Science • Technology • Quality • Regulatory • Community

PDA Letter

Volume XLIII • Issue #10

www.pda.org/pdaletter

November/December 2007

In This Issue…

TRI's new facility opened in September. Read all about it and see photos, pages 54–57

FDA Reps Present Five-Year Update to GMP Initiative at 2007 PDA/FDA Conference

1200 Professionals Attend the Conference, Exhibition and TRI Courses

Walter Morris, PDA

The U.S. FDA used the pulpit at this year's PDA/FDA Joint Regulatory Conference to highlight achievements and areas in need of further assessment regarding its 2002 GMPs for the 21st Century Initiative. The various elements of the initiative were covered during the two-and-a-half day conference, which included 4 plenary sessions, 12 break-out sessions, 8 breakfast sessions and 11 PDA Interest Group gatherings. Quality by design, process analytical technologies, design space and quality systems as well as a bevy of compliance-related topics dominated the agenda.

As has become the trend with this meeting in recent years, the 2007 event broke all attendance records for the Conference, Exhibition and PDA Training and Research Institute courses. The 1200 registrants represented the largest gathering for this and any PDA event in the Association's 61-year history. Attendees continue to travel from all over the globe to attend, with large contingents of registrants at this year's conference from China, Japan, India and South Korea. Representation from European countries has always been strong, and this year was no exception.

Facing a standing-room-only audience at the opening plenary session of the meeting, Program Committee Member and Session Moderator **Rick Friedman,** Director, Division of Manufacturing and Product Quality, CDER, oriented attendees to the Agency's current activities and thinking:

"Good morning. As all of you likely know by now, in August 2002 FDA announced a significant new initiative known as cGMPs for the 21st Century to modernize the regulation of pharmaceutical manufacturing and product quality. This initiative included veterinary and human drugs and certain human biological products, including vaccines and biotech. We've had many accomplishments since 2002 and reported many of them in our 2004 and 2007 updates which are on the FDA website.

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2008 PDA Annual Meeting

Science Driven Manufacturing: The Application of Emerging Technologies

THE BROADMOOR
COLORADO SPRINGS

April 14-18, 2008

Colorado Springs, Colorado

Conference	|	April 14-16, 2008
Exhibition	|	April 14-15, 2008
Career Fair	|	April 14-15, 2008
Courses	|	April 17-18, 2008

The PDA Annual Meeting is the one meeting each year dedicated to advancing the careers of pharmaceutical and biopharmaceutical professionals by focusing program content on science and technology innovation, offering extensive formal and informal networking opportunities and providing a forum to contribute to and influence the advancement of science and regulation in the industry.

Highlights of this year's conference program include:

- The patient point-of-view and how you and your organization may have contributed to their well-being and/or recovery
- Novel manufacturing technologies that enhance patient safety
- New contaminants implications, detection and exclusion

Complementing the conference are PDA Training and Research Institute (PDA TRI) training courses, an exhibition featuring today's leading pharmaceutical and biopharmaceutical companies, PDA's 4th Annual Career Fair and enhanced networking opportunities.

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TRI's new facility officially opened following the PDA/FDA conference

PDA Parenteral Drug Association

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2008 PDA/EMEA Joint Conference

European GMP: Current Issues and Future Developments

18-21 February 2008
Budapest, Hungary

Conference	|	20-21 February 2008
Exhibition	|	20-21 February 2008
Training Courses	|	18-19 February 2008
Workshop	|	18-19 February 2008

Register by 1 December 2007 and SAVE!

Don't miss the opportunity to learn about the fast evolving European regulatory environment directly from regulators and industry experts who will share their experience and knowledge. The conference agenda includes eight concurrent sessions and three plenary sessions, covering important topics such as:

- **Dedicated Facilities**
- **Annex 1**
- **QP Discretion**
- **Atypical Actives**
- **GMP Inspections**
- **ICH Quality Guidance**
- **Investigational Medicinal Products**
- **Excipient GMP**
- **Annex 2**
- **Variations**
- **New Guidance**
- **Future of Inspections**
- **And More…**

Most importantly, there will be an extraordinary number of speakers from the EMEA, the European Commission and the national authorities. Rarely have so many officials from so many authorities across Europe committed to present their views and participate in discussions on evolving GMPs. And never has interaction with European inspectors been this convenient.

See you in Budapest in February 2008!

www.pda.org/emea2008

Editor's Message

With the last issue of the *PDA Letter* for 2007, I want to take this opportunity to thank the volunteer Editorial Committee for all their help soliciting members for articles and reviewing member submissions. This was the second year in which we actively sought member submissions for our feature articles, and we had many good ones. We owe a debt of gratitude to our authors for taking time out of their extremely busy schedules to put their thoughts on paper for us.

Next year, we hope to have even more submissions from the membership. Our themes are as follows: January, **Quality Systems and Compliance;** February, **Contract Manufacturing;** March, **Supply Chain Management;** April, **Environmental Monitoring;** May, **European Regulatory Update;** June, **Novel Technologies for Drug Delivery;** July/August, **Sterile Products/ Aseptic Processing;** September, **New Trends in Validation;** October, **Pharmacopeial Harmonization;** November/December, **FDA Regulatory Update.** We are also on the lookout for "Technology Trends" for the Science & Technology Snapshot. For more information on submitting to the Letter, go to www.pda.org/pdaletter, and follow the "Authors Wanted" link on the right-hand side.

I also want to recognize the winner of the July/August issue cover art contest, **James Agalloco,** a former everything at PDA. He recognized the inside of the steam sterilization autoclave and also identified the brand! James' prize was a one-year membership renewal. A number of other contestants identified the photo successfully, and although their names were not drawn for membership renewal, we are in the process of sending them each a consolation prize.

Finally, I want to recognize the PDA staff for continuing to support the Letter. Our science and regulatory staff introduced the "Snapshots," our staff in Europe brought us the new Europe Section, our membership team significantly increased the volume of articles in their section, and TRI continued to add a personal touch to each issue.

Lastly, I want to introduce **Emily Hough** (pronounced Huff) as the new writer/editor for the *PDA Letter.* She started with PDA on November 12, replacing the former assistant editor, and has dived right in by writing an article on CAPA for next month's issue!

Visit www.pda.org/pdaletter

At the Letter's new website, you can read selected articles and link to the members-only archive *before* your hard copy arrives in the mail! Also, you can easily submit your comments and have them published as "Letters to the Editor." Click on the "Authors Wanted" link to learn about upcoming topics and how to submit articles!

The PDA Letter is published 10 times per year, exclusively for PDA members. Subscriptions are not available. Articles in the PDA Letter may be reproduced with permission—contact the PDA Letter Editor for details.

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2008 Aseptic Processing Training Program

The PDA Training and Research Institute's most popular training program returns in 2008. Held at the new PDA TRI facility in Bethesda, Maryland, this ten-day course offers an exceptional opportunity to:

- Relate and incorporate each component of aseptic processing into one operation for overall improved process and final product
- Describe the theory behind personnel gowning and aseptic technique qualification to minimize risk of manual product contamination
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- and more!

Four 10-day sessions are being held in 2008!

Session 1: January 28-February 8, 2008 **SOLD OUT!** February 25-29, 2008
Session 2: April 7-11 and May 5-9, 2008
Session 3: August 18-22 and September 15-19, 2008
Session 4: October 13-17 and November 10-14, 2008

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PDA LECTURE TRAINING RETURNS TO CALIFORNIA!

PDA Training and Research Institute returns to California in March 2008 for the San Francisco Training Course Series with **NINE** industry courses:

- Problem Solving Techniques in Nonconformance Investigations – ***New Course!***
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- Effective Application of a Quality Systems Approach to Pharmaceutical cGMPs in Compliance with the FDA Guidance – ***New Course!***
- Elements of Risk Management
- Auditing for Microbiological Aspects of Pharmaceutical and Biopharmaceutical Manufacturing – ***New Course!***
- cGMP Manufacturing of Human Cell-Based Therapeutic Products
- Fundamentals and Essentials of EU and US GMPs for API and Biotechnology Manufacturers
- Process Validation for Biopharmaceuticals
- What Every Biotech Startup Needs to Know about CMC Compliance

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The Power of Collaboration: My Welcoming Remarks at the 2007 PDA/FDA Conference

PRESIDENT'S MESSAGE

Bob Myers

I would like to welcome everyone. This is our biggest and most successful meeting every year, and this year is no exception. Roughly 1200 people will be participating in the various events during the week; it is certainly a credit to the committee and to the people who put on all the educational events and the workshops that are coming up this week. A look through the participant list and you will see people have come from all over the world—a truly global event. This year in particular, we have a lot of participants from Asia—from China, Taiwan, South Korea and Japan. A significant number, and I think that is a credit to the program and to the work of this particular collaboration that we have with the FDA. I know a lot of people are here also from Europe, and I know that is pretty typical of the participation, but the Asian participation this year is particularly high.

FDA and PDA collaborate on this, we co-sponsor it, which means, as you saw, there are a lot of people from the FDA who participate in the organization of the program. They have a lot of input as to what they think should be presented, and I think it is important that we provide this forum for them and for our membership as a way to communicate to our membership and to the public in general.

We have other collaborations with the FDA, and not necessarily co-sponsored events. Most of our meetings, even our scientific meetings, have a speaker generally from the FDA or from another regulatory agency. This year, we do have a second co-sponsored group of meetings, our Quality Systems meetings. And it is going to be pretty much a global presentation of this information. It starts in November in Bethesda, Dublin in December, and Beijing and Shanghai next year, which will be our first events in China. So that is something we are looking forward to, and I think we will be very successful over there with the support of the State FDA in China.

We have other collaborations. It starts with the EMEA in February of next year; that's our second EMEA/PDA conference. It will be in Budapest. R^3 Nordic in Stockholm this year, Modern Aseptic Production; we have a great relationship with R^3 Nordic…In November, ISPE and PharmaChemical Ireland, we are putting on a joint meeting in Cork, Ireland. That will be on technology and the science of sterile processing, as well as some other subjects; we will have an educational course there also. A formulary meeting in Europe next year with USP and EDQM. Kazakhstan Inspectorate training has been going on for three years. We've trained about 250 potential FDA staff from Kazakhstan starting in 2005. It has been a very worthwhile effort. We have exposed them to our science and the regulations here in the United States and Europe….It has been one of our outstanding achievements in the last few years. We have had talks with the State FDA in China, and we will probably be doing some Inspectorate training there in conjunction with our Quality System meetings next year.

TR-43 Announcement: PDA Publishes Glass Defects Technical Report

Graphical Examples of over 100 Different Glass Nonconformities Included

PDA Technical Report No. 43, *Identification and Classification of Nonconformities in Molded and Tubular Glass Containers for Pharmaceutical Manufacturing*, published in October 2007, provides detailed examples of glass nonconformities for molded and tubular glass containers. Lexicons of nonconformities for each glass type can be viewed on a CD that is provided with the report.

More than 100 photos and drawings in the lexicons demonstrate the most commonly found nonconformities in molded and tubular glass containers. TR-43 is the only available best practices guide that visually catalogs, identifies and classifies glass defects for molded and tubular glass for the pharmaceutical industry.

"Technical Report No. 43 is unique," said **Rich Levy,** PDA Sr. VP of Scientific and Regulatory Affairs. "The visuals on the CD complement the written report and help the reader to accurately identify the defects. The technical report moves the industry closer to a harmonized best practice for glass defect identification and control."

The Glass Task Force:

- **William Bogle,** Genesis Packaging Technologies
- **Alfred Breunig,** MGlas AG
- **Adeliya Chirina,** XOMA (US) LLC
- **David Davidow,** Gujarat Glass International, Inc**.**
- **Nicholas R. DeBello,** , Wheaton Industries Inc. (task force co-chair)
- **Michael N. Eakins,** PhD, Eakins & Associates
- **Jens H. Eilertsen,** Novo Nordisk A/S
- **Eric Engel**, Pfizer Inc**.**
- **Hans Engels,** DSM Pharmaceutical Products
- **Mads Espersen,** Novo Nordisk A/S
- **Carol Rea Flynn,** Gerresheimer Glass, Inc.
- **Kristy D. Fraizer,** Baxter Pharmaceutical Solutions LLC
- **Raymond P. Godlewski, Sr.,** Baxter International
- **Stephen W. Goodsir,** Wyeth, retired
- **Richard M. Johnson,** Fort Dodge Animal Health (task force co-chair)
- **Jan Gunnar Jorgensen,** Novo Nordisk A/S
- **Nadir Lahmeur,** Saint-Gobain Desjonquères
- **Alessandro Landi,** Nuova Ompi
- **Gerhard Mayer,** Nuova Ompi
- **Sarvang Mishra,** Wyeth
- **Tony Perry,** Schott North America, Inc.
- **Scott Ramseyer,** CSL Behring
- **Diane V. Rimer,** Baxter Healthcare
- **Mark Sanne,** Alcon, Inc.
- **Suzanne Seeley,** Merck & Co., Inc.
- **Lauren Shamitz,** Massachusetts Biologics Laboratories
- **Mike Silvola,** Hospira, Inc**.**
- **Bruce D. Smith,** Genesis Packaging Technologies, retired
- **Edward J. Smith,** PhD, Wyeth
- **Franco Stevanato,** Stevanato Group
- **Robert W. Swift,** Amgen Inc (task force co-chair)
- **Lynn Torbeck,** Torbeck & Associates
- **Hans Woerder,** Hawe Packing Consulting
- **Kirk Wolff,** Eli Lilly and Company
- **Andrew Yao,** Schering Plough Corporation

Science & Technology *Snapshot*

PDA's Ambitious Sci-Tech Agenda

Vincent Anicetti, Genentech, Inc. *(from remarks made at the PDA/FDA Conference)*

One of the things we try to do and are committed to as a Board is to make sure that we are listening to the membership. Over the past couple of years, through surveys and other forums, we've heard loud and clear that PDA needs to be focused, first and foremost, on science and technology and best practices, and let that drive our position on regulation, operational procedures and other aspects of our business. **John Shabushnig** has led the strategic planning committee effort over the last couple of years for PDA, and I'm very excited about some of the investments that we will be making to ensure that we remain a preeminent scientific organization.

The first is that we will be investing more funds and effort into our Journal of Pharmaceutical Science and Technology. You will see that more articles will appear in the Journal in upcoming years. We will be putting more effort in turning around those papers as quickly as possible.

Second is an effort to produce more and more timely Technical Reports. PDA Technical Reports are a great asset to many of us when we are thinking about developing operations and the best procedures for doing so. We have a goal of producing a technical report every two months. So we have a goal to produce six to eight per year. We also have a goal to make these consensus documents. And that is not consensus in terms of compromising the science and technology, rather it is consensus with the goal of making these global documents. We are a globally regulated industry, and we want to make sure that the documents we produce reflect the best thinking on the part of the major regulatory agencies. We've done a terrific job of that with two recent documents that were published, Technical Report No. 39, guidance for temperature controlled medicinal products, and our revision of Technical Report No. 1, moist heat sterilization.

As Bob mentioned, we also have a very ambitious program for scientific meetings. In the next year we expect to have 14 major scientific meetings in various regions of the globe.

Technical Report *Watch*

In Global Review: *Drafts of the following TRs are under review by the global PDA membership. To learn how to comment on any one of the drafts, contact Genevieve Lovitt-Wood at glovitt@mindspring.com.*

- ***Reprocessing of Biopharmaceuticals***

In Edit: *After global review, task forces responsible for the TRs consider the feedback received. TRs then undergo final technical editing.*

- ***Biological Indicators for Sporicidal Gassing Processes: Specification, Manufacture, Control and Use***
- **TR-14 (Revised 2007),** ***Validation of Column-Based Separation Processes***
- **TR-15 (Revised 2007),** ***Validation of Tangential Flow Filtration in a Biopharmaceutical Application***
- ***Microbial Data Deviations***

In Board Review:

Following technical editing, TRs are reviewed by PDA's advisory boards (SAB, BioAB). If/when approved, the PDA Board of Directors (BoD) makes the final decision to publish or not publish the document as an official PDA TR.

- **TR-26 (Revised 2007),** ***Sterilizing Filtration of Liquids***
- ***Quality Risk Management for Aseptic Processes***
- ***Filtration of Liquids Using Cellulose-Based Depth Filters***

Leadership *Opportunities*

Call For Authors

The following task forces are forming. Contact Genevieve Lovitt-Wood, gilovitt@mindspring.com, if you are interested in participating. You will be asked to present a CV prior to being selected for the task force.

- Disposable Manufacturing Technology Task Force
  Chair **Robert Repetto,** Wyeth
- Analytical Methods for Biopharmaceuticals Task Force
  Co-Chairs **Nadine Ritter,** PhD, Biologics Consulting Group, and **Gautam Maitra,** AC Immune
- Analytical Methods Development
  Chair **Steffen Krause,** Favrille.

Call For Reviewers

The following in-process technical reports will be undergoing public review. If you are interested in participating in helping PDA strengthen these reports, please contact Genevieve Lovitt-Wood, gilovitt@mindspring.com.

- *Reprocessing of Biopharmaceuticals* –
  Target Review: December 2007
- TR-3 (Revision), *Dry Heat Sterilization and Depyrogenation* – Target Review: March 2008
- *Steam in Place* – Target Review: March 2008
- *Moist Heat Sterilizer Systems* –
  Target Review: March 2008

In *Print*

Dispelling Validation Myths for Bioprocesses

Based on material from Bioprocess Validation: The Present and Future, *by Trevor Deeks, PhD, Emergent Biosolutions*

Process validation (PV) is generally considered as the demonstration that a process works. For a process to work effectively, safely and consistently, it must be executed within an environment that supports those goals—in other words, within a "quality assured" GMP-compliant environment. It is worth noting here that a true GMP-compliant environment is not one simply where the paperwork supports that claim, but one in which it is true in practice. For too long the pharmaceutical and biopharmaceutical industries have been driven by the dogma that "if it isn't documented, it didn't happen." There are many situa-

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Task Force *Update*

The Technical Report No. 30, *Parametric Release of Pharmaceuticals Terminally Sterilized by Moist Heat* Revision Task Force met at the PDA headquarters in Bethesda, Md., on Nov. 1 to review content drafted to date. Discussions centered on the sensitivity and statistical applicability of the sterility test for the evaluation of terminally sterilized products given the low probability of contamination as noted by USP.

The Technical Report No. 3, *Dry Heat Sterilization and Depyrogenation* Revision Task Force held a development meeting at PDA headquarters in Bethesda, Md. on Sept. 27 to review the draft revision of the technical report. Approximately 80% of the revised document is completed. Task Force members identified several benchmarking questions during the Sept. meeting for presentation at the PDA Technical Reports: A Sneak Peek conference on November 5 at Amgen's headquarters in Thousand Oaks, Calif. Task Force Co-Chair **Peter Lee**, Amgen, will represent the group during the Sneak Peek workshop and will solicit feedback from workshop attendees. The team will meet again to review the completed first draft in January with the goal of releasing the document for PDA peer review in March.

The Risk Management for Aseptic Processes Task Force met at Wyeth, September 17-18, to address and incorporate comments received during global review of this technical report. The team spent a great deal of time examining the qualitative and quantitative model examples given in the report to ensure they were illustrative of a practical application of risk management concepts provided in the technical report without prescription regarding aseptic processing. **Ruhi Ahmed,** BioMarin, will present the technical report draft at the PDA Technical Reports: A Sneak Peek conference, Nov. 5 at Amgen's headquarters.

The TR-14, *Validation of Column-Based Separation Processes*, Revision Task Force met at PDA headquarters Sept. 20-21 to address and incorporate comments received during global industry and regulatory peer review of the revised draft report. Task Force Co-Chair **E.J. Brandreth,** Favrille, agreed to present the draft at the PDA Technical Reports: A Sneak Peek conference.

The Steam in Place Task Force held a development meeting Sept. 23 prior to the PDA/FDA Joint Regulatory Conference in Washington, D.C. In attendance were Task Force Chair **Kevin Trupp,** Hospira; **Jose Goin,** Genentech; **Martin Kern,** Octapharma; **Genevieve Lovitt-Wood,** G.I. Lovitt;

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tions where the documentation belies the real situation. Perhaps the true measure of a GMP-compliant environment should be defined by another idiom, "If it works correctly every time, then it must be validated"—or, "If it delivers a product that is fit for purpose, then it is truly compliant."

The key question now becomes, "How do we monitor or measure the success of a process?" Indeed this provokes some heretical thoughts—perhaps the documentation is not quite so important after all. But, is this such a heresy? If we are able to scientifically demonstrate that the process consistently delivers a product fit for purpose, we must be doing something right and we must be employing good practices. Regardless of historical practice, it is the scientific demonstration of good practices that matters, not the overzealous generation of documentation. This also has been recognized in recent policy statements by the U.S. FDA on "risk-based approach" and process validation.[1, 2] Only in this way can the pharmaceutical industry move forward.

The demonstration of fitness for purpose of the product is an extremely difficult challenge in biologicals processes, and for these technologies more than any other, we need to be clear-minded about how we can substantiate the capability of a process to deliver a suitable product. The problem with guidances on GMP compliance is that they start from the principle that one rule fits all circumstances. This is certainly not the case for biological processes.

Thus, the main objective of process understanding studies should be establishing the capability of the process to deliver a product that is fit for purpose. End product testing of biological products may be a very poor indication of fitness for purpose, when compared with products from synthetic chemicals. This is mainly due to the lack of specificity, accuracy and precision of many of the analytical methods employed, but it is also due to the fact that the primary structure of a large molecule does not confer activity. It is the tertiary structure that counts.

The need for three conformance/ consistency batches is the first "sacred myth" that must be dispelled.

However, when this analytical information is combined with the large volume of in-process testing data, the product characterization testing performed, and a good understanding of how the process control parameters can affect these data, an overall pattern of process understanding starts to emerge.

This book attempts to address how this process understanding can be obtained and what part it plays in the overall process validation effort required to register a new product or process. In our fast-moving pharmaceutical environment, in which health economics, safety and profitability place competing demands upon the industry, the need for safer medicines and better treatments of resistant illnesses dictate that the industry must develop manufacturing processes and validate them in a quicker, more cost-effective and better way than it does at present. The tools for this are becoming more readily available and the regulatory environment is changing to permit this, despite the skepticism that persists about the rate of change. The application of risk management, process analytical technology (PAT) and the proposals concerning "design space"[3] are opening up new opportunities to move forward. This book examines the current norms and status of bioprocess validation—norms and expectations which are changing. They are moving away from the concept that three conformance batches signifies a robust, validated process and towards a concept that the understanding of the process and the limits within which it needs to be controlled are the most important factors in establishing process robustness, ensuring consistency, and thereby assuring product quality. An attempt is also made to define what is needed in the future to demonstrate robustness. This is not just a "wish list." Examples are taken from a large portfolio of industry experience to show how some of these innovative approaches are already a reality.

This change of approach needed must also be accepted by the regulators. The pharmaceutical industry needs to educate the regulators about what is now possible with PAT and convince them that this is the way forward. Some regulators do not need too much convincing and the change of approach is already starting to take place. It is often limited by the rate at which new technologies are able to develop, but it is clear that the approach to validation in the future will be very different. The need for three conformance/ consistency batches is the first "sacred myth" that must be dispelled. What do these batches tell us that we do not know already? The answer quite often is "very little." This is particularly true if there is already a good understanding of process capability before the consistency batches are started. In many cases the consistency batches are there to prove what we already know and this is not quite the same as validation. If

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we already know something, and have demonstrated it by scientific studies, then it is already validated, and to prove it again is a duplication. Three batches have never demonstrated consistency. This approach has no statistical significance and is commonly misleading, since it can give a false sense of security that the process works, only to discover that a few batches later problems occur with the process, indicating that it is not under control and does not work consistently. Validation is therefore becoming more closely linked with process development and process understanding studies. Such studies are often aimed at "finding out," but often result in a demonstration of consistency for a particular process step. Finding out cannot be associated with predefined acceptance criteria, but the knowledge gained needs to be applied appropriately to the control of the process. These studies are becoming increasingly important. This book examines the changes taking place within the industry, starting with the traditional approach and culminating in the new concepts now being promoted—the present and the future.

References

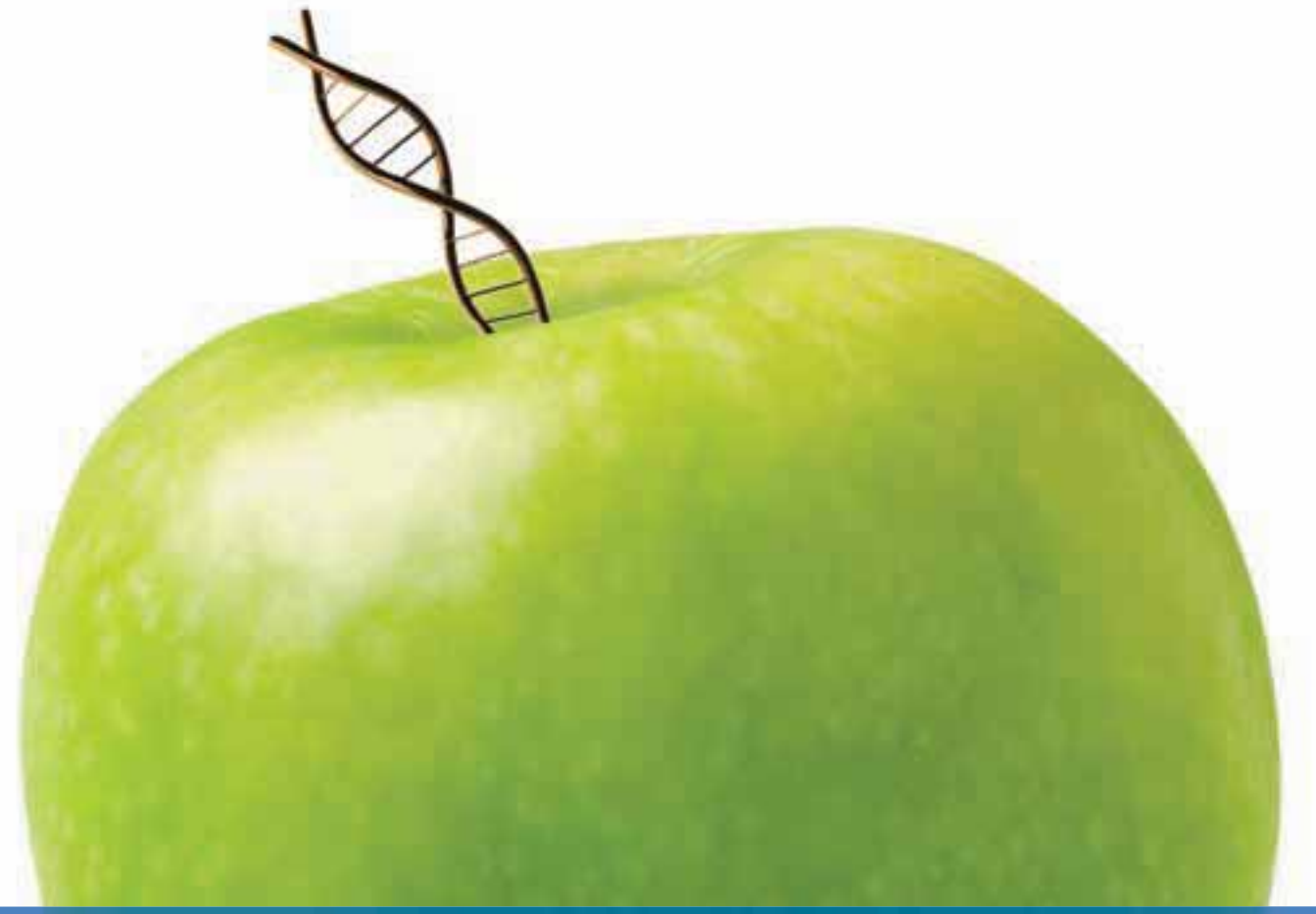
1. U.S. FDA. Press Release: Pharmaceutical GMPs for the 21st Century: A Risk-Based Approach, 2002; www.fda.gov.
2. U.S. FDA. Compliance Policy Guide (CPG 7132c.08): Process Validation Requirements for Drugs and Active Pharmaceutical Ingredients Subject to Pre-market Approval, 2004; www.fda.gov.
3. International Conference on Harmonisation. Quality Guideline Q8: Pharmaceutical Development, 2005; www.ich.org.

Task Force Update, continued from page 11

Anton Ponomarenko, Bayer; **Randy Wilkins,** Millipore; **Garth Corkill,** Pall; and **Dave Adams**, Baxter. The Task Force reviewed the first draft (75% complete), ensuring points of consideration for both sterilization and sanitization of SIP were addressed as applicable. The team targeted completion of the first draft by December and agreed to meet that month at a Genentech facility in Vacaville, Calif.

The Moist Heat Sterilizer Systems Task Force held a development meeting Sept. 26 at the PDA/FDA Joint Regulatory Conference. Task Force Co-Chairs **Chris Smalley**, Wyeth, and **Ron Nekula,** Bayer, were joined by **Matt Hofacre**, Steris; **Kimberly Brown,** Amethyst; **Charles Buckle,** Johnson & Johnson; **Michael Guyader,** Lonza; **Genevieve Lovitt-Wood,** G.I. Lovitt; **Anton Ponomarenko**, Bayer; and **Cody Riley,** Amgen. The team addressed document organization and the level of detail needed to provide useful global guidelines on best practices without prescription. This TR is being developed as a companion document to TR No. 1, and will address IQ/OQ and surrounding activities of moist heat sterilizer systems. The Task Force resolved to meet again to review the completed first draft in January 2008 at a Steris facility in Laguna Hills, Calif.

The TR-26, Sterilizing Filtration of Liquids Draft Revision Task Force was represented by **Co-Chairs, Paul Stinavage** (Pfizer) and **Maurice Phelan** (Millipore) at the PDA Filtration Interest Group Session at the PDA/FDA Joint Regulatory Conference. The co-chairs presented an update on the draft report with a request for feedback. Task Force member **Jean Bender,** Genentech agreed to present the draft at the PDA Technical Reports: A Sneak Peek conference.



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– FDA Guidance For Pharmaceutical cGMPs, September 2004

Applied Biosystems

PDA Survey on Analytical Methods for Cleaning Validation

Destin LeBlanc, Cleaning Validation Technologies

PDA conducted an online survey on the topic *Analytical Methods for Cleaning Validation* during the summer of 2007. This is the second of a series of surveys PDA is conducting on cleaning validation practices. The survey was designed by a team comprised of **Destin LeBlanc**, Cleaning Validation Technologies; **Liz Dallison,** Pfizer; **Jennifer Carlson,** Genentech; and **Paul Pluta,** Abbott.

The results of the 2007 survey are summarized below. Some of the responses in the results totaled more than 100% because more than one response was allowed per participant. Note that while there were a total of 83 valid participants, not all responded to every question. Unless otherwise specified, the percentages are percentages of those who responded to that specific question. In addition, some questions had the option of *Other,* with the opportunity to write in a response. *Other* responses we considered to be informative have been included in the summary below.

Survey Participation

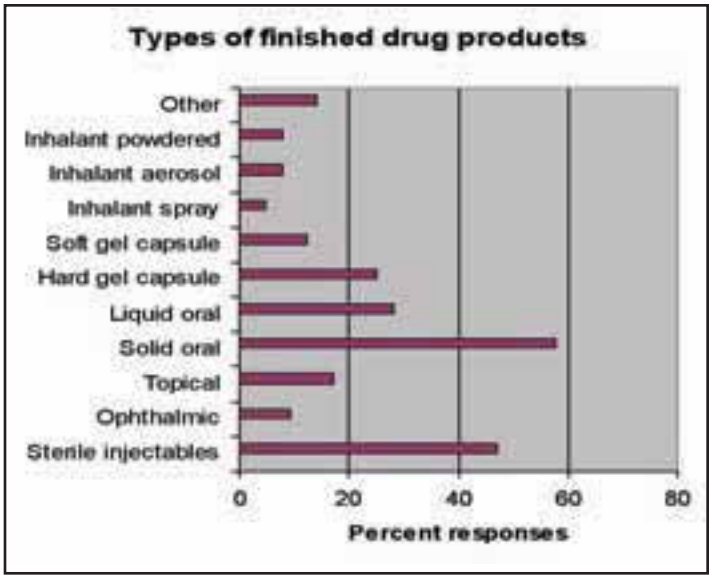
83 respondents participated, with 68% from North America, 19% from Europe and 13% from other locations. Participation by **department** was as follows: 31% from Validation, 23% from Quality Control/Analytical Support, 18% from Quality Assurance, 7% from Production/Manufacturing, 2% from Regulatory, 1% from Engineering and 17% from *other* departments.

By **facility type:** 67% were part of a multinational company, 12% were the sole manufacturing location for their company, 7% were part of a regional company, 7% were contract manufacturers and 6% were *other.* There were no responses from virtual companies.

By **type of product:** 64% made finished drugs, 43% made APIs, 7% made combination drug/device products and 6% made *other* products. There were no replies from companies that made diagnostics.

By **facility function:** 41% were commercial manufacturing facilities, 10% were clinical manufacturing facilities, 46% made both commercial and clinical products and 4% had *other* functions.

FIGURE 1



Manufacturing Methods for APIs

By **manufacturing method for APIs:** 69% used organic synthesis, 56% used biotechnology processes, 8% used natural products extraction and 8% had *other* responses.

Analytical Methods for APIs

For measurement of **residues of the API** in API manufacture, 40% preferred a specific method, 33% preferred a non-specific method, 26% used either specific or non-specific methods, depending on which was most appropriate and 2% had an *other* response.

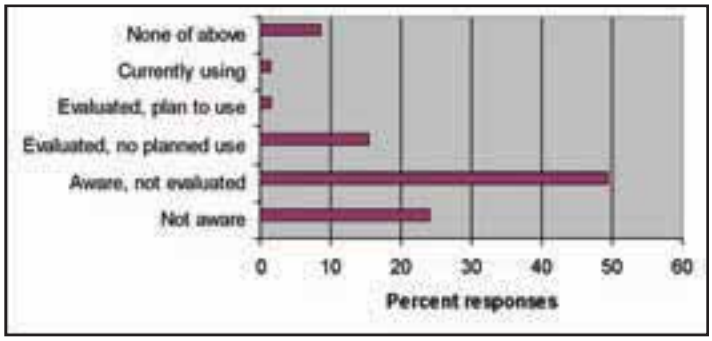
For measurement of residues of **aqueous cleaners** in API manufacture, 13% preferred a specific method, 54% preferred a non-specific method, and 26% used either specific or non-specific methods, depending on which was most appropriate, and 8% had an *other* response, including *no cleaning agent used* (which presumably meant they used water alone for cleaning).

For measurement of residues of **solvents** in API manufacture, 29% preferred a specific method, 10% preferred a non-specific method, 26% used either specific or non-specific methods, depending on which was most appropriate, 35% did not measure residues of solvents (presumably because the solvent were volatile), and 3% responded *other*.

Methods for Drug Products

For measurement of residues of the **small molecule APIs** in drug product manufacture, 66% preferred a specific analytical method, 7% preferred a non-specific analytical method, 23% used either specific or non-specific methods, depending on which was most appropriate, and 4% responded *other*.

FIGURE 2



For measurement of residues of **large molecule APIs** in drug product manufacture, 30% preferred a specific analytical method, 50% preferred a non-specific analytical method, and 20% used either specific or non-specific methods, depending on which was most appropriate. This shift from the responses for **small** molecule manufacture is as expected because of degradation of proteins in biotech manufacture.

For measurement of residues of **cleaning agents** in drug product manufacture, 31% preferred a specific analytical method, 49% preferred a non-specific analytical method, 15% used either specific or non-specific methods, depending on which was most appropriate and 5% responded *other*. This balance between specific and non-specific methods was very similar to the balance for large molecule APIs in finished drug manufacture.

Use of HPLC

Of respondents who used HPLC as an analytical method for APIs, 30% stated they *always* used HPLC, 40% stated they *usually* use HPLC, 6% *rarely* used HPLC because of degradation of the residue in the cleaning process, 21% *rarely* used HPLC because other methods were simpler and more convenient, and 3% chose *none of the above*.

Use of TOC

Of respondents who used TOC as an analytical method for APIs, 44% stated that TOC is the method of choice because of its convenience and simplicity, 19% stated that TOC was the method of choice because of degradation of the API in the cleaning process and 37% stated *none of the above*.

Use of FTIR and Ion Mobility

Figure 2 shows the variety of responses for the technology involving use of FTIR with a fiberoptic probe. Figure 3 displays the variety of responses for ion mobility technology.

Analytical Methods by Residue Type

Figure 4 gives the analytical methodologies used by respondents for measuring residues of **small molecule APIs** (which could be either in API synthesis or in finished drug manufacture). HPLC, UV/Vis, and TOC were the predominant technologies used. Almost every respondent (98%) used HPLC. *Other* responses included gravimetric (two responses), ICP/MS, GC and TLC. Note that the totals exceed 100% because of multiple methodologies used by most respondents.

Figure 5 gives the analytical methodologies used by respondents for measuring residues of **large molecule APIs** (which could be either in biotech bulk manufacture or in finished drug manufacture). TOC was the predominant methodology, followed by total protein and ELISA. *Other* responses included gravimetric. Note that the totals exceed 100% because of multiple methodologies used by some respondents. ➤

FIGURE 3

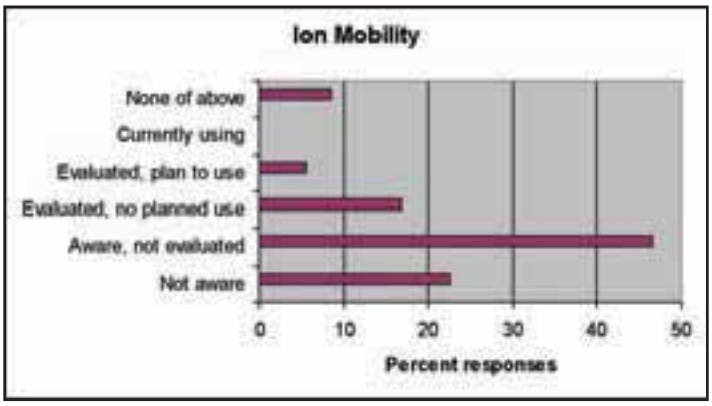


FIGURE 4

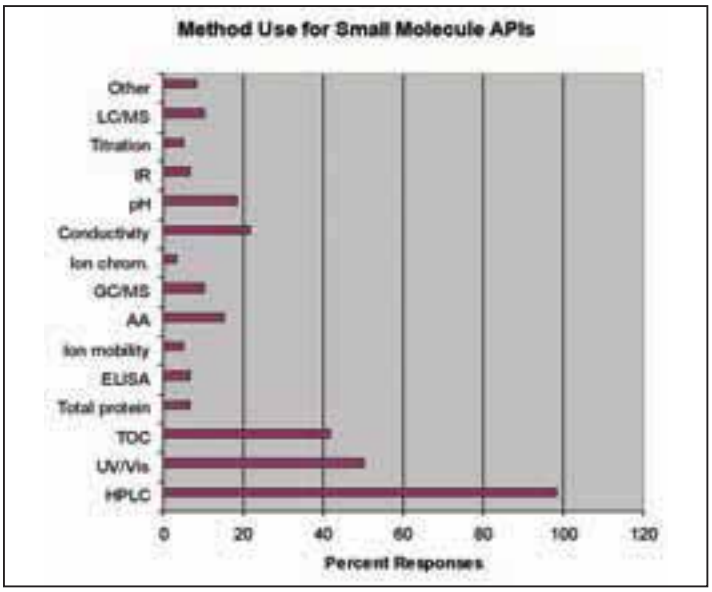


FIGURE 5

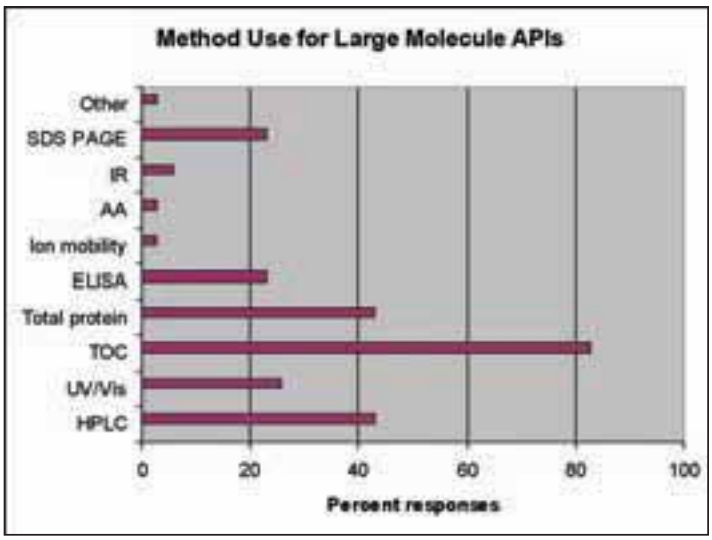


Figure 6 gives the analytical methodologies used by respondents for measuring residues of **cleaning agents/solvents** (which could be either in API manufacture or in finished drug manufacture). TOC was the predominant method, followed by conductivity, pH and HPLC. Other responses included surface tension, gravimetric (two responses) and air monitoring for odor.

Drivers for Method Selection

Figure 7 gives the drivers (reasons) for analytical method selection. Although sensitivity (detection or quantitation limit) had the largest percent of responses, all choices received significant responses. *Other* included cost, robustness and method developed by product development.

Analytical Method Validation

For **validating analytical methods,** 72% used ICH Q2 principles, 48% validated a method even if it was a USP or pharmacopeial method, 15% did not validate methods if they were USP or pharmacopeial methods, and 6% listed *none of the above*.

For selecting the **linear range** for validation, 57% used a range of *about 50-150%* of the residue limit, 20% used *about 10-100%* of the residue limit and 9% used *about 1X-8X* of the quantitation limit. *Other* responses included a variety of ranges from 2.5% to 1,000% of the residue limit.

TOC Issues

For **analytical method validation** for TOC, 58% performed method validation as they would for a specific method, 8% did not perform a separate validation because TOC is a pharmacopeial method, 32% performed limited validation such as precision and accuracy and 2% responded *other*.

For **systems suitability** for TOC for residues, 52% performed systems suitability before each set of samples, 11% performed it at least once a week, 24% performed it less frequently than every week and 9% responded *other*.

For the use of **online TOC for validation protocols**, 78% used lab instruments only for protocols, 13% used online TOC for rinse samples only, 9% had evaluated online TOC and were not satisfied with it, and 7% had *other* responses such as currently evaluating online TOC.

Considerations in Evaluating Responses

While this survey is not scientific in its selection of respondents, it does provide some basic information on current practices in analytical method use in pharmaceutical manufacturing. Note that these questions were asked in the context of analytical methods for cleaning validation, and answers might not apply to those same analytical methods used for other purposes. Caution should be applied in using this data. For example, in the responses on linearity ranges, the majority uses a range of 50-150% of the residue limit. While this range may be appropriate for an active in a product assay (50-150% of the specification), it may not be the best range for a cleaning validation residue limit, where the limit is not the target value, but the *upper limit*. However, in the selection of analytical methods, it should be recognized that no one method is ideal. The most important thing is that the method is validated and appropriate for its intended purpose.

FIGURE 7

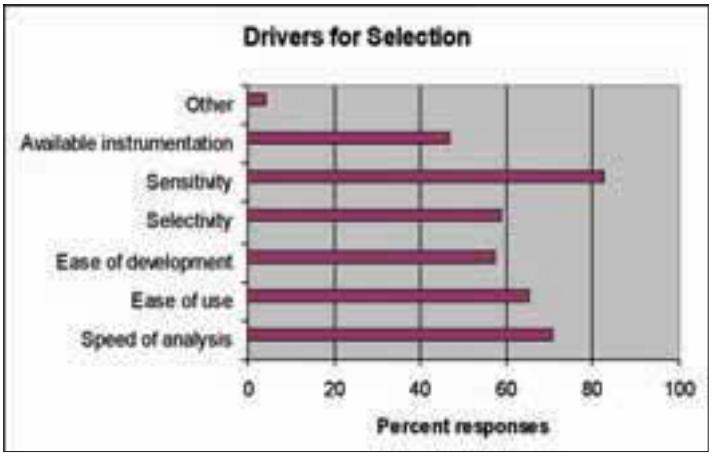
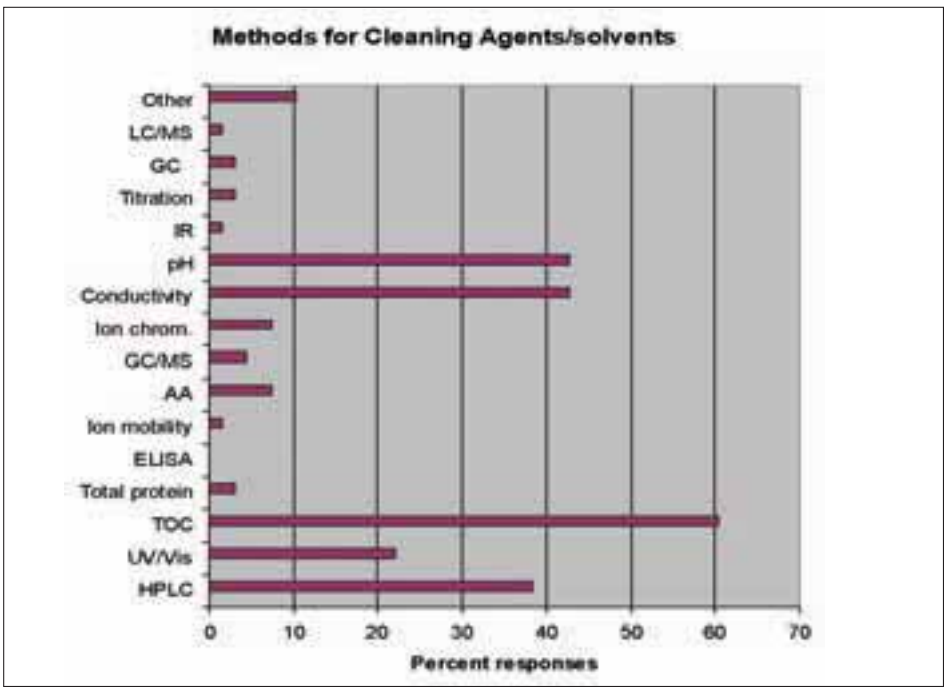


FIGURE 6



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. Any PDA member can join one or more Interest Group by updating their member profile (www.pda.org/pdf/join_IG_instruction.pdf). Please go to www.pda.org/interestgroups for more information.

North American Interest Groups

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*
Section Title	**Biopharmaceutical Sciences**	**Laboratory and Microbiological Sciences**	**Manufacturing Sciences**	**Pharmaceutical Development**	**Quality Systems and Regulatory Affairs**
Related IGs and Group Leaders	**Biotechnology** Group Leader: Jill A. Myers, PhD *BioPro Consulting* Email: jmyers@bioproconsulting.com **Lyophilization** Group Leader: Edward H. Trappler *Lyophilization Technology* Email: etrappler@lyo-t.com **Vaccines** Group Leader: Frank S. Kohn, PhD *FSK Associates Inc.* Email: fsk@iowatelecom.net	**Pharmaceutical Cold Chain** Group Leader: Rafik H. Bishara, PhD Email: rafikbishara2@yahoo.com **Microbiology/ Environmental Monitoring** Group Leader: Jeanne E. Moldenhauer, PhD *Excellent Pharma Consulting* Email: jeannemoldenhauer@yahoo.com **Visual Inspection of Parenterals** Group Leader: John G. Shabushnig, PhD *Pfizer Inc.* Email: john.g.shabushnig@pfizer.com	**Facilities and Engineering** Group Leader: Christopher J. Smalley, PhD *Wyeth Pharma* Email: smallec2@lwyeth.com **Filtration** Group Leader: Russell E. Madsen *The Williamsburg Group, LLC* Email: madsen@thewilliamsburggroup.com **Pharmaceutical Water Systems** Group Leader Theodore H. Meltzer, PhD *Capitola Consulting Co.* Email: theodorehmeltzer@hotmail.com **Sterile Processing** Group Leader: Richard M. Johnson *Fort Dodge Animal Health* Email: johnsor4@fdah.com	**Clinical Trial Materials** Group Leader: Vince L. Mathews *Eli Lilly & Co.* Email: vlm@lilly.com **Combination Products** Group Leader: Michael A. Gross, PhD *Chimera Consulting* Email: michaelgross.chimera@gmail.com **Packaging Science** Group Leader: Edward J. Smith, PhD *Wyeth Pharmaceuticals* Email: smithej@wyeth.com **Process Validation** Group Leader: Harold S. Baseman *ValSource, LLP* Email: hbaseman@valsource.com	**Inspection Trends/ Regulatory Affairs** Group Leader: Robert L. Dana *PDA* Email: dana@pda.org **Quality Systems** Group Leader: David A. Mayorga *Global Quality Alliance, LLC* Email: david@gqaconsulting.com

European Interest Groups

Related IGs and Group Leaders	**Biotech** Group Leader: Hannelore Willkommen, PhD *Reg. Affairs & Biological Safety Consulting* Email: Hannelore.Willkommen@gmx.de	**Visual Inspection of Parenterals** Group Leader: Markus Lankers, PhD *Rap.ID GmbH* Email: markus.lankers@rap-id.com	**Filtration** Group Leader: Roger Seiler *Sartorius SA* Email: roger.seiler@sartorius.com **Production and Engineering** Group Leader: Philippe Gomez *Sartorius SA* Email: Philippe.gomez@sartorius.com **Prefilled Syringes** Group Leader: Thomas Schoenknecht, PhD *Bünder Glas GmbH* Email: t.schoenknecht@gerresheimer.com	**Nanotechnology** Group Leader: D F Chowdhury *Aphton BioPharma* Email: Fazc@aol.com **Technology Transfer** Group Leaders: Volker Eck, PhD *PDA* Email: eck@pda.org Zdenka Mrvova *Zentiva* Email: zdenka.mrvova@zentiva.cz

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FDA Reps Present Five-Year Update to GMP Initiative at 2007 PDA/FDA Conference, continued from cover

"But the implementation stage continues, and that will be clear over the next three days as most of the presentations you see will refer to FDA's ongoing efforts to develop new quality management systems that encourage better product development, a modern pharmaceutical quality system, and early industry adoption of beneficial technological advances."

One element of the initiative that has surfaced as the linchpin for moving industry into a new paradigm of quality manufacturing, is "Quality by Design" (QbD). The three speakers in the opening plenary session spoke on QbD.

FDA's **Helen Winkle**, Director, Office of Pharmaceutical Science, CDER, gave the keynote presentation, "Implementing Quality by Design," in which she addressed:

- Why quality by design?
- Where are we in preparing for quality by design in CMC review programs?
- Opportunities and challenges

Picking up from Friedman on the cGMP initiative as a whole, Winkle commented, "Sitting in this room gives me a little bit of nostalgia, because as Rick said, in August 2002 we started the cGMP Initiative for the 21st Century, and our first workshop was actual held in this room in April of 2003….Here we are less than five years later, and I think we've made a tremendous amount of progress. We've made a lot of progress with the GMPs, making changes and such, but we've also made a lot of progress in the review side…and as Rick said, quality by design."

In discussing "why quality by design?" Winkle reviewed many of the now familiar problems with the current paradigm for manufacturing design and control. These problems include low-tech manufacturing controls, high rates of rejects and waste, limited capabilities to predict impact of scale on final product, inability to analyze or understand root causes of manufacturing failures, and little emphasis on manufacturing. The downside of these problems includes high cost of manufacturing, inefficiencies, drug shortages, technological stagnation, and a need for intensive regulatory oversight.

Winkle noted that the CMC pilot has given FDA great insight into the capabilities of companies in designing manufacturing and control strategies.

Quoting FDA Deputy Commissioner and Chief Medical Officer **Janet Woodcock,** Winkle explained that the whole purpose of the 2002 GMP initiative is to achieve the "Desired State": *A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight*—a goal, Winkle noted, is "a mutual goal of industry, society and the regulators.

5 QbD Submissions Approved in CMC Pilot

While all three groups might desire QbD, "implementation of quality by design is really in the hands of industry," stressed Winkle. "You are the ones who have to take those concepts and incorporate them into your application."

On the other hand FDA must be "prepared to review them. We have to have the science and knowledge to be able to do adequate reviews on this information and to provide you with additional information to help you."

And CDER's Office of New Drug Quality Assessement (ONDQA) has been working hard over the last two years to gear up for the New QbD submissions in the event that such submissions someday start pouring in. ONDQA has received a limited number of new drug applications with QBD under a pilot program for the Chemistry, Manufacturing and Control portion of the NDA.

"We asked the companies to submit information on quality by design and really try to have a quality by design application," stated Winkle. "We received in total a request for 11 applications to come in under the pilot. We have reviewed five of those and approved them."

Winkle noted that the CMC pilot has given FDA great insight into the capabilities of companies in designing manufacturing and control strategies. "When we started this initiative we really didn't know a whole lot about what the companies had as far as pharmaceutical development information. And we've learned a lot about their capabilities [through the pilot]. We've also learned a lot about how they do their manufacturing and about what some of the issues with manufacturing are. We hope very soon to have a workshop on the lessons we learned to help other companies in moving down the path of quality by design. But we are still in the process of evaluating that information."

Right now, ONDQA is working to implement post-market plans for supplemental filings for companies that are approved for QbD applications. "We'll have some kind of plan, what we've been calling the regulatory agreement, for those companies so that they will know specifically what they need to submit and what they don't as far as supplements," Winkle explained. "Then we'll have a really good look at what their risks are and base that decision on those risks in that post-market plan." She added, "We're even looking to make this available for companies that don't do quality by design."

Table 1: Traditional Pharma Lifecycle vs. QbD – *From Helen Winkle's Slides, 2007 PDA/FDA Conference*

ASPECTS	TRADITIONAL	QbD
Pharmaceutical Development	**Empirical;** typically univariate experiments	Systematic; multivariate experiments
Manufacturing Process	**Fixed**	**Adjustable** within design space; opportunities for innovation **(PAT)**
Process Control	In-process testing for go/no-go; offline analysis w/ slow response	**PAT utilized** for feedback and feed forward at real time
Product Specification	Primary means of quality control; based on batch data	Part of the overall quality control strategy; based on desired product performance (safety and efficacy)
Control Strategy	Mainly by intermediate and end product testing	**Risk-based;** controls shifted upstream; real-time release
Lifecycle Management	**Reactive to problems** & OOS; post-approval changes needed	**Continual improvement** enabled within design space

QbD Picture Becoming Clearer

After several years of discussing QbD, FDA is now giving a clearer explanation of the differences between the new paradigm and the traditional test-to-control system.

Winkle highlighted the differences during her talk, prefacing the discussion with the caveat, "it is not mandatory to do quality by design." However, she said, FDA does believe that "quality by design is going to lead you and FDA to a much better system of regulatory review. It is going to simplify that system, and it is going to give the companies much more control over the quality of their products."

The comparison presented by Winkle was broken down into the various aspects of the product lifecycle (see Table 1). Starting with pharmaceutical development, Winkle explained that traditional development is empirical. Under QbD, "we are really looking at systematic development of your products through multivariate experiments." Whereas a traditional manufacturing process is fixed, "we hope under quality by design it will be adjustable within the design space. And you will have a lot of opportunities for innovation here where you can change your product, where you can do process analytical technologies and analyze right online your product."

Today's process control involves the use of in-process testing for "go or no-go"; under QbD, "we are hoping you will be able to utilize information that you get from the feedback using PAT or some other system, and take that information and feed it forward at real time."

Specifications under QbD will move from sampling being set for quality control to being "part of the overall quality control strategy and based on desired product performance (safety and efficacy)." The control strategy will evolve from intermediate and end-product testing to upstream, risk-based controls. "One of the things that I'd like to say here," Winkle commented, "that really is sort of the basis for quality by design—to build quality and not test it in. This is really part of what we are looking for. In traditional we do a lot of testing to make sure our product is okay, if not we throw it away. Under control strategies for QbD, it is risk-based and controls are shifted upstream for real-time release.

"And last of all," she continued, "the lifecycle management: in the traditional we were reacting to problems, and we handled those problems based on how severe they were basically with post-approval changes needed. Under the new QbD, what we are hoping for is continual improvement, where you will have a design space or an area where you have a safety to do anything you want to that product because you will completely understand that area within the design space and what any changes will do to affect it."

Abbott Shares Advantages of Process Data Management

Two industry representatives gave their perspective on QbD following Winkle's talk: Amgen's **Anurag Rathore,** PhD, Director, Process Development, and Abbott's **Azita Saleki-Gerhardt**, PhD, Division VP for Manufacturing Science and Technology.

Saleki-Gerhardt explicated several "tools" used by her firm to implement QbD: process data management, first principles, six sigma/lean, design of experiments, risk management and mechanistic studies. While each tool is of equal importance, Saleki-Gerhardt's talk demonstrated the criticality of a strong process data management system to the entire QbD program.

Consolidation of information from the entire manufacturing process, including raw material and in-process and analytical testing, opens the door to greater process understanding and continuous improvement. "This ability to consolidate and have it available electronically gives the scientists and ➤

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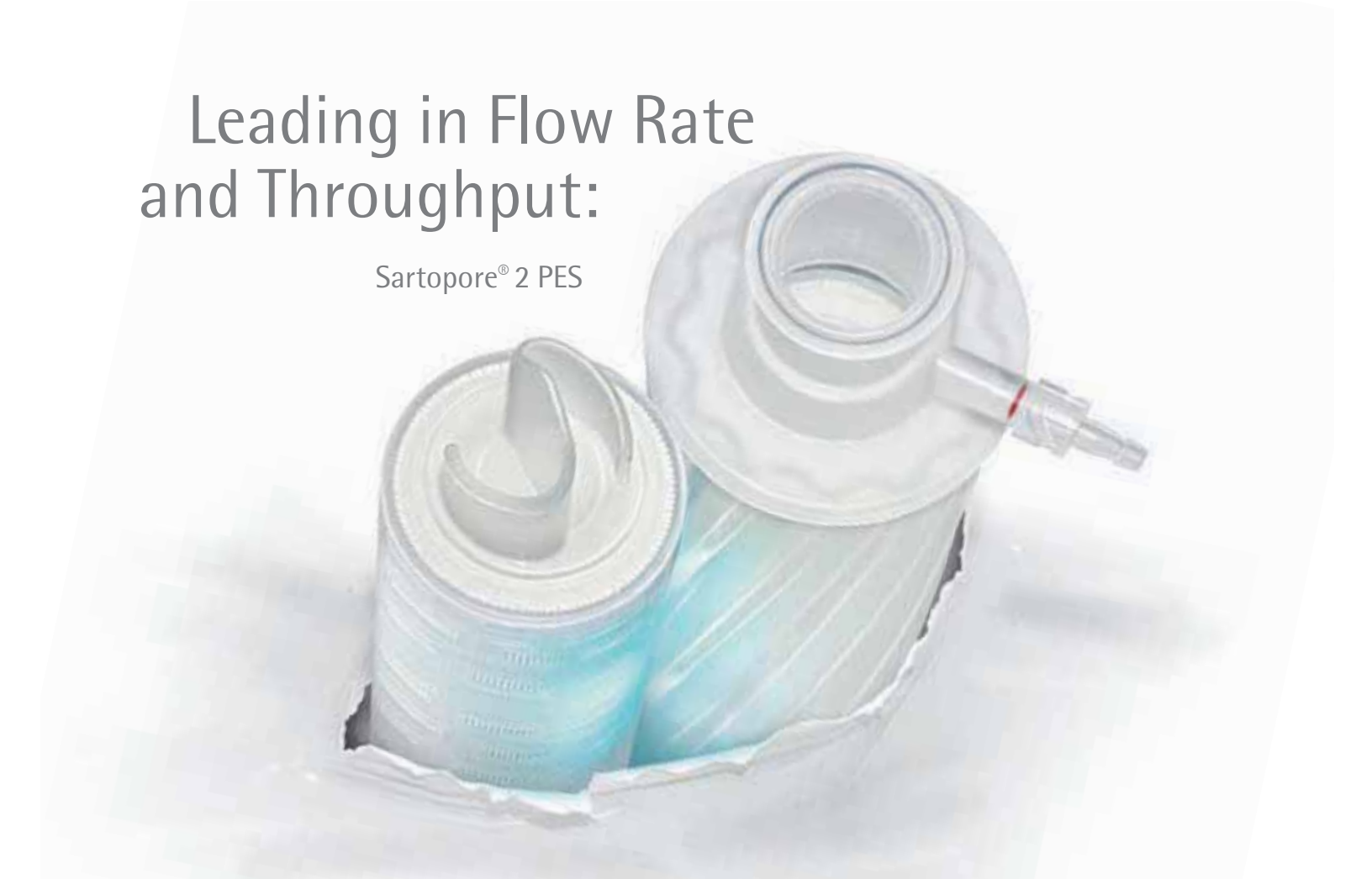

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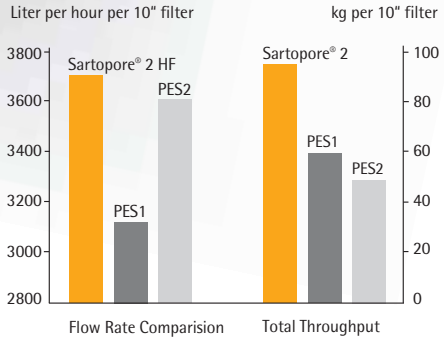

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engineers significant ability to see the product performance, and it really saves them a lot of time to be able to react to the issues and also to be able to do continuous improvement," explained Saleki-Gerhardt.

"You can use the standardized tool set [visualization, analysis, business logic] to do automated trending, ad hoc reporting and advanced analysis," she added (see Figure 1).

Abbott reaps a number of advantages from this consolidated system:

- Complete investigations more quickly and thoroughly: "Instead of spending through the paperwork and trying to find the data, the data is available to the scientist online."
- Improve process robustness: Justify specification limits and testing criteria.
- Proactive trend monitoring and automated "dashboards": Early fault detection; automated yield and cycle time reporting; summaries of testing results/conformance for analysis
- Continuous improvement enabler
- Annual reporting: Extracts facilitate Annual Product Reviews and Facility Audit Reports

Saleki-Gerhardt shared an example of a continuous improvement to a dissolution specification resulting from the use of this system to identify a trend and a six sigma approach to solve the technical problem.

The firm took a close look at dissolution data for 243 lots of a certain product and identified an upward trend. While the firm spotted the trend prior to the point of failure, but it "really didn't have an idea what was the root cause for this upward trend," said Saleki-Gerhardt.

"What we found out as a result of that," she explained, "was that the root cause for the upward trend was related to the raw material property change. So even though the raw material met ➤

FIGURE 1

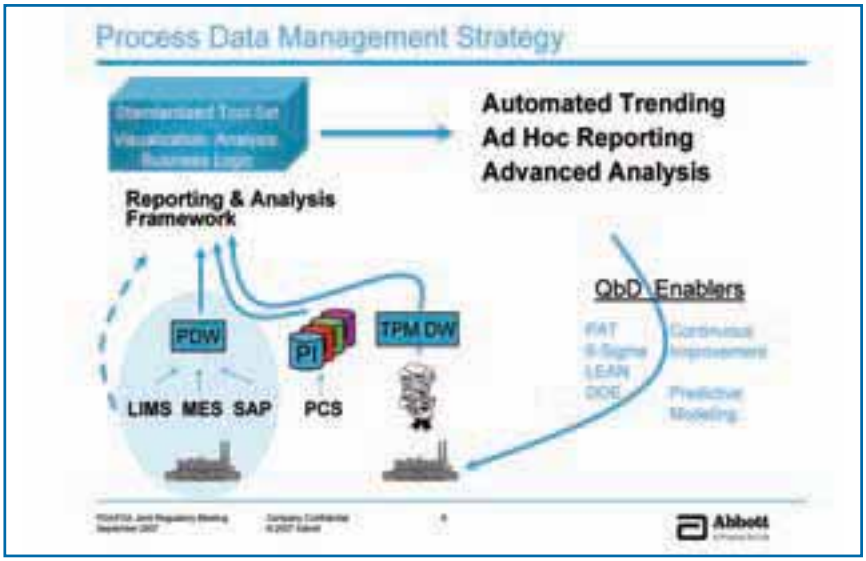

FIGURE 2

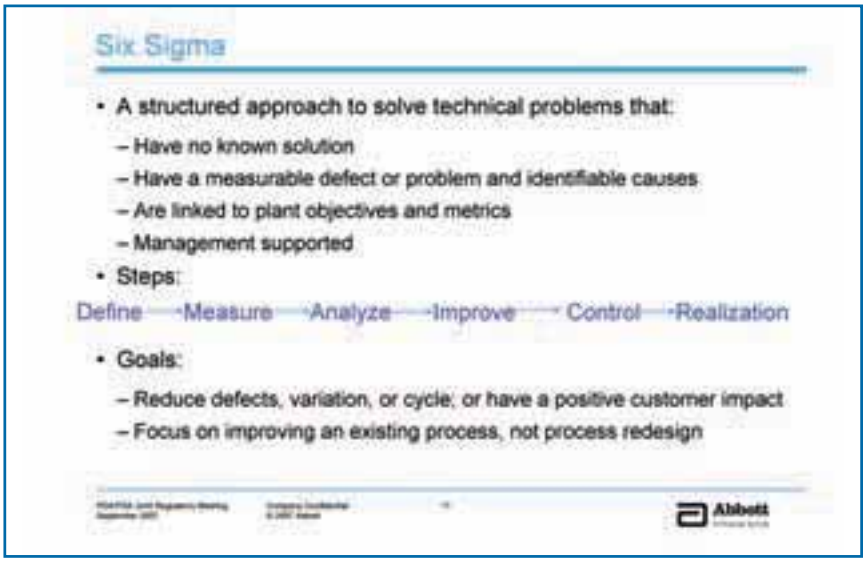

FIGURE 3

PDA Parenteral Drug Association

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the specification, some internal properties had changed to a point that it had the product impact and caused the upward trend in dissolution."

To find the problem, she stated that a six sigma process was launched. This six sigma approach is defined in Figure 2 (see page 24). To correct the situation, Abbott worked with the raw material vendor and defined a "new design space" and performed a new characterization. "The specification was filed, approved and implemented, and, as you can see from the result [Figure 3, see page 24], the dissolution was realigned with what we would expect.

"The power of this is actually looking at the data before actually you have an issue, looking if there is a trend, and going back and correcting."

Saleki-Gerhardt also touted the "power of PAT," noting its applicability at various levels. "We can do it in development when we identify our critical process parameters, during the scale up, and we can do it overall to the manufacturing process. PAT basically covers the entire process, a great opportunity to be able to get real time information…for continuous improvement."

In the end, Abbott has established "an intelligent processing system." Using PAT, the firm has the ability to "actually online and in real-time" trend information about the process. "In this model, if there is subtle variability in the raw material, using the adaptive process within your design space, you can compensate for raw material. The ultimate goal in this case would be that you have a consistent product attribute for the patient every time. And that [is] moving from a traditional system to quality by design."

Quality by Design: The FDA Center-Field-Center Link

Following **Helen Winkle's** talk at the PDA/FDA Conference, an audience participant asked her how CDER ensures that the field investigators are on the same page as the Center regarding the evolving expectations. Below is the transcript of the question (read aloud by session moderator **Rick Friedman**) and Winkle's response.

Question: How invested in QbD are the field investigators? Is it part of their training? Is CBER on board? To what extent are the Office of Regulatory Affairs (ORA) and other FDA offices involved in QbD training programs?

Winkle: Well, we feel that the field (and ORA) is a valuable part of the whole quality by design process, and we have had a number of training sessions with the field, especially the pharmaceutical inspectorate. If you remember, the cGMP initiative for the 21st Century actually established a pharmaceutical inspectorate, and we are in the process of filling that cadre of inspectors with additional knowledge on the whole aspect of the initiative, and this includes looking at risk management, quality by design and quality systems. We are hoping that they will be well educated.

I will be very honest with you, it has been a slower process than we had originally intended. One of the things we are hoping to do [is] look at the difference between how someone from the pharmaceutical inspectorate does an inspection as opposed to how [investigators] might have done it ten years ago, five years ago—trying to get some data from some companies; we have a study under CRADA [Cooperative Research and Development Agreement]…and this is one of the things that we hope to look at. But we've been making every effort to educate them and every effort to work together with them—both [CDER's] review area and office of compliance.

We also have a new pilot for small molecules. We have worked with an inspector from the pharmaceutical inspectorate for each one of those applications. We've had the inspector either on the phone or in person during the meetings with the industry so that they can become more knowledgeable about what's going on with these particular applications.

We all understand that [training in the field] could make it or break it. If you make a decision to review, and the inspector later goes out and contradicts that decision, it will cause problems. And everyone in industry will know about it….

Another part of the question was on CBER. I work with CBER every week. They are at a different rate of implementing quality by design, but doing many of the same things we are doing.

[**Editor's Note**: Upcoming issues of the *PDA Letter* will include additional coverage of the 2007 PDA/FDA Conference.]

Foreign Inspection Program Detailed at PDA Japanese Regulatory Workshop

Walter Morris, PDA

PDA hosted a Japanese Regulatory workshop immediately following the PDA/FDA conference. The workshop was designed to expand on discussions that took place at the Japanese Regulatory Workshop held at PDA's Annual Meeting in March 2007, and address regulatory topics important for manufacturing and marketing products under the Japanese Pharmaceutical Affairs Law and GMP Inspections.

In the keynote presentation, Japan National Institute of Health Sciences official **Yukio Hiyama**, PhD, Third Section Chief, Division of Drugs, opened the meeting with his talk, "Japanese Pharmaceutical Affairs Law, Regulations and International Collaboration." His presentation focused primarily on changes to Japan's Pharmaceutical Affairs Regulation of 2002, effective 2005.

The most significant difference in the new law for manufacturers was the change from a manufacturing license to marketing authorization. This "allowed licensees to contract out manufacturing activities," explained Hiyama. And that, he added, "actually drove a series of regulation changes."

First was passage of the "GQP" regulation, which stipulates the Marketing Authorization Holder's responsibility for quality management. Second was the requirement to include process control and manufacturing process information in the marketing applications. The establishment of a drug master file system represents a third regulatory change emanating from the new Pharmaceutical Affairs Regulation.

The fourth regulatory change implemented by the Japanese health authorities as a result of the Pharmaceutical Affairs Legislation was the consolidation of the legal position of GMP. "GMP became a requirement for product approval," explained Hiyama. Prior to the revised statute, GMP compliance was required for manufacturing facility licensure, not for product approval.

With the regulatory change, he stated, "naturally GMP inspection prior to approval will be conducted. Also, periodic GMP inspection in post-marketing phase is there." Another aspect of the regulation important to U.S. and EU-based manufacturers is that there "is no distinction between foreign sites and domestic sites," Hiyama said. "So we started GMP inspections in foreign sites."

PMDA, he noted, is a new organization created by the revised Pharmaceutical Affairs Legislation to carry out the review of drug applications and pharmacovigilance activities.

The Japanese Pharmaceutical and Medical Devices Agency (PMDA) has the authority in Japan to conduct inspections. An overview of the overseas inspection programs was provided at the PDA workshop by PMDA's Hirokazu Hasegawa, Director, GMP Inspection, Office of Compliance and Standards.

PMDA, he noted, is a new organization created by the revised Pharmaceutical Affairs Legislation to carry out the review of drug applications and pharmacovigilance activities. GMP inspections fall under the post-marketing safety operations in PMDA, although "we carry out prior-approval inspections," Hasegawa noted. "It is our normal practice to cooperate with review officers in carrying out prior-approval inspections."

He outlined the four requirements for gaining marketing approval in Japan: "The first requirement is that the NDA must be reviewed for quality, safety and efficacy. The second requirement is the manufacturing site of the product should be judged to be in compliance with the GMP regulations. The third requirement is the company responsible for marketing the product should have a license for marketing pharmaceuticals in Japan. And the fourth requirement is the manufacturing site of the product must have a license for the drug manufacturer, in the case of Japanese manufacturer, or obtain accreditation for drug manufacturer in the case of a foreign manufacturer."

Prior to the revision to the pharmaceutical legislation, a manufacturer had to produce products in Japan. After the revision, the licensee "doesn't necessarily need a manufacturing site in Japan, and the company may contract out the manufacture of the product."

Marketing applications trigger the preapproval GMP inspection and regular compliance post-approval GMP inspections. "There are other types of inspections for issuing a manufacturing license to a domestic manufacturer and issuing an application to foreign manufacturers. Those inspections focus on buildings and facilities," said Hasegawa. "Those inspections focus on building and facilities, and currently

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Quality & Regulatory *Snapshot*

ICH Advancing the Q8-Q9-Q10 Trilogy

Bob Dana, PDA

Hello and welcome to this month's edition of the Quality and Regulatory Snapshot. For our "Health Authority Special Report," our colleagues in Europe have provided summaries of two recent meetings held at the EMEA in London. The first provides information about the "Interested Parties" meeting; an annual meeting held in conjunction with a conference of the EMEA GMP/GDP Inspectors Working Group. The second provides an update on a briefing on ICH Q10. PDA was well represented at both meetings. In addition, the International Conference on Harmonisation concluded meetings of their Steering Committee and working groups in Yokohama, Japan (Oct. 29-Nov. 1). At these meetings, ICH reached agreement on a new annex on Pharmaceutical Development (Q8). This annex focuses on quality by design and design space throughout the life cycle of a pharmaceutical product. PDA will review the annex when it becomes publicly available and will submit formal comments if appropriate.

ICH also agreed to establish an Implementation Working Group on the new ICH quality and manufacturing guidelines (Q8, Q9 and Q10). The working group will concentrate on responding to questions from stakeholders and developing training materials to enhance implementation. According to the press release issued at the conclusion of the meeting, ICH is also considering the development of a guideline on Development and Manufacture of Drug Substances, with a decision on whether to proceed expected in the coming months.

Closer to home, last months issue of the Quality and Regulatory Affairs Snapshot included a brief discussion of our Regulatory Affairs and Quality Committee and the work they do. I'm happy to inform everyone that **Sue Schniepp** was just elected to membership on this Committee. As you may be aware, Sue was Chairperson for the recently concluded and very successful 2007 PDA/FDA Joint Regulatory Conference (see cover story).

We welcome your feedback on the contents of the Quality and Regulatory Snapshot, as well as your ideas and suggestions for future topics of discussion and improvements. Just email us at snapshot@pda.org. Farewell until January 2008.

Health Authority *Spotlight*

History of ZLG

Jim Lyda, PDA

In the simplest terms, the purpose of ZLG is to compensate for a decentralized regulatory system and provide a unified international voice to the German regulation of marketed medicinal products and medical devices. For historical reasons, government functions in Germany, including the regulation of health care products, are delegated to the 16 states, or Laender, which make up the Federal Republic of Germany. Tasks that may be assigned to the central government in most EU member states—such as approving medicinal products and inspection of manufacturers for GMP compliance—are handled by 16 independent regional agencies.

In the 1990s, European harmonization of medical device rules to ensure free trade generated the need for a unified way of representing all of the 16 authorities in Germany. In 1994, a treaty established ZLG for this purpose. The HIV concerns related to blood/blood products showed the need for centralized quality monitoring of medicinal products made in Germany and the need for training of specialists. In 1999, ZLG became the central coordination point in Germany for the establishment and maintenance of the quality assurance system of the GMP inspectorates, both human and veterinary. ZLG can be viewed as the partner of the German institutions BfArM (drug assessment) and Paul-Ehrlich Institute (biologics assessment). Guidance documents that were developed together with the expert groups and published by ZLG have to be implemented in the quality systems of the state inspectorates.

[**Editor's Note:** This history of ZLG is a follow-up to the interview Jim conducted with ZLG's Sabine Paris in the September *PDA Letter,* page 32.]

Health Authority *Special Report*

EMEA Holds Q10 Briefing and Interested Parties Meeting

Jim Lyda, PDA

Editor's Note: On September 26, 2007, EMEA sponsored an "EMEA/Industry Briefing and Outlook" meeting on "ICH Q10 in Europe" and an "EMEA Interested Parties Meeting" in London. PDA was represented at both meetings by Jim Lyda and a number of active members. The following are edited and abridged notes prepared by them based on their observations and participation in the meetings. The full, unedited reports are posted at www.pda.org/regulatorynews under the "Europe" link.

ICH Q10 in Europe

Pete Gough, David Begg Associates; Gabriele Gori, Bausch & Lomb; Claudia Nardini, Kedrion; Jim Lyda, PDA

This special briefing was held at the EMEA offices in London in conjunction with the Interested Parties meeting reported elsewhere in this issue, and was chaired by **Emer Cooke,** Head, Inspections Sector, EMEA. The briefing featured presentations by three members of the Q10 Expert Working Group: **Jacques Morénas,** AFSSAPS; **Ian Thrussel,** MHRA; and **Neil Wilkinson,** AstraZeneca and EFPIA representative.

The Q10 draft reached Step 2 of the ICH process in early May 2007, with public comment in the EU open until Nov. 30. It is anticipated that the Q10 draft will reach Step 4, the equivalent of final approval, by summer of 2008. Following summaries of the development, milestones, content and structure of Q10, the briefing ventured into the more pragmatic and undefined implementation aspects of the guidance.

Regulator Perspectives

The following summarize the main points presented by the two health authority representatives.

Q10 adoption would:

- Encourage a preventive action culture
- Improve quality monitoring and review
- Provide greater assurance of no unintended consequence from continual improvement activities
- Complement and serve as a bridge between regional GMP regulations
- Link development and manufacturing through product lifecycle
- Reinforce the well-accepted ISO 9000 structure within a pharmaceutical context
- Facilitate appropriate levels of regulatory scrutiny (e.g., post approval change, inspections)
- Foster innovative approaches to process validation

It is anticipated that the Q10 draft will reach Step 4, the equivalent of final approval, by summer of 2008.

Challenges to future successful implantation of Q10:

- Clear understanding of the stakeholders' (regulator and industry) needs and options
- Trust—industry and regulator openness in working together
- Culture—overcome internal conservatism and 'silo' thinking, both industry and regulator

Other unknowns:

- Will Industry really be comfortable with the lifecycle approach?
- Will inspection of product transfer activities take GMP inspectors into development?
- Will the Q10 approach disadvantage small and medium companies?
- Will Q10 ultimately raise expectations for GMP (i.e., Q10 become the de facto standard for all?)

The answers to these questions will be developed in the coming years as the industry and the regulators grapple with the opportunities and challenges. But there are several commitments that will help pave the way.

Industry Perspectives

The following represent industry's perspectives as presented by EFPIA's representative.

Issues resolved at Step 2 of the Q10 draft:

1) The content of ICH Q10 that is additional to current GMP requirements is optional.

2) Regulatory approaches for a specific products or manufacturing facilities should be commensurate with the level of product and process understanding, the results of quality risk management, and the effectiveness of the Pharmaceutical Quality System (PQS—term used in place of Quality Management System).

3) Q10 should be applied in a manner that is appropriate and proportionate to each of the product lifecycle stages.

4)The effectiveness of the PQS can normally be confirmed during a regulatory inspection at the manufacturing site.

How will the implementation of Q10 occur? Firms and/or sites that wish to develop a Q10 quality system will undertake a gap analysis of their current QS against the Q10 guideline and derive action plans covering site and corporate aspects of the PQS. Internal evaluations will confirm when a site is believed to be Q10 compliant. Each site that intends to comply with Q10 must be able to demonstrate this at the site level, describing the integration of any corporate aspects of the PQS as appropriate. Once a site has been confirmed as having an effective Q10 PQS the opportunities described in the Q10 Annex could then be pursued, with regulators taking the initiative.

How can we work together to ensure consistent implementation? At the

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North America Events

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

Conferences

November 1-2, 2007
PDA/FDA Co-sponsored Conference Series on Quality Systems
Bethesda, Maryland

November 6-8, 2007
PDA Extractables/Leachables Forum
Bethesda, Maryland

April 14-18, 2008
PDA 2008 Annual Meeting
(Conference, Courses and Exhibition)
Colorado Springs, Colorado

May 19-23, 2008
2008 PDA Biennial Training Conference
(Conference, Courses and Exhibition)
New Orleans, Louisiana

Training

Lab and Lecture events are held at PDA TRI, Bethesda, Maryland unless otherwise indicated.

Lab Courses

November 13-16, 2007
Validation by Design (R): DoE Basics for PAT Applications

November 14-16, 2007
Developing an Environmental Monitoring Program

November 14-16, 2007
Pharmaceutical Water System Microbiology

December 5-6, 2007
Developing and Validating a Cleaning and Disinfection Program for Controlled Environments

January 16-18, 2008
Developing an Environmental Monitoring Program

Lecture Courses

October 29-31, 2007
Managing Quality Systems

Course Series

November 27-29
San Diego Course Series
San Diego, California

Chapters

November 14, 2007
New England Chapter
Steam Sterilization

November 14, 2007
Puerto Rico Chapter
Cleaning Validation

November 15, 2007
West Coast Chapter
Current Biopharmaceutical CMC Issues

November 19, 2007
Canada Chapter
Annual Conference

November 28, 2007
Delaware Valley Chapter
Utah Medical Prevails in Court over FDA Charges

November 29, 2007
Southeast Chapter
Biofilm Conference dedicated to the Pharmaceutical and Biopharmaceutical Industries

December 6, 2007
Capital Area Chapter
Minimizing Risk in Your Raw Material Supply Chain

Europe/Asia-Pacific Events

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

Europe

November 13, 2007
PDA Workshop Series on *Technical Report No. 1, Revised 2007, Validation of Moist Heat Sterilisation Processes: Cycle Design, Development, Qualification and Ongoing Control*
Milan, Italy

November 13, 2007
Ireland Chapter
Pharmachemical Ireland/PDA/ISPE Quality and Innovation Conference

November 13-15, 2007
European Training Course Series in Berlin
Berlin, Germany

November 15-16, 2007
Cork, Ireland Training Course Series
Cork, Ireland

November 27-30, 2007
The Universe of Pre-filled Syringes and Injection Devices
Berlin, Germany

December 4-6,2007
Practical Aspects of Aseptic Processing
Basel, Switzerland

December 10-11, 2007
PDA/FDA Co-sponsored Conference Series on Quality Systems
Dublin, Ireland

December 12-14, 2007
Dublin, Ireland Training Course Series
Dublin, Ireland

December 10-11, 2007
PDA/FDA Co-sponsored Conference Series on Quality Systems
Dublin, Ireland

January 22, 2008
Investigational Medicinal Products Workshop
Paris, France

February 18-21, 2008
2008 PDA/EMEA Joint Conference
Budapest, Hungary

Asia-Pacific

November 13-14, 2007
Japan Chapter
Chapter Annual Meeting

December 2007
Japan Chapter
Sterilized Product GMP

April 21-22, 2008
PDA/FDA Co-sponsored Conference Series on Quality Systems
Beijing, China

April 24-25, 2008
PDA/FDA Co-sponsored Conference Series on Quality Systems
Shanghai, China

Health Authority Special Report, continued from page 29

EU level regular industry-regulator interactions should occur to address implementation confirmation, opportunities and optional (Q10) versus mandatory (GMP) expectations. The two sides also should work towards a common understanding of lifecycle and knowledge management.

At the ICH level both the EU regulators and industry are supportive of the establishment of an Implementation Working Group (IWG) for Q8, 9 &10 together, including the engagement of the non-ICH regions. At the PIC/S level industry supports the development of aide-memoires, but it is probably too early for this.

The briefing concluded that both industry and regulators were committed to safeguarding public health and that Q10, together with Q8 and Q9, will enable a flexible regulatory approach that will foster innovation for the benefit of all parties.

EMEA Interested Parties Meeting

Stephan Rönninger, F. Hoffmann-La Roche Ltd; Pete Gough, David Begg Associates; Peter Reichert, Novo Nordisk; and Jim Lyda, PDA

The Interested Parties Meeting is usually held once per year in conjunction with a meeting of the EMEA GMP/GDP Inspectors Working Group (formerly the Ad hoc Inspection Services Working Group). Attending the meeting were representatives of the inspectorates from each of the 27 EU Member States, 2 accession countries, the 3 EEA countries and a representative of the European Commission. The meeting was chaired by **Emer Cooke,** Head of the EMEA Inspections Sector. Also attending was **Sabine Atzor** of the European Commission. Readers should look for the official EMEA summary to be posted on the EMEA website in the near future.

The conference included updates to the following topics:

- EudraGMP Database
- Mutual Recognition Agreements
- Compilation of Community Procedures
- Changes to EU GMP Guide
- EMEA "Reflection Paper on QP Discretion"
- Atypical Actives

Actions to extend the scope of the MRA with Japan will be extended to sterile products and biologics are ongoing.

1) The EudraGMP Database went partly online in April 2007 for regulators. Public access to the database is planned for early 2008.

2) All existing MRAs will be expanded to cover GMP for API. Actions to extend the scope of the MRA with Japan will be extended to sterile products and biologics are ongoing. MRA negotiations with the United States remain inactive, but the EMEA stated that there is routine and productive information exchange with the U.S. FDA apart from the MRA.

3) Compilation of Community Procedures (a summary of inspection and related information in the EU) is being amended in the following areas:

- Conduct of Inspections–marketing authorization holders obligations, new annex on API inspections, concept of risk-based inspections
- New procedure for dealing with serious GMP noncompliances
- A model for risk-based inspection planning
- Handling of suspected quality defects–the introduction of a Quality Risk Management approach and inclusion of Investigational Medicinal Products

Access the Compilation at www.emea.europa.eu/Inspections/GMPCompproc.html

4) Changes to EU GMP Guide include a new introduction and revisions to Parts I and II, as part of the ICH Q9 implementation. Most revisions are expected to be completed by the end of 2007.

5) EMEA "Reflection Paper on QP Discretion": A unified industry position was presented by EFPIA with the following key points in response to the Reflection Paper:

- The Reflection Paper is welcomed as a step forward
- The scope should be extended to include various types of deviations (common cause, one-off planned, non-critical OOS
- There needs to be an agreed definition of what constitutes a minor deviation
- Industry supports adoption of the principals of the Reflection Paper into Annex 16 of the GMP Guide.

EMEA noted that all competent authorities currently agree on the content of the reflection paper. The individual industry comments on this issue (including the PDA survey data, see the October *PDA Letter*, pp. 31 and 32) were studied by the working group, and they are sympathetic to the points raised. Options for moving forward have been discussed. All interested parties have made the point to directly include all these comments in a revised Annex 16, without issuing a revised reflection paper first and without waiting for the approval of the revised variations regulations.

6) Atypical Actives: There was an industry presentation on examples of problems experienced with atypical actives—materials that are common food or pharmaceutical excipients that can be registered as API's (e.g., citric acid). The European Commission is aware of the issue and are considering how to respond. In the meantime, inspectors are being encouraged to adopt a risk-based approach to individual cases.

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EMD

Volunteer Spotlight

Name: **Lothar Hartmann, PhD**

Company: F. Hoffmann – La Roche Ltd.
Basel, Switzerland

Title: Head of External Relations
Global Quality Department

Education: Diploma, Technical Chemistry
PhD Biotechnology (Water Treatment)
Technical University of Berlin, Germany

PDA Join Date: Over 10 years ago

PDA Volunteerism and Awards:

- Current member of PDA Science Advisory Board (SAB)
- Current co-chair of PDA Program Advisory Board (PAB)
- Chair of PDA/EMEA 2008 Joint Conference, *European GMP: Current Issues and Future Developments,* February 2008, Budapest, Hungary.
- Chair of PDA conference, Biopharmaceutical Manufacturing and Development, June, 2006; in association with the European Biopharmaceutical Enterprises (EBE), a sub-group of EFPIA representing the biotech pharma industry in Europe.
- Head of EBE Biopharmaceutical Manufacturing Committee.
- Member of the ICH Q7 Expert Working Group, and leader of PDA's European Steering Committee for organizing the three Q7a training workshops in Europe in 2003. Awarded special PDA award of recognition in May 2004 for this work.
- Co-author and lead-author of various industry perspective guidance documents, for example, integrating GMP into ISO 9001.
- EFPIA task force supporting ICH Q10 experts.

Interesting Fact about Yourself:
When not at work I spend all the time I can with my family. We enjoy relaxing and going on a lot of excursions together.

Of your PDA experiences, which stand out the most?
I was very involved in the genesis of ICH Q7, GMP for Active Pharmaceutical Substances. When PDA was chosen to do the worldwide training on the guidance after it reached Step 4, I helped with the development of the European sessions, all of which were very successful. The enthusiasm, camaraderie, and professionalism of everyone involved helped me realize the strength and reach of PDA. I knew from that point that I wanted to stay involved.

Which member benefit do you most look forward to?
I like many of the member benefits including the PDA Journal, the continuing series of helpful Technical Reports, and the *PDA Letter.* But the main benefit for me is the ability to stay in touch with so many people all over the world. I have been to the PDA/FDA conference and the PDA Annual Meeting several times. The concentration of people is really impressive; there is something, someone at those events for everybody. This is a real strength of PDA, being able to gain access, contacts and support from all sectors of our industry. We are building this kind of PDA networking connection in Europe and it will pay off for everyone.

Which PDA event/training course is your favorite?
Right now I'm excited about the PDA/EMEA Joint Conference next February in Budapest. I am co-chairing a planning committee of excellent volunteers from the inspectorates and the industry membership. The EMEA and **Emer Cooke** have been wonderful in their support. **David Cockburn,** my co-chair from the EMEA Inspections Sector, is really making things happen. Long-time colleague, **Steve Bellis** has rounded out the leadership team. Our topic is the current status of the European GMP, and for sure there is much to cover. This conference is like no other event in Europe.

How has PDA benefited you professionally?
In so many ways. Roche is a world class multinational in every sense of the word. But in healthcare delivery to the patient, we operate in the personal realm. In between we have to comply with many complex requirements in over 150 countries. So we face every challenge and opportunity at every level of the pharmaceutical spectrum. As Head of External Affairs, my role in the company is to ensure that we understand and comply with the necessary quality standard throughout the world. PDA is a perfect platform for me to pursue my professional and business goals, and my colleagues at Roche recognize this. If PDA did not exist, I think we would have to invent it. Just that simple!

If you have comments or questions about the volunteer spotlight, contact Walt Morris at morris@pda.org

PDA Puerto Rico Chapter Holds Second Educational Event

Evelyn Marchany (Schering-Plough), Puerto Rico Chapter President Elect

The Puerto Rico Chapter made its mark on the Island by bringing professionals a mix of education and application in different areas of the pharmaceutical and parenteral industry. Our second event took place on July 18, and accommodated 89 industry professionals and six U.S. FDA representatives from the San Juan District Office. The event marks the solid establishment of the chapter as a valuable resource in Puerto Rico.

The conference was held at the Condado Plaza Hotel in San Juan, and resulted from the joint effort of the FDA, the industry (Wyeth, Puerto Rico) and the chapter members. The conference addressed how the regulatory environment around quality by design (QbD) impacts the industry and how process analytical technology (PAT) is being applied.

The FDA guidelines on the Quality Systems Approach to Pharmaceutical cGMPs and on PAT, along with the ICH documents Q8, Q9 and Q10, represent a clear message that the future for a pharmaceutical manufacturing process will be determined at the design phase by the application of "continuous real-time quality verification" and adequate "real-time" process controls.

PAT is defined as a system for designing, analyzing and controlling manufacturing processes through timely measurements of critical quality and performance attributes of raw and in-process materials and manufacturing processes. The goal of PAT is to "understand" and to effectively "control" the process so that the risk to the product quality is minimized. The concept of QbD is based on the same principle—design the process to minimize the potential for quality nonconformances.

Wyeth is moving towards pharmaceutical manufacturing innovation and "real-time" quality assurance by building programs and strategies that include the use of PAT tools. Currently, Wyeth-Puerto Rico is implementing PAT applications for parenterals and solid dosages. The applications include: refractometry, headspace oxygen analyzer, tunable diode laser absorption spectroscopy (TDLAS), NIR, particle size analyzer (laser diffraction), and light induced fluorescence (LIF), among others.

FDA presented its position on promoting the QbD and PAT applications as a joint effort with the industry to better understand manufacturing processes in "real time." As part of its support to the industry for new methods of process understanding, the FDA continues to grant safety, efficacy and purity of the products to the consumer following GMP regulations.

Stability, EU GMPs and CAPA on the Marquee at Southeast Chapter Annual Fall Meeting

Ta-Mela Jeffries, PDA

Over 100 attendees and 30 exhibitors attended the PDA Southeast Chapter's successful 2007 Annual Fall Meeting in Durham, N.C., on September 4, and participated in the variety of educational seminars and exhibitions offered.

During the full day conference chapter leaders introduced the new Southeast Chapter website, which will facilitate better chapter-to-member communication, and announced new online registration, which will ease the process of event registration.

The first educational seminar was presented by **Anthony Polletta**, who presented "On-Going Stability Programs for Approved Drugs." Polletta discussed drug stability evaluations, mandated stability testing and the process of testing approved drugs for stability. (Stability testing for approved products must take place on samples representative of what is in the field. Storage must support label claims.) Polletta also coved stability testing results, regulatory expectations and situations where stability test results can be questioned.

Kathy Wessberg, Director, Regulatory Operations, Abbott, delivered "EU Directive of API's Compliance with GMPs." Wessberg discussed the importance of the EU in today's global market and gave several strategies an organization can utilize to comply with EU regulations and expectations, including:

- Insure APIs comply with EU GMP through audits (internal and external)
- Create a communication channel between API auditing groups and quality persons at sites using the APIs
- Create and agree to use a QP Declaration of API GMP Compliance template
- Create and agree to use a technical specific to API GMP Compliance

Wade Speir presented "FDA CAPA Compliant Root Cause Investigation and Documentation," which covered:

- Conduct robust root cause analyses on unexpected discrepancies
- Understand and eliminating recurring problems by selecting appropriate corrective and preventative actions
- Document investigation data analysis to prevent FDA 483s, inspection findings and warning letters

The PDA Southeast Chapter can attribute the success of this meeting to the speakers, volunteers and attendees involved. We give special thanks to them for leading interesting and educational discussions and making the conference an intellectual and career-advancing opportunity for everyone involved.

Inside the Global Regulatory Dialogue™

IPQ
INTERNATIONAL PHARMACEUTICAL QUALITY

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IN THIS ISSUE: THE QUALITY BY DESIGN/GMP RELATIONSHIP will need to be further defined to make sure that reviewers and investigators in different regulatory agencies are on the same page. Industry will be looking for assurances from regulators that the new risk-based QbD paradigm under which CMC applications will be developed and approved will be understood and appropriately evaluated by investigators during GMP inspections. While the new FDA and ICH quality systems guidelines provide a conceptual umbrella for the interconnection, further guidance is being recommended to help clarify and harmonize the role inspections will play under the new paradigm and how GMP expectations will evolve. FDA is redoubling its efforts to partner with countries with mature regulatory processes to help free up the much needed resources to help with drug quality oversight in regions where the regulatory structures are less strong and the manufacturing and supply chain rapidly growing.

–BILL PAULSON, EDITOR-IN-CHIEF

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INDUSTRY WILL BE LOOKING to regulatory agencies to further define the relationship between quality by design and GMP to make sure that reviewers and investigators are on the same page as the new risk-based quality regulatory paradigm evolves.

There should be written procedures for production and process controls. So they need to be designed to assure the drug has... quality and purity. So we are saying that the written procedures for your operatiyon, all of the things that you are telling the operator to do, the way you have designed the specific details of the operation are right to make sure that the process has the same output time after time, day after day. Buildings and facilities. All this is in design and all this is looked at by the inspection.

Now you do submit into an application something very important. And this is what we are doing at CDER, where we are changing from a chemist based approach to review to more of a design based approach to review. In the P2 summary, we are encouraging you to put QbD in there too. It is informational. We want you to do it. The reason our reviewers want you to do it is a very good reason. They want to make sure they make the best decisions on product attributes that are the requirements in the application. And they can't do that unless they really know how you developed the process and what the process capability is, at least provisionally, it is early so you can't really calculate cpk at that early stage, but at least get a very good idea. And know what the process vulnerabilities and weaknesses are. They want to make the best decisions. And they realize that only focusing on chemistry and end product testing wasn't enough.

So we want to get out expert scientists in our review groups more involved with processes. What we don't want to do, either in review OPS or office of compliance, we are working on 314.70 revisions so we don't lock in too much of that so you can make revisions over time. But we do want to look at design work.

The point is that much learning takes through process experience. Basically what we are submitting in a drug application is predictions of whether the process is going to be in control. When the rubber hits the road, you will see if the process really performs the way you expected and predicted. But there are extrapolations and other things that you are doing that are rough estimates. And there is never at least one or two things that you learn upon commercialization that you say, oh we are going to tweak that, or we will do more than tweak that, that wasn't as

INSIDE THE GLOBAL REGULATORY DIALOGUE

For more information on *IPQ* please visit:

www.ipqpubs.com

International Pharmaceutical Quality (*IPQ*) is published in collaboration with Bill Paulson former Executive Editor of *"The Gold Sheet"*. Published bi-monthly with supplements issued quarterly, all *IPQ* publications will directly target the relevant issues surrounding international harmonization and help further the discussion about regulatory approaches appropriate for advancing products and processes. Each issue will provide an in-depth analysis of a problem area or developing regulatory initiative. It will seek to improve understanding of issues and aid the development of harmonized global regulation of pharmaceutical quality and corporate quality systems.

IPQ staff will report on key conferences and workshops where proposals for industry and regulatory guidances and initiatives are being presented. As a key driver of the evolving regulatory model and the harmonization effort, the US Food and Drug Administration will be an important component of *IPQ*'s coverage. Also included in the new publication's purview will be international quality initiatives and harmonization efforts involving industry associations, regulatory agencies, pharmacopeias and standard-setting organizations around the globe.

IPQ™
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New England Chapter Talks About Project Portfolio Management

Louis T. Zaczkiewicz (Hyaluron Contract Manufacturing), PDA New England Chapter President

The PDA New England Chapter sponsored a half-day workshop called "Project Portfolio Management" at the Boston University Corporate Education Center (BUCEC) on Sept. 12. Our speaker was **Dan Stavola,** a certified project management professional and member of the BUCEC faculty. The meeting was organized by chapter member **Bruce Rotker,** Sparta Systems.

Project portfolio management is both an art and a science, as it applies knowledge, skills, tools and techniques to a collection of projects to meet an organization's goals. The enterprise vision and mission is first broken down into a collection of strategies. Each of the strategies will in turn have a collection of objectives met by specific projects. Understanding the strategy will drive how projects are managed along with the business model. Each potential project is to be evaluated by the executive management team to assure alignment with the vision and mission. Many different types of scoring models are used to choose which projects a company is to pursue. In the end, project portfolio management will ensure a strategic alignment of projects to the business strategy of the firm, ensuring that a company's vision is achieved.

We were pleased with the member attendance and with **Ta-Méla Jeffries** attending from PDA's headquarters. We owe Ta-Mela a special "Thank You" for this event since this was the first time we used online registration and accepted credit card payment. Ta-Mela served as our registrar and handled everything so smoothly, down to the nametags, that we have decided to make online registration for our events permanent.

Finally, we appreciate and thank Masy Systems (www.masy.com) for sponsoring this event. Besides providing quality products and services (ISO 9001:2000 certified and ALA ISO/IEC 17025:2005 accredited), Masy Systems has always been a strong supporter of PDA and the New England Chapter. Sponsorship allows us to keep meeting prices down and allows our members to learn about technologies that will help in doing their jobs.

100 New Members Attend PDA/FDA Breakfast

Hassana Howe, PDA

For the first time PDA hosted a New Member Breakfast at the PDA/FDA Joint Regulatory Conference in an effort to orient new PDA members with their member resources. Over a 100 new members attended, making it one of the most successful New Member Breakfasts to date.

The success of this event can be attributed to the Board Members, Volunteers, Chapter Leaders and PDA Staff Members involved. Board Member, **John Shabushnig,** PhD, Pfizer and the Program Planning Committee Chair **Susan Schniepp,** Hospira, Inc., gave insightful presentations on their PDA membership experiences and informed members how to utilize PDA's *career-long learning*™ opportunities. In addition, special thanks are given to PDA chapter representatives who represented the Australian, Capital Area, Delaware Valley, Puerto Rico, West Coast and the Japan Chapter. These representatives gave members an opportunity to learn more about their chapter events and volunteer opportunities.

If you are a new PDA member and were unable to attend the breakfast, you can view the PDA Membership Orientation presentation online at www.pda.org/membership. The next PDA New Member Breakfast will be hosted at the 2008 PDA Annual Meeting in April 2007. If you would like more information please visit www.pda.org/annual2008 and click on "Networking Opportunities" or contact the Membership Department at info@pda.org.

PDA Chair-Elect John Shabushnig, Pfizer, greets new members

Delaware Valley Chapter Takes a Look at EMEA

Chapter's September Meeting Draws 200 Participants

Susan Speth (GlaxoSmithKline), PDA Delaware Valley Chapter Operating Committee Members

Two hundred representatives of pharmaceutical and biopharmaceutical companies congregated at the Desmond Hotel and Conference Center in Malvern, Pa., Sept. 27 for the PDA Delaware Valley Chapter's "A Focus on EMEA (European Medicines Agency) Considerations" conference and annual Vendor Night Extravaganza.

The evening commenced with displays from 31 area vendors. Here participants received hands-on information about the latest technologies, resources and supplies as well as the opportunity discuss the latest and greatest tools of the trade with technical experts from these valuable suppliers.

Following the vendor displays, 125 participants heard presentations on the EMEA inspection process from keynote speaker **Roger Smith,** Quality Manager, GlaxoSmithKline presented "A Focus on EMEA Considerations." He opened by providing the audience with the mission statement and structure of the EMEA, which is headquartered in London, UK, and is responsible for the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use.

Smith explained that complying with EMEA expectations is more involved than just interpretation of writings from the agency. It requires firsthand experience that is not easily obtained through conference-type discussions. His presentation covered the EMEA's role for products produced in the European Union or imported to the European Union. He also reviewed typical challenges faced when handling EMEA inspections such as language and culture.

Smith also discussed the Pharmaceutical Inspection Cooperation Scheme (PIC/S), the UK's Medicines & Healthcare products Regulatory Agency, mutual recognition agreements, the role of the EU Qualified Person, and some unique differences between FDA and MHRA.

At the close of his presentation, Smith entertained questions and shared ideas with the attendees. He also provided attendees with relevant web links for further information. As always copies of the presentation were forwarded to all attendees by Chapter leaders.

New Chapter Websites Up and Running

For In September, PDA unveiled the first of many new chapter websites! These new, full service websites give chapter leaders the opportunity to better service their membership. The new sites offer chapter-specific event calendars, a networking forum for members, direct contact abilities to chapter leaders as well as the ability for online event registration. Special thanks to the New England Chapter for allowing us to use their site as a test site.

PDA wants to congratulate all of our participating chapters on their new websites! If you are interested in seeing any of the new chapter sites, please visit:

www.pdachapters.org/newengland
www.pdachapters.org/puertorico
www.pdachapters.org/southeast
www.pdachapters.org/midwest
www.pdachapters.org/canada
www.pdachapters.org/southerncalifornia
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If your information appears inaccurate in this list, please visit www.pda.org to update your profile or email changes to info@pda.org.

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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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www.pdachapters.org/puertorico

Southeast Chapter
Areas Served: NC, SC, TN, VA, FL, GA
Contact: Patrick Sabourin
Email:
psabourin@clarkstonconsulting.com
www.pdachapters.org/southeast

Southern California Chapter
Areas Served: Southern California
Contact: Saeed Tafreshi
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saeedtafreshi@inteliteccorporation.com
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Areas Served: Northern California
Contact: John Ferreira
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The 2008 Annual Meeting: Science Driven Manufacturing: The Application of Emerging Technologies

Colorado Springs, Colo. • April 14-18 • www.pda.org/annual2008

Maik Jornitz (Sartorius-Stedim), Program Committee Chair and PDA Treasurer

In a world of information and communication, the most valuable means of discussion is still face-to-face conversation and networking with industry and regulatory colleagues and peers.

Each year, the PDA Annual Meeting creates a most advantageous platform to exchange information; either as speaker, recipient of highly qualified presentation, PDA Interest Group participant or active volunteer.

The theme of the PDA 2008 Annual Meeting is *Science Driven Manufacturing: The Application of Emerging Technologies*, and the meeting will focus on new grounds of science and technology within a highly regulated manufacturing environment.

Manufacturing technologies and entire processes are evolving rapidly in response to new requirements and challenges within the pharmaceutical and biopharmaceutical production settings. Implementation of new technologies, beyond the transfer of technologies, will be discussed, since production locations are no longer localized.

Innovative detection methodologies, which are essential to prevent novel and known contaminants to disrupt product processing and quality requirements, will also be addressed. Additionally, industry representatives will discuss the removal or inactivation of such contaminants.

A variety of manufacturing and quality science subjects will also be covered, including new aseptic and downstream processing approaches, filling technology advances, and implications of up-coming regulations.

In addition, a main focus of the PDA 2008 Annual Meeting will be the patient. For this reason, we will hear directly from former patients and how a drug supplied changed their life, and how you and your organization contributed to their well-being or recovery. To be able to take note of their experience creates for us the motivation to strive to investigate new routes of development, manufacturing and compliance. Our keynote speakers, **Linda Armstrong Kelly** and **Shelley Morrison,** are two of such patients and will share their experiences with us. We would like to thank them for their contribution and support.

On behalf of the Program Planning Committee, I hope that you will join us at the PDA 2008 Annual Meeting, April 14-18, 2008, at The Broadmoor in Colorado Springs, Colorado to take advantage of this unique opportunity to achieve the highest value for you and your company.

Twelve Top Government Speakers Confirmed for 2008 PDA/EMEA Joint Conference

Budapest, Hungary • Feb. 20-21 • www.pda.org/emea2008

If you have a stake in European GMP, take a look at the 2008 PDA/EMEA Joint Conference, *European GMP: Current Issues and Future Developments.* This comprehensive conference covers GMP issues for manufacturers, distributors and importers of medicinal products and related materials in Europe. The agenda includes eight topical tracks and four plenary sessions featuring a wide range of speakers. PDA has confirmed 13 top level regulators from the EMEA, the European Commission and the National Authorities; additional government speakers are invited.

Rarely have so many European officials, from so many authorities, participated in common discussions on evolving GMP. Confirmed government speakers are (in order of appearance):

Emer Cooke, EMEA Inspections Sector
Sabine Atzor, EU Commission
Katrin Nodop, EMEA Inspections Sector
Eija Pelkonen, NAM, Finland
David Cockburn, EMEA Inspections Sector
Paul Hargreaves, MHRA, UK
Jacques Morénas, AFSSAPS, France, and current chair PIC/S
Ian Rees, MHRA, UK
Sabine Paris, ZLG, Germany
Tor Graberg, MPA, Sweden
Chris Cullen, IMB, Ireland
Jean-Louis Robert, Ministry of Health, Luxembourg, and current chair QWP.

If your job is to keep current and informed regarding GMP, you will not want to miss the 2008 PDA/EMEA Joint Conference. See you in Budapest!

See what the 2006 conference attendees had to say*:

The goal in 2006 was a platform for open discussion and exchange on regulatory and technical issues	**Yes**
Was this goal achieved?	**86%**
Should this conference take place again?	**95%**
Would you come again?	**93%**

(*128 evaluations collected from 250+ attendees)

The

2007 PDA/DHI Technical Books Distinguished Editor/Author Awards

will be presented at

2008 PDA ANNUAL MEETING

April 14-18, 2008
Colorado Springs, Colorado

Awards will be given to the top two editors/authors of a PDA-DHI co-published book. This is a "members' choice" award, your participation will determine the winners. Please take a moment to cast your vote online at **www.pda.org/bookstore**. Polls are open from December 1, 2007 through December 31, 2007.

Nominees:

Trevor Deeks, PhD: *Bioprocess Validation: The Present and Future*

Steven S. Kuwahara, PhD and **Simon Xiuwei Li**: *Chinese Drug GMP: An Unofficial Translation Including Related Sections of the Taiwanese, U.S., and ICH-API GMP*

Richard Prince, PhD and **Diane Petitti**: *Confronting Variability: A Framework for Risk Assessment*

Nigel Halls, PhD: *Essential Microbiology for QP Candidates*

Anne F. Booth: *Ethylene Oxide Sterilization: Validation and Routine Operation*

Nigel Halls, PhD: *Pharmaceutical Contamination Control: Practical Strategies For Compliance*

Scott Sutton, PhD: *Pharmaceutical Quality Control Microbiology: A Guidebook to the Basics*

Jeanne Moldenhauer, PhD: *Systems Based Inspection for Pharmaceutical Manufacturers*

Stephan O. Krause, PhD: *Validation of Analytical Methods for Biopharmaceuticals: A Guide to Risk-Based Validation and Implementation Strategies*

Pharmaceutical and Biopharmaceutical Career Opportunities Abound...

www.pda.org/careers

PDA Career Center

World Wide Possibilities

Whether you are actively seeking employment, or just want to see what you might be missing, PDA's Career Center delivers a wide range of opportunities. Post as much or as little information as you like. Our 100% confidential and secure job-searching network allows you flexibility and ease-of-use without the risk.

- Register for free
- Feel comfortable in a 100% secure and confidential online environment
- Experience a flexible and user friendly interface
- Create a variety of resumes to target different career profiles
- Participate in PDA Virtual Career Fairs
- Explore a wide range of local and international opportunities
- Gain new perspective on how to make a smooth career transition

PDA's Career Center is updated regularly with important news and information on the companies and careers that are important to you. Visit often to view the latest "Hot Jobs" and start turning job possibilities into career opportunities at www.pda.org/careers.

PDA℠
Parenteral Drug Association

Consider Your Entry for the 2008 Trainers' Choice Award

Entries Due by January 31, 2008

Bill O'Connor (Genzyme Corporation), 2008 PDA Training Conference Committee

Are your training programs and materials something to be admired? Don't sell yourself short, there's always a fresh approach out there and it might be yours! Don't keep it to yourself, share it and be recognized as a leader by your peers, your company and PDA. Perhaps you have a perfectly structured on-the-job program or an in-depth classroom manual with a trainer's guide. Maybe you've developed a great video tutorial, or developed e-learning. Past entrants have showcased this type of training, as well as, self-designed intranet sites or interactive board games, game shows or competitions with a sports theme.

Since the 2002 PDA Biennial Training Conference, participants have had the opportunity to view, interact and select the winners of the prestigious Trainers' Choice Award. This year's conference, at the Ritz Carlton, New Orleans, May 19-23, will be no different with the exception of yet another group of extremely creative finalists expected. The Awards are presented for outstanding achievement, creativity and originality in design and delivery of CGMP and technical training programs or materials, and will be awarded on the final day of the conference.

Categories may include: (based upon acceptance at preliminary judging awards will be given for each category)

- Multimedia Presentation
- Classroom Training Manual
- E-learning Program / Web Page Design
- Experiential/Interactive Training
- Other Creative Approaches

All trainers currently employed in the pharmaceutical, biotechnology, medical device, biologics or related health science industries are eligible. (Consultants or vendors to such industries are not eligible.) The materials must have been designed by internal staff and subsequently owned by that company.

All submissions will be subjected to preliminary judging by the PDA Training Conference Committee, and finalists will be required to display/demonstrate the materials at the 2008 PDA Biennial Training Conference. Winners will be chosen by vote of the conference participants. Finalists will be recognized and the winners announced at the Trainers' Choice Awards Ceremony on the final day of the conference.

Enter and be recognized by your fellow trainers! The deadline is January 31, 2008.

Visit www.pda.org/Training2008 for all submission information and to complete the application outlining your entry. Please address all questions to: **Jason Brown,** coordinator, Programs and Meetings, PDA +1(301) 656-5900, ext. 131, or brown@pda.org.

PDA
Parenteral Drug Association

www.pda.org/training2008

2008 PDA BIENNIAL TRAINING CONFERENCE

NEW ORLEANS
LOUISIANA

Focus on Performance: Partnering For Business Success

Join colleagues and connect with thought leaders at the ***2008 PDA Biennial Training Conference*** and take home the knowledge and skills you need to train your workforce. The conference is designed for anyone with training responsibilities in the bio/pharmaceutical industry and will provide the most current information needed to strengthen your training expertise. **Training and medical device experts and FDA representatives** will provide valuable insight on how to:

- Implement best training practices in a highly regulated environment
- Improve the performance of your employees
- Apply the latest training trends and techniques
- Inform your team of the most current regulatory requirements

Complementing the conference are PDA Training and Research Institute (PDA TRI) training courses and an exhibition featuring vendors who provide excellent services in support of training efforts.

CONFERENCE

MAY 19–21

EXHIBITION

MAY 19–20

TRAINING COURSES

MAY 22–23

Faces and Places: PDA/FDA Conference—The Sessions


Program Chair Sue Schniepp, PDA President Bob Myers and PDA Chair Vincent Anicetti kick-off the 2007 PDA/FDA conference

GMPs for INDs: (l-r) Kathleen Wessberg, Abbott; Jamie McElvain, Amgen; and Monica Caphart, FDA

Opening plenary session moderator Rick Friedman, FDA, and keynote speaker Helen Winkle, FDA, watch a presentation

Opening plenary session speakers Anurag Rathore, Amgen, and Azita Saleki-Gerhardt, Abbott field questions

Rapid Methods: (l-r) Bryan Riley, FDA; Pankaj Amin, FDA; Tim Wozniak, Eli Lilly; Sue Schniepp, Hospira; and Alan Rhoden, Pfizer

ICH Q8: (l-r) John Towns, Eli Lilly; Anurag Rathore, Amgen; Liam Feely, Abbott; and Moheb Nasr, FDA

Quality Systems: (l-r) Robert Sausville, FDA; Kim Trautman, FDA; Martin VanTrieste, Amgen; Joe Famulare, FDA; and Maria Guazzaroni Jacobs, Pfizer



Did all 1200 attendees pack into the opening plenary session?

(l-r)) Paul Stinavage, Pfizer, and Maurice Phelan, Millipore address the Filtration IG session

The Quality Systems IG holds a cozy discussion

(l-r) Trevor Decks, Janny Chua, Amy Davis, and Richard Prince

Ed Trappler leads the Lyophilization IG session

Regulatory & Quality Issues for Biologics: (l-r) William Egan, PharmaNet Consulting; Lizzie Leininger, StemCells; and Donald Fink, FDA

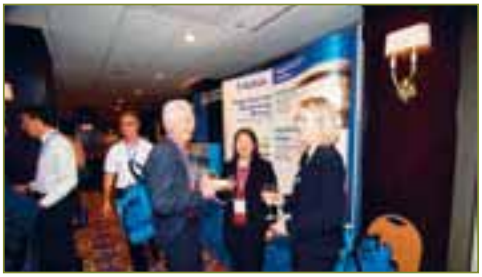
Day 1 Joint Clinical Trial Materials & Pro. Val. IGs: (l-r): Vince Mathews, Eli Lilly; Nate Milton, Eli Lilly; Mark Roache, Bayer; David Radspinner, Thermo; and Hal Baseman, Valsource

Day 2 of the Joint Clinical Trial Materials & Pro. Val. IGs session draws healthy discussion

More day 2 of Joint Clinical Trial Materials & Pro. Val. IG

Faces and Places: PDA/FDA Conference: Exhibits and Networking















Faces and Places: GPP: Good Party Practices
















Chair's Message: TRI Officially Opens Doors in Bethesda

Vincent Anicetti, Genentech, Inc. ***(From His Opening Remarks at the 2007 PDA/FDA Conference)***

Many of you probably are aware of the Training and Research Institute. Until this year, it was located outside of Baltimore. What really differentiates PDA in many ways in terms of a pharmaceutical training and education institute is the fact that we can provide hands-on training. And one of the things that has been unique and exceptional about PDA was our ability to conduct laboratory-based courses and conduct aseptic and sterile filling operations through the training and research institute.

Unfortunately, the location that we had was difficult to travel to for many of us. Our goal has been to co-locate TRI with the corporate headquarters in Bethesda, Md. We will open the new TRI Institute in Bethesda this week. It is a very exciting event. I've seen the facility: it is a state-of-the-art pharmaceutical facility. We have two microbiology laboratories there, a specialized biotech suite, and we can fully duplicate sterile filling operations including component prep and autoclave procedures. So it is a great asset for all of us as professionals in the pharmaceutical industry to have this center; now that we have it in Bethesda, I think it is going to be more accessible than ever. Many thanks to **Bob Myers** and the entire PDA staff for achieving that this year.

The other thing that made this possible was the very generous donations of many of our corporate sponsors and many individuals. I'm very proud and grateful to say that we have received over a million dollars in donations for the new TRI. It has really been a wonderful effort, and we are very fortunate to have so many supporters in our organization. I wanted to take a few moments just to recognize three groups of these contributors. The first our Platinum Supporters. Our second group are our Annual Supporters who have made an annual commitment to support the TRI facility. And lastly, the many other organizations that have made a contribution to support TRI. If you are chagrined that your organization is not listed up there, it is not too late. We are always happy to talk to anyone that will support this important endeavor.

The opening of TRI in Bethesda represents a new and exciting era for the Institute and for PDA, and one that will see, I'm sure, even greater success.

TRI Celebrates a New Beginning

On September 26, PDA's Training and Research Institute celebrated the opening of its new facility in Bethesda, Md. The ribbon-cutting ceremony involved members of the Montgomery County Maryland Economic Development Office, the PDA Board of Directors, contributors to TRI and various other VIPs. On the following two pages are photos of the event.

PDA Chair Vince Anicetti cuts the ribbon with fellow Board members and staff watching

PDA Board of Directors in attendance: (l-r) Laura Thoma, Rebecca Devine, Nikki Mehringer, Steve Mendivil, Vince Anicetti, Eric Sheinin, Martin VanTrieste, Kathleen Greene, Lisa Skeens, Bob Myers, Amy Scott-Billman, Louise Johnson, Anders Vinther, and John Shabushnig

Groninger's Lothar Bruger and Wenzel Nowak pose with the prefilled syringe unit, the company generously donated

Giuseppe Fedegari poses with the state-of-the-art autoclave his company Fedegari Autoclavi donated

PDA Board member Steve Marten tours the aseptic filling area with PDA's Hassana Howe

Taking a close look at the Micro Lab are (l-r) Berit Reinmüller, Bengt Ljungqvist, Hassana Howe and J.P. Jiang

PDA's Feng Chen (far left) translates for Suming Fang, Bob Myers, Yuhua Lou and Weijun Gu

continued on next page

Gail Sherman (far right) poses with Vectech Officials

Here to help! FDA's Janet Woodcock is greeted by Vince Anicetti and Bob Myers outside the cleanroom

Current Chair Vince Anicetti speaks with former Chairs Bob Myers and Nat Kirsch

Before and After

Destruction…

…construction…

…education

The autoclave on arrival…

…during installation and training…

…and in use during the first Aseptic Processing Training

Endotoxins: Joint PDA/SFSTP Collaboration Ongoing

Philippe Gomez, Sartorius-Stedim, and Volker Eck, PDA

When talking about endotoxins, according to specialists, one can still have difficulties in setting up a suitable control procedure. It appears to be somewhat difficult to select the right procedure to apply and, even more, to justify this choice.

Despite the fact that extensive and valuable literature exist, specialists and users feel that a more concrete guideline should exist to help in the design endotoxin controls that are scientifically sound and robust. During discussions of this topic at past PDA meetings, participants have made a number of comments suggesting that guidance is necessary, particularly with respect to setting procedures for nonsoluble products and justifying the limits for biotech products when the variability of the method is large.

SFSTP (Société Française des Sciences et Techniques Pharmaceutiques) and PDA started introducing to our stakeholders in 2006 the idea of creating a common PDA/SFSTP working group on endotoxins. Announcements were made during the PDA France Chapter conference *Contaminant Removal* in December 2006, and the first PDA conference on *Good Practices for IMPs* in May 2007. The feedback was overwhelming, and at the end, around 30 people volunteered to participate.

The creation process went on, and the face-to-face inaugural meeting was held Oct. 23 at the SFSTP premises in Paris. Twenty experts participated, including representatives from regulatory bodies like AFSSAPS (the French Health Authority).

The main point, as expressed during the meeting, was the urgent need of a scientific and technologically sound guide covering not only updates of existing regulations and newly introduced technologies, but also the basic procedures in relation to the product itself (e.g., soluble/non soluble, biotech product, etc.).

The participants identified other issues to be covered, including:

- Present measurement methods (harmonization between pharmacopoeias, selectivity, inhibition, reliability)
- Sampling procedures, particularly for raw materials, components, medical devices, and sample pre-treatment and preparation
- Result interpretation and comparison between different methodologies and practices ➤

Before and After

Evolution of a cleanroom

Ompi Day

Georg Roessling, PDA

On October 5, 2007, Nuova Ompi, located near Venice, Italy, and a major supplier of glass syringes and related material to the pharma industry, scheduled their "2007 Ompi Day." More than 150 people attended a seminar and examined Ompi's new glass syringe manufacturing line. This state of the art facility is an impressive example of the synergy of pharmaceutical quality understanding and high tech engineering. Many of the participants were PDA members and friends of PDA. For sure many will meet again at the PDA Prefilled Syringe Conference in November in Berlin.

Also attending Ompi Day:
Prof. Alessandro Rigamonti, President of AFI (Associazione Farmaceutici Industria), the pharmaceutical industry association of Italy.

"The Hosts of Ompi Day, the Ompi management team (l-r): Marco Stevanato, PhD; Sergio Stevanato, President of Stevanato Group; and Franco Stevanato, PhD. "

Delegation from PDA Japan Chapter Visits PDA Europe

Georg Roessling, PDA

Two representatives of the PDA Japan Chapter met at the PDA Europe office in Berlin to discuss opportunities for working together. The 2008 conferences on Compendial topics with EP, JP and USP, April 1-2, in Frankfurt, and the Visual Inspection Conference in October in Berlin were some of the many topics discussed. Many more activities are planned for 2008.

PDA Japan visitors to the PDA Europe headquarters (l-r): Shigeto Hirabara and Daikichiro Murakami, both of Taikisha Ltd, Japan; and Georg Roessling, PDA

continued from previous page

- The expected 3 log reduction value in depyrogenation processes
- Currently proposed limits, are they satisfactory?
- Known and alternative technologies for bacterial endotoxins/pyrogen removal and their acceptability

Luc Pisarik, Merial/SFSTP, and **Philippe Gomez,** Sartorius-Stedim/ PDA launched this discussion and will co-chair the working group.

The next meeting is planned in Paris during the PDA Conference called *Investigational Medicinal Products: Negotiating the GMP/GLP/GCP Interface* Jan. 22. The group will gather and discuss progress on the work assigned as a result of this first session and plan to go ahead for the next meeting already scheduled in March 2008.

Volunteers are from major biopharmaceutical companies, regulatory agencies and industry suppliers residing in France and neighbouring countries. They were very motivated and look forward to issuing a useful document that could serve as a basis for professionals in this field.

With that in mind, it would be even more beneficial to extend participation to a wider and more international basis. Therefore, PDA is promoting this effort and will contribute to proliferating the information on a global level. Individuals from North America, Asia and other regions are encouraged to participate as well so that the discussions and work can be turned into a PDA technical report with scientifically justified practical hints and suggestions. If you want to contribute, please feel free to contact **Philippe Gomez** at philippe.gomez@sartorius.com.

Special thanks go to the French society of pharmaceutical science and technology (SFSTP) and particularly to **Cecile Oger** for her help and most valuable support.

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carried out by document check only in most cases." His division also conducts "for-cause" inspections following recalls or the occurrence of other quality problems or upon request from MHLW.

The Japanese authority will rely on "document checks" under certain circumstances, but recognizes "that all the inspections should be done on site," said Hasegawa. However, "it is time and resource consuming, and we don't have enough resources at present. On the other hand, current regulations mandate the need to apply for GMP inspection and obtain confirmation of GMP compliance." As such, "we can decide the GMP compliance by document check only for some of the applications."

Preapproval inspections are carried out on-site for all domestic facilities. For foreign firms, a number of criteria are involved in deciding to conduct an on-site inspection or a document check. Hasegawa elaborated: "If the product is covered by MRA [mutual recognition agreement] or MOU [memorandum of understanding], only a document check will be done. If the manufacturing site is located in a member country of PIC/S, we will put our emphasis on a document check only, and anon-site inspection will be preferred for the manufacturing sites outside the member countries of PIC/S.

On-site inspection will be conducted for high-risk products, including biotechnology products and new chemical entities. Other factors to be considered are the past history of GMP inspections and history of recalls."

The conduct of overseas inspections is "basically" the same as that for domestic sites. "Usually," said Hasegawa, "each inspection is done by two inspectors, but in some cases of specific products, including biological products, additional experts may participate. We are asking the applicant to employ interpreters to be able to facilitate the inspection and to avoid misunderstanding. Normally the inspection period is three or four days, depending on the size of the site and the complexity of the manufacturing process."

"…Some interpreters told us that it is quite exhausting to continue interpreting a GMP inspection for a long time…"

Firms are notified about three to six weeks in advance of the inspection date. "Because an inspection should be done within the limited time and such limitation of time is more important factor for foreign inspections, we ask the applicant to submit some information relating to…focus points to be checked during the inspection," Hasegawa explained. "If this information is not submitted, there is a possibility of extending the inspection period."

Like the U.S. FDA, PMDA employs a systems approach to inspections, examining the quality system, buildings and facilities, storage, manufacturing, packaging and labeling, and laboratory. "In the case of foreign manufacturing sites," said Hasegawa, "since frequent visits are difficult, we will cover all the subsystems in one visit."

Use of interpreters is very important, he explained. "Based on our experience, two interpreters are preferable. Some interpreters told us that it is quite exhausting to continue interpreting a GMP inspection for a long time. To avoid a bias, one or more interpreters should be independent from the company. To avoid misunderstanding, word for word translation is preferable, even if it takes time. Translation between Japanese and the local language is preferred, but Japanese and English may be acceptable. We will ask to interpret what is written in some documents during a document check. In cases of employing professional interpreters, they should know technical terms related to GMP."

Between the start of the foreign inspection program in October 2005 and July 2007, PMDA conducted 75 overseas inspections, with 40 sites visited in North America, 28 in Europe and 7 in other regions.

PMDA Office of Compliance and Standards GMP Expert **Takashi Nagashima** discussed "Check Points During GMP Inspection" following Hagesawa's presentation. Following an inspection, he noted, firms will receive written observations in Japanese typically within three weeks of the inspection. A written response from the firm, also in Japanese, is required three weeks after receiving the observations.

The company's response should include photographs or drawings to demonstrate corrective actions. A summary report for any additional validation tests performed and copies of any revised SOPs also should be incorporated into the response. Finally, a schedule of actions to be taken and the anticipated time of the final report should be outlined if corrective action is merited.

After evaluating 25 vendors, the European Medicines Agency (EMEA) selects TrackWise as its enterprise Quality Management System (QMS).

Claus Christiansen...
Integrated Quality Management Auditor for the EMEA,
gave these reasons for the selection:

- "Quick and smooth implementation."
- "Overall breadth of the TrackWise solution."
- "Ease of configuration."
- "Ability to integrate with existing software."
- "Audit trail and electronic signature."
- "Pharmaceutical industry experience."
- "Manages critical quality processes and global risk analysis."

TRACKWISE®
The Ultimate Quality Management Software

ABOUT THE EMEA

The European Medicines Agency coordinates the evaluation and supervision of medicinal products for its 25 European Union (EU) member states. It has implemented TrackWise to replace paper based and spreadsheet systems used by the agency to manage its quality processes. Implementation took only four months, meeting set timetables and budget goals.

ABOUT SPARTA SYSTEMS' TRACKWISE SOFTWARE

Sparta Systems is the recognized global leader for enterprise quality and compliance management software. Over 200 companies and 300,000 users rely on TrackWise, including quality assurance, manufacturing, customer support and regulatory professionals. TrackWise is a complete solution with unlimited flexibility to meet the precise needs of each customer. Sparta Systems also offers full support services and best practices for implementation.

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