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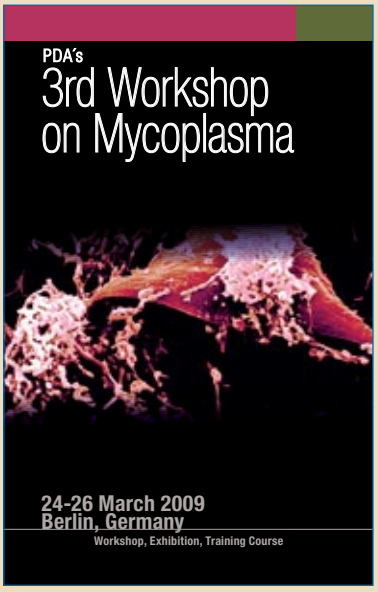
PDA Letter

Volume XLV • Issue #1

www.pda.org/pdaletter

January 2009

In This Issue:



PDA
Parenteral Drug Association

Connecting People, Science and Regulation®

PDA Teams with PIC/S for Regulator-Industry Dialogue on Annex 1, QRM

Jim Lyda, PDA

PDA worked with the Pharmaceutical Inspection Cooperation Scheme (PIC/S) and the International Society of Pharmaceutical Engineers to bring together regulatory and industry representatives for two days to discuss the application of quality risk management in aseptic processing. The highly successful event was held November 13-14, 2008, in Geneva, Switzerland.

The workshop covered the manufacture of sterile medicinal products in the context of the revised EU/PICS GMP Annex 1. In keeping with PIC/S focus on inspections and GMP issues, the subtitle of the workshop was "New and Possible Uses of Quality Risk Management." The concept was originally suggested by PIC/S as a way to bring authorities and industry together in a "safe" environment to have open and frank discussions on technical issues and the application of QRM principles to the production of sterile medicinal products. While the workshop was sponsored by all three organizations, PDA was responsible for organizing the event.

The three major goals of the workshop, in priority, were:

- To build a safe and constructive platform for technical discussions between inspectors and industry
- To better interpret and implement the latest revision of EU/PICS revised GMP Annex 1
- To explore the potential uses of QRM in the manufacture of sterile medicines

Registration for the workshop totaled 96 individuals, including the inspector, industry and staff planning team. There were 42 inspectors participating from 24 different countries and one representative of the European Directorate for the Quality of Medicines and HealthCare (EDQM). The representatives came from Australia, Canada, Cyprus, Czech Republic, Estonia, Finland, France, Germany, Greece, Indonesia, Iran, Ireland, Italy, Latvia, Malaysia, Norway, Romania, Singapore, Slovenia, South Africa, Sweden, Taiwan, Republic of China, United Kingdom and the United States.

Perspectives on Annex 1

The workshop opened with an introduction by **Jacques Morénas**, Current Chairman of PIC/S. This was followed by a summary of the changes and interpretations around revised GMP Annex 1 by **Paul Hargreaves,** Principal Medicines Inspector, MHRA. A presentation on regulator "true stories" was made by **Andrew Hopkins,**

continued on page 19

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Table of Contents

Volume XLV • Issue #1 www.pda.org/pdaletter

Cover art:
Implementation strategies for EMEA Annex 1 were covered at the workshop for industry and regulators presented by PDA & ISPE with PIC/S.
Photo collage by James Austin Spangle.

Coming Next Issue:
Supply Chain

PDA's 4th Annual Global Conference on Pharmaceutical Microbiology

October 5-8, 2009 | Bethesda, MD

Call for Abstracts / Case Studies

The 2009 PDA Pharmaceutical Microbiology Program Committee invites you to submit a scientific abstract for presentation at PDA's 4th Annual Global Conference on Pharmaceutical Microbiology. The theme of this year's conference is **Bringing Microbiology to the Manufacturing Floor**. Suggested topics include, but are not limited to:

- **Case studies, such as:**
  - » Satisfying global regulatory requirements
  - » Meeting pharmacopeial expectations
  - » Quality risk assessment/ Quality by Design (microbial control)
  - » Application of RMM in manufacturing setting
- **Trends in environmental monitoring**
  - » Sampling, detection and data analysis methods
  - » Scientific principles on sampling efficiency
  - » Viable but non-culturable organisms
- **Setting alert/action limits**
  - » Use of statistics in qualification of new methods
- **New and/or alternative methods**
  - » Rapid Microbiological Methods (RMM)
- **Advances in Aseptic Processing**
- **Emerging technologies in microbiology**
- **Biotechnology Manufacturing**
- **Microbial identification in the pharmaceutical industry**
- **Objectionable organisms**
- **Recent compliance issues in non-pending cases (FDA enforcement officers/auditors)**
- **Microbiological programs in non-sterile environments**
  - » Viable and non-viable monitoring
  - » Microbial challenges
- **Medical devices/Combination products**
- **Media fill design**
- **Microbiological aspects of cleaning validation**
- **Sterilization, disinfection and preservation**

Abstracts must be received by April 30, 2009 for consideration.

Visit https://www.pda.org/microbiology2009 to submit your abstract.

Case studies are particularly desired. Commercial abstracts featuring promotion of products and services will not be considered. After July 1, 2009, you will be advised in writing of the status of your abstract. PDA will provide one complimentary registration per podium presentation. Additional presenters are required to pay appropriate conference registration fees. All presenters are responsible for their own travel and lodging, with the exception of health authority speakers.

QUESTIONS?

Contact PDA:
Leslie Meritt
Sr. Programs and Meetings Coordinator
Tel: +1 (301) 656-5900 ext. 124
Fax: +1 (301) 986-0296
Email: merritt@pda.org

ALL ABSTRACTS WILL BE REVIEWED

All submitted abstracts will be reviewed by the Program Planning Committee for inclusion as a podium presentation or for poster presentation.

ATTENTION EXHIBITORS

PDA is seeking vendors who provide excellent products/services in support of this conference. Space is limited and is on a first-come, first-serevce basis. To reserve your space, please contact Nahid Kiani at kiani@pda.org or +1(301)656-5900 ext.128.

Editor's Message

Annex 1 Changes Effective in March

Many of the new provisions in the revised Annex 1 go into effect in 2009, so the *PDA Letter* starts the New Year off with two articles on the regulation. The cover story, by PDA's **Jim Lyda,** summarizes a meeting PDA sponsored in cooperation with PIC/S on Annex 1 implementation and risk management. As Jim relates, the meeting was very successful in generating dialogue between the inspectors and industry representatives in attendance. Out of respect to the attendees who were promised an environment for open discussion, the article does not include specific quotes from the various discussion segments of the meeting. A participant in the meeting, **Martyn Becker,** submitted the second feature article on Annex 1—a commentary on implementation strategies. Martyn believes many firms are right on top of the new provisions in the Annex, so they will not need to change much by due date in March. However, he outlines three specific areas of the document that firms might need to do some last minute adjustments in order to be in compliance.

Annex 1 and how it fits in with existing regulatory guidances worldwide is an important subject for most PDA members. It is clear from Jim's article that the EMEA intends to continue the dialogue with industry as the new rules come into effect. Martyn points out that the "biggest single" change in the document pertains to capping, which does not become effective until March 2010. I encourage readers to contact me if they have comments about the feature articles or if they would like to contribute to the dialogue in a future issue.

With the New Year underway, PDA welcomes new members to our volunteer Board of Directors. Our "News & Notes" announcement about the new BoD includes photos and brief bio information of the new members.

The "Science & Technology Snapshot" opens the year with a message from PDA Sr. VP **Rich Levy,** PhD, on the Associations 2008 accomplishments in Science and Technology. The "Quality & Regulatory Snapshot" also includes a 2008 retrospective from PDA VP **Bob Dana.**

Correction: Finally, we would like to apologize to **Miguel Montalvo.** In the October issue of the Letter, we incorrectly stated that he was the President of PDA's Puerto Rico Chapter; he is a Member-at-Large.

PDA Letter

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2009 PDA Annual Meeting

Sponsorship and Exhibition Opportunities

Las Vegas, Nevada

Exhibit Schedule:

Pre-Conference	April 19, 2009
Conference	April 20 - 24, 2009
Career Fair	April 20 - 21, 2009
Post-Conference	April 23, 2009
Courses	April 23 - 24, 2009

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Secure your place as an exhibitor/sponsor to reach your target audience and drive your company's success. Every year, the Exhibit Hall at the *PDA Annual Meeting* attracts hundreds of pharmaceutical and biopharmaceutical professionals with purchasing power to network, learn about new products and inquire about new career opportunities. Don't miss this opportunity to showcase your company's merging technologies, products and services.

The *2009 PDA Annual Meeting* offers a number of exciting sponsorship opportunities, including the passport raffle drawing, the 3rd Annual PDA Golf Tournament sponsorship, refreshment breaks, and much more! Tabletops still available!

PDA's 5th Annual Career Fair

The PDA Annual Meeting provides a unique venue of employers to scout new employees. Each year PDA's signature Career Fair draws hundreds of bio/pharmaceutical professionals to meet face-to-face with potential employers. This successful networking event will provided you industry specific job seekers who are eager to share their insight and skills with you. Private rooms and scheduled interviews appointments are available to make for meaningful and successful connections.

Pre- and Post-Conference Workshops

Tabletop/Sponsorship space is available for both the *PDA Workshop: Cleanroom Technology and Contamination Control* (April 19th) and *PDA Workshop: Process Validation* (April 23rd). Limited tabletops are available, so secure your space early!

Photos courtesy of Bayer Healthcare and Sartorius Stedim Biotech

For more information or to reserve your spot as a an exhibitor or sponsor, contact Nahid Kiani at + 1 (301) 656-5900 ext.128.

www.pda.org/annual2009

2009 PDA Board of Directors

The PDA Board of Directors welcomes two new members in 2009: **Junko Sasaki,** who works for Sumitomo Pharmaceuticals and is responsible for Global Submission of Investigational New Drugs to the U.S. FDA, and **Christopher Smalley,** Director of Compliance, Wyeth.

Sasaki is a Regulatory Affairs and Quality Committee (RAQC) Committee member for Asia and the first female board member of the PDA Japan Chapter. She is an active member of the Quality Assurance/Quality Control Committee and Development QA Committee of Japan Chapter.

Smalley, in the 1980's, was a member of the PDA Training Committee and took over as Chairman of the committee in 1991. He has been the Chair of the Facilities and Engineering Interest Group since 1991, and is a member of the Science Advisory Board. Smalley has also served on numerous task forces and committees.

PDA also is proud to announce the re-election of two directors: **Steven Mendivil,** Executive Director of Corporate Quality Compliance for Amgen, and **Amy Scott-Billman,** Head of Worldwide Regulatory Strategy for Cancer and Chronic Disorder Immunotherapeutics at GlaxoSmithKline.

Mendivil is currently the Chair of PDA's Regulatory Affairs Quality Committee (RAQC) and has served twice on the PDA/FDA Conference Committee. Previously Mendivil served as Co-chair of the PDA/FDA Quality Systems Conference and has presented for PDA in Bethesda,Maryland; Dublin, Ireland, Beijing and Shanghai, China. Mendivil has also led PDA Task Forces organized to draft PDA comments on Biologic and Good Manufacturing Practice issues.

Scott-Billman has also served as a member and Chairperson of PDA's Regulatory Affairs/Quality Committee (RAQC), the Training and Research Institute Advisory Committee (TRIAC), the PDA Strategic Planning Committee and is currently a member of the Biotechnology Advisory Board (BioAB). She served on the PDA/FDA Annual Conference committee from 1998–2004, served as Chair in 2000 and has been a chair or member of numerous PDA task forces and document review committees.

Outgoing members include: **Yoshihito Hashimoto,** Senior Executive Engineer, Pharmaceutical Project, Chiyoda Corporation, and **Gail Sofer,** Consultant, SofeWare Associates. Hashimoto has served on the PDA Board of Directors and has served as the Director of the PDA Japan Chapter. Sofer has served on PDA's Board of Directors, Science Advisory Board of PDA and has also co-chaired PDA's Biotech Advisory Board. She has also chaired a PDA Task Force on virus filters. Sofer currently is a member of BioAB and an author of PDA's *Technical Report No. 41 (revised 2008) Virus Filtration.*

2009 Directors

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ValSource

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Science & Technology Snapshot

Science and Technology Has Banner Year, Looks Ahead

Rich Levy, PhD, PDA

As we close 2008, I would like to take the opportunity to thank all of our volunteers and PDA members who have contributed to our efforts in Science and Technology. This was a banner year on multiple fronts, and I would like to take a brief opportunity to update all of you on our achievements.

For the first time ever, PDA published five technical reports in one year. At least five others were in the final draft stages, and should be published in the first two quarters of 2009. Many other task forces are in various stages of completion, and we anticipate another record year in 2009.

Our Advisory Boards: SAB, BioAB and AGAB, have been very busy developing strategic and tactical plans, as well as other duties. One of our ABs' main functions is to provide oversight over task force leadership and scope statements, and the scientific content of our technical reports and regulatory comments. Between the three Boards, 29 ballots were reviewed and voted on and 25 approved—an active year and one measure of our increasing activity and hopefully influence on issues that matter to PDA members. And this year, more than in the past, the scientific Boards have been assisting the RAQC in the development of regulatory responses.

In 2008 we added several new Interest Groups (IGs) as we have expanded overall member participation. Three new IG's were established: a North American component of the existing Prefilled Syringe IG, Clean Room Design and Contamination Control, and Risk Management. And, as part of our globalization efforts, most IGs now have co-leaders from both the Americas and Europe.

And this year, more than in the past, the scientific Boards have been assisting the RAQC in the development of regulatory responses.

Our scientific meetings continue to do well, led by our signature Annual Meeting, Prefilled Syringe and Injector Devices, Global Pharmaceutical Microbiology, Cold Chain, and Viral Safety meetings. And we added several new topics to our repertoire, including Clinical Trial Materials, Sterilization Technology, and Supply Chain Integrity meetings. These new offerings were initiated from member feedback. And finally, we have been taking several of our new Technical Reports on the road as workshops in the United States, Canada, Europe and China.

Finally, we have taken steps to move to electronic publishing for both the Journal and Technical Reports. This step is necessary to further expand our industry influence, as well as adjusting to increases in Journal submissions and Technical Report output. **Walt Morris,** Director of Publications, and I have been leading an effort to implement a HighWire Press solution to transforming our Journal into a 21st century communication tool. We anticipate launching the new site in June of 2009, opening up the possibility of both rapid publications of accepted articles to full searches of past Journal content. All accessed through your membership.

In *Print*

Thermal Death Time Verification

The following is excerpted from the chapter, "Contributing Factors to Variability in Biological Indicator Performance Data," by Jeanne Moldenhauer, PhD, Excellent Consulting. The chapter appears in the recently published PDA/DHI book, Biological Indicators for Sterilization Processes, *edited by Moldenhauer and Margarita Gomez, Ocean Spray Cranberries, Inc. References have been removed for this excerpt, but can be found in the book.*

In the past few years, there has been a change in emphasis by regulatory and compendial requirements to require that pharmaceutical manufacturers verify the accuracy of the thermal death time (D-value) and organism control counts for biological indicators used. Although the requirements were presented in draft form through compendial documents, only when the documents were officially issued did many pharmaceutical manufacturers first initiate verification procedures. When implementing these procedures, numerous discrepancies were found between the labeled values and the verification values. This chapter presents concepts on how these discrepancies may be resolved, as well as, how to prevent them in future verification studies.

Thermal death time evaluations (D-value determinations) are very susceptible to variation in results. This variation may arise from procedural differences, spore crop variations and equipment differences. Some of the factors affecting the heat resistance of biological indicators are:

- Size of the inoculum
- Type of organism
- Sporulation
- Growth media composition
- pH
- Phase of spore maturity
- Incubation temperature for recovery of organisms

In the past, many pharmaceutical manufacturers accepted biological indicator testing results on the basis of the certificate of analysis from the biological indicator manufacturer. Companies typically did not perform extensive reviews of the biological indicator manufacturer's procedures and practices, nor did they periodically verify the values obtained.

In December 1993 the FDA published and later (1994) issued a guidance document for data to be submitted in product applications in support of sterility assurance validation. In this document there is a statement that indicates that that the drug company using a biological indicator is responsible for verification of the thermal resistance. Companies submitting new

continued on page 13

Leadership *Opportunity*

Combo Products Experts Needed

PDA's Scientific Advisory Board recently authorized the formation of the Combination Products Task Force. The task force is organized as a committee of the Combination Products Interest Group which was originally established in 1998. The task force is co-chaired by **Michael Gross,** PhD, Principal Consultant, Chimera Consulting, and Leader of PDA's Combination Product Interest Group; and **Lisa Hornback,** Principal Consultant, Hornback Consulting and member of PDA's Scientific Advisory Board.

The Combination Products Task Force and subcommittees need additional PDA members with experience in combination products to serve in this effort. If you are interested in joining the Task Force and serving on one of the sub-committees described below, contact **Iris Rice** at PDA by email (rice@pda.com) and attach your resume or a biographical summary emphasizing your interest and experience in combination products.

The Combination Products Task Force has been formed to identify membership needs and to help determine PDA's future role in combination products. The task force is currently developing activities and programs focused on the development, manufacture and marketing of all types of combination products. Such programs and activities concerning combination products will include:

- **Articles, meeting proceedings, books and/or other print or electronic publications** on quality and regulatory matters related to combination products.
- **Conferences, workshops and training programs** on combination products.
- **Establishing working relationships** with regulatory bodies and other professional associations interested in combination products.
- **Responding with comments** on proposed regulations and/or guidance issued by regulatory bodies related to combination products.

The task force has established three subcommittees:

- **The Education Subcommittee** is responsible for the development of conferences, workshops and training programs. It is currently serving as the program planning committee for a conference on combination products that will be held in September 2009 in conjunction with the PDA/FDA Joint Conference. The Education Subcommittee is chaired by Michael Gross.
- **The Regulations Subcommittee** is responsible for organizing task groups to respond to proposed regulations and guidance on combination products and for managing relationships with

continued on page 13

Recent Sci-Tech Discussions: Light Sensitive Products Packaging

The following unedited remarks are taken from PDA's Pharmaceutical Sci-Tech Discussion Group, an online forum for exchanging practical, and sometimes theoretical, ideas within the context of some of the most challenging issues confronting the pharmaceutical industry. The responses in the Sci-Tech Discussions do not represent the official views of PDA, PDA's Board of Directors or PDA members. Join at www.pharmweb.net/pwmirror/pwq/pharmwebq2.html.

I had a bewildering query related to the study of light exposure time. My question is that, do we really need any specific data to define a specific timeline for the light sensitive products they can be kept at normal daylight?

This query comes into picture when the processing of materials in a manufacturing unit is in process, it is kept under controlled lighting conditions, but in most of the cases/manufacturing systems it is common that during the packing of such substances they are least bothered about the light sensitivity of the product.

In cases of larger batch sizes, the packing quantity is kept in normal room lighting for hours without care. Would the use of amber colored vials help as an anticipatory practice? If yes, to what extent can we rely on their use?

Dear forum members, I would welcome suggestions regarding any…guidelines for the specification of lighting controls for the same.

Respondent 1: Hi [Questioner], The use of amber colored vials *cannot* help as an anticipatory practice. This color *does not* have efficacy of light protection.

Respondent 2: I 100% agree with [Respondent 1].

That is why, e.g., Mecobalamin (Methycobal) injection is packed in a light barrier packing despite being filled in amber colored ampoules.

Questioner 2: Further to this topic does anyone have a specification for lights used in production/QC when producing light sensitive products?

Respondent3: Dear [Questioner 2], I think this is easy. Whatever you choose, prove it. It will always be site and product specific. And watch out, a change in formulation can change the light sensitivity of the product.

Questioner 2: [Respondent 3], thanks for the input. Let me clarify: I am trying to determine what light/lens to use for the lights in the room, what wavelengths to filter and how to validate the room after installation. Thanks

Respondent 4: For photolabile products, it is suggested that appropriate light and time controls be implemented during manufacturing and inspection. This is an ICH guideline. Also, if the product is UV-sensitive, blocking films to cover the lights, during processing, can be applied.

Respondent 5: 700 lux is the minimum for a good work environment, and if the product is light sensitive, then use colored bulbs to eliminate the issue.

Respondent 6: [Questioner 2], When involved in the production and testing of truly light-sensitive drugs, all critical operations took place in rooms lit by *low-pressure* Sodium D-line bulbs.

No other readily available visible lighting was of sufficiently low intensity and long wavelength so that light exposure was *not* detrimental to the drug, which was nifedipine.

Hopefully, this information will be helpful to you.

Respondent 7: My dear [Questioner 2], some people use yellow light in working area when handling photosensitive materials. Light intensity depends on the type of work and sensitiveness of the product being handled. In QC, some people use dark room light (Red) also.

As regards [Questioner 1's] first question (whether data to define a specific timeline for the light sensitive products they can be kept at normal daylight is needed), I recall that we had a practice of carrying out such studies in the past.

Hope this helps. I would appreciate to hear if some one else has some more ideas.

Respondent 8: Addition to [Respondent 5's] reply: lighting level varies from 200–750 lux depending on simple/medium/normal/difficult visual requirements (300–500 lux may be sufficient to check the cleanliness in non-sterile clean rooms/equipment)

And I would recommend manufacturing and packing under colored bulbs along with necessary coated color films (or black) for windows and doors (to avoid the direct contact of day light).

Respondent 2: For light sensitive product in my experience, we painted the shades/coverings of light with red/dark pink paint and measured the light intensity with the help of lux meter till it met our specification of light intensity less than 10 lux.

The in-process testing also includes the measurement of light intensity with the help of lux meter.

Hope that helps.

Respondent 9: When I needed to protect my product from light I had found that neither the amber vials or yellow lighting did the job. For my product I had to block a different wave length of light. I used red fluorescent tube sleeves to protect the product-similar to photography lighting. The sleeves just slide over the tubes.

Respondent 10: Hi [Questioner 1], photochemical reaction is a very complex process; many variables may be involved in the photolytic degradation kinetics.

The velocity of the photochemical reaction may be affective not only by the light source, intensity, and the wavelength of the light, but also by the size, shape, composition, and color of the containers.

To properly determine the deleterious effects of light on the quality of a drug or drug product properly, standard light stability testing should consider all the aforementioned variables, once uniform standard light-stability testing procedures are instituted, proper primary and secondary packaging (yellow-green or amber glass offer considerable protection from ultraviolet light, but little protection from infrared light since they can not block the wavelength of the infrared light), storage environment, and expiration date for the light sensitive drug or drug product can be calculated.

Leadership Opportunity, from page 11

regulatory bodies and trade associations with an interest in combination products. Two proposed combination product regulations, one on quality systems and the other on safety reporting are anticipated in the near future. Lisa Hornback is the Chair of the Regulations Sub-committee.

- **The Publications Subcommittee** is responsible for all written documents on combination products that will be published by the Task Force. This may include articles, meeting proceedings and books. The sub-committee is currently working on establishing a PDA SciTech Discussion Forum on combination product quality and regulatory matters. The Publications Sub-committee is chaired by **Tracy Meffen**, Director, Quality, Angiotech.

In Print, Thermal Death Time Verification, continued from page 11

product applications may need this information for approval of the product by the FDA.

Several years ago at the USP conference in Marco Island, Fla., the consensus of those attending the biological indicator session was that microbial count resistance standards of commercially manufactured biological indicators needed to be developed. At that time, users were experiencing some difficulty in verifying both microbial count per indicator as well as microbial resistance performance data. While USP at that time permitted a -0.3 logarithmic reduction in microbial count, many individuals expressed that a standard population, such as at least 1.0 × 106 sterilization resistance spores, needed to be present on an indicator. Additionally, there was an interest to convert from time at temperature conditions to inactivate the indicators to a more measurable and descriptive D-value label claims statement. In that regard, subsequent USP proposed drafts and eventually the compendial chapter relating to biological indicators included changes that impacted biological indicator label claims. During the tenure of the USP 1995 through 2000 Microbiological Subcommittee for Revision, a new draft proposal of the USP BI Performance Requirements Chapter was written. The compendial chapter was modified to require that the biological indicator count should equal the label claim count. Further, since certain vagaries and variations can exist in the precise determination of D-values, the USP Chapter related to Biological Indicator Performance maintained the acceptability of a + or -20% variation of D-value of the stated label claim.

In response to the proposed USP Chapter, both users and manufacturers of BIs took issue with the fact that the microbial count level of a level of a label claim had to be confirmed with no allowance for values below the stated label claim. During the 1998 New Orleans USP Open Conference, users expressed that they could not always reproduce the exact microbial levels and needed some degree of flexibility around the count requirement. They indicated that variation in count methodologies resulted in variance around the count level at times. Further, manufacturers of commercial indicators were adamant about relief. In response to these concerns it is anticipated that the revisions to this chapter will revert to the original requirement in no less than a -0.3 logarithmic reduction in spore count. However, the requirement to produce indicators with at least the population stated on the label claim is a manufacturer's responsibility as seen by the USP Subcommittee. If manufacturers have the license to apply count levels lower than the stated label claim this may provide the use of spores with higher resistance values to meet a kill-time performance window.

During the USP Open Conference it was pointed out to participants that if a label claim of -0.3 logarithmic count (50% arithmetic reduction, below that stated on the label claim) was acceptable and a -20% variation occurred in the D-value, which was acceptable to the USP, the user has to critically assess whether the biological indicators are adequate for the cycle development purpose. This concern was expressed because the USP could permit the use of biological indicators with 1 × 104 per indicator, and this associated with a -20% reduction in D-value could permit a "weak" biological indicator.

It is important to know as much as possible about how the biological indicator's manufacturer performs the test and what type of controls are used to ensure that the results are accurate and reliable, prior to purchase of the biological indicators.

[**Note:** The remainder of the chapter contains the type of information that should be reviewed and/or considered prior to selecting biological indicators, or when results are obtained which are significantly different from the labeled values.]

PDA Interest Groups & Leaders

PDA Interest Groups are divided into five sections by subject matter. This aligns them for improved effectiveness, supports increased synergies and provides the opportunity for Interest Group members to play a more active role in Task Forces. The five sections are Quality Systems and Regulatory Affairs, Laboratory and Microbiological Sciences, Pharmaceutical Development, Biotechnological Sciences and Manufacturing Sciences. PDA's goal is for each group to have co-leaders from the three major regions in which the Association is active: Asia, Europe and North America. Any PDA member can join one or more Interest Group by updating their member profile (www.pda.org/volunteer). Please go to www.pda.org/interestgroups for more information.

SECTION TITLE

Biopharmaceutical Sciences	Laboratory and Microbiological Sciences	Manufacturing Sciences	Pharmaceutical Development	Quality Systems and Regulatory Affairs

SECTION LEADER

Frank S. Kohn, PhD *FSK Associates*	David Hussong, PhD *U.S. FDA*	Don E. Elinski *Lachman Consultants*	Sandeep Nema, PhD *Pfizer Inc.*	Robert L. Dana *PDA*

RELATED IGS AND GROUP LEADERS

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Implementation Strategies for EU GMP Annex 1

Martyn Becker, Martyn Becker and Associates

In February 2008, EU GMP Annex 1 was republished in revised, rather than rewritten, form. There were improvements, including some harmonization with the U.S. FDA guidance and some realignment of the 5 micron particle per cubic meter figure with ISO 14644. By now, industry has had plenty of time to consider EU GMP Annex 1, yet many firms might still be sorting out what is new and what is unexpected.

Although published in February 2008, many of the changes do not come into effect until March 2009, now only two months away, with the capping requirements being delayed until March 2010. Do we really need implementation strategies beyond those employed with previous versions of the annex?

Anyone paying attention to these things has already been invested in implementing this, so that it was not a surprise. The process simulation requirements have been harmonized with the logical and sensible requirements in the U.S. FDA aseptic processing guidance, which were interestingly generated through the highly-successful FDA/industry collaborative Product Quality Research Institute (PQRI) process in 2003. **[Editor's Note:** For more on the PQRI/FDA collaboration and PDA's role in the process, see the July/August 2005 *PDA Letter*.**]** There should be no issues there since harmonization is indeed what the industry has been crying out for.

Some implementation strategies are indeed necessary simply because some of the changes require a different way of thinking. The following are three areas of the guidance that have either been amplified by the revision or are completely new, and, as such, firms should carefully consider how they impact their current practices:

Qualification/Classification Requirements

Clean rooms are expected to be classified in accordance with ISO 14644-1 "Clean rooms and associated controlled environments—classification of air cleanliness," and the process of classification should be clearly segregated from routine monitoring, which makes sense and is here clearer than previous iterations of the annex. The number of locations is identified by the calculation in ISO 14644-1 as is the preferred method of sampling, so that the requirement is clear. Industry has been moving to the use of this classification logic over the last decade so that the implementation strategy, if not already in place, should be based on this process.

Routine Particulate Monitoring Requirements

Here we see a requirement for a formal risk management strategy with regard to monitoring locations linked to the locations used for classification. We also see a statement that is not initially clear in its intent: "[f]or Grade A zones, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly […]." Does this mean that routine, regular samples should be taken over the duration of, say, an operational shift, as was the case with the stated interpretation of the word "continuous" in the 2003 edition of the annex? The requirement continues "[t]he Grade A zone should be monitored at such a frequency and with suitable sample size that all interventions, transient events and any system deterioration would be captured and alarms triggered if alert limits are exceeded […]."

This can surely only mean truly second-by-second continuous monitoring, since how else could you capture all interventions and transient events? How do we strategize for this, and is it even necessary?

To be sure, truly continuous critical location monitoring needs to be evaluated using a different rationale than the one used for the evaluation of point-in-time samples such as the ones that have been common with the use of turret-type manifold systems. With truly continuous

Some of the newly-added items are straightforward enough to be "no-brainers" for those who have been keeping their eyes on the regulatory climate over the last decade or so, for the signs for their formal requirement have all been there.

Some Annex 1 requirements have been present from its first publication in 1989, e.g., the 5 micron requirement, redundant filtration, A-D grading system, and steam sterilization time/temperature/pressure relationship. These should have been rationalized, justified and/or implemented by industry for almost twenty years. Some of the newly-added items are straightforward enough to be "no-brainers" for those who have been keeping their eyes on the regulatory climate over the last decade or so, for the signs for their formal requirement have all been there. Examples of these are isokinetic probes for particulate monitoring (many companies have already been using them for years) and the per-batch pre-sterilization bioburden for terminal sterilization and sterile filtration, which was mandated by the EU Committee for Proprietary Medicinal Products in 1996.

monitoring, out-of-acceptable-range spikes will certainly be detected. Finding such a spike with discrete samples was one thing, since an investigation would no doubt be triggered. Here however, the focus should be much more on accumulated data translated into process information regarding the state of environmental control at that sample point. So trend evaluations become more important than knee-jerk reactions to single spikes, since a single non-repeated spike may not mean that there is actually anything amiss.

While continuous monitoring at critical locations (say, close to the fill head) might perhaps provide a more complete picture of environmental conditions at that point, we need to understand the context. Why? Even truly continuous monitoring is still a sampling process, and simple mathematics will identify the tiny proportion of the environment that you are actually sampling. It is therefore important to apply an appropriate rationale to this, because the obtained results define only what is in the sample, not what is in the Grade A environment as a whole, in the same way that a process simulation using growth medium only gives absolute assurance for that particular fill (not for every fill) even though it is used to impart a level of assurance to the whole. The evaluation strategy should take this into account, alongside the operational limitations of the sampling equipment in terms of background noise and so on. Procedures should therefore be established and documented to guard against over-reaction to individual events, to evaluate trends in real time and to be able to detect drift from the defined state of environmental control.

Capping Environment

In this author's opinion, the biggest single issue to come out of the new edition of the annex was vial capping, with opposing EU regulatory views leading to the final wording being something of a compromise between two extremes. One regulatory opinion indicated that capping was required to be undertaken within a Grade A/B aseptic area with no exceptions, while others took the perspective that it was unnecessary and that the annex should not be published with that specific requirement as the only way to achieve the end. The compromise text therefore allows for application of sterile caps in aseptic Grade A/B, or alternatively as a clean process under a "Grade A air supply."

Studies have been undertaken within industry… that demonstrate the effectiveness and risk-averse nature of capping outside the aseptic processing area.

The text in clauses 116 to 124 references the kind of unsupported statement that industry is constantly criticized for: "The container closure system for aseptically filled vials is not fully integral until the aluminium cap has been crimped into place on the stoppered vial [.....]" (Clause 118). While this is a back-stop risk-averse position, it does not take into account the kind of process challenge that is routinely carried out in industry, such as the microbiological container closure integrity challenge. If the closure is specified as being closed and integral without a crimped cap in place, then it must be up to the individual company to demonstrate by means of closure integrity validation of the un-capped container that this is actually the case. Arguments are made for the sealing ability of stoppers and vial necks without caps, and this is the way to demonstrate that it all works as stated. A benefit of undertaking this process is that it challenges not only the stoppering but also the potential for raised or misaligned stoppers that may or may not be detected by the raised stopper detector, which has been one regulatory argument for the statement above.

There are, of course, two potential outcomes to this kind of challenge process:

1. It passes, meaning that the containers can indeed be regarded as sealed.
2. It fails, and the company has to accept that the statement in clause 118 actually holds true in that case.

For the first outcome, there would perhaps be no need for either capping under aseptic conditions or maintenance under a "Grade A air supply" following exit from the aseptic area while in the latter case, protection would be necessary using either of the options listed. The implementation strategy would therefore benefit from inclusion of a container closure integrity evaluation process in order to determine which route should be pursued. This integrity process must be fully rationalized and documented on a scientific basis using realistic methodologies and acceptance criteria. If uncapped integrity can be confirmed then the way forward is simpler than if it cannot. If it cannot be confirmed then a decision should be made on how the units should be protected up to the point of capping.

Studies have been undertaken within industry (and supplied to the EMEA Inspectors' Working Group during feedback prior to publication of the Annex 1 update) that demonstrate the effectiveness and risk-averse nature of capping outside the aseptic processing area. If the decision is therefore taken to cap as a clean process outside the aseptic core in the absence of a clear indication of what a "Grade A air supply" means, further rationalization will need to be made concerning the actual required environmental conditions. If "Grade A air supply" means the full Grade A requirements as normally operated within an aseptic core, then there would be no difference in expectation—and such a workstation located outside an aseptic core could not possibly comply with those

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PDA Teams with PIC/S for Regulator-Industry Dialogue on Annex 1, QRM, continued from cover

Sr. GMP Inspector, MHRA, followed by industry perspectives by **Wolfgang Fischer,** Bayer Schering Pharma.

The workshop participants were assigned to four separate working groups distributed by inspectorate, company, countries and so forth. The goal was to distribute the participants, particularly inspectors and industry, as evenly as possible to breakdown "silos." The working groups met with assigned facilitators to work through the five case studies in a predefined rotation. Each case study was introduced by the topic leaders (authors) of the study who stayed with the group to assist as needed. The five case studies were:

T1: Capping of vials

T2: Media fills

T3: Continuous monitoring, clean area classification and ISO norms

T4: Sterilization of contact parts and containers

T5: Depyrogenation of contact parts and containers

The outcomes of the case studies were presented by the working groups during the closing plenary session on November 14. The outcome of T5 was presented by the topic leader with group discussion. For T1–T4, a spokesperson for the working group made the presentation, followed by comments from the other three groups. To facilitate this process, PDA staff collected report templates from each of the groups following each session, 20 report templates in all. These were collated into a slide presentation by the staff during the workshop and displayed in the closing plenary. A summary of the report outcomes and discussion from the closing plenary is being prepared by the PDA staff and, the planning team for publication after review, by PIC/S. The workshop closed with comments from PIC/S First Deputy Chair, **Tor Gråberg,** Chief Inspector, MPA.

Hard Work Pays Off

This was one of the most labor-intensive events ever organized by PDA. The idea was first put forward by PIC/S Chairman **Jacques Morénas** in the early 2008. Those of us who have worked with him, know his openness to new thinking and to getting things done. What was striking to me was the eager and professional approach by everyone involved, especially the "topic leaders," usually one-each from the regulator and industry side for each topic. This process worked very well with help arriving from colleagues as needed. For example, **Paul Sexton** of the Irish Medicines Board stepped in for colleague **Stan O'Neill,** when Stan was called away for other duties; **Ingeborg Kraemer-Pittrof,** F. Hoffmann-La Roche took the lead for colleague **Stephen Roenninger,** when Stephan was called to the ICH meetings in Brussels, etc.

There was a true eagerness to bridge the knowledge gap between industry practitioners and the health authority inspectors–both of whom share responsibility for ensuring that medicinal products pose minimal risk to the patient. I also need to acknowledge the four facilitators who worked diligently over two days to help the working groups reach their conclusions. **Kate McCormick** (ISPE), **Friedrich Haefele** (Boehringer Ingelheim), **Bill Miele** (Pfizer), and **Ingo Presser** (Boehringer Ingelheim) were the glue that kept this process together. Rarely, if ever, have so many inspectors from across the globe ➤

Opening Remarks

The following are selected remarks by the opening speakers at the *PDA & ISPE with PIC/S Workshop for Regulators and Industry on Annex 1 Manufacture of Sterile Medicinal Products: New and Possible Uses of Quality Risk Management.*

"I am very proud, as PIC/S Chairman, to inspectors from so many different countries participating in discussions between inspectors and industry. For PIC/S this is a unique occasion to build a safe and constructive platform for technical discussions between inspectors and industry. From these discussions we can better understand the concerns of industry and the concerns of inspectors. And maybe we can match these concerns together and find a solution for the future.

"At the EMEA level we worked for five years to reach an agreement on the current revision of Annex 1, which is now part of the EU guide and also the PIC/S GMP guide. It is important to have a common interpretation."

— Jacques Morénas, PIC/S Chairman, opening the workshop.

[for this workshop]… there is no wrong answer, no unique right answer, and nobody is going to take notes. That's the concept behind this workshop. So enjoy the discussions and share your ideas, your knowledge, and your thoughts."

— Véronique Davoust, Pfizer, representing PDA

"…we have a philosophy of good manufacturing practice. So when you read a sentence in Annex 1 you must look at it in relation to your own quality system, in relation to your sterility assurance systems. Look at it in respect of you procedures, your equipment, your facilities. How does this fit in? So how you interpret a sentence, paragraph or chapter is up to you. But it must fit in with your own systems. Each chapter of the EU GMP guide, each Annex, starts off with a "Principle". If you have any doubt about the intent of the sentence or the paragraph, go back to the principle to find the answer that you actually need.

"For Annex 1, the principle is to minimize the risk of microbiological contamination, particulate contamination and pyrogen or endotoxin contamination. So, you can interpret it in your own way to make sure you are meeting the principle. That is the guiding light to what the GMP guide, the philosophy of GMP is trying to achieve. If you look at it in that way, everything will become a lot, lot clearer."

— Paul Hargreaves, MHRA on interpreting the EU GMP guide

worked so closely and professionally with their industry colleagues to that end. As an ex-inspector myself, I could not have felt more honored and privileged to have been a part of this effort.

Based on the workshop evaluations, we can only conclude that the hard work paid off. Nearly an equal number of industry and regulatory representatives shared their views with us by filling out evaluation forms (the results are represented in the box below, with returns being about equal from industry and inspectors).

The case studies were each different in content and structure and were evaluated separately. All case studies were rated very useful. Topic one was rated highest in the evaluation, corresponding with the known interest in capping. Topic one and topic three were regarded as the most complex, requiring the most time and focus by the working groups. Topic four was completed the fastest, except for topic five which forced the working groups to classify risks in a 30 minute window.

From the discussions at the workshop it is clear there are still differences in the interpretation of Annex 1 by the users. To further improve a common interpretation, it has been reported that PIC/S and EMEA/EU Member States will work together on a set of Questions & Answers in order to facilitate a harmonized implementation of the annex.

Acknowledgements

PDA and ISPE sincerely thank those mentioned and the following individuals who worked long hours in the preparation, planning and delivery of the workshop.

Bruce Davis, AstraZeneca

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Jean-Luc Clavelin, Eli Lilly

Lina Ertle, AFSSAPS

Véronique Davoust, Pfizer

Martyn Becker, Martyn Becker Associates

The PIC/S QRM workshop planning team meets the evening before the workshop (l-r): Paul Sexton, Irish Medicines Board; Peter Reichert, Novo Nordisk; Martyn Becker, MB Associates; Véronique Davoust, Pfizer; Tor Gråberg, MPA; Bill Miele, Pfizer; Friedrich Haefele, Boehringer Ingelheim; Ingeborg Kraemer-Pittrof, F. Hoffmann LaRoche; Jacques Morénas, AFSSAPS; Ingo Presser, Boehringer Ingelheim; Lina Ertle, AFSSAPS; Bill Paulson, IPQ; Paul Hargreaves, MHRA; Georg Roessling, PDA (Attending but not shown: Andrew Hopkins, MHRA; Wolfgang Fischer, Bayer Schering Pharma; Kate McCormick, ISPE & Jim Lyda, PDA/photo taker)

Format of workshop:	4.3*
Value of Workshop to me and my Job:	4.4*
A key concept was inspectors and industry working together. Was this helpful?:	Yes: 34, No: 0
Do you think we should do this again?:	Yes: 34, No: 0

(*Scale from 1-5, 1 being the lowest rating and 5 the highest)

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Implementation of EU GMP Annex 1, continued from page 16

expectations because of the environment and potential interventions.

A critical part of operational design, therefore, needs to be the engineering-out of mechanical issues. For example, locating the capper as close as is possible to the aseptic out-feed and installing screw-feeders rather than conveyor belts to route the units into the capper, which would mitigate the risk of units falling over. There is a potential complication here since a raised stopper detector is normally located between the aseptic out-feed and the capper. One needs to consider which route is of lesser risk—minimal track distance post-out-feed but no raised stopper detector, or longer track including the detector? It may be that the value of the detector might be outweighed by the benefit of the short track and the potential for non-intervention by operators, which might lead to a reduced potential for contamination—but this would need to be rationalized and justified on a case-by-case basis.

If the track length is minimized, a screw feeder is implemented and the detector option not used, then there is minimal necessity for personnel intervention so that it may be possible to rationalize and risk assess the location of the capping process into a controlled, but formally unclassified area. If the detector is in place and therefore a longer feed track, there is increased potential for human intervention so that it may be necessary to place it in a formally classified area such as Grade D. Once decided, it is then perhaps a case of deciding what aspects of a genuine Grade A environment would be appropriate to be monitored. Then again, High Efficiency Particulate Air (HEPA) coverage of a connecting track is one thing, but is it possible to apply the same environmental criteria to a connecting tunnel as you would to the environment within the capper, where the crimping mechanisms are liberating aluminium particles? That would seem counter-intuitive. The air emerging from the HEPA filter should of course be of the same standard as that emerging within a unidirectional aseptic background in both cases; the difference lies in the background into which it is emerging and this should feature in the determination of which background and limits are most appropriate. The EU regulators themselves do not appear to be harmonized regarding what a "Grade A air supply" means in practice, and so a logical, scientific and justifiable approach is required to not only understand the key potential contaminants at this point of the process, but also to implement appropriate conditions and acceptance criteria that make the monitoring process truly value-adding in terms of sterility assurance.

In reality, neither side of the fence has the monopoly on knowledge and expertise in this area

Industry-Regulatory Dialogue Important

Product sterility is all about probabilities: the probability of a non-sterile unit existing in the environment in the first place, plus the probabilities of being able to detect and then locate it. Regulators and industry are ultimately aiming at the same target, which is the safety, protection, health and well-being of the patient and it makes sense to apply real and meaningful criteria to the assessment of our processing environments so that we do not head up the GMP spiral just for the sake of it. This is why it is so important for regulators and industry to be able to talk together in a reasonable manner and discuss the science and logic of how we should approach the manufacture of products purporting to be sterile.

In reality, neither side of the fence has the monopoly on knowledge and expertise in this area, regardless of how much one or the other side might think it does. In Europe, we could do far worse than take a leaf out of FDA's book, when the Agency decided (admittedly initially against its will) to discuss specific issues concerning aseptic processing with the industry and others in 2002/2003 under the *aegis* of PQRI. The end product of that process was real success in understanding, appreciating and implementing scientific solutions for critical issues such as process simulation output, and the inclusion of this particular rationale into Annex 1 is a *de facto* product of industry liaison. Just think of the potential benefits of the European regulators if they could do the same.

About the Author

Martyn Becker is now managing Director of Martyn Becker Associates, Ltd., a consulting company in the UK. He previously worked for Merck, SmithKline Beecham in the UK and as an inspector for the MHRA, where he attained the title of Senior Inspector (steriles and biologicals) and then ultimately as Southern Regional Manager. He has served on a number of regulatory liaison committees, including the PQRI Aseptic Working Group with successfully provided recommendations to FDA for inclusion into the 2004 FDA aseptic processing guidance. More recently he has formed part of an EFPIA expert working party that has input to the EMEA on the recent updating of EU GMP Annex 1 on sterile medicinal products.

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Quality & Regulatory Snapshot

A Look Back at 2008, and Forward to 2009

Bob Dana, PDA

2008 was a busy year on the regulatory front. The year began with PDA submitting comments on two U.S. FDA proposals relative to annexes to ICH Q4B and the proposed changes to the U. S. GMPs. In addition, we also commented later in the year on FDA's Draft Guidance for Industry entitled, *Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes.* We currently have a Task Force of PDA volunteers drafting comments for the newly released FDA Draft Guidance on potency testing for cellular and gene therapy products.

At the end of the year, FDA released their long-awaited Draft Guidance entitled, *Process Validation: General Principles and Practices* on November 19. PDA quickly mobilized a task force to draft comments and arranged for a series of workshops on the document.

We have been equally busy in Europe this year, with comments being prepared and submitted on revisions to GMP Annex 2: *Manufacture of Biological Medicinal Products for Human Use*, the Annex to ICH Q8, *Pharmaceutical Development*, Chapter 4 of the GMP Guide (*Documentation*) and Annex 11 to the GMP Guide (*Computerised Systems*).

We are very grateful to the leaders of these Task Forces and all the PDA volunteers who worked so hard to prepare our comments.

Besides the preparation of our regulatory comments, there has been a lot of other goings on in the Quality and Regulatory area. **Zena Kaufman** completed her two year stint as Chair of the Regulatory Affairs and Quality Control Committee in June. **Steve Mendivil** assumed the role of Chair in July and **Stephan Roenninger** stepped in to fill the role of co-chair. This process helps ensure a succession plan for our RAQC leadership is in place and smoothes the transition process when the change occurs. Thanks Zena, and good luck Steve and Stephan. RAQC also strengthened some of our governance controls with the approval of some updated operating procedures this year, thanks to the hard work of the members on one of our strategic project teams.

2008 was also a good year for our regulatory conferences. We kicked the year off with the second PDA/EMEA Conference in Budapest, Hungary. Like the first PDA/EMEA Conference held in London in 2006, the second one featured more than 50 regulators from across all of Europe, and was attended by over 300 persons. Just concluded in Europe was the first ever European Workshop jointly sponsored by PDA and ISPE with PIC/S. This workshop focused on the theme of: *New and Possible Uses of Quality Risk Management in the Manufacture of Sterile Medicinal Products* and how the recently revised Annex 1 fits with that concept.

Your colleagues in Europe also responded to a unique opportunity in advance of the PDA/EMEA Conference in February. PDA supported EMEA in their efforts to exchange views prior to the submission of written comments in the public consultation process for Annex 2. Members of the drafting group that worked on the Annex revision participated in a consultation and open discussion of the Annex prior to the closing of the consultation deadline. The outcome of this consultation provided additional information to the authorities in preparation of the final content of the Annex. This open meeting, which PDA administered, provided much useful information to EMEA for their consideration in the finalization of Annex 2.

In addition, at the request of EMEA, PDA staff and volunteer scientists met with EMEA representatives in June to review our comments on the *Guideline on the Production and Control of Monoclonal Antibodies*. And finally, our European colleagues will be meeting with representatives of the EMEA Inspectorate at the upcoming interested parties meeting later this month.

Regulatory conferences also took place in the United States, highlighted by another successful Joint PDA/FDA Regulatory Conference in September. Always a signature of our conference schedule, this year's conference had more than 900 attendees and featured more than 100 regulators from around the world as speakers and participants. Immediately following this conference, we held a conference, again jointly sponsored with FDA, on ensuring the quality and integrity of pharmaceutical ingredients in the supply chain. This conference was so successful it is being repeated in San Diego in early December.

continued on page 27

Supply Chain *Guidance*

CBER Import FAQs

On November 19, 2008, the U.S. FDA Center for Biologics Evaluation and Research updated their guidelines for importing regulated products in the United States. Below are their recommendations and rules for imports, listed in frequently asked questions (FAQs) format. The complete listing is available at http://www.fda.gov/cber/faq/specimenfaq.htm.

What standards apply to imports that are regulated by the Center for Biologics Evaluation and Research (CBER)?

CBER regulates biological and related products, including blood and blood products (which includes certain kinds of devices), vaccines, allergenics, tissues, and cellular and gene therapies. CBER also regulates the medical devices involved in the collection, processing, testing, manufacture and administration of licensed blood, blood components and cellular products and all HIV test kits used both to screen donor blood, blood components, and cellular products and to diagnose, treat, and monitor persons with HIV and AIDS. In order to import a CBER-regulated product into the United States, the product must meet FDA's regulatory requirements. Foreign firms which manufacture products regulated by CBER that are directly or indirectly imported into the United States must comply with applicable FDA requirements before, during, and after importing into the United States. FDA does not recognize regulatory approvals from other countries. General information about CBER is available at http://www.fda.gov/cber/about.htm. You can find more information about standards for vaccines at http://www.fda.gov/cber/vaccines.htm, for blood and blood products, including plasma derivatives, at http://www.fda.gov/cber/blood.htm, for allergenics at http://www.fda.gov/cber/allergenics.htm, for cell and gene therapy at http://www.fda.gov/cber/gene.htm, for CBER-regulated devices at http://www.fda.gov/cber/devices.htm, and for tissues at http://www.fda.gov/cber/tiss.htm.

What role does FDA play when an FDA-regulated article is offered for import?

If the article being imported falls under FDA's jurisdiction, it is subject to FDA review. Section 801 of the Federal Food, Drug, and Cosmetic Act (21 USC 381) sets out basic standards and procedures for FDA review of imports under its jurisdiction. Section 801(a) provides for examination of imports and also authorizes FDA to refuse admission of imports that appear, from examination or otherwise, to violate FDA requirements. FDA regulations at 21 CFR 1271.420 set out the basic import standards and procedures for human tissues. As

continued on page 27

Guidance *News*

U.S. FDA Posts New Level 2 Guidance on the cGMP Q&A Website

The following are new questions and answers that the U.S. FDA posted to the "Production and Process Controls" portion of the cGMP Q&A website, which was updated on November 12. The answers on the website might contain additional links and contact information not provided below.

The U.S. FDA launched the drug cGMP Q&A section of its website as part of the 21st century initiative. The goal is to provided timely answers to questions about the meaning and application of cGMPs to drug products. PDA will publish updates to the website as they become available. To view the full cGMP Q&A listings, go to: http://www.fda.gov/cder/guidance/cGMPs/default.htm.

In 2004, FDA issued a guidance entitled "PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance" that encouraged industry to modernize manufacturing through enhancements in process control. How can I implement PAT (Process Analytical Technology)?

The objective of FDA's PAT program is to facilitate adoption of PAT. In our 2004 guidance, we discuss FDA's collaborative approach to promote industry uptake of new and beneficial technologies that modernize manufacturing operations and enhance process control. FDA recognizes that firms should be encouraged to promptly implement new systems that improve assurance of quality and process efficiency. Accordingly, our approach to PAT implementation is risk based, and includes multiple options:

1. PAT can be implemented under the facility's own quality system. CGMP inspections by the PAT Team or PAT certified Investigator can precede or follow PAT implementation.
2. As another quality system implementation option, FDA invites manufacturers to request a preoperational review of their PAT manufacturing facility and process by the PAT Team (see ORA Field Management Directive No.135).
3. A supplement (CBE, CBE-30 or PAS) can be submitted to the Agency prior to implementation, and, if necessary, an inspection can be performed by a PAT Team or PAT certified Investigator before implementation. This option should be used, for example, when an end product testing specification established in the application will be changed.
4. A comparability protocol can be submitted to the Agency outlining PAT research, validation and implementation strategies, and time lines. Following collaborative review of the general strategy outlined

continued on page 29

2009 PDA/FDA Joint Regulatory Conference

Save the Date

September 14-18, 2009
Washington, D.C.

Conference	September 14-16
Exhibition	September 14-15
Courses	September 17-18

www.pda.org/pdafda2009

The *PDA/FDA Joint Regulatory Conference* offers the unique opportunity for you to join FDA representatives and industry experts in face-to-face dialogues. Each year, FDA speakers provide updates on the current state of initiatives impacting the development of global regulatory strategies; while industry professionals from some of today's leading pharmaceutical companies present case studies on how they employ global strategies in their daily processes.

Hear directly from FDA experts and representatives of global regulatory authorities, and take home best practices for compliance. You won't find this level of direct information exchange with FDA and other global regulators at any other conference!

PDA is also offering an exhibition during the conference, and the PDA Training and Research Institute (PDA TRI) will host courses immediately following the conference.

Supply Chain Guidance, CBER Import FAQs, continued from page 25

explained in more detail below, FDA and CBP have coordinated their efforts and work together to ensure the smooth processing of FDA-regulated imports.

How does the U.S. Customs and Border Protection (CBP) notify FDA of entries of FDA-regulated products?

FDA receives electronic information about most FDA related entries from CBP. FDA currently receives this information through its Operational and Administrative System for Import Support (OASIS).

When submitting an entry notification, a filer will determine the appropriate Harmonized Tariff Schedule (tariff) code for each product being offered for importation. CBP uses the tariff code, in part, to determine if other government agencies also need to make an admissibility determination. However, a tariff code may cover a wide range of products and may include both products that are subject to FDA jurisdiction and products that are not subject to FDA jurisdiction. When this is the case, filers are usually given the option of "disclaiming" FDA jurisdiction. This is accomplished by disclaiming the "line" in the entry that applies to those products. (Each distinct category of product in an entry will have its own "line" in the entry. For example, if a shipment of a vaccine consisted of both multi-dose vials and pre-filled, single dose syringes, the vials would be one line and the syringes another line.)

What information is submitted to CBP and FDA about an FDA-regulated product?

The entry information submitted to CBP and then to FDA includes:

- The identification of the product by the tariff code
- The entry type
- The entry number
- The arrival date
- The port of entry
- The port of unlading
- The carrier code
- The vessel name and voyage, flight or trip number
- The importer and ultimate consignee
- The quantity
- The value
- The country of origin
- The bill of lading or airway bill number
- The manufacturer
- The importer of record
- The ultimate consignee

The tariff codes are flagged to indicate which products will require FDA review. The additional information that is currently transmitted to FDA includes:

- The FDA manufacturer
- The FDA shipper
- The FDA Country of Production (country of origin)
- The complete FDA product code
- A description of the article in common business terms
- The quantity for each FDA line
- Affirmations of Compliance

Affirmations of Compliance (AOC) are voluntary data elements that a customs broker or self-filer currently may use when transmitting certain information to FDA through the CBP's electronic interface with OASIS. Each AOC provides a mechanism to indicate (or affirm) compliance with a specific FDA regulatory requirement. For example, for a licensed biological product, the AOC would be the Biologics License Number or Submission Tracking Number, while for an investigational biological drug product, it would be the Investigational New Drug Application Number.

A Look Back at 2008, and Forward to 2009, continued from page 24

So 2008 was a busy and productive year. What will 2009 bring? Hard to predict. But as mentioned above, we are already hard at work developing comments on two new FDA regulatory guidance documents. The planning process is underway for the third *2009 PDA/EMEA Regulatory Conference*, to be held in Berlin, Germany in October 2009. Planning for the *2009 PDA/FDA Joint Regulatory Conference* gets underway in December. We anticipate some additions to our RAQC Committee in early 2009 as we seek to broaden our base and expertise on that Committee. RAQC also has some strategic initiatives underway that you'll hear about later in 2009. After over three years in this job, the one thing I will predict is that 2009 will be a busy year, filled with a few surprises, and will be one that we will be able to look back at a year from now with pride in our accomplishments, all of which are due to the hard work of you, our volunteer members: a heartfelt *Thank You!* And to those of you who weren't able to contribute directly to any of our work products and deliverables in 2008, I encourage you to become involved in one of our projects or Task Forces next year.

Regulatory Briefs

Regulatory briefs are compiled by PDA member volunteers and staff directly from official government/compendial releases. Links to additional information and documentation are available at http://www.pda.org/regulatorynews.

North America

Cooperative Manufacturing Arrangements for Licensed Biologics Guidance Available

A guidance from the U.S. FDA is available, entitled, *Guidance for Industry: Cooperative Manufacturing Arrangements for Licensed Biologics*. This November 2008 Guidance provides information concerning cooperative manufacturing arrangements applicable to biological products subject to licensure under the U.S. Public Health Service Act. It describes the licensing strategies for meeting the increased need for flexible manufacturing arrangements.

The guidance finalizes a draft of the same title which was originally issued in August 1999 and modified in July 2007.

Comments Solicited for Draft Guidance on Process Validation

A draft guidance entitled, *Process Validation: Principles and Practices,* is now available. The draft guidance outlines the general principles and approaches that the U.S. FDA considers to be appropriate elements of process validation for the manufacture of human and animal drug and biological products, including active pharmaceutical ingredients (APIs).

Comments must be submitted to FDA by January 20, 2009 for consideration as they develop the final Guidance on the subject. To contribute to PDA's comments, please see the link to the On-Line Review Tool on the PDA website (www.pda.org) and provide your comments no later than December 10, 2008.

Europe

Danish Medicines Agency Releases Guidelines on Parallel Import of Medicinal Products

The Danish Medicines Agency has issued guidelines on parallel import of medicinal products. These guidelines replace the Guideline on parallel import of medicinal products, no. 40 of July 2, 2007.

To date, the main objective of the Danish Medicines Agency's consideration of an application for a parallel import marketing authorization is to establish whether the required identity exists between the medicinal product distributed directly and the medicinal product for which an application for a parallel import marketing authorization has been submitted.

If the Danish Medicines Agency is not able to obtain all information about a parallel imported medicinal product, the application will be rejected if, upon a concrete evaluation of the case in question, the Danish Medicines Agency finds that there may be significant differences in the therapeutic effect of the parallel imported product and the directly distributed medicinal product.

Guidance News, continued from page 25

in the comparability protocol, the regulatory pathway can include implementation under the facility's own quality system, a pre-operational review, CGMP inspections (either before or after PAT implementation), a combination of these, or another flexible approach.

Manufacturers should evaluate and discuss with the Agency the most appropriate option for PAT implementation. For products regulated by the CDER, contact the Process Analytical Technology Team with any questions.

How do I contact CDER's Process Analytical Technology Team?

Manufacturers are encouraged to contact the team via *email* regarding any PAT questions at: PAT@cder.fda.gov

To contact our PAT Team via *mail*, please see the PAT Web page (under the section "Contact Us") for our new mailing address at White Oak.

All correspondence should be identified clearly as "Process Analytical Technology" or "PAT."

Please also refer to the web page to keep abreast of the latest information on PAT.

How do I contact CBER's Process Analytical Technology Team?

Manufacturers should contact the appropriate review division in CBER to discuss applicability of PAT to CBER-regulated products.

References

"PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance"

Contact Information

PAT Questions (CDER):
PAT@cder.fda.gov

PDA Metro Chapter Discusses Revised USP Chapters, Supplier Quality Management and Bowls a Strike

Bob Seltzer, Schering-Plough

On September 25, two microbiology subject matter experts, **Donna Foti,** Microbiology Group Leader, Catalent Pharma Solutions and **Frank Matos,** Quality Control Manager, Wyeth compared the new and old versions of two USP chapters: <61> General Chapter on Microbial Enumeration Tests and <62> Tests for Specified Microorganisms.

This panel first provided the audience with answers to frequently asked questions, e.g.,

- "If I have already validated an alternative bioburden, plate count method do I need to re-validate against the new Chapter <61>?"
- "Can you use less than 10 g of 10 ml of sample? Under what conditions?"
- "Do I have to cross validate the rapid microbiology method against my old USP method?"
- "If I don't have a microbiological test specification for a raw material or for a finished product, do I need to validate against the new test?"

It was a practical microbiology manager's and analyst's potpourri of Q&A for some voluminous revalidation or novel validation work on nonsterile drug product microbial release and stability testing.

Supplier Quality Management

On October 21, **Steve Sharf's,** Compliance Manager, GMP, Schering-Plough, almost two hour talk and Q&A ran through a gamut of information that answered the following questions:

- "What are suppliers and why do we need to audit them?"
- "How do we develop a risk assessment tool?"
- "How do we develop an audit schedule?"
- "How do we train our auditors and keep them current?"
- "How do we certify those suppliers that have demonstrated consistency in their material?"

Among Steve's many recommendations was that, when certifying a supplier for a particular raw material, not less than ten successfully tested/accepted batches are needed. He also debunked a company's purchasing group's over-emphasis on delivery timing metrics as opposed to the QA group's material specifications metrics.

Bowling, Social & Networking

On November 18, the PDA Metro Chapter hosted a rare evening of pure fun and networking at a bowling alley in central New Jersey. Much fun was had swapping stories and anecdotes.

Visit PDA's New Online Offerings: Facebook, LinkedIn and Wikipedia

Hassana Howe, PDA

PDA extends a special invitation for you to join our new online groups through *LinkedIn* and *Facebook*. This is a great opportunity for you to share information, network and stay on top of important developments both in your field and at PDA.

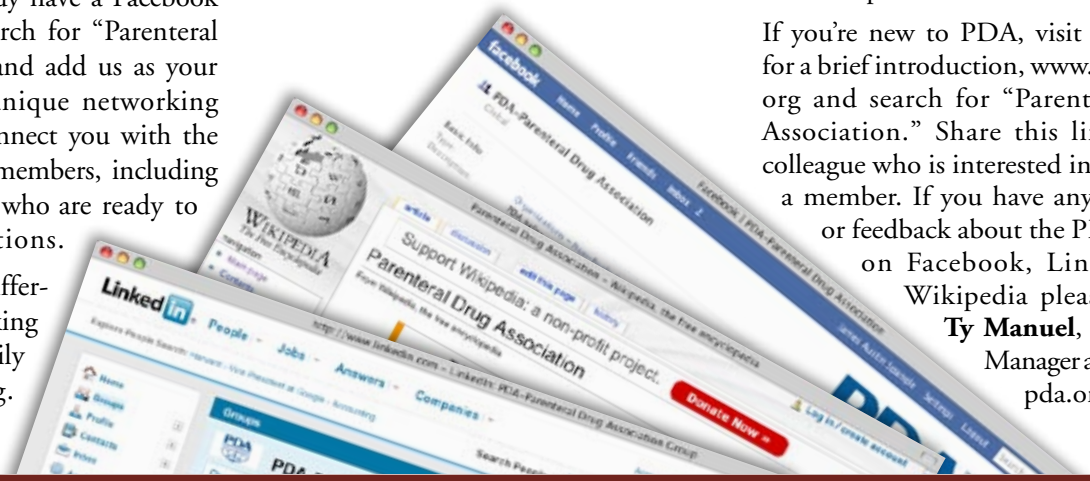
Facebook.com is a social networking interface where users create profiles and build their network of friends and groups. If you already have a Facebook account, simply search for "Parenteral Drug Association" and add us as your new group. This unique networking opportunity will connect you with the already 100 online members, including PDA staff members who are ready to answer your questions.

Linkedin.com is a different kind of networking tool focused primarily on career building.

LinkedIn helps individuals connect with past and present colleagues and employers, find new business opportunities and/or share advice with industry experts. Just like Facebook, individuals build their own personal profile and then begin searching for people and groups they would like to associate with. The following tools are unique aspects of LinkedIn's career building focus:

- Find clients, service providers, subject experts, partners and new job opportunities by indicating your needs/search in your profile
- Search for job based on narrow or broad search criteria
- Post and distribute job listings
- Get introduced to other professionals through LinkedIn networking connector
- Participate in discussion forums

If you're new to PDA, visit Wikipedia for a brief introduction, www.wikipedia.org and search for "Parenteral Drug Association." Share this link with a colleague who is interested in becoming a member. If you have any questions or feedback about the PDA Group on Facebook, LinkedIn, or Wikipedia please contact **Ty Manuel**, PDA Web Manager at manuel@pda.org.



PDA Midwest Chapter Holds Event Focusing on QbD & CMOs

Scott Hartman, Safis Solutions

On October 17, the PDA Midwest Chapter held a training event at the Eli Lilly and Company Manufacturing and Quality Learning Center in Indianapolis, Ind. More than 90 attendees from 36 companies and 5 different states gathered to hear talks on Quality by Design (QbD) in the morning and Contract Manufacturing Organizations (CMO) in the afternoon. The two sessions featured presentations and panel discussions from experts from the industry.

The morning session of the event began with the presentation "Product Commercialization and Quality by Design Implementation at Lilly," by **Joanne R. Barrick**, which highlighted some on the driving forces behind the QbD initiative and some of the steps Eli Lilly has taken in their commitment to QbD.

Next, **Steven Nail**, PhD, presented, "A Quality by Design Approach to Development and Scale-Up of Freeze Dry Cycles." Steven provided general comments about QbD and discussed ways in which Baxter has begun to apply QbD in their operations with freeze dryer and spectroscopy technology.

The final presentation in the morning session was by **Paula Hudson**. Paula discussed how Eli Lilly has implemented QbD in product and process development. Reviewing the product lifecycle from the patient profile to the process design review, she highlighted ways in which applying QbD effectively will provide knowledge and flexibility to efficiently manage and support products throughout their lifecycle.

Following the presentations, **Richard Van Doel** joined the speakers on the stage to take part in a panel discussion. The discussion included numerous questions about the participant's experiences with the application of QbD. Specific topics of discussion included: future trends for QbD, additional examples of the application of QbD, and application of QbD by CMOs.

After lunch and networking, the afternoon session on CMOs began with a presentation by **Lisa Schuster**, entitled, "Overview of Regulatory and Quality Requirements of Contract Manufacturers." She reviewed the requirements for these organizations, sources of these requirements, and common considerations for selecting a CMO.

Next, **John Steichen** presented "Contract Manufacturing Organizations: Auditing & Oversight." As a part of this discussion, he reviewed common deficiencies with quality systems, material systems, product systems, facilities and equipment, laboratory control systems, and packaging and labeling.

John Lockwood provided the final presentation of the afternoon session. His presentation, "Selection & Qualification of Contact Manufacturers," expanded on the earlier discussion of considerations for selecting CMOs, to include advantages of using a CMO, common complaints about working with CMOs, and finally, key selection criteria such as experience, reputation, price, customer service, and quality.

James Copp and **Steve Thomas** joined the speakers on the stage to participate in a panel discussion. Specific topics of discussion included: frequency of audits, audit certificates and auditor certification, managing the CMOs, dealing with compliance and quality issues, and an additional discussion of common audit deficiencies.

The PDA Midwest Chapter holds monthly dinner events in Northbrook, Ill., an annual golf outing in Chicago, Ill., and an annual event in Indianapolis, Ind. For more information about these events, or to get involved as a volunteer, please contact **Peter Noverini** at peter_noverini@baxter.com, or **Scott Hartman** at shartman@safis-solutions.com.

PDA's *Who's Who*

Joanne R. Barrick, RPh, Global Process Validation Support Manager, Manufacturing Sciences and Technology, Eli Lilly

James Copp, Senior Director, Manufacturing and Supply Chain Management, Targanta Therapeutics

Scott Hartman, Manager, Sales and Marketing Account, Safis Solutions and PDA Midwest Chapter Volunteer

Paula Hudson, Manager, CMC Regulatory Affairs, Eli Lilly

John Lockwood, CPM, CQA, Senior Compliance Advisor, Safis Solutions

Steven Nail, PhD, Senior Baxter Research Scientist, Baxter Pharmaceutical Solutions

Peter Noverini, Research Associate II, Sterility Assurance, Baxter and PDA Midwest Chapter President

Lisa Schuster, Compliance Advisor, Safis Solutions

John Steichen, RAC, Senior Compliance Advisor, Safis Solutions

Steve Thomas, Director of Quality Assurance and Control GMP, Targanta Therapeutics

Richard Van Doel, President, Performance Validation

All PDA Chapter Events are listed on the global calendar: **www.pda.org/calendar**

NEPDA Election Results, Facility Tour and Meeting Make for Landslide

Myron Dittmer, MFD & Associates

The New England PDA chapter held its last dinner meeting and facility tour of 2008 on November 12 at the Holiday Inn in Tewksbury/Andover; about 100 people attended.

The facility tour was at Wyeth Biotech's Andover facility and included a brief slide presentation on the history and product development activities there. Because of the facility's outstanding U.S. FDA inspection history, the FDA recently decided to forgo a preapproval inspection for a new product registration. The tour included a visit to a cleaning validation laboratory, where various cleaning procedures and technologies are researched and validated. These include cleanability and swab recovery studies, cleaning efficacy studies and cleaning simulations using vessels and equipment prototypes. Analytical testing includes total organic carbon measurements, conductivity, sodium dodecyl sulfate and polyacrylamide gel electrophoresis (SDS-PAGE), spectrophotometry, as well as other procedures.

The next area visited were suites in the E/F process utility area which included a tour of the clean-in-place utility system. Engineers described the operation of the many pumps, valves, and control system needed to direct cleaning fluids and water rinses to the various two-story bioreactors, media and buffer tanks located above.

The tour continued in the A/B Multivalent Pneumococcal suites for the cell culture production stream, which consisted of a number of clean rooms dedicated to upstream bioreactor production containing 30 L, 250 L and 2,500 L bioreactors. Downstream processing included centrifugation, filtration, and ultrafiltration. The bulk product produced is a multivalent pneumococcal vaccine.

The last stop on the tour was the E/F suites for product development/commercial development, which contained 5 bioreactors ranging in size from 100 L to 6,000 L. The E/F suites are one of Wyeth's several cell culture bioreachot and media buffer areas. Located in adjacent suites were support tanks such as harvest and media/buffer tanks. Also, two purification suites were viewed containing centrifuges. These suites are set up to accommodate other purification technologies

After relocating to the Holiday Inn for the dinner meeting, chapter elections were held for board members for 2009-2010. NEPDA Nominating Committee co-chairs **Myron Dittmer** and **Bruce Rotker** announced the results of the ballots cast that evening.

The first presentation given at the meeting was entitled, "Technical Report 29: Initiating Good Cleaning Practices - Vision, Scope, and Progress" was prepared by **John Hyde** and was presented by **Richard Jushchyshyn.**

(l-r) Louis Zaczkiewicz, Hyaluron Contract Manufacturing; Richard Paiva, Hyaluron Contract Manufacturing; Bruce Rotker, Sparta Systems; Peter Harris, B & V Testing; Chris Meyer, JM Hyde Consulting; Jerry Boudreault, Drug Development; Myron Dittmer, MFD & Associates; Melissa Smith, MJ Quality Solutions; Mark Staples, Cusp PharmaTech; Maryellen Brown, The Christholm Corporation

PDA's *Who's Who*

Myron Dittmer, Principal Consulting, MFD & Associates and NEPDA Nominating Committee Co-chair

John Hyde, Founder and CEO, Hyde Engineering & Consulting

Richard Jushchyshyn, Principal, Hyde Engineering & Consulting

Kathleen Kendrick, Validation Technology Manager, Wyeth

Nahid Kiani, VP, Membership Services & Sales, PDA

Bruce Rotker, Director of Sales, Sparta Systems and NEPDA Nominating Committee Co-chair

Richard provided a summary on the PDA Biopharmaceutical Cleaning Validation Task Force which is in the process of revising TR-29 in an effort to transition from traditional approaches to more risk-based approaches for cleaning validation. Besides discussing small molecules, the revised TR will discuss new landscapes for monitoring and validating biopharmaceutical cleaning processes and operations. Richard compared differences between the traditional approaches (such as establishing highly controlled procedures and using three consecutive commercial runs) versus risk-based approaches (such as validation design and execution based upon risk analysis and management, and establishing process design space) for cleaning validations. He also discussed the new landscapes for validating and monitoring cleaning operations including the use of process analytical technology methodologies and data for basis of cleaning validation studies, and application of statistical process controls among many others. The final objectives of the revised TR-29 are to:

- Document current principles and practices for the cleaning validation processes for biopharmaceutical manufacturing equipment systems ➤

- Provide the industry with practical, experience-based methodologies for implementation of cleaning validation based on current best practices

Richard noted that the draft document will be available for general review and comment during the 1st quarter of 2009 and is expected to be submitted for publication in the 3rd quarter of 2009.

The second presentation entitled, "Maintaining Good Cleaning Practices," was given by **Kathleen Kendrick.** Kathleen provided a discussion and information on the "Cleaning Program Lifecycle" used at Wyeth Biopharma.

She reviewed general cleaning regulations (national and international), the importance of establishing effective standard operating procedures and training procedures, major elements to maintain the cleaning process, cleaning process record keeping, preventive maintenance recommendations and the necessity of ongoing monitoring of cleaning activities. Kathleen also described a number of regulatory citations of firms related to cleaning as a way of demonstrating the importance of maintaining a proper cleaning program. She also stressed the need to trend monitoring data by developing and maintaining control charts with upper and lower process limits based on sound scientific reasoning.

Kathleen emphasized the importance of establishing a cleaning verification and revalidation program to address both automatic and manual cleaning processes and how a formal change control program will assist in maintaining control of the cleaning program. In summary, she noted that an effective cleaning program can be achieved by:

- Robust procedures and training
- An effective maintenance program for equipment
- A cleaning monitoring program
- A revalidation assessment program

Following the presentations, **Nahid Kiani** presented to the outgoing chapter president**, Louis Zaczkiewicz,** an award for his service to PDA on the Membership Advisory Board, North American Chapter Council Co-Chair and particularly for his efforts over the past two years as NEPDA chapter president.

Other awards were also presented to those who served the NEPDA either as chapter officers or committee chairs over the past several years.

PDA's *New Chapter Leaders*

Jerry Boudreault, President, Drug Development Resource and PDA New England Chapter President

Maryellen Brown, Marketing Specialist, Sales, The Chrisholm Corporation and PDA New England Chapter Treasurer

Sarvang Mishra, Sr. Packaging Manager, HGT, Shire and PDA New England Chapter Secretary

Russell Morrison, Commissioning/ Validation Manager, Commissioning/ Validation and PDA New England Chapter President-elect

Melissa Smith, Senior Consultant, Quality and Analytical Consulting, MJ Quality Solutions and New England Chapter Member-at-Large

Louis Zaczkiewicz, Senior Engineer, Engineering, Hyaluron Contract Manufacturing and New England Chapter Immediate Past President

Volunteer Spotlights

Anita Derks

Global Quality Manager (Biotechnology), F. Hoffmann-La Roche Ltd.

Education: BSc(Hons), Microbiology, Otago University

PDA Join Date: 1996

Areas of PDA Volunteerism: BioAB (member); Biotech Interest Group (member); *PDA Letter* (contributor); 2007, 2008 PDA Biopharmaceuticals Conference (speaker); 2009 PDA/EMEA Conference Planning Committee (member)

Why did you join PDA and start to volunteer? I like PDA as an organization, and the high professional standards of PDA staff members; this has created an ability to generate highly regarded robust technical reports and comments. The members and the networks are always respectable and comprise of a good mix of technical and scientific knowledge. I have met very nice people and developed excellent working relationships through the PDA events and discussions as it is so important to meet others and hold discussions outside your own working environment.

Of your PDA volunteer experiences, which stand out the most? The technical discussions and involvement in these discussions for a variety of expertise and experiences.

How has volunteering through PDA benefited you professionally? I have a chance to learn and discuss professional and work related topics with many people from all parts of the world. It is good to be challenged and have a chance to discuss ideas and experiences.

Which member benefit do you most look forward to? Meetings and the technical reports and the PDA letter.

Which PDA event/training course is your favorite? Smaller technically specific meetings.

What would you say to somebody considering PDA membership? Get involved as this is an important learning and sharing opportunity that will benefit you and the organization that you are working for or involved in. It is a great way to meet like-minded people.

I like PDA as an organization, and the high professional standards of PDA staff members

Barbara J. Potts, PhD

Principle Scientist, Genentech, Inc.

Education: BSc and MSc, Zoology, Montana State University; PhD, Experimental Pathology, The University of California; Staff Fellow, Neurology Institute (NINCDS), The National Institutes of Health (NIH); Senior Staff Fellow, Allergy and Infectious Disease, NIH.

PDA Join Date: 2002

Areas of PDA Volunteerism: Biotechnology Advisory Board (BioAB); Mycoplasma Task Force (co-leader); Cell Substrate Task Force (member); 2005, 2008 and 2009 Mycoplasma Workshops (co-chair); 2008 PDA Virus /TSE Forum (committee member and speaker)

Professional Awards Won: U.S. Public Health Service National Institutes of Health NIH Director's Award for special efforts in the recruitment and employment of physically handicapped employees in NINCDS NIH; Genentech, Inc. Diversity Champion, 2005; Genentech, Inc. 2004 Safety Team "Thinking Outside of the Box" award for Quality Control Safety Improvement Team video; Genentech, Inc., 2004 Safety team "Outstanding Contributor "award

Why did you join PDA and start to volunteer? Initially I presented at a few meetings and found I wanted to get more involved. My first "real" job with PDA was the organization of the 2005 Mycoplasma in Plant Peptones workshop with John Geigert. This workshop led to the organization of the Mycoplasma Task Force and the publication of Proceedings in 2007. Again all of this was done with John's guidance and help. I was soon asked to join the BioAB and I am on several other Task Forces.

Of your PDA volunteer experiences, which stand out the most? Co-leading the Mycoplasma Task Force is fun and challenging. We have approximately 60 members in this Task Force and approximately 30 attend our 2–4 hour Task Force face-to-face meetings for the preparation of three technical reports. This group includes many of the experts in the mycoplasma field from academia and industry making the discussions always interesting.

How has volunteering through PDA benefited you professionally? In my volunteering at PDA activities, I must always make sure that my activities are in alignment with Genentech's goals. The information I collect from my activities help me give direction and advice back to Genentech. I have also gained experience in managing a large project with volunteer participants who are making time in their busy day for my requests. This experience has given me wonderful management experience.

Which member benefit do you most look forward to? The *PDA Letter* and PDA Technical Reports.

What would you say to somebody considering PDA membership? Professionally, it is the best deal in town. I cannot believe how much PDA accomplishes with so few staff members.

Please Welcome the Following Industry

Tajuddin Akasah, National Pharmaceutical Control Bureau

Ali Alijani, Althea Technologies

Susan Atherholt, Enviro Pharma Services

Dilek Aydin, CSL

William Bagley, Talecris Biotherapeutics

Peter Baker, Purdue Pharma

Bryan Ball, Ben Venue Laboratories

Vidyadhar Bapat, Sandoz

Barbara Bassi, Chiesi Farmaceutici

Ron Bates, Allergan

José Berdoz, Swissmedic

Paula Bergin-Holbrook, Genentech

Ross Berkeley, Shire Pharmacueticals

Patrick Berreby, Shire Pharmacueticals

Qiao Bobo, MedImmune

Katherine Boeskin, Regeneron Pharmaceuticals

Massimo Bormetti, Gambro

Colin Bosch, Novartis Pharmaceuticals

Elizabeth Bramhall, Bristol-Myers Squibb

Steve Brown, Halozyme Therapeutics

Maggie Buccambuso, Protherics

Stacy Burke, Baxter Healthcare

David Burney, Meda Pharmaceuticals

Sharon Burns

Rosemary Bushby, Biocompatibles

Christopher Butler, Baxter Healthcare

Jared Byrne, Amgen

Maria Calimano, Micrylium

Juan Cardenas, Laboratorios Sophia

Robert Caren, Genentech

Cheryl Carr, Teva Parenteral Medicines

Carrie Cascio, Ipsen Biopharm Limited

Jennifer Catour, Gilead

Hector Cervoni, Abbott

Matthew Chapas, Ben Venue Laboratories

Clint Christensen, Ultradent Products

Andreas Christodoulou, Septodont

Frantisek Chuchma, State Institute for Drug Control

Michele Cianchini, Baxter Healthcare

Joseph Cipollo, AstraZeneca

Julia Cox, Clarkston Consulting

Catherine Cunningham-Shinabarger, Pfizer

Mary Ann Czech, Catalent Pharma Solutions

James Davidson, Lachman Consultants

Denise Dawson, Map Pharmaceticals

Doug Dawson, Dawson Logistics

Justin Dawson, Raven Biological Laboratories

Jeanne De Long, De Long Quality & Compliance Services

Ed DeLuise, Baxter Healthcare

Olivier Desplat , Bausch & Lomb

Lucia Di Nardo, Baxter Healthcare

Willow DiLuzio, Millennium Pharmaceuticals

Dimitrios Dimas, National Organisation for Medicines

Viorica Dinga, Biotechnos

Dorde Dmitrasinovic, Agency for Medicinal Products & Medical Devices Slovenia

Rudy Duke, Osteotech

Martin Eisenhawer, Swissmedic

Roy Elder, BioMarin Pharmaceutical

Kathryn Elwell, Solstice Neurosciences

Cynthia Ely, Amgen

Roni Engelstein, Hadassah Hebrew University Medical Center

Etty Feller, Sol-Gel Technologies

Frederic Field, Safety Syringes

Joseph Firca, McCormick

Todd Forthaus, Covidien

Michelle Fortin, Kriegar School Johns Hopkins

Anthony Frankland, Fisher

Stephen Franks, TM Electronics

Adriana Galindo, Cardinal Health

Asher Gamliel, Aminolab-Pharma

Mario Gargiulo, Bristol-Myers Squibb

Paul Genest, Millipore

Leonardo Gherardini, Novartis

Vinay Goel, Goel Enterprises

Anthony Gould, TGA

Patty Graham, Fresenius Medical Care

Darlene Grennon, Baxter Healthcare

Jill Gresens, Cook Pharmica

Silke Gries-Bartenschlager, Talecris Biotherapeutics

Melissa Gulmezian, Allergan

Bindhu Gururajan, AstraZeneca

Richard Hammond, Baxter Healthcare

Yoshihiko Hanaura, Seikagaku BioBusiness

Britt Hanto, Photocure

David Hardy, Therapure Biopharma

Deborah Harsha, Pfizer

Andrew Hartman, Alkermes

Michael Hartman, Sanofi Pasteur

Naoreen Hasan, SNC Lavalin

Ayako Hasegawa, Allergan

Vicki Heath, BioMerieux

Erin Hegarty-Pasquale, Novartis

John Henshaw, Mt. Wachusett Community College

Sam Herald, ImClone Systems

Bonnie Heredia, Baxter Healthcare

Rusty Hertzler, Abbott

Andrea Hiser, Aptuit

Belinda Holdsworth, Jacobs Engineering

John Hriczo, Six Sigma

Togi Hutadjulu, National Agency of Drug & Food Control

Radosveta Ivanova Filipova, Ministry of Health of Bulgaria

Leaders to the PDA Community

Stuart Jaffe, Invitrogen

April Jocson, Althea Technologies

Melanie Jordan, Midwestern University

Enrique Juarez, Sage Products

Colette Jue, Genentech

Jim Kaiser, Bausch & Lomb

Hiroyuki Kanazawa, Seikagaku BioBusiness

Charles Katzer, Discovery Laboratories

Nishikawa Kazuyoshi

Brigid Kealy, Genentech

Youngsun Kim, VaxInnate

Oliver Kirby, Shire Pharmacueticals

Carol Kirchhoff, Pfizer

Janice Kitson, ImClone Systems

Chris Kobus, MedLine

Lior Koriat, Teva

Andreas Kouri, Shire Pharmacueticals

Phuong Kwan, Grifols Biologicals

Athena Kyriakou, National Organisation for Medicines

Paul Landesman, Allergan

Marie-Eve Latendresse, Axcan Pharma

Terry Layo, Sparta-Systems

Greg Lea, Bioproperties Pty

Nick Lee, Innocoll Technologies

Karl Leitner, Octapharma

Filomena Leonardi, Spencer Stuart

Cory Lewis, Althea Technologies

Hans Lien, LigoCyte Pharmaceuticals

Richard Lilischkis, BTF BioMerieux

Allan Lin, Daiichi Sanyko

Lin Lingli, Schering Plough

Chris Lombardi Lombardi, AstraZeneca

Carmen Lopez, Amylin Pharmaceuticals

Paul Lovett, J&J

Peter Lowry, PhilaBiologics Associates

Xujin Lu, Bristol-Myers Squibb

Xiaofeng Lu, PDL BioPharma

Karen Mack-Wilson, Sanofi-Aventis

Antonella Maggio, Generex Biotechnology

Ritesh Mahna, Glaxo SmithKline

Lin Mai, Bayer

Walter Maldonado, Amgen Manufacturing Limited

Lynn Malik, Genentech

Almut Malone, Bayer Schering Pharma

Richard Mangiavas, Lantheus Medical Imaging

Liliana Manzatu, Biotechnos

Helen Mao, Endo Pharmaceuticals

Hugh Mark, Pfizer

Yuichi Maruyama, M`s Science

Tamaki Masuda, Seikagaku BioBusiness

Herbert Matheson, Validation Technologies

Iris McCallister, Ultradent Products

Robert McDonough, Biokinetics

Todd McLaren, Hyde E+C

Sergio Medina Servin, PyMPSA

Priyanka Mehta, Pfizer

Andrea Mesaros, Ben Venue Laboratories

Karen Migliaccio, Migliaccio Consulting

Charles Miller, Talecris Biotherapeutics

Doug Milliken, Caliber Infosolutions

Takao Mimura, Daicel Chemical Industries

Makoto Miyazaki, Seikagaku BioBusiness

Joseph Morwald, Evolution Scientific

Gamal Mostafa, Elkendi

Sri Mudumba, Macusight

Norbert Mueller, Regierungspraesidium Darmstadt

Lukmani Muhammad, National Pharmaceutical Control Bureau

Motoki Mukai, Seikagaku BioBusiness

Amelia Mutere, Genentech

Raed Naji, Naratech Pharmaceutical Consultancy

Dan Napradean, Sindan Pharma Srl.

Paul Nawrocki, NAMSA

Anna Marie Noche, Genentech

Jean Francois Noel, Sanofi Pasteur

Jean-Marie

Noel, Baxter Healthcare

Heather Novak, APP Pharmaceuticals

Brianne O`Callaghan, BCCA - Investigational Drug Program

Conny Oerlemans, Quco

Ryo Okada, Seikagaku BioBusiness

Bjorn-Egil Olsen, Norwegian Medicines Agency

Ricardo Ortega, Abbott

Charles Osborn, PTI Industries

Vincent O'Shaughnessy, Wyeth

Yongsoon Park, Samyang Genex

Jae Ha Park, Berna Biotech Korea

Mukesh Patel, Val-Pharma

Ray Patrick, Sealed Air

Gilda Petersen, Solstice Nuerosciences

Antonio Pinto

Ralitsa Pramatarova, CU Therapeutics

Naomi Pule, Medicine Control Council South Africa

Karen Quarford, ZymoGenetics

Dorothy Raish, Sanofi Pasteur

Michela Rapucci, Baxter Healthcare

Barbara Rellahan, U.S. FDA

Jose Restituyo, Schering Plough

We welcome more of this month's new PDA members on the next page ➤

Please Welcome the Following Industry Leaders to the PDA Community

continued from previous page

Jennifer Reynolds, Medtronic

Paul Rice, Astra Zeneca

Maud Richard, Duoject Medical Systems

Tulio Rivera, Sirion Therapeutics

Wanda Rivera, Baxter Healthcare

Rosa Ria Riyadi, Schering Plough

Anthony Robert, Catalent

Dennis Rodman, Evolution Scientific

Sergio Rodrigues, Pall

Zuleika Rodriguez, Abbott

Theodore Ronningen, Battelle

Christina Rosato, J&J

Richard Rossi, World Courier

Scott Runkle, GlaxoSmithKline

Mike Russ, Genentech

James Ruta, Merck

Abbas Saeda, Medical Product Agency

Hiroaki Sakamoto

Anthony Samsa, The University of Tennessee Health Science Center

Christopher Savitz, GlaxoSmithKline

Carol Savvas, Slayton Search Partners

Juliette Schick, Scilog

Cordula Schneider, Talecris Biotherapeutics

Brian Schultz, Baxter Healthcare

Sharon Sclechter, Ch2m Hill

Gordon Scott, GlaxoSmithKline

Jesse Scott, Ortho Biotech

Kenny Seaver, Solvay Pharmaceuticals

Ian Sellick, Pall Life Sciences

Christopher Servais, Greenbox

Sarah Seyedgavadi, Amgen

Michael Sherriff, Applied Biosystems

Li Shi, Genzyme

Bahman Shimiaei, Spectrum Pharmaceuticals

Seon-Mi Shin, Celltrion

Aquiles Amparo L. Silva, Laboratório Químico Farmacêutico Bergamo

Diorio Simone, Baxter Healthcare

Michael Sinclair, Microcheck

Sarah Singleton, Eli Lilly

Paul Skerker, Millennium Pharmaceuticals

Peter Skutnik, BD

Henry Slodkowski, Meridian Medical Technology

Elaine Smith

Melinda Smith, CRB Consulting Engineers

Heather Smith, Biovail

Stefanie Smulders, Janssen Pharmaceutica

Inger Soerensen, Bang & Olufsen

Brian Spry, APP Pharmaceuticals

Laurence Stauch, Teva Parenteral Medicines

Ursula Steinle, Pfizer

Roy Sturgeon, Lachman Consultant Services

Guo Ming Sun, Eli Lilly

Srividya Talanayar, Vaxinnate

Shigeharu Tamakoshi, Rohto Pharmaceutical

Shaila Tamragouri, Abraxis Bioscience

Lori Testerman, SAIC

Sehloho Tohlang, Medicine Control Council South Africa

David Toledo-Velasquez, Merck

Manuel Torrado, Allergan

Kerry Tripp, IDT

Bruce Truesdale, Chick Companies

Tony Tse, Genentech

Meredith Uebersax, MedImmune

Shinsuke Ueyama, JCL Bioassay

Sydney Ugwu, NeoPharm

Antonia Retno Utami, National Agency of Drug & Food Control

Inge Van Der Schoot, Janssen Pharmaceutica

Miek Van Loon, J&J

Peter Vasquez

Jacqueline Veivia-Panter, Abbott

Maria Adelaida Veridiano, Pacific BioLabs

Marie-Christine Viel, Sandoz

Annie Villamil, Cerexa

Myriam Visschedyk, Solvay Pharmaceutical

Liesbeth Voeten, J&J

Regina Voges-Haas, Biotest

Hong Vu, Intercell

Geraldine Walker, Yonkers Industries

Amber Walsh, 1st Source Network

Michael Waters, Ovation Pharmaceuticals

Min Wei, BD

Lonny White, Coldstream Laboratories

Anita Whiteford, Mallinckrodt Baker/ Covidien

Lakiya Wimbish, Lonza

Jesusa Wirth, Nexgen Pharma

Tim Wortley, GE Sensing

Christine Wright, Millipore

Qia Xie, Bayer

wang xinming, NCPC North Best

DongGon You, Celltrion

Denise Young, Amgen

David Zabele, J&J

Camellia Zamiri, PDL BioPharma

Zohar Zehavi, Teva Pharmaceutical

Roujian Zhang, ImClone

If your information appears inaccurate in this list, please visit www.pda.org to update your profile or email changes to info@pda.org.

Chapter Contacts

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

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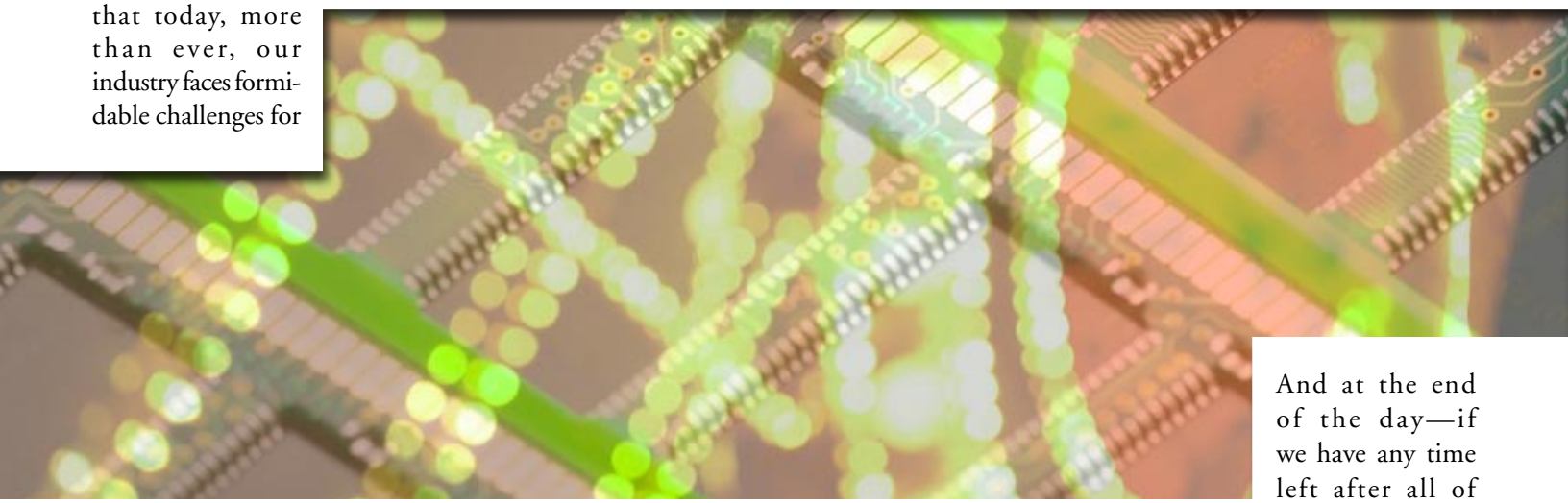
Don't Be Left Behind: Attend the 2009 PDA Annual Meeting

Las Vegas, Nev. • April 20–24 • www.pda.org/annual2009

Hal Baseman, ValSource and Vice Chair of the 2009 PDA Annual Meeting Program Planning Committee

I would like to take this opportunity to invite you to the *2009 PDA Annual Meeting*, being held from April 20th to the 24th at the Red Rock Casino, Resort and Spa outside of Las Vegas, Nev. This is always a worthwhile event, with many pharmaceutical and biological product development and manufacturing professionals gathering, networking, and participating in lectures, meetings, and workshops. But this year the meeting is especially important.

We would all agree that today, more than ever, our industry faces formidable challenges for improving efficiency and reducing the cost of manufacturing, while maintaining, improving, and assuring product quality. One of the ways to meet this challenge is the recognition and use of modern technologies. This year the theme and focus of the PDA Annual Meeting will be the impact of technology on our industry.



Over the past 30 years, technology has been developed and utilized to meet the challenges of new product requirements, beneficial dosage forms, improved manufacturing and testing methods, product quality and operational efficiency. The effective use of such technology presents challenges. These include maintaining awareness of new technologies, understanding and controlling complex systems, realizing and meeting regulatory expectations, adjusting existing operating and quality systems, and developing effective validation techniques.

The objective of this conference will be to focus our attention on the use of technology in our industry in an effort to better understand its current and potential use, the global regulatory expectations, and ways to meet challenges associated with its use. If you are or plan to be involved in the development, manufacturing, testing, distribution, or validation of sterile pharmaceutical, medical devices, or biological products—this is the most important conference you can attend this year.

The meeting will begin with a key note address by **Ian Morrison,** Consultant, followed by U.S. FDA commentaries from **J. David Doleski,** Consumer Safety Officer, and **Nicole Trudel,** Consumer Safety Officer, on the future of our industry and the impact of technology. Then over 75 papers and poster sessions will then be presented on topics ranging from Manufacturing Product Science to Data Management to Quality Science, Process Development, Science, and Validation; including updates on six new or revised PDA Technical Reports. In addition, 14 PDA Science and Technology Interest Groups will hold meetings on the recent developments in their respective areas. More than 100 technology and support company vendors will exhibit. Over 1,200 peers and colleagues are expected to gather to network and exchange ideas. At the end of the conference the PDA Training and Research Institute will offer eight useful courses in topics related to Risk Management, Validation, Microbiology, Cleanroom Management and Quality Programs.

And at the end of the day—if we have any time left after all of these intellectual happenings—I am told there are some entertainment and distractions available at the Red Rock Resort and the surrounding area; including several special events organized by the PDA conference committee and staff. And you may want to try out some of your own risk-based experiments in one of the many venues provided for just such a purpose.

In all seriousness, there is no comparable meeting and conference in our industry. PDA offers its members and attendees the unique opportunity to gather, learn, discuss, and influence trends and the direction of our industry. You do not want to miss that opportunity or this meeting. Not this year.

I hope to see you in Las Vegas in April.

2009 PDA Cold Chain Conference/Training Course Rapidly Approaching

Bethesda, Md • March 23–24 • www.pda.org/coldchain2009

Bob Dana, PDA

PDA began our Cold Chain conferences in March 2006. Our first Cold Chain conference took place in Bethesda, Md, with about 75 persons in attendance. The meeting was one of the key steps in the revision process for PDA *Technical Report No. 39, Guidance for Temperature Controlled Medicinal Products: Maintaining the Quality of Temperature Sensitive Materials through the Transportation Environment*. The process culminated with the publication of the revised TR in 2007.

In March 2008, I recall standing in front of the more than 200 attendees at the Cold Chain Conference (back in Bethesda), marveling at how much had transpired in such a short time. Our conference registration had almost tripled, the Pharmaceutical Cold Chain Discussion Group (PCCDG) had morphed into the Pharmaceutical Cold Chain Interest Group (PCCIG), the revision to Technical Report 39 had been prepared, a new PDA Training and Research Institute (PDA TRI) course series had been developed and we had expanded our Cold Chain conference series to include annual meetings in Europe. The U.S. Cold Chain conference had also attracted the attention of global regulatory authorities and had expanded to include products requiring controlled room temperature storage as well.

It is clear to me that cold chain and the control of temperature-sensitive products has become a big deal. We are now poised to present the *2009 PDA Pharmaceutical Cold Chain Management Conference*: *From the First to the Last Mile – Management of the Distribution of Temperature-Sensitive Pharmaceutical Products*. It will be held March 23–24, 2009 at the Hyatt Regency Hotel in Bethesda, Md. The Program Committee, chaired by **Rafik Bishara,** has put together an impressive agenda over the two day conference. Industry experts involved with managing the distribution of temperature-sensitive pharmaceutical products will discuss how modern technologies and the use of mean kinetic temperature help ensure that the controls applied to distribution systems provide a quality product to the most important person in the supply chain—the patient. Several sessions will address compendial and global regulatory expectations and findings, with presentations from U.S. FDA and other regulators expected.

Transportation system partners are key to helping ensure delivery of a quality product and a series of presentations will describe the ways packaging materials and systems and transportation service providers contribute to the delivery of products meeting manufacturer's and regulatory expectations, as well as patient needs. In addition, the historic, ongoing and planned future work of the PCCIG's contribution to the process will be described. Finally, a unique training initiative developed and delivered through a PDA/WHO partnership will be presented.

In a first for the Cold Chain Conference, a series of poster sessions will also be held, allowing attendees to meet and speak first-hand with the presenters in an informal setting.

Immediately following the conference (March 25–26), the PDA TRI will present a two-day training program entitled, *Global Regulations and Standards: Influences on Cold Chain Distribution, Packaging Testing and Transport Systems*. This course will provide participants with an introduction to global regulatory expectations and will also explore TR-39.

Registering for both the conference and the TRI Course will get participants a discount on the registration fees for each. Check the PDA and TRI websites (www.pda.org and www.pdatraining.org) for more details, including the full conference agenda and course description.

I have been really impressed at how rapidly the technology and expectations for transportation of temperature-sensitive pharmaceuticals have progressed over the past three years, and how well PDA has delivered timely knowledge on the subject to our members. If you are involved in the manufacture, testing and distribution of temperature-sensitive pharmaceutical products, or the design and evaluation of these distribution systems, you won't want to miss this conference.

If we're lucky, the timing may even coincide with the blossoming of the cherry trees in Washington, D.C.; a spectacular sight not to be missed. I look forward to seeing you next March in Bethesda, Md. for what is sure to be an outstanding and informative conference and training program.

Faces and Places

Training Workshops on *PDA Technical Report 1* and *PDA Technical Report No. 26 Revised 2008*

(l-r) Weijin Gu, JPT Consulting; Jerry Martin, Pall; Rich Levy, PDA; Maurice Phelan, Millipore; Petra Motzhau, Sartorius Stedim Biotech

The highly anticipated new 2008 edition of TR-26 is shipping to PDA members now and available at our PDA Bookstore online

Attendees listened with great interest at the Training Workshops

Forbidden City Images ©2008 Jerry Martin

Presenters enjoyed the picturesque Forbidden City in Beijing, China

Michael Sadowski, Baxter, delivered a captivating presentation on PDA TR-1

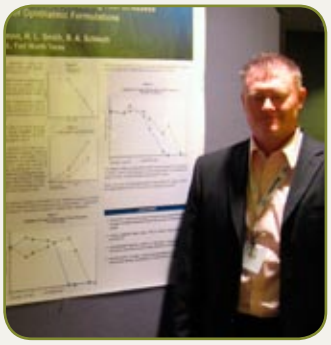
PDA's 3rd Annual Global Conference on Pharmaceutical Microbiology

(l-r) James Agalloco, Agalloco & Associates; Donald Singer, GlaxoSmithKline; Radhakrishna Tirumalai, USP; Anthony Cundell, Schering-Plough Research Institute; Sven Deutschmann, Roche Diagnostics

(l-r) Anthony Cundell, Schering-Plough Research Institute; Colin Dykes, OpGen; Jaspreet Sidhu, Molecular Epidemiology; Mareike Wenning, Technical University Munich

(l-r) Michael Miller, Eli Lilly; Andrew Hopkins, MHRA; Tor Graberg, MPA; Rick Friedman, FDA; John Metcalfe, FDA

(l-r) Andrew Bartko, Battelle Memorial Institute; Pascal Yvon, AES-Chemunex; Kimberly Benton, FDA; Michael Miller, Eli Lilly



Paul Shannon, Alcon Research, smiles next to his poster on the Lonza MicroCompass System

Christian Supina, Baxter, stands next to his poster that spelled out the use of a silkworm larvae plasma test to quantify peptidoglycan and beta glucans

Steve Randall, Baxter, poses next to his poster that diagrams a case study in human error reduction

Suman Kathuria, Siegfried, smiles next to her poster on microbial failure investigations

Exhibits sparked conversations among the crowd

Attendees listen to a session given by Berit Reinmuller, Royal Institute of Technology; Jette Christensen, Novo Nordisk; Bengt Ljungqvist, Royal Institute of Technology; Gilberto Dalmaso, A.L. Co. Industries; Michael Miller, Eli Lilly

Attendees discuss the thought provoking ideas they heard at their sessions—in and out of the lecture hall.

Faces and Places

PDA Conference on the Development and Regulation of Clinical Trail Supplies | November 10–11, 2008

(l-r) Asenath Rasmussen, Pfizer; Jamie Tsung, Baxter; Eugene Johnston, Biologics Consulting Group; Suman Patel, BPDS&S

(l-r) Sarvang Mishra, Shire Pharmaceuticals; Larry Sweeney, Genzyme International; Robert Lesnefsky, Fisher Clinical Services; Rafik Bishara, PDA

(l-r) Judith Sernatinger, Stryker Biotech; Anne Bechet, OctoPlus; John Amedio, John Amedio and Associates

(l-r top) Bob Dana, PDA; Vijai Kumar, Excel Life Sciences; (l-r bottom) Andrea Zobel, Parexel International; David LeProhon, Stryker Biotech

(l-r top) Sarvang Mishra, Shire Pharmaceuticals; Howard Levine, BioProcess Technology Consultants (l-r bottom) Robert Haggerty, Hyaluron; Karen Migliaccio, Migliaccio Consulting

(l-r top) Tatyana Touzova, Biolex; Meena Subramanyam, Biogen Idec; (l-r bottom) John Gasdaska, Biolex Therapeutics; Taylor Burtis

Meeting Students' Needs: Pre-Lecture Communication

Walter Morris, PDA

PDA Training and Research Institute (TRI) faculty dedicate a lot of their precious free time preparing for their lab and/or lecture courses to ensure that students receive the best instruction for their equally precious dollars. At the *PDA's 3rd Annual Global Conference on Pharmaceutical Microbiology,* one faculty member shared with us his strategy for tailoring his course to the students' specific needs.

Barry Friedman, PhD, consultant and TRI instructor, attended the conference to teach his TRI lecture course "Microbiology of Water in a cGMP Environment," an area he has gained significant experience in over his 25-year career in biotechnology, aseptic processing and medical devices. The course description indicated that students would learn about: *water sources, microbiological problems associated with water sources, development of test requirements, and frequency of testing and specifications of the various waters available.*

Because of his extensive knowledge in this area, Barry understands going into a course that it is difficult to address all of the nuances pertinent to each individual student. As such, the veteran lecturer has developed a strategy of pre-lecture communication with registered students to help him tailor his message to their specific needs.

It is a rather simple strategy for any lecturer to follow, yet it is very effective. A few weeks prior to the course, Barry sent via email the following message to all the registered students:

> *My name is Barry Friedman and I will be providing the training for the upcoming PDA seminar "Microbiology of Water in a cGMP Environment." If you have a moment, I would appreciate feedback on what you would like to obtain from this one day seminar. Or, if there exists a particular area that you would like to explore, I also would be interested in hearing about it and what I might be able to do to expand in those areas.*
>
> *Again, thanks for planning to attend this course on Thursday, October 23 in Chicago.*

A majority of the students replied, helping Barry hone in his message and organize his materials to ensure the specific topics raised were covered during the one-day course. The following is a sampling of comments received by Barry:

> *I would like to learn agency expectations for plant water used in sterile manufacturing; testing, specifications [and] daily testing required. Also, sources of contamination, risk, what to look for on audits, etc. Basically, anything relevant to Quality Assurance that I should know!*
>
> *1. How do most firms qualify RO systems? 2. What recirculating temperature is considered "self sterilizing" in the industry today? Our stance is that any system validated at 80°C would need to be revalidated, as would any process that used that water if recirculation temperature were lowered.*
>
> *What I would like to get out of this seminar is related to the requirements and future expectations in the U.S. and Rest of World for water purity used in APIs and excipients; in particular the testing performed and frequency. We do not have any sterile environments or aseptic products, but do have products marketed as low endotoxin. Also, I am interested in the impact of typical water issues on the quality of the downstream API's and exicipients, so that I can bring back to my operations people the importance of having an effective water purification system*
>
> *I'm new to Water monitoring. My background is EM of clean rooms, bioburden testing of materials/products, and sterility testing. I'm looking for general information on setting up a GMP compliant routine monitoring schedule for water and clean steam systems and troubleshooting any failures. Also, qualification guidelines would be useful as my organization will be qualifying an new WFI system in the next year or so.*

How effective was Barry in utilizing this pre-lecture information in his actual presentation? Well, according to the industry veteran, "I received greater than an 80% response, which I thought was great and demonstrated the interest of the perspective attendee. Once we were in the classroom setting, that interest was confirmed."

About the Lecturer

Barry Friedman, PhD, is a biotechnology/aseptic processing consultant. He has over 25 years of experience in biotechnology, aseptic processing and medical devices and has been the Quality Control Director for contract manufacturing organizations specializing in Phase 1, 2, and 3 and commercial operations for the past eleven years. He is the past president of the PDA Capital Area Chapter and has presented seminars on Aseptic Processing and Contract Manufacturing of Clinical Trial APIs.

A Look Back at PDA's Quality by Design Conference in Frankfurt

Program Chairs Mohammed Barkat, Patheon, and Michiel Rook, Global ConSeptS

One wouldn't normally use the phrase "looking back" when speaking about the concept of "Quality by Design" (QbD), because QbD means looking to the future of our industry. However, in this article we are taking a look back at the highly successful QbD conference PDA sponsored last October in Frankfurt, Germany.

The conference is a perfect example of looking back to the achievements many companies have reached over the past years by embracing the principles of QbD. From their experiences, other companies can learn that QbD is not something for the future; the principles can be applied successfully today, and thus are relevant to any biopharmaceutical and pharmaceutical company. Obviously, Quality by Design is here to stay. For those people who believe this is yet another "brilliant idea" from the regulatory authorities that soon will fade away, bad luck, it will not.

The case studies presented at the conference were unambiguous, and provided examples of the strength of applying QbD principles in a variety of ways:

- A medical device process went out of control. Applying the principles of QbD the process was brought back to its specifications and yields were significantly improved over the original process
- Implementation of a design space to support Real Time Release for a medicinal product
- In-line control of a lyophilization process based on product temperature measurements

The format of the conference was based on the logical flow of a QbD process. It started with determining the impact of QbD concepts on the process and an organization. This session had some remarkable presentations on how to present a concept like QbD to your senior management and how to get their buy-in. One thing is clear: QbD should be proposed to senior management as Good Business Practice to get their support.

The second phase of the QbD process is to find out the critical parameters and attributes of the process. Risk assessment is one element to establish the critical quality attributes, but so is prior knowledge based on existing processes and products. Remember, Quality by Design is based on good science and knowledge management. One particular presentation in this session captured each aspect: putting the patient at the center of the design space, and from that point link the critical quality attributes to the safety and efficacy of the medicinal product.

The third part of the QbD process is to write protocols for Design of Experiments and perform multivariate statistical analysis on the test data in order to find out what control parameters are critical to the process and the medicinal product and which are not. This phase is where the scientific foundation for a process and the drug product is set. Obviously, it is the place for scientists and statisticians to establish the correct techniques and mathematical models. This session of the conference was packed with presentations on different statistic techniques and models to use. Although not all of us enjoy models and mathematics, there is a whole bunch of people to whom this looks like a piece of cake and on whom we can trust. New software packages are commercially available that enable more people to get through this phase. The data obtained is pivotal to the next phase of the QbD process; hence, models and their outcome should be challenged to represent the actual process.

The fourth step in the QbD process is to shape the design space. Whereas for many people the design space seems something "virtual", setting a design space is not that difficult provided you have the scientific data to support it. The presentations regarding design space made it obvious that companies by now are using design spaces to manufacture medicinal products. Nevertheless, the concept of design space is complex and needs more attention to be better understood by all members of the bio-pharmaceutical society.

Now that you have your process parameters confined within the design space, incessant improvement of the process starts. The critical parameters need continuous monitoring and this is where Process Analytical Technology (PAT) comes into scope. PAT applications for small molecules are relatively accessible, when it comes to complex molecules a lot of investigation still need to be done. Likewise, standard techniques in aseptic processing such as lyophilization could do with PAT applications. Based on presentations given during this session soon such method could be available. Real Time Release becomes more feasible due to the PAT applications that are being employed today, strongly supporting the continuous improvement that is part of the product and process lifecycle.

The conference saw the attendance of a significant number of regulatory authorities' staff. Both European and FDA representatives were present including the chair of the EU PAT team. Once more, it is confirmed that the regulatory bodies are open to receiving QbD driven applications for new and existing processes and procedures to obtain marketing authorisation for QbD driven processes are in place. The industry needs to change paradigm with respect to regulatory people; they are no police officers, they are partners helping you to obtain market authorisation provided the basic QbD process principles of good science and knowledge management are respected.

At the end of the conference, three parallel workshops were organized. The first workshop discussed the development and maintenance of a design space throughout the product lifecycle. The second focused on how to handle a transition from a current quality system to a system based on the Q10 guideline and the last workshop was on how to create a design space and

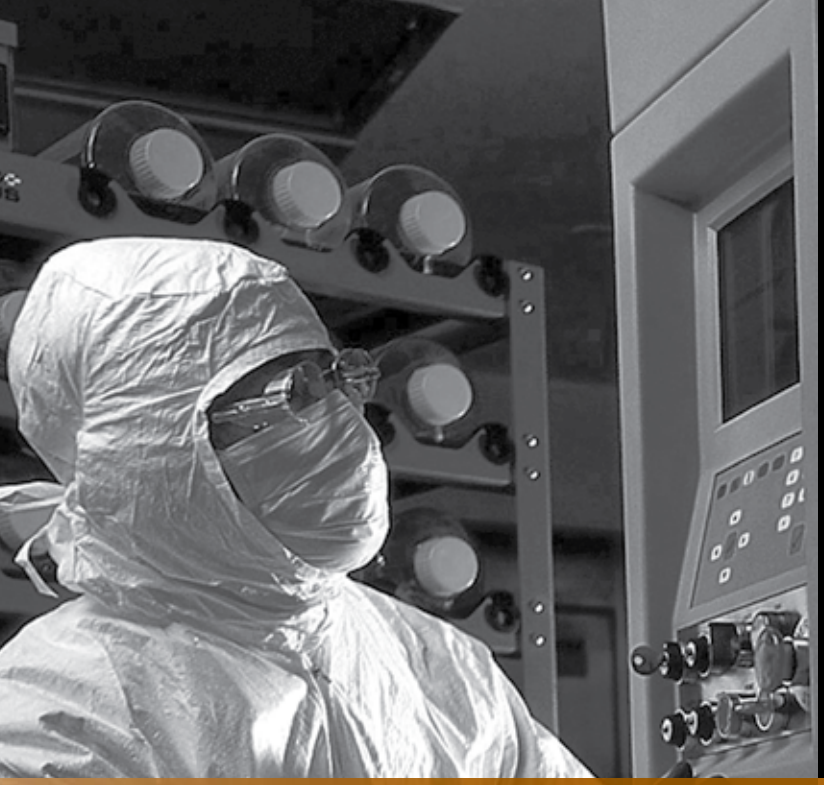
the initial steps to take in formulation development. These workshops proved to be of excellent value as the discussion in these groups were answering many open questions from the audience.

Taken as a whole, the conference was a great success, and given its attendance (over 100 people were present), the subject of Quality by Design is one that not only has a lot of interest; it has many people whom see the need to progress in this direction. With no doubt, the primary target of Quality by Design is to further increase the safety of the patient by producing medicinal products with processes that are better understood and more robust. Better understanding and more robust processes will target the second goal of QbD; producing products at a lower cost. These two reasons explain why QbD is good business practice in the bio-pharmaceutical industry.

Conclusion

- Quality by Design has two major drivers. The first is to enhance patient safety by providing medicinal products of a higher quality produced by processes that are more robust and better understood. The second driver is to reduce costs, which relates back to better-controlled processes.
- Quality by Design is a proven concept in many other industries (e.g., petro-chemical, aviation and car industry). There is no reason whatsoever why this concept would not apply to the bio-pharmaceutical industry.
- Many bio-pharm companies have embraced the concept of QbD. These companies in part already benefit from the proceeds of applying QbD principles. Given the current focus of reducing costs in the bio-pharmaceutical industry, companies that do not apply QbD have not much choice other than adopt the QbD principles.
- Intense teamwork between product and process development, technology transfer, production, regulatory affairs and quality assurance/control departments is key to the success of Quality by Design. Only when a team approach is applied, Quality by Design will become a successful concept.
- QbD is good business sense. Better products and robust processes will lead to extra cost-effective production. In the end, cost reduction should increase company profits.
- QbD is not "another good idea" from the regulatory authorities. FDA and the European regulatory organizations have significantly changed their position and organization compared to the past. They would like to see new technology and techniques being applied, adopt real time release and PAT applications as long as the basis, good science and knowledge management, is correctly applied.

The chairs would like to thank the PDA and the organizing committee for their excellent work. Due to their efforts, this meeting was a true success. We will be back in 2009.



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