have the opportunity to provide comment to the document "Addition to Chapter 6 to the EU Guide to Good Manufacturing Practice", Titled: On going stability. PDA is an international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical and biopharmaceutical manufacturing and quality. Our comments were prepared by a committee of experts in this field.

Following please find a 'track change' version of the draft text for 'On going stability' that embraces the comments from our expert committee. We agree this addition to the GMP Guide is timely and needed. It has long been PDA policy to promote harmonization among the major markets, and to recommend changes to new guidance that promotes a unified international standard. Many of our comments are thus to encourage such consistency.

The rationales for our suggested changes are as follows:

6.23 Delete the word continuous, or change to 'on going'. Clarification and consistency.

6.24 The purpose is "to confirm that the product remains within specification". Clarification.

6.25 The original wording on bulk packs was open to interpretation. We have offered clarification that testing of bulk pack is only necessary in certain circumstances.

6.26 This section needs rewording. We believe it says the protocols should be prepared for each product, and reports on the results prepared, but we're not sure. The reference to 6.29 seems an error.

6.27 Delete reference to different batch sizes in bullet point 1. This is not necessary and is burdensome.

6.28 Change 'continuing' to 'ongoing'

6.29 Delete first sentence regarding 'trend analysis' as such a requirement is open to interpretation, and exceeds requirements of other regions. The balance of the requirement in consistent with requirements in other regions.

6.30 Delete first sentence. Requiring 'worst case situations' is open to interpretation and invites speculation by the inspectorates. It also exceeds the written requirements in other regions. In balance of the section revise to state 'that studies be considered' after any significant change….

6.31 No comment

6.32 Delete this section. As written it exceeds requirements in other regions. The requirement to notify the competent authority is adequately described in 8.7 and 8.11 of the GMP guide.

6.33 No comment

Sincerely,

Victoria Ann Dedrick
Vice President, Quality and Regulatory Affairs
PDA

30 June 2004

Marijke Korteweg
EMEA
7 Westferry Circus
Canary Wharf
London E14 4HB
Email: iqmanagement@emea.eu.int

Ref: Addition to Chapter 1 to the EU Guide to Good Manufacturing Practice

Title: Product Quality Review

Dear Mrs. Korteweg,

PDA is pleased to have the opportunity to provide comment to the document "Addition to Chapter 1 to the EU Guide to Good Manufacturing Practice", Titled: Product Quality Review. PDA is an international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical and biopharmaceutical manufacturing and quality. Our comments were prepared by a committee of experts in this field.

Following please find a 'track change' version of the draft text for Product Quality Review (PQR) that embraces the comments from our expert committee. We agree a requirement for PQR is timely and needed. It has long been PDA's policy to promote harmonization among the major markets, and to recommend changes to new guidance that promotes a unified international standard. Many of our comments are thus to encourage consistency with the long-standing industry expectations surrounding the USA requirements for PQR.

The rationales for our suggested changes are as follows:

1. PQR components:

a. (ii) - 'representative' is consistent with current FDA expectations

b. (vi) & (x) - Wording has been added that those variations and commitments that 'impact on product quality' should be reviewed.

c. (xi) - Delete this section – the assessment step of the PQR (next paragraph) addresses the issue of revalidation. The listing described here is impractical, burdensome, and exceeds requirements in other markets (Note: Processes are normally validated, not procedures).

d. (xii) - Delete this section – much equipment is multi-use, and would have to be listed again and again in different PQRs. Equipment re-qualification is adequately covered in existing GMP systems. Preparing such a list is impractical, burdensome, and exceeds requirements in other markets.

2. Marketing Authorization Holder (MAH):

a. The MAH, if different from the manufacturer, normally cannot conduct the PQR as only the manufacturer has the necessary data.

b. This requirement adds significant administrative burdens with unclear value.

c. It also exceeds requirements in other markets.

d. For the above reasons, the role of the MAH has been modified, and the requirement for a 'technical agreement' with the MAH should be deleted.

e. Instead, we suggest that a copy of the PQR be shared with the MAH.

3. **Stability –** The paragraph relating to stability should be deleted and included with the GMP addition to chapter 6 for 'Ongoing stability.'

4. Qualified Person:

a. The PQR is a quality review. The Quality Unit should be responsible for the conduct and accuracy. This is consistent with Annex 18 (ICH Q7A) which describes the PQR but does not describe QP responsibility.

b. We see no advantage (and some complications) in assigning this responsibility to the QP.

c. We recommend deletion of this paragraph.

Sincerely,

Victoria Ann Dedrick
Vice President, Quality and Regulatory Affairs
PDA

The following booklets have been selected from the chapters of

Microbiology in Pharmaceutical Manufacturing

Editor: *Richard Prince*

(2001, Item No. 17185 Price: US$ 240 Member/US$ 299 Nonmember)

These booklets offer a complete overview of a specific topic and provide practical advice for anyone interested in current aspects of microbiology in pharmaceutical manufacturing.

A Basic Primer On Pharmaceutical Microbiology

Author: *Hans van Doorne*

57 Pages, ISBN: 1-930114-75-3
Item No. 17228
Member: US$ 75
Nonmember: US$ 95
Government: US$ 30

This booklet provides a basic primer on pharmaceutical microbiology by focusing on the essential properties of microorganisms.

Topics include the three major types of microorganisms of concern to pharmaceutical scientists – bacteria, fungi and viruses.

Designing A Contamination Control Program

Author: *Sandra A. Lowery*

67 Pages, ISBN: 1-930114-76-1
Item No. 17229
Member: US$ 75
Nonmember: US$ 95
Government: US$ 30

This booklet focuses on the various aspects of sterile product manufacturing that must rely on classical aseptic processing methodologies for bulk processing, aseptic filling or both.

Microbiological Validation Master Plan

Author: *Trevor Deeks*

42 Pages, ISBN: 1-930114-67-2
Item No. 17230
Member: US$ 50
Nonmember: US$ 65
Government: US$ 20

This booklet describes the contents of the Microbiological VMP and the factors that influence the validation requirements. The reader will gain an appreciation of the planning required within the microbiology laboratory to support a company's overall validation effort.

Validation Of Sterilization Processes

Author: *James Agalloco*

51 Pages, ISBN: 1-930114-68-0
Item No. 17231
Member: US$ 50
Nonmember: US$ 65
Government: US$ 20

This booklet describes approaches and methods that can be used to validate sterilization procedures. The booklet stresses the commonality of methods and practices used in the validation of different sterilization methods.

Practical Considerations for the Development, Validation and Transfer of Analytical Test Methods

Author: *Diane Petitti*

28 Pages, ISBN: 1-930114-69-9
Item No. 17232
Member: US$ 35
Nonmember: US$ 45
Government: US$ 15

This booklet provides guidance for performing effective and efficient method validation studies. It also focuses on the important practical usefulness of the validation exercise for the routine testing laboratory and how it may affect the release process.

For more information on these and other publications, please visit our e-store at **www.pda.org/estore**

04101903

Risk Management and Harmonization

Mark Lynch, PAREXEL Consulting

[Editor's Note: The following summary of session C3: *Risk Management and ICH Harmonization* of the 2004 PDA/FDA Joint Regulatory Conference was prepared by session moderator Mark Lynch, Parexel Consulting. The summary includes a review of each speakers' remarks and selected questions posed by the audience. Mr. Lynch indicates whether the speaker answered each question, and in some cases what the answer was. In preparing this summary, Mr. Lynch inserted his own commentary for certain questions, as indicated by parentheses. See page 30 for a list of session speakers.**]**

Attendees learned the principles of risk and risk management, which apply readily to international harmonization, hierarchy and levels of risk management models, and high-level and low-level tools from Dr. Claycamp. It became clear that Dr. Claycamp had worked with the FDA workgroups on the FDA site ranking model as well as ICH Q8 and Q9 drafts. Dr. Claycamp answered questions from the audience pertaining to the subjectivity of the Risk Assessment Team, use of the ISO Risk Management Standard in Q8 and Q9, the role of the level of detection in risk estimates, and the composition of the ICH working group for Q8 & Q9.

Brian Hasselbalch explained how the FDA Manufacturing Site Risk-Ranking Model for prioritization of cGMP inspections was developed. He explained the model contained risk factors in the separate areas of product, process, and facility. He clarified how the process risk factors were estimated using a "Expert Elicitation Survey" because the FDA has limited data on manufacturers' processes. He provided some ideas about how the unit operations in a production process might be evaluated as well as how the product, process, and facility information was combined and evaluated. In the question and answer period Mr. Hasselbalch clarified how the results of the activity were being used currently and what information might be publicly available to industry.

Frank Matarrese provided the linkage of Risk Management to the ICH Q8 and Q9 documents and suggested that this was an appropriate topic for all steps in the pharmaceutical development life-cycle.

Selected Questions from Cards

Dr. Claycamp

How will the ICH Risk Management Guidance be similar or different from the ISO Risk Standard? Answered

Risk assessment can be subjective based on the team composition. Can you please comment o the "subjectivity of risk assessment?" from A. H. Mollah, Baxter Healthcare.

His presentation says there are cultural and individual biases.

In determining risk level, you considered probability of occurrence and severity. What about level of detection (as in FMEA)? Do you consider detection in risk estimate? (Answered)

Who is on the Q9 Expert Working Group?

(Answered by naming a few individuals, chair Greg Guyer, and referring to ICH Web page.)

Mr. Hasselbalch

Will the risk-ranking model be applied to manufacturing sites currently audited by Team Biologics?

(Answered no, because not the same resource shortfall per number of sites as for CDER.)

Can you define "less frequent" inspections? 3 yrs, 5 yrs., vs. traditional 2 yrs. For general inspections?

(Answered, but I don't think he could be specific.)

How does risk-ranking inspections comply with CFR requirement of inspecting each facility every two (2) years?

(Answered, it does not as this is not currently possible.)

Are the results of the "Expert Elicitation" available for industry? It would be highly useful in our conducting risk assessment.

(Answered. I do not believe the agency plans to release elicitation information. I think Mr. Hasselbalch questioned the need for this, because he felt the company should know more about the risk of their own products and processes that the FDA.)

Since much of the desired data (process) is not readily available to the FDA, why not ask sites to complete a survey to gather the relevant data, i.e. mitigation factor and volumes?

(Answered. They thought it that but were subject to the OMB paperwork reduction restrictions.)

Can you tell us again how the SRP (Risk-Ranking Model) will be used by FDA in scheduling inspections in 2004 and beyond? (i.e. a test run?)

(Answered. I believe he estimated that about half of district surveillance inspections to be conducted would be as a result of the risk-ranking model. It did not appear that the survey addressed API manufacturers until I looked at his slide15, which says all drug industry facilities, whether inspected or not, from Field Accomplishment and Compliance Tracking System (FACTS) from 2000 - 2004. Therefore, this should include API and foreign sites. There were no specific questions during the session, but Dan

PDA
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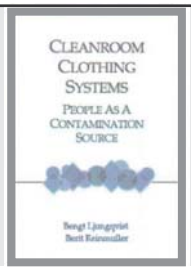
Your source for scientific, technical and regulatory information.

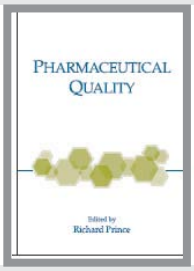
2004 New Technical Book Releases!

Cleanroom Clothing Systems: People as a Contamination Source
By Bengt Ljungqvist & Berit Reinmueller



If you have responsibilities for maintaining a cleanroom environment, this book is a must-read guide that provides comprehensive observations from case studies performed in a dispersal chamber.

Item No. 17206
US$ 135 member/US$ 169 nonmember

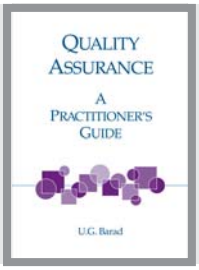


Pharmaceutical Quality
Edited by Richard Prince

This book offers examinations of quality from international, government, industry, and individual perspectives. It is a must-have reference guide for both pharmaceutical and biopharmaceutical professionals.

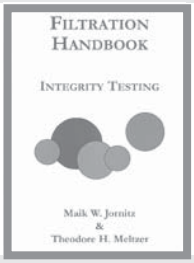
Item No. 17207
US$ 240 member/US$ 299 nonmember

Quality Assurance: A Practitioner's Guide
Author: U. G. Barad



This is an indispensable tool for students, beginners and experienced professionals working in pharmaceutical companies – large and small. It covers most of the prevailing regulatory requirements and expectations worldwide.

Item No. 17212
US$ 185 member/US$ 229 nonmember



Filtration handbook: Liquids
Authors: Maik W. Jornitz & Theodore H. Meltzer

This training guide provides both an overview and a comprehensive training course that is invaluable to filtration professionals at all levels.

Item No. 17208
US$ 185 member/US$ 229 nonmember

Good Practice and Compliance for Electronic Records and Signatures, Part 3, Models for Systems Implementation and Evolution

Part three of the series Good Electronic Records Management, this document, produced by the PDA Part 11 Task Group, provides further discussion for enhancing information technology practices used in the engineering of new computing environments, the remediation of already-installed computing bases, and the subsequent maintenance of both types of computer systems.

Item No. 13003
US$ 95 member/US$ 190 nonmember

PDA Technical Report No. 32 revised:
Auditing of Suppliers Providing Computer Products and Services for Regulated Pharmaceutical Operations

This current revision to the technical report by the PDA Industry Advisory Board (IAB) reflects the lessons learned in four years of successful implementation. Also described is how the original Supplier Auditing and Qualification Task Group developed and tested a Process Model and Data Collection Tool. Use of these tools will provide consistent audit information that can be shared within the industry.

The audit information, presented as an audit report, is useful in supporting procurement activities and in inferring structural integrity of supplier products when engineering and validating computer systems, helping to meet the FDA challenge.

Item no. 01032 Paper version
Price: US$ 100 member/US$ 295 nonmember

Item no. 01132 CD-ROM version
Price: US$ 75 member/US$ 270 nonmember

For additional information or to place an order, visit
www.pda.org/estore

Gold asked me afterwards about API sites. International inspections have historically been driven by ANDA/NDA submissions, therefore it would be interesting to know the number of international sites selected for inspection this year. Also, if this is a "pilot", then it should be evaluated against specific criteria before continuing as a routine practice, 2005, 2006, 2007).

How will your ranking model work with sites manufacturing multiple product types? For example, solid dose, topicals, and metered dose inhalers (MDIs) at the same site?

(Not answered due to time.)

When using recall data, specifically the frequency, how do you compare a single lot recall for a multiproduct site versus a single product site?

(Not answered due to time.)

Can you speak to how, in the risk-ranking model, you come up with an overall score versus the individual risk areas? That is, if you have a high risk in a minor area how do you factor this into the overall inspection strategy?

(Not answered due to time.)

Can firms learn their "Scores"?

(Not answered due to time. This is an important issue because it approaches the concept of a "list" [good firm/bad firm list]. If firms are impacted negatively due to the list, then they must be able to know where they stand [due process] as well as to be able to submit information to convince the Agency to change their status. Another issue is, if the scoring is publicly available, then contractors and vendors may make decisions based on it as well as any audit or other information available to them. And lastly, if there is not sufficient oversight, there is a chance that the Agency will not update the scores on a continuing basis to reflect the results of the most recent inspection. Therefore, this process should have a limited retrospective window, e.g. to look back over the last two or three years, or over the last x inspections. FDA has either not thought about these issues or not formulated a policy on the matter that can be publicly discussed yet.)

The following three experts discussed risk management and ICH harmonization at the 2004 PDA/FDA Joint Regulatory Conference:

Gregg Claycamp
Center for Veterinary Medicine

Brian Hasselbalch
CDER, FDA

Frank Matarrese
Frank Matarrese GxP Consulting

Session participants also had a chance to meet **Stephen Stachelski**, Chair PDARAQC Task Force for ICH Q9 Comments.

Matthew A. Clark
Director, Marketing Services, Membership & Chapters

Director's Message

New PDA Membership Types

With each passing day, communications technology transforms the world into a digital village even as the global marketplace expands exponentially. News, information, research and discoveries routinely travel the globe in nanoseconds. The promises of an exciting new drug can be presented to a packed auditorium in Chicago and a field hospital in Kenya simultaneously.

Embracing the rapidly unfolding opportunities of this exciting era, PDA membership is being restructured to include greater contribution and participation from more new members worldwide.

PDA's Board of Directors has added three new membership types with an eye towards developing a broader base of international collegiality and scientific endowment. The three new membership categories are Developing Economy, Academic and Student. All are individual memberships and include full PDA member benefits and privledges.

Developing Economy: Capital investments in human resources, facilities and research and development are being made in every corner of the planet. Every nation, every culture and every environment has the potential to impact our industry now and for generations to come. The new Developing Economy membership provides all professionals the venue to teach, learn, share and grow. A complete list of countries eligible for developing economy status can be found at www.pda.org/join. Rate: US$ 100.

Academic: Throughout its 58-year history, PDA has relied on academicians to enhance many of our educational and research efforts. The Academic membership brings professors, educators and institutional researchers full circle and to the epicenter of furthering industry knowledge. To qualify for an Academic membership, individuals must be employed full-time by an accredited academic institution of higher learning working in an industry-related discipline. Rate: US$ 80.

Student. The Student membership provides an affordable advantage to young and redirected mid-career professionals who are pursuing their places in our industry. This membership category provides an incredible opportunity for assimilation, education and networking. Any student who is enrolled full-time and is pursuing industry-related studies at an accredited academic institution of higher learning is eligible for this membership. Rate: US$ 30.

These three new membership options will increase the accessibility of PDA to thousands of individuals around the world, affording them the resources to grow professionally, create life-long connections, and build foundations for the advancement of good science. For more information on PDA membership, or to join online, go to www.pda.org/join.

PDA Member Volunteers Launch 2004 PDA/FDA Conference

Walter Morris, PDA

PDA Capital Area Chapter Presidents Opens 2004 PDA/FDA Conference

PDA Capital Area Chapter President Barrie Friedman (Cambrex BioScience) welcomed over 800 members of the PDA community to the 2004 PDA/FDA Joint Regulatory Conference, Sept. 20-22.

The conference represented the largest PDA event to date and was one of the most informative in light of all the new guidances, reports and policy changes released by the U.S. FDA a week following the conference. By meeting with stakeholders days before the publication of these materials, FDA's top experts involved with the reforms were able to place each document in context and prepare attendees for the challenge of implementation.

Friedman pointed out that the conference fostered many opportunities for industry attendees to interact with FDA officials, and he encouraged all to do so, noting the value Capital Area Chapter participants derive from their close proximity to the agency's headquarters.

Friedman took the opportunity to discuss some of the recent accomplishments of the Capital Area Chapter. One of the biggest is the biotech scholarship the Chapter is sponsoring for University of Maryland-Baltimore County students.

The Chapter is also proud of its ongoing efforts to advance education. Its quarterly dinner meetings are focused on advancing PDA member understanding of pertinent issues and the latest developments at FDA.

To learn more about the PDA Capital Area Chapter and to become involved, go to its Web site, www.pda.org/chapters/CapChap/contact.html.

PDA Chair Nikki Mehringer Praises Association's Unique Global Community

Following PDA Capital Area Chapter President Barrie Friedman's words of welcome at the 2004 PDA/FDA Joint Regulatory Conference, PDA Chair Nikki Mehringer (Eli Lilly and Company) credited PDA members for their influential role in advancing sound science and regulations for the entire community.

PDA is a "unique global community" of "teachers and students, regulators and regulatees, authors and readers, multinationals and laboratory start-ups," stated Mehringer

"The fun of being a PDA member," she said, is the ability "to engage in conversation with people of such different backgrounds."

Regarding the 2004 PDA/FDA conference, Mehringer pointed out that PDA has been involved with FDA's 21st Century initiative since it began. This involvement stems from the mission of the Association and the strong belief of all our members that "good science should be the basis for everything we do," she declared. Just as important, "science-based regulations should absolutely be 'harmonizable' regulations across all plants, countries and continents."

Mehringer identified a number of groups that benefit from PDA's activities, including regulatory agencies, companies and, most importantly, patients.

In closing, the PDA Chair encouraged all in attendance to become involved with PDA. To do so, she said, is "very simple….Volunteer!"

PDA/FDA Program Chair Lauds Diverse Committee's Strong Effort

Allen Burgenson (Cambrex Bio Science) lauded the strong effort of the 2004 PDA/FDA Joint Regulatory Conference program planning committee—a group he chaired.

The group represented "an integration of industry and regulators into one team to present one cohesive program," said Burgenson. The broad experience of planning committee members, which included international representation, was reflected in the "breadth of attendees" at the conference.

Burgenson noted that the conference provided attendees a "unique opportunity" to interact with FDA officials on a number of topics related to the 21st Century drug cGMP initiative, including:

- resources and constraints,
- biotech,
- advances in pharmaceutical science and manufacturing technology,
- quality management, and
- globalization.

Chapters Contacts

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

Asia Pacific

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E-mail: ken_dibble@millipore.com

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dmakhey@nicholaspiramal.co.in

Japan Chapter
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Web site: www.j-pda.jp

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E-mail: jun_yeon_park@pall.com

Southeast Asia Chapter
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Web site: www.pda-it.org

Prague Chapter
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E-mail: hwick@hwmr.ca
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Capital Area Chapter
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E-mail:
barry.friedman@cambrex.com
Web site: www.pdacapitalchapter.org

Delaware Valley Chapter
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Midwest Chapter
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Mountain States Chapter
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New England Chapter
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Puerto Rico Chapter
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E-mail: bladues@wyeth.com

Southeast Chapter
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Web site: www.pdase.org

Southern California Chapter
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Contact: John Spoden
E-mail: pdasc@pdasc.org
Web site: www.pdasc.org

West Coast Chapter
Areas Served: Northern California
Contact: Randall Tedder
E-mail: randall@iconnova.com
Web site: www.istep.com/~randallt/wccpda

A Hunger For Knowledge

Eggs benedict, coffee and juice for breakfast as well as shrimp salad, sourdough and iced tea for lunch are perfect place settings for scientists and engineers who hunger for knowledge. The PDA/FDA Joint Regulatory Conference (September 20-22) sponsored some incredible—and of course, edible—presentations that satisfied both mind and body. Leftover samplings from the breakfast and lunch menus are certainly worthy of an entrée presentation.

Paul McKellips, PDA

Nooners—Lunch, Monday September 20

Change Control for Biotech Products

Moderated by **John Geigert**, PhD, President, Biopharmaceutical Quality Solutions, this opening day lunch session tackled change control and product comparability for biotech products. Topics included the impact of ICH Q5E, FDA's guidance on comparability protocols for biotech products and the possible impact of PAT on biotech change control.

Keith Webber, PhD, Acting Director, Office of Biotechnology Products, CDER, FDA and **Anthony Lubiniecki**, PhD, Adjunct Professor of Chemical and Biochemical Engineering, UMBC, prepared tasty presentations. Dr. Lubiniecki identified the four key principles of comparability and Dr. Webber discussed the FDA and industry standards for a successful protocol.

Laboratory Data Use to Improve Quality

Moderated by **Vince L. Matthews**, Quality Consultant, Eli Lilly and Company, this luncheon feasted on the notion that there's more to utilizing laboratory data than what meets the eye. Making improvements to laboratory and production operations is a central use of critical data. Panelist **Amy R. Barker**, PhD, Senior Analytical Chemist, Eli Lilly, pointed out that there are many types of charting, tracking and measurement standards with a variety of uses and functions. But by monitoring standard data beyond system suitability, it is possible to determine root causes, troubleshoot analytical and instrumental issues, isolate analytical variability from process variability and, most importantly, be proactive. **Mary Oates**, PhD, Senior Director of Global Quality Analytical Resources, Pfizer, built her presentation around the six key ingredients of data that must be tracked:

- Release and stability results
- Laboratory investigations sorted by assignable cause
- Planned and unplanned deviations from approved procedures and requirements
- Instrument information (use, maintenance)
- Right-first-time indicators (metrics) for lab operations
- Resources required per task

Guidance for Industry on Changes to an Approved NDA or ANDA

Moderated by **Brent Conatser**, Associate Quality Consultant, Eli Lilly, this opening day luncheon featured a sizzling discussion of the FDA guidance on changes to an approved NDA or ANDA, which lays out the Chemistry, Manufacturing and Control supplemental submission expectations for post-approval changes. FDA uses a four-tiered approach involving preapproval supplements for the most serious changes, changes-being-effected 30-day supplements for less serious changes, changes-being-effected supplements for moderately serious changes and annual reports for changes of little concern. **David J. Cummings**, Chemist, Office of Pharmaceutical Science, CDER, FDA, conveyed that a supplement or annual report must include *a list of all changes…*in *enough detail* to allow FDA to *quickly determine* whether the appropriate *reporting category* has been used. For *supplements*, this list must be provided in the *cover letter* (§ 314.70(a)(6)). In *annual reports*, the list should be included in the *summary section* (§ 314.81(b)(2)(i)). The applicant must describe each change fully in the supplement or annual report (§ 314.70(a)(1)).

Fresh Starts—Breakfast, Tuesday September 21

Orientation to FDA: An Introduction to Working with the Agency

Moderated by **Allen L. Burgenson**, Senior Regulatory Affairs, Cambrex BioScience, this breakfast was fortified with three representatives from FDA who covered the basic aspects of the FDA organization, including the CBER, CDER and ORA missions. The three panelists, **Robert C. Coleman**, National Expert Investigator, ORA, FDA, **Seamus O'Boyle**, Public Affairs Specialist, CBER, FDA, and **Mary Krezmner**, PharmD, Senior Health Promotion Officer, CDER, FDA, helped the audience digest a frequently confusing maze of acronyms and offices.

USP Committee of Experts: The Application and Selection Process

Moderated by **Janeen Kincaid**, Senior Manager Technical Affairs, Pfizer, this breakfast workshop had participants chewing over the foundation of USP's standards-setting activities, which is comprised of hundreds of expert elected volunteers who serve as the scientific decision-makers for USP. These volunteer experts establish and maintain the authoritativeness of USP's standards, information, and patient safety activities, and the credibility of the continuous revision processes that establish and revise the United States Pharmacopeia and the National Formulary (USP–NF). **Eric B. Sheinin**, PhD, Vice President, Department of Standards Development, U.S. Pharmacopeia, talked about USP's First Annual Scientific meeting which was held in Iselin, New Jersey in late September. **Susan J. Schniepp**, Manager, Compendial Services, Hospira, illustrated a ten-step recipe for standard submission and adoption by the USP.

Ten-step recipe for standard submission and adoption by the USP

1 Standard is Submitted to USP
2 Expert Committee (EC) Approves for Publication
3 USP Scientists Review Item
4 Item is Published in *Pharmacopeial Forum*
5 Public Comment is Received
6 EC review/responds to USP Scientists
7 USP Scientists compiles/analyzes comments
8 **If no further revision is required:** Adopted in Official Publications
9 **If further revision is required:** Republished in Pharmacopeial Forum
10 Process repeats until issues are resolved

Luscious Lunches du Jour—Lunch, Tuesday September 21

BSE/TSE: Implications for Pharmaceutical Manufacturing

Moderator **Amy Scott-Billman**, Executive Director, Adult & Pediatric Vaccines U.S. Regulatory Affairs, GlaxoSmithKline, ensured that luncheon participants had an easy time swallowing all the latest U.S. regulations impacting the manufacture of pharmaceutical products. Experts from various U.S. regulatory agencies and industry explored the science-based risk assessment approach versus the geography-based approach to sourcing. An update on current policies, procedures, sanctions, etc., from the U.S. Department of Agriculture and an update on the status of analytical tests for detection of BSE were provided by **Taryn Rogalski Salter**, Director Global Regulatory Policy, Merck, **William Egan**, PhD, Director, Office of Vaccines Research and Review, CBER, FDA, and **Lisa Ferguson**, Senior Staff Veterinarian, Animal and Plant Health Inspection Service, U.S. Department of Agriculture.

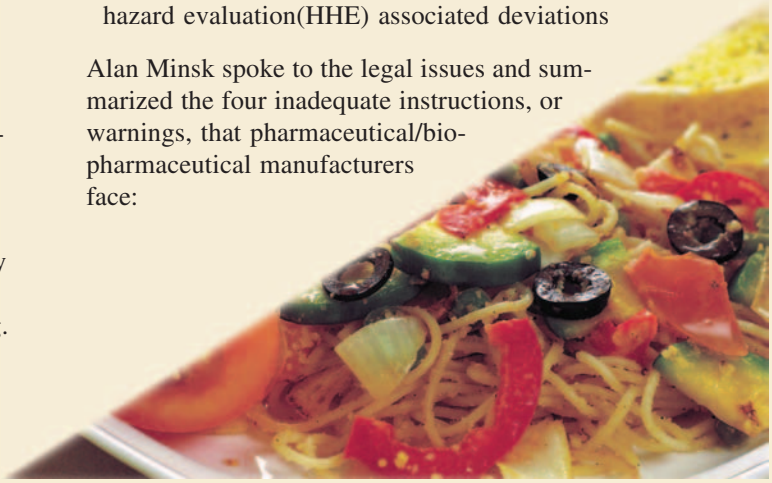
QA/QC Interest Group

This luncheon was a virtual smorgasbord of information. Moderated by **Don E. Elinski**, Validation Manager, Eli Lilly and Company, the QA/QC Interest Group feasted on a panel discussion involving **John Ayres**, MD, Health Hazard Evaluation Physician, Eli Lilly, and **Alan Minsk, JD,** Arnell Golden and Gregory, on the topic of health hazard analysis from the regulatory, industry, and legal perspectives. Risk Assessment is becoming a common statement in our industry today, and FDA released three new draft guidance on the use of risk assessment tools for health hazard analysis last spring.

Dr. Ayres identified six key components to proactive risk management:

- ❖ Requires strong partnership of Marketing, Medical, Safety, Quality and Manufacturing to ensure high quality processes are in place to document batch production, adverse experiences and product complaints.
- ❖ Absolute emphasis on manufacturing process & release specifications
- ❖ Evaluating link between product complaints and Adverse Events (AE)
- ❖ Considering AEs in context of product formulations, manufacturing process or process deviations and the impact on safety.
- ❖ Physician and toxicological evaluation of manufacturing processes
- ❖ cleaning validation
- ❖ deviations
- ❖ formulation or process changes
- ❖ Close prospective monitoring of released lots with health hazard evaluation(HHE) associated deviations

Alan Minsk spoke to the legal issues and summarized the four inadequate instructions, or warnings, that pharmaceutical/biopharmaceutical manufacturers face:



- Failure to instruct or warn is a major basis of liability for manufacturers
- When health-care providers are adequately informed of the relevant benefits and risks associated, they can reach appropriate medical decisions regarding which product is best for specific patients
- Sometimes a warning serves to inform health-care providers of unavoidable risks that are inherent in the use of the product
- By definition, such warnings will not aid the health-care provider in reducing the risk of injury to the patient by taking precautions in how the product is used, but it might allow the provider, and thereby the patient, to make an informed choice whether to use the product

Visual Inspection of Parenterals Interest Group

Moderated by IG leader **John G. Shabushnig**, PhD, Senior Manager, Global Quality Technical Services, the Visual Inspection IG was served a summary of recent FDA observations in the area of visual inspection and provided updates on the progress of the Technical Report #37 (Strategies for Effective Visual Inspection of Parenterals) Task Force. **Julius Knapp**, Research and Development Associates, made a sweeping and comprehensive presentation to a packed room. He stated that the Knapp-Abramson analysis of visible particle contamination in injectable products has, since 1980, used probability of particle detection in defined groups to evaluate batch quality. He reminded attendees that the Accept/Reject decision is probabilistic and is not simply repeatable.

Breakfast on the Run—Wednesday September 22

The CBER to CDER Transition

This breakfast session was moderated by **John Geigert**, PhD, President, Biopharmaceutical Quality Solutions, and featured a discussion on the current status of the FDA reorganization for biotech products. The main course included the identification of areas that have been confusing to industry and possible solutions for helping industry work more effectively with FDA through this transition. **Chiang Syin**, PhD, Chief, Manufacturing Review Branch One, CBER, FDA, and **Carolyn Renshaw**, PhD, Biologist, CDER, FDA, were the two panelists.

Compendial Issues: USP and Other Pharmacopeias

Susan J. Schniepp, Manager, Compendial Services, Hospira, moderated this breakfast session on compendial issues. Attendees recieved several morsels on international pharmacopeia harmonization. CBER/CDER transition implications for USP/monographs and PAT from global compendial perspectives were discussed and analyzed by **Eric Sheinin**, PhD, Vice President, Department of Standards Development, USP, and **Janeen Kincaid**, Senior Manager Technical Affairs, Pfizer, Inc.

ICH Q5E Comparability Protocols

This breakfast workshop was packaged to keep conference participants on schedule! Moderator, **Elizabeth Leininger**, PhD, Sr. Consultant, Biologics Consulting Group, served up this delicacy featuring **Christopher Joneckis**, PhD, Senior Advisor for CMC Issues, CBER, FDA, and **Rebecca Devine,** PhD, Regulatory Consultant. The panelists identified leading scientific and regulatory considerations for the comparability of biological products and up-to-date information concerning current and future regulatory expectations.

The breakfasts and luncheons were a very popular addition to the 2004 PDA/FDA Joint Regulatory Conference. These extra-conference sessions allow meeting participants to attend an hour-long topical lecture and enjoy a good meal. Look for more breakfasts and luncheons in upcoming PDA events.

The breakfasts and luncheons at the 2004 PDA/FDA Joint Regulatory Conference drew large numbers of hungry participants

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2005 PDA Extractables/Leachables Forum

Diane Paskiet, Program Planning Committee Chair (Monarch Analytical Laboratory)

Container/closure extractables have been recognized by PDA as a challenging issue facing industry and a special forum was presented in 1996 to bring awareness to the topic and communicate industry's concerns with the implementation of an extractable/leachable program. An effort to explore the issue of "how far to go," the PDA re-visited the topic in the November 2001 forum, *The Extractable Puzzle: Putting the Pieces Together*. The forum highlighted the regulatory, materials, chemistry and toxicological aspects of extractable/leachable studies, and a survey was conducted to communicate the perspective of industry.

In light of new advances in drug delivery, materials and regulatory expectations, it is time to evaluate the concerns of industry today. **The Extractables Puzzle: An Integrated Team Approach** will be presented May 23-25, 2005 at the Marriott North Bethesda Hotel and Conference Center. This forum will provide significant value to pharmaceutical and biotechnology professionals and bring together the regulatory, materials, chemistry and toxicology functions regarding: when to look?, where to look?, how to find and what to do when addressing extractables and leachables challenges. Extractable and leachable issues relating to different drug product categories, packaging systems, drug product delivery systems, and drug device combination products and processing equipment will be considered.

Bring your questions, experiences and best practices to facilitate the continued discussions of the chemical and toxicological characterization of extractables from packaging, process materials and drug product leachables. If you are new to the field, attend an introduction course to the world of leachables and extractables. If you are a veteran, learn about the latest industry trends and consensus opinions. Either way, you will gain an understanding of the current and best strategies for testing and qualifying packaging and processing materials.

The conference will include several relevant topics:

- **Analytical testing:** Analytical testing is related to the level of concern for the drug product and its route of administration as described in Table 1 of the 1999 *Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics*. Is there sufficient guidance for your product? This forum will afford time to address your interests.
- **GMP:** What action is needed to assure compliance with respect to extractables and leachables? How does the cGMPs translate to an extractable/leachable study, what approaches have been successful, what approaches have failed? The new demands placed on industry will be featured at this forum.
- **International regulatory perspectives:** The forum will provide representation from FDA, EMEA, MHLW and Health Canada. Topics will include the integration of critical functions throughout the drug development process, managing information between vendors and pharma manufactures, profiling materials, analytical test methods, evaluation of processing materials, assessment of safety, stability, suitability and quality control.
- **Guidance on the pharmaceutical development process:** The information needed to get a product through review, guidance on testing that should be performed on separate container/closures verses final products, comparison of pharmacopoeial and ISO standards and their utility, correlation of extractables and leachables, and guidance on what constitutes a complete toxicological qualification, will also be covered.
- **The Product Quality Research Institute (PQRI) L&E Working Group** plans to provide an update on its activities on dealing with leachables and extractables in orally inhaled and nasal drug products (OINDP).

Additionally, the conference will offer attendees the opportunity for direct participation in roundtables and breakout discussions. Regulatory authorities will be present during panel discussions to answer your questions. Results of a survey, which will be circulated in advance of the conference to examine where industry stands today, will be presented at the conference. The forum will also include poster sessions.

The Extractables Puzzle: An Integrated Team Approach

May 23-25, 2005

Bethesda North Marriott
Bethesda, Maryland

Go to **www.pda.org** for more information on the conference and to take the **PDA Extractables Survey.**

2005 PDA International Congress: *Bringing Practicality To Science*

Paul McKellips, PDA

The "eternal city" of Rome, Italy serves as the backdrop for this year's PDA International Congress, Courses and Exhibition—a three day exchange of solutions to meet regulatory compliance in a changing, global market.

The 2005 PDA International Congress will focus on time-critical trends in science, industry and regulatory affairs, through the examination of dozens of industry case studies and the latest updates from regulatory authorities throughout the world.

Pharmaceutical and biopharmaceutical entry-level, managers, directors and senior executives will come together to exchange ideas in the following areas.

Presentations will be given by senior-level experts representing the pharmaceutical and biopharmaceutical industries and health authorities in Europe and the U.S. The following is just a taste of the presentations offered for the 2005 PDA International Congress:

CGMP Guidance for Phase I Clinical Trials, Christopher J. Joneckis, PhD, CBER, FDA

Virus Filter Challenge and Nomenclature Standardization: A FDA/FDA Task Force Update, Kurt Brorson, PhD, CDER, FDA

Q10: A New Quality Management Initiative, Joyce Ramsbotham, Solvay Pharmaceuticals

Case Study: Robust Validation Testing to Avoid OOS Results, Dr. Bernd Renger, Vetter Pharma-Fertigung, GmbH & Co, KG

Case Study: Process Analytical Technology (PAT) at AstraZeneca, Dr. Staffan Folestad, AstraZeneca (invited)

2005 PDA International Congress:

Bringing Practicality to Science

Rome Italy

Rome Cavalieri Hilton

March 1-3: Conference

March 1-2: Exhibition:

March 4: PDA TRI Training Courses

Go to www.pda.org/rome2005

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The Congress will take place at the Five Star Rome Cavalieri Hilton. Situated on a 15-acre Mediterranean private park, the Cavalieri overlooks the Colosseum, St. Peter's Cathedral, Trevi Fountain and the historic city center. The Catacombs, Vatican and Spanish Steps are only minutes away by foot.

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