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PDA Letter

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January 2008

In This Issue…

PDA Parenteral Drug Association

Connecting People, Science and Regulation®

Getting to "Preventative" Through Strong Quality Systems

Emily Hough and Walter Morris, PDA

Pharmaceutical companies and regulators are placing a heavier emphasis on the "P" in Corrective and Preventative Action (CAPA) plans. Current examples of drug recalls and other quality problems indicate that companies are still reacting to problems rather than proactively targeting quality deficiencies.

Experts at the PDA/FDA co-sponsored conference on Quality Systems stressed the need for a more proactive and efficient approach that would better serve patients and move the industry closer to six sigma. The conference on Quality Systems was held in Bethesda, Md., on Nov. 1-2. Presenters spoke about the impact that CAPA has—from the manufacturing site all the way to the marketplace—in the context of robust pharmaceutical quality systems.

Martin Van Trieste, VP, Quality, Amgen, spoke about the need for an enhanced structure of CAPA, as the pharmaceutical industry is lagging behind other industries. He said during his presentation, *"Evolving Systems: CAPA,"* the CAPA system would provide significantly greater business benefits if industry acted in a more proactive systematic manner. "Mature quality systems prevent problems, so you don't ever have problems in the first place," Van Trieste said.

Neil Wilkinson, PhD, Senior Director of Global Quality, AstraZeneca, agreed the industry needs to learn from its past mistakes. "I bet you, I could walk in today and look at your records and look back five years ago and I will find the same issues that are happening now—were happening then and that is a sad reflection of us as an industry."

Wilkinson said that more of a change in thinking is required so that a preventative culture is moved toward, rather than a corrective one. He estimated that the industry is at a 90% corrective mode. Wilkinson said that he would like to see that change to 10% so that "most of our actions are preventive, rather than reacting to nonconformances that have already occurred in the past."

FDA's **Kim Trautman**, GMP Expert, CDRH, agreed that problems need to be avoided, not just fixed. "It is not just about the correction to the specific problem or product problem, but what the systematic correction is. What can we do proactively, to really truly take preventive steps?...There are monitoring

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2008 PDA Annual Meeting

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Colorado Springs, Colorado

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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.

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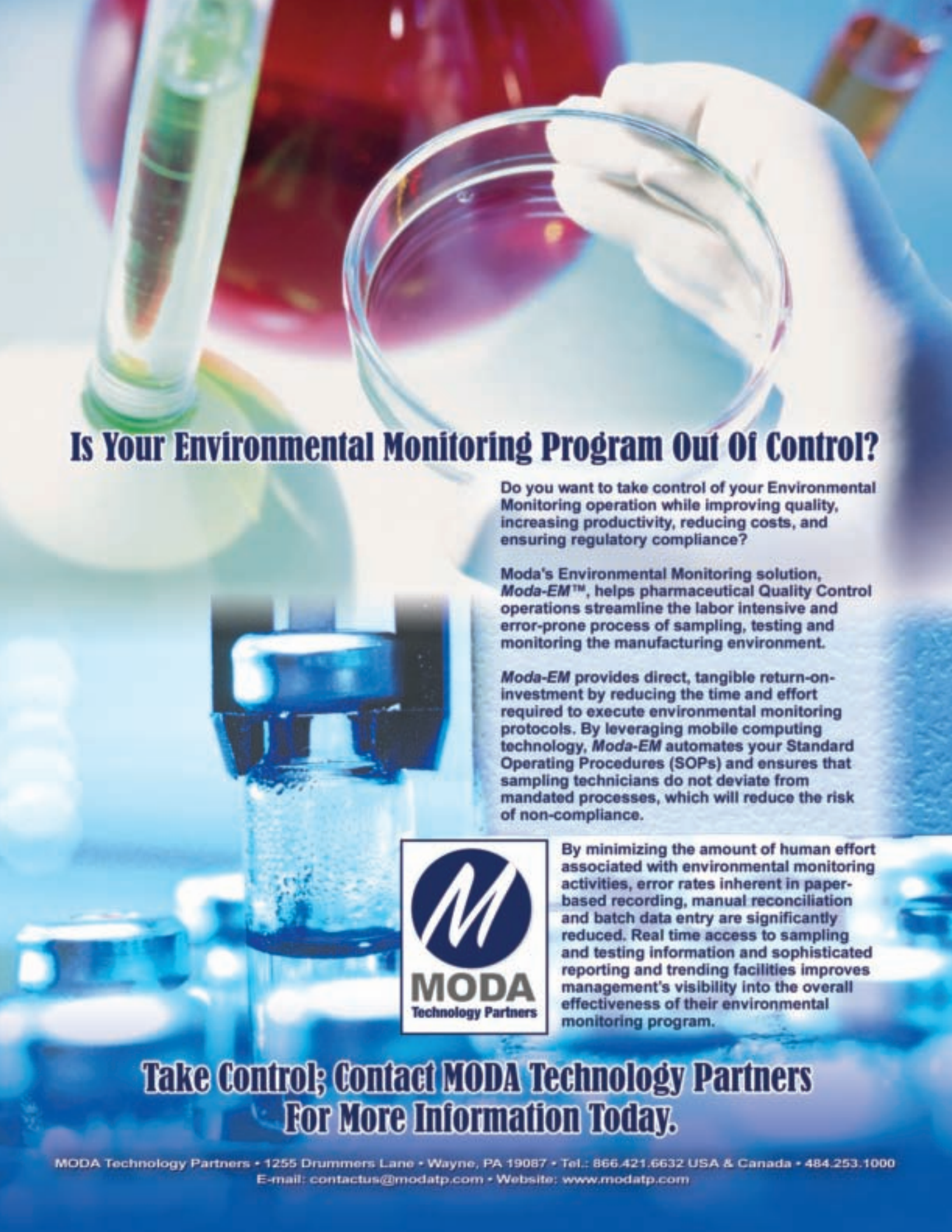

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Cover art: *While it is commonly accepted that microchip manufacturers utilize more robust quality systems than pharmaceutical firms, can the same be said about potato chip manufacturers? An article in The Wall Street Journal says so and was discussed at the PDA/FDA cosponsored workshop on Quality Systems in Bethesda last November.*

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Editor's Message

In this issue, new *PDA Letter* writer/editor **Emily Hough** reports on the 2007 PDA/FDA Co-Sponsored Workshop on Quality Systems in Bethesda, Md. (cover story). Her focus is on discussions about CAPA systems and how more of an emphasis needs to be placed on the preventative aspect.

PDA member **Stephan Roenninger,** in collaboration with PDA's **Jim Lyda,** provides an informative report from recent ICH meetings in Yokohama, Japan (see page 32). At that meeting, ICH Q4B on pharmacopeial harmonization reached Step 4. The ICH Steering Committee also agreed to the formation of a single Implementation Working Group for Q8, Q9 and Q10.

Henry Kwan, PDA's consultant for Chapters and long-time PDA member/volunteer, reports in with another "Tales from the Trail" (p. 37). Speaking of solid PDA volunteers, this issue we provide two Volunteer Spotlights: **Jean Louis Saubion** and **Michael Miller.**

This issue is also the "show issue" for the upcoming PDA/EMEA Joint Conference in Budapest. Please be sure to read about the event in the articles listed on the cover page. Keep up with PDA's other doings in the Science & Technology and Quality & Regulatory Snapshots, TRI Talk, and the Programs & Meetings and Europe sections.

Finally, in the spirit of Quality Systems and Corrective and Preventative Actions, the **PDA Letter** staff must take responsibility for some snafus which occurred in the prior two issues. First, in the October issue, our very own president—**Bob Myers**—was misidentified as "Bill" Myers in the "President's Message." We are still trying to figure out how we missed that one. Second, in the November/December issue, long-time volunteer and former board member **Tim Marten** was misidentified in the TRI photos as **Steve Marten,** not to be mistaken with long-time funnyman **Steve Martin.** Since we are still here, we assume Bob has forgiven us, and we hope Tim can do the same! We assure all readers that we will be much better now that we have Emily on board. Thanks for your patience.

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!

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John Shabushnig Ascends to PDA Chair

John Shabushnig starts as PDA Chair in 2008 after serving two years as Chair-Elect following the 2005 PDA elections. Outgoing Chair **Vincent Anicetti,** elected directly to the position in 2005, now serves as Immediate Past Chair until the end of 2009. **Maik Jornitz** was elected by the membership as the current Chair-Elect, and will ascend to the Chair in 2010.

Rebecca Devine joins the Executive Committee as Secretary, and **Anders Vinther** joins as Treasurer following the 2007 autumn election.

New Directors elected to the Board for two-year terms are: **Harold Baseman, Véronique Davoust, Lothar Hartmann, Stephan Köhler** and **Michael Sadowski. Laura Thoma** was re-elected as a Director.

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Martin Van Trieste, *Amgen*

PDA wants to thank outgoing members of the Board for serving the Association and the membership: **Nikki Mehringer, Lisa Skeens, Tim Marten, Eric Sheinin,** and **Kathleen Greene.** PDA looks forward to their continued participation and contribution.

New Releases from the PDA Bookstore

Check out these newly released titles in the PDA Bookstore, your source for pharmaceutical and biopharmaceutical science, technology and regulatory information.

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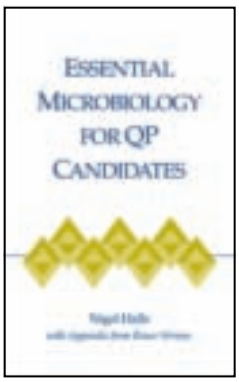

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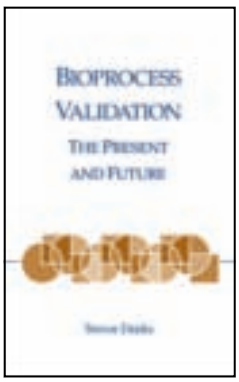

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PDA Technical Report No. 43, Identification and Classification of Nonconformities in Molded and Tubular Glass Containers for Pharmaceutical Manufacturing Prepared by PDA Glass Defects Task Force

The purpose of this technical report is to provide consistent, standardized quality criteria that can be used by pharmaceutical companies for the visual inspection of incoming glass containers.

Two detailed lexicons (collection of color photographs of glass defects) visually illustrate glass nonconformities that have been developed: one for molded glass and one for tubular glass. This digital lexicon collection accompanies *Technical Report No. 43* and is included in this purchase price.

Supplement Volume 61, No. S-3
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Science & Technology *Snapshot*

Your Technology Trends Article can Contribute to the Advancement of Our Industry

Rich Levy, PhD, PDA

As part of the Science & Technology Snapshot, we want to present information on the latest technology trends relevant to the PDA community. In 2007, we published several "Technology Trends" from various sources, including a dialogue from a PDA workshop on TR-1 and articles contributed by PDA members. Our goal is to include a "Technology Trend" in five of the ten Snapshots published in 2008.

We feel this component of the Snapshot has a great deal of potential to keep our membership informed while individual members gain experience and some recognition by their peers.. The concept is simple. Write about a technology trend that has impacted you and your company and share it with PDA for publication. The Technology Trend does not have to reference cutting-edge technology, but rather can discuss a well-known technology that is new to our industry or being applied in new ways. Examples of this are disposable manufacturing systems discussed in the June 2007 issue and the E-beam sterilization technology featured in the October 2007 Snapshot. In both cases, each technology is already well-established, but there is an up tick in their application industry-wide. In the case of E-beam, the application of this technology to aseptic processing systems is noteworthy.

Even if you don't want to write an article yourself, let us know about a technology trend that is important to you. We can do the follow-up, or even locate an expert willing to write the article for us.

PDA does expect that all articles will provide details on how the technology is being used today in the industry, preferably from a manufacturer's perspective. One caveat. We don't intend to publish "info-articles" from technology enablers in the Letter. Enablers are welcome to submit Technology Trends as long as they are able to discuss the actual application of their technologies in a pharmaceutical facility, even if they must leave out specific company names. Co-authored articles from enablers and users are encouraged.

So, now that you know the process, get involved in Technology Trends.

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),** ***Validation of Column-Based Separation Processes***
- **TR-15 (Revised),** ***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),** ***Sterilizing Filtration of Liquids (Board Ballot)***
- ***Quality Risk Management for Aseptic Processes (SAB Ballot—Just Approved)***
- ***TR-44, Filtration of Liquids Using Cellulose-Based Depth Filters (Board Ballot)***

Journal *Preview*

November/December 2007 Journal

Lee Kirsch, PhD, University of Iowa

The last issue of PDA Journal of Pharmaceutical Science and Technology for 2007 is loaded with excellent research articles. A two-manuscript series on the mechanisms of vial breakage during freezing describes the use of specially designed strain gauges to evaluate the effects of processing conditions and solute characteristics on this potential failure mode usually associated with freeze-drying operations but also relevant to the manufacture of cryogenic pharmaceuticals. The manuscripts entitled "Mechanistic Studies of Glass Vial Breakage for Frozen Formulations I" and "II" are a collaborative effort for a group of co-authors and investigators including **Ge Jiang, Mike Akers, Manish Jain, Jeremy Guo, Adrian Distler, Rob Swift, Manpreet-Vick Wadhwa, Feroz Jameel, Sugu Patro** and **Erwin Freund.**

continued on page 10

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
  Chair **Robert Repetto,** Wyeth
- Analytical Methods for Biotech Products
  Co-Chairs **Nadine Ritter,** PhD, Biologics Consulting Group, and **Gautam Maitra,** AC Immune
- Analytical Method Validation for Commercial Biopharm Products
  Chair **Stephan 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.

- 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

Task Force *Update*

A Peek at the "Sneak Peek"

The following Task Forces presented their work at the "Sneak Peek" on Nov. 5, hosted by Amgen at its Thousand Oaks, Calif., headquarters:

Co-chair **Peter Lee**, Amgen, of the **Task Force for the revision of TR-3, *Validation of Dry Heat Processes used for Sterilization and Depyrogenation***, noted that the group is holding a follow-up meeting in January to review the completed first draft. He is hopeful that a draft will be released for formal peer review in March 2008.

A co-chair of the **Task Force for the revision of TR-14, *Industrial Perspective on the Validation of Column Based Separation Processes for the Purification of Proteins*** represented the team in Thousand Oaks; **E.J. Brandreth,** Favrille, received several useful suggestions for monitoring levels of various types of chromatography from audience participants. He commented that the feedback will be discussed at the next meeting of the task force.

The Task Force for the revision of TR-15, *Industrial Perspective on the Validation of Tangential Flow Filtration Systems in Biopharmaceutical Applications,* was represented by **Chris Bussineau**, BioVascular. The draft revision to TR-15 had recently undergone global industry and regulatory peer review. The document generated many questions regarding inclusion, particularly the portion on PAT. Chris agreed that PAT could be applied in this operation. He noted that the feedback received at the "Sneak Peek" will be considered by the task force at its next planned meeting in December.

Jean Bender, Genentech, made the short trip to Amgen to represent the **Task Force for the revision of TR-26, *Sterilizing Filtration of Liquids.*** Interest in the assessment of extractables and leachables was high, as evident by discussion of the draft document. All agreed that while these are certainly important to monitor, filter contact with process fluid is minimal as compared to long term container/closure contact.

The Task Force for the new technical report on Reprocessing of Biopharmaceuticals was represented by **Harold Van Deinse,** Baxter Healthcare. Discussions with the audience centered around defining reprocessing, particularly with respect to labeling and freeze/thaw and use of risk management in the decision to reprocess both proactively and reactively.

Journal Preview, continued from page 9

The development of an intravenous dosage form for vitamin A using emulsion technology is the subject of a fine offering from Thailand entitled the "Physicochemical Properties of Lipid Emulsion Formulated with High-load All-trans-Retinoic Acid." Co-authors **A. Chinsriwongkul, P. Opanasopit, T. Ngawhirunpat, N. Chareansriwilaiwat, W. Sila-On** and **U. Ruktanonchai** report on the stability and drug release properties associated with formulation sources of variation. PDA Journal readers can also take a quick look at the entire table of contents of the 3rd and 4th quarter issues of the 2007 Thai Journal of Pharmaceutical Sciences.

The use of statistical models to characterize drug release from HPMC matrix tablets containing cyclodextrin-complexed glipizide is the subject of a manuscript by **H. N. Shivakumar, B.G. Desai, S. Pandya** and **S. S. Karki** entitled "Influence of-cyclodextrin Complexation on Glipizide Release from Hydroxypropyl Methylcellulose Matrix Tablets." In addition to studying drug release, the authors characterized the complexation properties using Fourier Transform Infrared Spectroscopy, Differential Scanning Calorimetry, X-Ray Diffraction and Nuclear Magnetic Resonance.

A short manuscript on evaluation methodologies for iontophoretic drug delivery is entitled "Homogenization Technique for Analysis of Post-Iontophoretic Acyclovir Content in Porcine Skin" by **J. Shaji** and **S. Marathe.**

The occurrence of red cell aplasia was linked to the leaching of various phenolic compounds from pre-filled syringes due to the presence of surfactants in the drug formulation. The efforts of a group of scientists to isolate and identify the leachables using LC-MS and Electrospray Ionisation Tandem Mass Spectrometry is described in "Recognition and Identification of UV-absorbing Leachables in EREX® Pre-filled Syringes: An Unexpected Occurrence at a Formulation-Component Interface" by **J. Pang, T. Blanc, J. Brown, S. Labrenz, A. Villalobos, A. Depaolis, S. Gunturi, S. Grossman, P. Lisi** and **G. Heavner.**

Stay tuned, we already have some great manuscripts lined up for next year.

December Top 10 Bestsellers

PDA℠ Parenteral Drug Association

1. **Essential Microbiology for QP Candidates** *New*
   By Nigel Halls, PhD *with Appendix from Bruce Vernon*
   Item No. 17265, PDA Member $225, Nonmember $279
2. **Environmental Monitoring: A Comprehensive Handbook, Volume I, Volume II and Protocol CD**
   Edited by Jeanne Moldenhauer, PhD
   Item No. 17239, PDA Member $530, Nonmember $659
3. **PDA Archive on CD-ROM – PDA Archive Retrieval Index - 30% Off**
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4. **Risk Assessment and Risk Management in the Pharmaceutical Industry: Clear and Simple**
   By James L. Vesper
   Item No. 17219, PDA Member $235, Nonmember $289
5. **Bioprocess Validation: The Present and Future** *New*
   By Trevor Deeks, PhD
   Item No. 17248, PDA Member $225, Nonmember $279
6. **Risk-Based Software Validation: Ten Easy Steps**
   By David Nettleton and Janet Gough
   Item No. 17256, PDA Member $200, Nonmember $249
7. **Pharmaceutical Contamination Control: Practical Strategies for Compliance**
   Edited by Nigel Halls, PhD
   Item No. 17246, PDA Member $255, Nonmember $315
8. **PDA Technical Report 1, Revised 2007, Validation of Moist Heat Sterilization Processes Cycle Design, Development, Qualification and Ongoing Control**
   Item No. 01001, PDA Member $150, Nonmember $250
9. **PDA Technical Report 43, Identification and Classification of Nonconformities in Molded and Tubular Glass Containers for Pharmaceutical Manufacturing**
   Item No. 01043, PDA Member $100, Nonmember $225
10. **GMPs Training CD Program, 10 programs on Sub-Parts B through K, Good Manufacturing Practice Regulations, 21 CFR Parts 210-211**
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Recent Sci-Tech Discussions: ICH Q10 vs. ISO 9000 and Oil Free Air

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

ICH Q10 vs. ISO 9000

The ICH Q10 is a bridge between regulatory requirements (including ISO standards), helping industry and regulators to achieve harmonization of the pharmaceutical quality system throughout the lifecycle of a product.
I remember that ISO certification audits are used to certify all types of companies, but in the pharmaceutical field, only packaging material and medical devices because of the ISO audits are very general and a look at the whole system and not really concerned with the product integrity.

Do you consider more appropriate for Active Pharmaceutical Ingredient and Drug Product the ICH Q10 strategy instead of ISO 9000? It is a fashion of some auditors to ask for ISO certification.

Respondent 1: ISO 9000 and ISO 13485 (for the medical device sector) inspections are not limited to general issues. In many cases there are more frequent audits under the ISO schemes than occur with pharmaceutical regulatory agency inspections (e.g., two per year), and audits between recertification visits usually address only part of the quality system and so can be very detailed.

As always, the quality of the audits is to some extent related to the quality of the auditor (but that is not limited to the ISO sector!).

Questioner: [Respondent 1], does it makes sense to certify with ISO 9000 a pharmaceutical company that produces active pharmaceutical ingredients if you already have implemented the ICH Q10, which harmonized requirements of ISO 9000 for the pharmaceutical industry? I have been told that the ISO certification opens doors.

Respondent 2: I believe that ICH Q10 is still only in draft form. In any case the GMPs for APIs is well established in EudraLex, so I am confused as to what you are trying to achieve by referring to ISO?

Respondent 1: ISO 9000 certification of API manufacturers is a good starting point, but note that the QP has to confirm that the API manufacturer complies with European GMPs for APIs for use of the API in the EU. ICH Q7 is the standard against which they will judge compliance. ICH Q10 has yet to be implemented.

Respondent 3: I agree with [Respondent 1] that ISO 9000 is a starting point, but where I have great problems is that while ISO 9000 gets a company in the mindset to need systems and documentation, it does not provide much guidance into the regulators expectations for API industry GMP compliance. In my experience companies that tout their ISO 9000-ness the most, have the hardest time meeting GMPs.

Questioner: [Respondent 3], ISO standard never has substituted the specific standard of the industry, nevertheless I agree with you. Do you know API pharmaceutical companies certified by ISO 9000?

Respondent 4: Having followed the chain I don't think that it has been made clear enough. All the signatories to ICH Q7A—USA, Japan, EU—and those countries that have also implemented the standard have made it mandatory that the GMP requirements are implemented for APIs. For drug products 21 CFR Part 11, All the EU Directives and GMP Rules Volume 4, TGA Rules and the Rules in many other countries mandate that these are followed. There is no debate.

For packaging components and devices various ISO standards can be implemented.

The biggest difference between the GMP requirements and ISO requirements is that the GMP requirements set specific standards that are monitored and enforced by government agencies. The detailed requirements are published. For ISO requirements companies tend to set their own standards, and are audited by the accreditation agency to which the company pay an annual fee.

If somebody auditing an API manufacturer asks for ISO, I think the answer is simple. We do not have it, it is optional, the GMP requirements are mandatory. Hope this clarifies the situation

Respondent 5: [Dear Questioner and Respondent 3], ISO 9000 is nothing but starting point only, and there is no legal requirement stating need of ISO certification for API facility. Better to go with ICH Q7 (one of the easiest ICH guidelines) and APIC guidelines. More consideration to be given on cleaning validation, facility validation and risk management. ICH Q10 is yet to be implemented.

Quality management system and management responsibilities as described in ISO guidelines and Q7 is similar. Even it matches with U.S. FDA six system inspection model, QSIT guidelines and quality system regulations.

Respondent 6: My two paisa. ISO 9000 is a general system being used for all type of industry. It also says document what you have performed/done, perform/do what you have documented. ICH Q7A is specific to API pharmaceutical industry.

I have seen and was part of industry where ISO 9000 and ICH Q7a has been wonderfully sewn together in one system. ISO requirements were wonderfully incorporated into SOPs being followed under ICH Q7A requirements.

Oil Free Air

We have a number of applications in which oil free air is needed for sterile and aseptic processes. I recall that the standard dew point temperature is -20°C but for the life of me I cannot find the correct reference (I think that it is more a EU issue than USP). Can any one help?

I have the ISO standard but it doesn't classify the needed air according to the application so it is not a big help.

Also, how do we translate the dew point temperature from the 8 barg pressurized air to the atmospheric -20°C?

Respondent 1: Just a reminder just because the compressor is oil free you still need "oil filters"

Respondent 2: I am not aware of any specific dew point recommendations from a regulatory agency (or a pharmacopeia) for the application you describe. The "standard" or "typical acceptance criteria" I have seen (for validation, anyway) are actually -40°C and -100°C.

That said, I believe this is a topic in the industry that could benefit from scientific rationale and risk analysis. One should not only understand what the numbers really mean, but also the potential impact to product.

Is there product contact and could the product be sensitive to the contents of the air (in this case, water vapor at those levels)? Is there concern for impact to mechanical or electronic components contacted by the air? Is there simply a desire to avoid condensation in the air line? Without answering these questions, I feel the only option is to follow some "industry standard," even if it means shouldering unnecessary resource burdens in system design, operation and/or testing.

Also, how do we translate the dew point temperature from the 8 barg pressurized air to the atmospheric -20°C? I believe that a pressure dew point of around 5.9°C at 8 barg would result in a dew point (atmospheric) of -20°C. I obtained that information from an online moisture calculator from alphamoisture systems (I do not know the calculations behind it).

It does beg the question, however, should we be interested in dew point, in pressure dew point, or both?

I hope this information helps and is not simply a repeat of past threads.

Respondent 3: I have mostly seen people use process compressed air between classes 1,2,1 and 1,4,1 according to ISO 8573-1. (particles, dew point, oil)—you mentioned that you had this standard.

For dew point, I have not seen a reference to -20°C (ISO 3) as a standard but would be interested to hear from other members about that. We use ISO 2 (-40°C) for dew point, excessive you might say but it definitely gives a comfort factor.

For Instrument air you might want to reference ANSI - ISA - 7.0.01 – 1996 (Quality Standard for Instrument Air) which specifies that IA must have a dew point at least 10°C below the minimum value to which any part of the AI distribution system is exposed and a pressure dew point not greater than 4°C. I guess you can translate that to process air too.

I think the conversion for dew point value at 8 barg to atmospheric is in ISO 8573-3. My European perspective.

Respondent 3: [Respondent 2], I think you raise an interesting question. Some discussion of the compressed air ISO 8573-1 values people use would be of value.

People might say how boring or find it mundane to discuss compressed air standards, but in reality there are some expensive overkill decisions taken when it comes to deciding what ISO quality air to use for what application. I guess for the reason you state.

For example, its easy to specify ISO 1 for particles ("medical air") without taking into account how costly it is to maintain such a system and keep it in a qualified state with that specification, or correctly sample the air in the distribution system.

What compressed air ISO classes do other forum members work to and for what? Are you willing to share that information?

Respondent 4: [Respondent 3], we used ISO 2/3/2 in an OSD project two year ago. In France we used to use what was known as "pneurop publication," before ISO 8573; besides there are two publications in STP pharma about pharma compressed air. One of them raised the approach of nonqualifying all POU, just beginning end and some other points (critical ones, "par embranchements") for particulates/dew point/oil content. And even though we used a dry screw compressor, AQ asked to check ALL the POU.

PDA Interest Groups & Leaders

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

SECTION TITLE

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

SECTION LEADER

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

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Getting to "Preventative" Through Strong Quality Systems, continued from cover

techniques; there are control techniques that can move us more to a preventive world and not so reactive."

According to Trautman, "Both in the device side and in the pharmaceutical side (and biological) we are still very much…reacting to complaints, reacting to information and litigation. We need to move a little bit more progressively so that we can be in front of that curve instead of firefighting from behind."

The automotive and semiconductor industries have successfully implemented preventative quality systems. Van Trieste, in his presentation, conveyed how both industries improved after undergoing extreme external cost pressures, competitive pressures and increasing consumer demands for improved reliability.

The semiconductor industry underwent performance and quality improvements to produce more powerful and reliable products and in turn provided tremendous consumer value in order to survive as a company. Remember "there was extreme external pressures forcing them to get their product to the market fast and then make rapid improvements," Van Trieste said.

"When [microchip producers] would launch a product, their yields would be low. For example a new product might have 40% yields, and they made their money from how fast they could go from 40 to 99.99% yields. They already had the competition taking their business….Reliability is very important. So the electronic industry adopted six sigma to meet these challenges."

The auto industry, in turn, went from one dominated by U.S. manufacturers and their well known "planned obsolescence" strategy to one dominated by Japan and total quality management. While this shift led to improved product quality, the car industry still has room to improve. If it were as

The PDA/FDA Co-Sponsored Workshops on Quality Systems

Walter Morris, PDA

In the U.S. FDA's continuing effort to help industry implement more robust quality systems, the Agency partnered with PDA to stage workshops on the subject. FDA announced the effort in the Sept. 20, 2007 Federal Register:

The Food and Drug Administration (FDA) is announcing a series of educational workshops on quality pharmaceutical production under current good manufacturing practice (CGMP). The workshops, which will be held in collaboration with the Parenteral Drug Association (PDA), are intended to educate participants on current methods for compliance with good manufacturing practices (GMP). The workshops are being offered to help ensure effective CGMP programs and to further the common goals of FDA and providers of quality.

FDA joined with PDA to create a program that provides "information and training opportunities for industry as well as CGMP compliance officials." Through close collaboration with officials from CDER, the program committee developed an agenda that provides "information on specific topics designed to educate and guide participants on methodologies and implementation of CGMP as applied to quality drug manufacturing. Presentations by both FDA and industry will provide a regulatory and practical perspective on the current relevant critical topics."

The committee also included a solid mix of experts from around the global pharmaceutical marketplace to help build a program beneficial to pharmaceutical professionals in each major region: North America, Europe and Asia. As such, FDA agreed to participate in the program on three continents, with the first stop in North America in Bethesda (Nov. 1-2), the second workshop in Dublin, Ireland (Dec. 10-11), and two stops in China—Beijing (Apr. 21-22) and Shanghai (Apr. 24-25). The following experts from industry and the Agency comprised the planning committee (see below).

From the various presentations at the Bethesda workshop, it was clear that participants will gain valuable insights into the evolving concept of quality systems as defined by FDA and ICH. The current regulatory push for the implementation of robust quality

continued from page 15

management systems only reflects internal efforts for improved systems. As pointed out by various speakers, companies long have been seeking new ways of finding and eliminating root causes of manufacturing problems. Often, companies felt it best to follow the lead of the regulators in their efforts to improve.

For example, over a decade ago, it was typical for firms to track only those deviations that were deemed significant, and this tracking was done at the facility level. As a result, the overall picture regarding the state of manufacturing control across the entire enterprise was not very clear. After a time, regulators advised firms to develop a more comprehensive approach, and in some cases, demanded it through regulatory action.

Next, many companies expanded their tracking capabilities to include all types of quality incidences. The resultant overload in data overwhelmed many a firm's ability to adequately investigate and correct serious problems. Quality systems at this time were still very much reactive and not very good at finding root causes, and really not able to provide preventative actions. Again, the regulators wanted improvements—urging companies to develop better systems for investigating manufacturing problems and requiring the highest levels of management to take responsibility for corrective actions.

That is where the industry and the regulators are right now. Through the Quality Systems workshops, companies of all sizes have an opportunity to learn from experts representing the largest companies and regulators to gain a better understanding of where the quality system paradigm is heading.

Case studies by Abbott, Amgen, AstraZeneca, Eli Lilly, Pfizer and other large companies demonstrate how the involvement of upper management in the quality system and the use of risk management principles lead to marked improvements in the manufacturing area.

In one example, a presenter noted how the institution of management review and risk mangement helped the firm come to grips with a huge backlog in deviation entries in their CAPA system. After careful consideration, the corporate quality group developed a three-tiered classification for prioritizing noncomformances, with the highest priority deviations receiving immediate attention.

Part of the challenge for that firm was to assure plant-level quality personnel that they were following company policy by not acting too conservative when classifying noncomformances. The senior executive imprimatur of the risk-based classification system was very important in overcoming this potential problem.

With a strong commitment to the new system and strong oversight and input from the corporate quality group, the firm feels it is making significant progress both reducing its backlog and finding root causes for nonconformances that have a true impact on the patients.

The presenter of the case study asserted that the regulators like the approach because the firm's investigations are robust, resources are being applied in a rationale manner so that serious problems can be addressed as quickly as possible, and the firm is still capable of tracking all nonconformances—both big and small.

For information on the upcoming QS workshops in China, go to www.pda.org/qualsys.

It has been well-documented at industry forums over the last five years that drug companies have not had the same market pressures to strive for six sigma manufacturing processes, but, nevertheless, have achieved a level of quality that rivals most other consumer product industries.

efficient as the semiconductor industry, Van Trieste observed "a Rolls Royce would cost only $50, it would circle the globe twice on only half a gallon of gas and its top speed would be 2.5 trillion miles per hour."

Another type of chip that has a tremendous record of quality—the potato chip—was also used as an example by Van Trieste. He cited an article from *The Wall Street Journal* which asserted potato chip manufacturers have more advanced manufacturing practices than the pharmaceutical industry. Because these manufacturers have robust processes, he said, they have very few failures. In fact, when he thought about it, he couldn't remember ever having a stale potato chip in his life.

Six Sigma Adoption Slower in Pharma

It has been well-documented at industry forums over the last five years that drug companies have not had the same market pressures to strive for six sigma manufacturing processes, but, nevertheless, have achieved a level of quality that rivals most other consumer product industries. In turn, microchip, ➤

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auto and other consumer industries are not saddled with the regulatory environment governing pharmaceutical development and manufacture—one of the most restrictive for any industry.

All of this is changing. For the last decade, health authorities worldwide have been looking to loosen manufacturing rules to help spawn innovation. Moreover, in recent years, pharmaceutical companies have been feeling the powerful tug of market forces. Where high profit margins driven by successful new product launches once allowed the industry to tolerate relatively high incidences of manufacturing waste, new price pressures directed by governments (particularly growing pressure in the world's largest market—the United States) are forcing companies to consider ways of lowering costs. Likewise, as the number of products flowing out of new drug pipelines slows, research-based companies are going to lose the economic cover afforded them by the lack of competition as more of their products go off patent with fewer blockbuster replacements.

FDA's compliance data shows that the industry as a whole is not operating in the preventative mode yet. The rate of drug recalls and the problems faced are the same now as they were a decade ago. Frequent problem areas are dissolution, contamination, impurities, sterility, labeling, and misbranding, to name a few. **Joseph Famulare,** Deputy Director CDER's Office of Compliance, presented two charts showing the number of drug recalls that have occurred from 1997 to 2007 (see Figure 1 and Figure 2). While the number of recalls remained steady in that period, those classified as most serious and second most serious (Class 1 and 2) have increased.

Van Trieste ended his talk with the following observation: "As an industry, I know we can move to a more proactive rather then r eactive system. We are around 20 to 25% with our cost of quality and the electronic industry is at 1 to 3%. It's amazing the power of doing six sigma. Now will we ever get there? I'm hopeful with the current economic and regulatory environment. However there are signs that the economics in our business will change and I am very encouraged with the various worldwide regulatory agencies focus on quality by design and their desire to help us create cultures of continuous improvement."

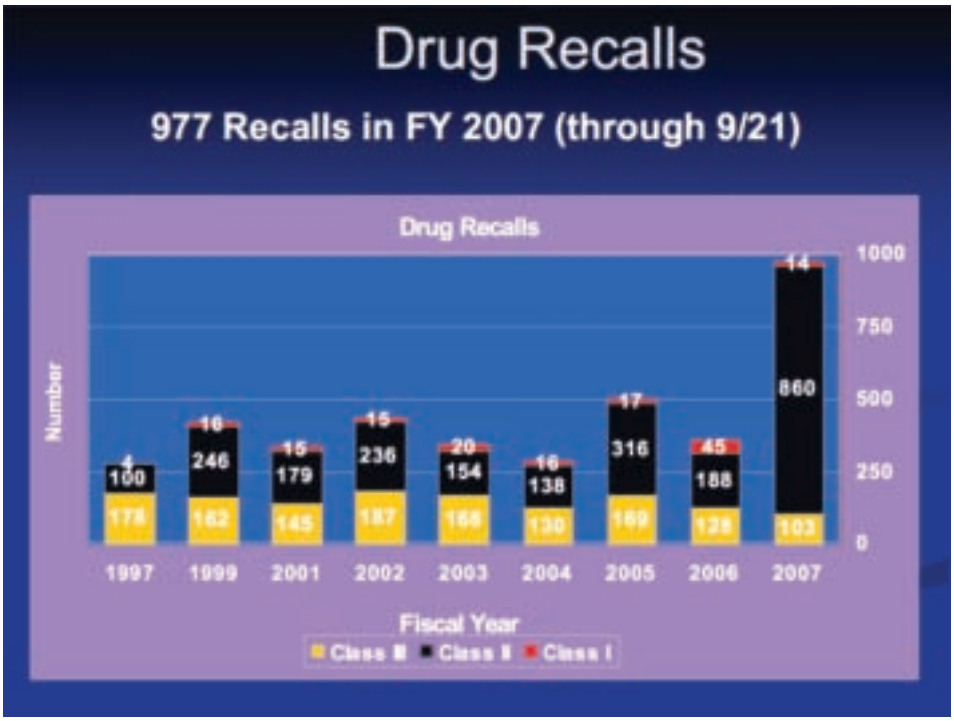

Figure 1: FDA Data for Total Drug Recalls, Fiscal Years 1997-2007

Figure 2: FDA Data for Drug Recalls Adjusted for Multiple-Recall Incidents

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Strong Quality Systems Should Prevent Data Fraud

Data Integrity Issues on the Rise—U.S. FDA

Emily Hough, PDA

The U.S. FDA is seeing an increase in the number of data integrity cases in recent years. Data integrity and manipulation that the agency encounters occurs both in the early stages of drug development and during commercial manufacturing for various FDA regulated products.

Part of the push for strong quality systems in the pharmaceutical industry is driven by the health authorities' intent to see companies across the spectrum apply more vigilant controls to ensure data integrity.

CDER Office of Compliance official, **Edwin Rivera-Martinez** said recently that the preapproval inspection program is one place where FDA tries to identify data fraud. Sponsors unable to demonstrate the ability to operate with integrity will not receive approval for their new drug or abbreviated new drug applications. Speaking at the 2007 PDA/FDA conference, he said that "Quality by Integrity" is just as important as Quality by Design. The two go hand in hand, he said, to assure the safety and efficacy of drug products.

> ***A frequent target of intentional data manipulation is chromatograms.***

FDA field investigators serve as the ground troops in combating fraud. During preapproval inspections, investigators will verify that the data submitted in marketing applications is authentic. The CDER reviewers, on the other hand, can only review the data as submitted. The Office of Compliance's role is to serve as a liaison between the field and review offices. It receives and processes establishment evaluation requests, monitors the status of inspections, reviews reports and forwards their recommendations to the review offices.

A frequent target of intentional data manipulation is chromatograms. In some cases, firms cut and paste chromatographic data so that initial out-of-specification (OOS) test results appear to be in spec. Some companies have changed chromatogram processing parameters to achieve compliant results. FDA also has seen companies substitute aliquot results from passing

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lots for the results of failing lots. Other fraudulent behavior includes altering weights of samples and standards in analytical calculations.

Similar types of fraud are found during GMP inspections. Investigators have noted manipulation of chromatograms by lab chemists without justification and changing of calculations to bring out-of-specification results within specification. Chemists, in this instance, then placed the in-specification assay results into the batch production and control record.

Rivera-Martinez pointed to a specific case where a contract manufacturer/laboratory submitted unreliable analytical results for degradants without notifying the sponsor. The contractor failed to submit initial OOS results obtained using original approved methods filed with the FDA. Passing results reported to the FDA were obtained from an unapproved analytical method not filed with the agency.

When fraudulent activity like the above is suspected, the Office of Criminal Investigations (OCI) works in conjunction with other agencies, including federal, state and local law agencies. OCI, which is part of FDA's Office of Regulatory Affairs (ORA), initiates and conducts criminal investigations under all statutes administered by the Agency. Based on their findings, OCI provides recommendations to the Agency's Office of the Chief Counsel on referrals of criminal cases to the U.S. Department of Justice for further investigation or prosecution.

To ensure that information they receive is correct, the FDA has committed itself to follow up on leads and on information regarding data manipulation and fraud, provide more specialized training of investigational staff on uncovering data integrity, data manipulation and fraud, and to focus more on the manipulation of data during preapproval inspections.

The managers have stated that the conspiracy was directed by the highest levels of the company, including the CEO.

According to Rivera-Martinez, of ten audits that were assigned to the ORA Field Offices by CDER in the 2006 fiscal year, three were revealed to contain data of questionable reliability. They are currently under review by CDER's OC.

Six Able Managers Prosecuted

The case of Able Laboratories, a company that fraudulently changed data and was caught in 2005, was reviewed by Rivera-Martinez. [**Editor's Note**: For more on Able Laboratories, see the PDA Letter, September 2005, page 25.] So far, six defendants in the case—the VP of QA/QC, four QC managers/supervisors and an R&D manager—have plead guilty to a broad-based conspiracy to alter records and flout mandated controls involving a series of drug products. Their criminal conduct ranged from improperly changing test parameters to obtain satisfactory test results to a secret project which included forging data in chemist laboratory notebooks and binders in order to obtain FDA's approval to manufacture a new generic drug product. The managers have stated that the conspiracy was directed by the highest levels of the company, including the CEO.

All six face a statutory maximum penalty of five years in federal prison and a $250,000 fine. A press release issued in March 2007, by the U.S. Department of Justice District Attorney's Office in New Jersey, said that the misconduct at Able Laboratories ruined the lives of many people. U.S. District Attorney **Christopher Christie** said, "Consumers were put at risk, a company that employed 500 people was destroyed, and shareholders were left with nothing at the end. This is the legacy of the fraud perpetrated at Able Labs by these defendants."

While the Able Labs case is certainly a extreme kind of fraud rarely seen in the pharmaceutical industry, Rivera-Martinez said that companies need to vigilantly train employees on proper data handling and reporting, assure reliability of data reported in applications and manufacturing records and emphasize that everyone in the company is responsible for data integrity. All of these are elements of a robust quality management system.

Quality & Regulatory *Snapshot*

FDA Proposes GMP Amendments

Bob Dana, PDA

Happy New Year to all our readers. If you're like me, you are wondering where 2007 went and what new things will be coming along in 2008.

Here is a partial answer to that question. On Dec. 4, 2007, the U.S. FDA published a Direct Final Rule to amend the GMP regulations for finished pharmaceuticals, 21 CFR parts 210 and 211. The Agency intends that the Direct Final Rule will amend the GMP regulations by modernizing and clarifying some of the requirements as well as harmonizing some of the requirements with those of other foreign regulators and other FDA regulations.

The Agency stated its belief that the amendments are consistent with current industry practice and decided to issue the amendments as a Direct Final Rule because it expects no significant adverse comments. However, in the event they do receive such comments, the Agency also published a Proposed Rule, encompassing the same amendments. If significant adverse comments are received, the Direct Final Rule will be withdrawn, and the comments received to the Proposed Rule will be evaluated.

Some of the areas affected by the revisions include sections dealing with plumbing, asbestos filters and verification by a second individual. In addition, several sections of the regulation which impact aseptic processing and sterile products are targeted for revision.

In providing background information supportive of their planned revisions, FDA noted the work done by the Product Quality Research Institute's (www.pqri.org) Aseptic Processing Working Group, chaired by PDA's **Glenn Wright,** Eli Lilly.

At the time of publication, PDA was considering whether to prepare and submit comments on the Direct Final and Proposed Rules.

continued on page 24

Interest Group Briefing

Jentges to be Europe Co-Chair of Inspection Trends/Regulatory Affairs IG

Barbara Jentges

Barbara Jentges, PhD, has agreed to be the Europe co-chair of the Inspection Trends/Regulatory Affairs Interest Group. The U.S. co-chair is **Bob Dana,** who has been leading this Interest Group for many years.

Barbara is based in Switzerland. She is the Managing Director of PhACT GmbH; a company that provides advice and service in drug regulatory affairs, with a specialty in EU regulatory submissions with a focus on biotechnology. Barbara has had more than 17 years of experience in regulatory affairs and previously worked with the Federal Institute for Drugs and Medicinal Devices (BfArM)—the German Health Authorities.

Like all PDA interest groups, the Inspection Trends/Regulatory Affairs IG offers a special networking and communications opportunity in a particular area. In this case, those members with an interest in regulatory, compliance and inspection issues. The IG is a great opportunity to network and exchange information about these topics. Jentges suggests the following topics might be considered when the European portion of the IG becomes active: Clinical Trials Directive, Variations (supplier change, new processes, technical transfer), Advanced Therapies Regulations, Preparation of Scientific Advice, etc. Proposals are welcome and can be sent to Barbara at barbara.jentges@phact.ch.

There will be a face-to-face meeting of the IG at the PDA/EMEA Conference in Budapest on Feb. 20-21, 2008. If you would like to be involved in the IG, please contact **Frederike Graeper,** PDA, at graeper@pda.org.

Regulatory *Trends*

Top 10 Sterile Product Surveillance Inspection Findings

The following data are the top U.S. FDA inspector findings from routine GMP inspections specific to the manufacture of sterile drug products during the Agency's fiscal years 2005-2007. **Tara Gooen,** Chemical Engineer, Office of Compliance, CDER, pulled the data and submitted it to PDA.

The cites are listed by GMP section and subsection in the order of the frequency they appear on the FDA-483's per fiscal period. An interesting quirk in the data occurred in FY '06. The top five observations were each cited the same number of times, and the following 12 citations were also cited an equal number of times. Therefore, all 17 problem areas are listed in two groups—Top 5 and Next 12.

The establishment of/adherence to appropriate sterile manufacturing procedures, 211.113(b), was the third most common problem in '07, a top problem in '06, and the top problem in '05. QC unit responsibilities/procedures not in writing or not fully followed—211.22(d)—and investigations into batch discrepancies/failures—211.192—were the top problem areas in both FY '07 and '06.

Also of note, FDA visited 76 sterile product manufacturers in FY '07, 10 more than each of the two previous fiscal years, 65 and 66 respectively. Moreover, the rate at which investigators issued 483s was much higher in FY '07 compared with the previous years: two-thirds (52) of the 76 inspections resulted in FDA-483s in 2007 compared to 43% (28/65) in '06 and 56% (37/66) in '05.

FY2007

1. 211.22(d) Quality control unit responsibilities and procedures are not in writing or fully followed
2. 211.192 Lack of or incomplete investigation into batch discrepancies or failures
3. 211.113(b) Appropriate sterile manufacturing procedures were not established or fully followed
4. 211.113(b) Inadequate validation of sterile manufacturing
5. 211.160(b) Lack of scientifically sound laboratory controls
6. 211.192 Investigation into batch discrepancies or failures did not extend to other products which may have been affected
7. 211.42(c)(10)(iv) Inadequate system for environmental monitoring

continued on page 24

In *Print*

Disinfection Programs—A Primer

From Essential Microbiology for QP Candidates, *by Nigel Halls, PhD, International Academy of GMP Training*

A reliable cleaning and disinfection program is an essential component of microbiological contamination control in pharmaceutical manufacture.

Disinfectants are chemical agents that inactivate microorganisms. Those that inactivate bacteria are called bactericides. Those that inactivate bacteria and bacterial and fungal spores are called sporicides. Those that inactivate fungi are called fungicides, most, but not all, fungicides are also sporicides.

Most disinfectants only function reliably and predictably on clean surfaces. Most disinfectants in current use are obtained as proprietary brands from commercial sources. None are simple solutions of an active agent in water, all contain other substances—perhaps buffers to ensure that the active operates at its optimum pH, surfactants to ensure better wetting of the disinfected surfaces, or even detergents in combined cleaning-disinfecting agents. The choice of a disinfectant may therefore be contingent upon if it is going to be used on surfaces which are intrinsically "dirty" (e.g., floors in non-sterile manufacturing facilities), or highly clean (e.g., aseptic Grade A/B areas)

For the most part, the active constituents of proprietary disinfectants fall into only a limited range of types—

1) Bactericides

- Alcohols (e.g., 60–70% ethanol or iso-propanol).
- Biguanides (e.g., 2–5% chlorhexidine) most commonly used in conjunction with other agents.
- Phenols (e.g., 2–5% chloroxylenol). Inclusion of detergents in proprietary products allow cleaning and disinfection in one step.
- Quaternary ammonium compounds (e.g., 0.5–1.0% cetrimide or cetylpyridium).

2) Sporicides:

- Aldehydes (e.g., 2% glutaraldehyde). Aldehydes are sporicidal but require long contact times and produce irritating vapours.
- Halogen-releasing agents (e.g., 1–5% sodiumhypochlorite and iodophores).

continued on page 26

FDA Proposes GMP Amendments, continued from page 22

In addition, FDA has withdrawn the May 1996 proposed rule amending the GMP regulations for finished pharmaceuticals. They indicated they were taking this step because of a change in approach to regulation of CGMP, consistent with changes occurring in other industries and other countries. This change in approach will include an incremental approach to the revision of the regulations, rather than the comprehensive approach taken in the May 1996 proposal.

So, that's the big regulatory news from the U.S. to kick off 2008.

Elsewhere in the Quality and Regulatory Snapshot, there is a summary of the frequency of findings from FDA's sterile drug surveillance program for Fiscal Years 2005–2007. We hope you will find these data interesting and instructive, and hope to be able to provide similar results for other FDA compliance findings in the future.

In the global arena, this issue includes copies of the PDA comments on the EMEA draft Guideline on the Production and Quality Control of Monoclonal Antibodies and Related Substances. These comments were developed by a PDA Task Force chaired by **Anita Derks** of F. Hoffmann LaRoche. If you are interested in working on future PDA Task Forces, please be sure to forward an email indicating your interest and area(s) of expertise to **Iris Rice** at rice@pda.org.

Also included in this issue is an extensive review of the recently concluded ICH meeting in Yokohama, Japan, written by **Stephan Roenninger** of F. Hoffmann LaRoche. The article describes the outcomes of the discussions on Quality topics from that meeting.

As always, we welcome your feedback on the concept and the contents of the Quality and Regulatory Snapshot as well as any suggestions for future issues. Just email us at snapshot@pda.org. See you in February.

Regulatory Trends, continued from page 23

8. 211.100(b) Manufacturing procedures were not followed or documented at the time of performance
9. 211.63 Inadequate equipment design, size, and/or location
10. 211.67(a) Inadequate equipment cleaning, sanitizing, and/or maintenance

FY2006

Top 5 (tie):

- 211.192 Lack of or incomplete investigation into batch discrepancies or failures
- 211.22(d) Quality control unit responsibilities and procedures are not in writing or fully followed
- 211.160(b) Lack of scientifically sound laboratory controls
- 211.165(e) Inadequate test method validation
- 211.110(a) Adequate in-process manufacturing controls were not established or fully followed

Next 12 (tie, cited once less than FY06 Top 5):

- 211.63 Inadequate equipment design, size and/or location
- 211.22(c) Quality control unit does not have the responsibility for approving or rejecting all procedures or specifications
- 211.192 Incomplete written record into investigations of batch discrepancies or failures
- 211.42(c)(10)(iv) Inadequate system for environmental monitoring
- 211.194(a)(8) Inadequate sign-off by a second person for laboratory records
- 211.186(a) Inadequate preparation of manufacturing and control records
- 211.160(a) Inadequate laboratory controls and changes
- 211.113(b) Inadequate validation of sterile manufacturing
- 211.113(b) Appropriate sterile manufacturing procedures were not established or fully followed
- 211.68(b) Inadequate controls over electronic master formula records
- 211.67(b) Inadequate equipment cleaning procedures or procedures were not fully followed
- 211.67(a) Inadequate equipment cleaning, sanitizing and/or maintenance

FY2005

1. 211.113(b) Appropriate sterile manufacturing procedures were not established or fully followed
2. 211.192 Lack of or incomplete investigation into batch discrepancies or failures
3. 211.100(b) Manufacturing procedures were not followed or documented at the time of performance
4. 211.63 Inadequate equipment design, size, and/or location
5. 211.22(d) Quality control unit responsibilities and procedures are not in writing or fully followed
6. 211.67(a) Inadequate equipment cleaning, sanitizing and/or maintenance
7. 211.160(b) Lack of scientifically sound laboratory controls
8. 211.110(a) Adequate in-process manufacturing controls were not established or fully followed
9. 211.113(b) Inadequate validation of sterile manufacturing
10. 211.188 Incomplete batch production and control records

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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

In Print, continued from page 23

Use of Disinfectants

From a regulatory standpoint, EU Good Manufacturing Practice (GMP) Clause 3.2 points out that premises "should be cleaned and, where appropriate, disinfected according to detailed written procedures." In the United States, the Code of Federal Regulations (CFR 211.42 (c) (10) (v)) indicates that for aseptic processing there should be "a system for cleaning and disinfecting the room and equipment to produce aseptic conditions." A program of disinfection is clearly necessary for clean rooms used for manufacture of sterile products, and most regulatory recommendations with regard to disinfection focus on this aspect of pharmaceutical manufacture. However, there is also a practical necessity for microbiological control in facilities used for manufacture of non-sterile dosage forms, but to differing extents, according to the microbiological limits and patient risks associated with contamination of the various different types of non-sterile dosage form.

The single biggest usage of disinfectants is for decontaminating floors. Most floors in pharmaceutical manufacturing areas are mopped every day, sometimes more than once a day. Walls may be wiped down with disinfectants, but less frequently than floors. In non-sterile manufacturing facilities the frequency of wiping down the walls with a disinfectant is likely to be very low. In ancillary areas supporting sterile manufacturing applications—Grade C/D—this might be weekly or monthly. In Grade A/B areas it could be daily, but more probably less often. Manufacturing equipment may be wiped down with disinfectants. This may extend from open work-surfaces, to protected (unidirectional air flow) work stations, machine cabinets and even to the external surfaces of major equipment like fluid bed driers. The product-contact parts of manufacturing equipment are generally cleaned without recourse to disinfectants—this is because of the possibility of leaving residues which could lead to product contamination (adulteration) of a non-microbiological kind. The exception to this may be that washed and rinsed product-contact parts are dried off with alcohol dissolved in water of the same quality as that which is prescribed as ingredient water in the formulation of the finished dosage form. In clean rooms for manufacture of sterile dosage forms, there is a likely need for extensive disinfection of equipment and machinery. The extent to which this may be required is particularly processs pecific, depending on the type of facility and equipment, availability of clean-in-place (say for cytotoxic manufacture), application of fumigation (fogging) techniques, etc. This should certainly be carried out:

- After a shut-down in which aseptic disciplines have been relaxed (and there are various reasons why this should happen)
- In response to environmental problems, particularly if a sporicide is to be used
- On some sort of routine cycle, say weekly or monthly

Disinfectant solutions should not be "topped up" and at least for sterile applications, shelf-lives should be applied (EU GMP Annex 1.38).

Preparation of Disinfectants

Various types of presentation of disinfectants may be of significance to the final use. They may be best supplied in bulk for dilution for floor mopping, or supplied in spray bottles for localized applications. Some suppliers provide specific quantities of disinfectant concentrate in sachets sufficient for making up a "standard" bucketful, which may be of considerable convenience to the end user.

Disinfectants should be dissolved in Water for Injections for all sterile parenteral Grade A/B applications. For ophthalmics this may be relaxed to Purified Water unless the Grade A/B clean room is also used for parenteral manufacture, in which case only Water for Injections may be used.

In Grade C/D ancillary areas of sterile manufacturing and in non-sterile manufacturing areas, disinfectants may be dissolved in potable water except where they may be used in applications which are sensitive relative to exposure of manufacturing equipment, in which case Purified Water may be better used.

For Grade A/B applications disinfectants must be sterilized:

- Where sterilization is done in-house, the preferred method is by bacteriaretentive filtration. In many facilities this may be most conveniently done via the filter train used for sterile filtration of liquid products. The filters should be tested for integrity before and after filtration in the same way as liquid product filters.
- It may be possible and economical to purchase pre-sterilized disinfectants; this can have a considerable impact on operational practices. The presentation should be supplied in double or triple bags to ensure that it can be taken through air-locks into aseptic manufacturing areas.

All diluted disinfectants should be held in clean (or where appropriate clean and sterile) containers. Disinfectant solutions should not be "topped up" and at least for sterile applications, shelf-lives should be applied (EU GMP Annex 1.38).

Rotation of Disinfectants

There is a regulatory view that a single type of disinfectant should not be

used for prolonged periods of time. For instance EU GMP Annex 1.37 states that "Where disinfectants are used, more than one type should be employed." This is called rotation of disinfectants.

The necessity for rotation has been challenged as a result of some scientific studies that may or may not be pertinent to the regulatory reasoning.

Microorganisms do not acquire genetic resistance to disinfectants in the way they can acquire genetic resistance to antibiotics (e.g., MRSA).

However, the prolonged use of a particular disinfectant may encourage the survival and increase of a resistant type of microorganism which is already in the general environment, by killing off all of its competitors. This is called selection, and can be particularly problematic in relation to bacteria which form endospores.

Rotation of disinfectants is neither costly nor complicated. It should be considered as a regulatory necessity in areas used for sterile manufacture (Grades A, B C and D) and practical good sense in other areas.

Validation of Disinfectants

Validation of disinfectants is sometimes perceived as confined to microbiological testing of their effectiveness. It is a far larger topic, which includes:

- Health and safety risk assessment—all disinfectants act on microorganisms by damaging their intracellular metabolic processes, many of which may also be part of human biochemistry
- Company restrictions on suppliers' quality systems
- Company restrictions on documentation provided by the supplier, e.g., Certificates of Analysis for each batch, or particular types of labeling, etc.
- Supplier qualification by audit and in-house chemical testing against supplier's quality control (QC) standards
- Compatibility testing of disinfectants against local materials for corrosion, discolouration, staining, etc.

Microbiological effectiveness testing is only necessary for disinfectants to be used in areas designated for manufacture of sterile products. In these cases the focus of the testing must be on the use of local isolates on local surface materials.

The correct ways of using disinfectants must be described in sufficient detail

There are two broad types of microbiological effectiveness test:

- Suspension Tests. A suspension of a challenge microorganism in the disinfectant is left for a pre-determined period, it is then neutralized and the numbers of surviving organisms counted. Typical acceptance criteria would be for 5 log reductions for bacteria (fewer for molds) within 60 minutes.
- Suspension tests do not mimic the way disinfectants are used in practice, nor are they predictive of performance. However a prospective disinfectant which fails against local isolates in the suspension test is unlikely to comply with simulated-use surface testing criteria, and suspension tests are considerably easier to perform.
- Simulated-use Surface Tests. The principle of simulated-use surface tests is for the challenge microorganisms to be dried on to a surface. No mechanical action is included. After a pre-determined contact period the numbers of survivors are counted. Typical acceptance criteria are for 3 log reductions.
- Local surface materials must be used. Recovery of the challenge in sufficient numbers after drying has often proved difficult.

Practicalities of Disinfection

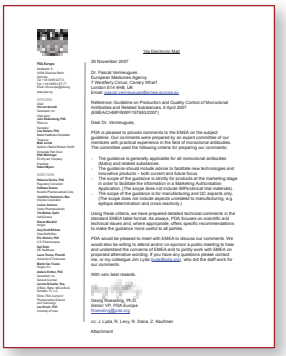
The correct ways of using disinfectants must be described in sufficient detail in the procedures for use as practical training aids for personnel required to perform these tasks. Most techniques used for mopping the floors of Grade A/B areas are variations on the three-bucket technique.

- The first bucket contains the disinfectant solution; the mop is dipped into the disinfectant solution, and the floor is mopped.
- The second bucket either contains water (in the case of Grade A/B —areas this should be sterile and of Water for Injection quality) or the same disinfectant as in the first bucket. After mopping the floor, the mop head is rinsed in this second bucket.
- The third bucket is empty and has a strainer or a wringer mounted over it. The rinsed mop is wrung out into this bucket. Thus the mop is "dry" and absorbent enough to begin the process all over again, dipping the mop into the first (disinfectant) bucket.
- Wiping is used for disinfection of manufacturing equipment, laminar flow benches, etc. Three applications should be considered—so-called "deep cleaning", "routine disinfection" and continuous disinfection.
- Some parts of aseptic manufacturing equipment must be sterilized. Thereafter many other pieces and parts of manufacturing equipment, work stations, chairs, communication systems, trolleys, etc used in Grade A/B areas are probably both unnecessary and impractical to sterilize. Documentation should be in place to ensure that these are periodically "deep-cleaned," generally after shut-

continued on page 44

PDA Submits Comments on EMEA Mabs Guide

For the comments grid, visit www.pda.org/regulatorycomments.



Via Electronic Mail

30 November 2007

Dr. Pascal Venneugues
European Medicines Agency
7 Westferry Circus, Canary Wharf
London E14 4HB, UK
Email: pascal.venneugues@emea.europa.eu

Reference: Guideline on Production and Quality Control of Monoclonal Antibodies and Related Substances, 5 April 2007 (EMEA/CHMP/BWP/157653/2007)

Dear Dr. Venneugues,

PDA is pleased to provide comments to the EMEA on the subject guideline. Our comments were prepared by an expert committee of our members with practical experience in the field of monoclonal antibodies. The committee used the following criteria for preparing our comments:

- The guidance is generally applicable for all monoclonal antibodies (Mabs) and related substances
- The guidance should include advice to facilitate new technologies and innovative products—both current and future focus
- The scope of the guidance is strictly for products at the marketing stage in order to facilitate the information in a Marketing Authorisation Application. (The scope does not include IMPs/clinical trial materials).
- The scope of the guidance is for manufacturing and QC aspects only. (The scope does not include aspects unrelated to manufacturing, e.g., epitope determination and cross-reactivity.)

Using these criteria, we have prepared detailed technical comments in the standard EMEA table format. As always, PDA focuses on scientific and technical issues and, where appropriate, offers specific recommendations to make the guidance more useful to all parties.

PDA would be pleased to meet with EMEA to discuss our comments. We would also be willing to attend and/or co-sponsor a public meeting to hear and understand the concerns of EMEA and to jointly work with EMEA on proposed alternative wording. If you have any questions please contact me, or my colleague Jim Lyda (lyda@pda.org), who did the staff work for our comments.

With very best regards,

Georg Roessling, Ph.D.
Senior VP, PDA Europe
Roessling@pda.org

The following PDA volunteers participated on the task force for these comments:

Anita Derks, F. Hoffman La Roche, Ltd (Chair)
Carol Van Auwelaer, Eli Lilly
Rebecca Devine, PhD, Consultant
Ronald Imhoff, Centocor
Mihaela Marian, Amgen
Per Rexen, Novo Nordisk
Gabriele Schaeffner, PhD, NDA Regulatory Science
Kathryn Stein, MacroGenics, Inc.
Randall Tlachac, University of Minnesota

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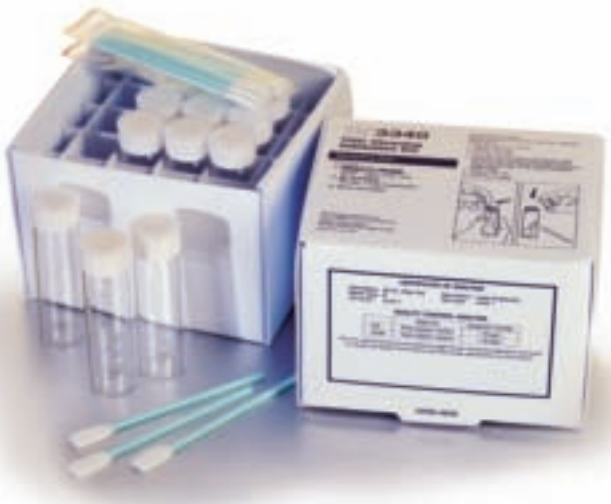

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Peering into the Crystal Ball: The Future of Good Cold Chain Management Practices

Rafik H. Bishara, PhD, Technical Advisor and Chair, Pharmaceutical Cold Chain Interest Group (PCCIG), PDA

There has been a significant increase in regulatory oversight and pharmacopeial standard creation for medicinal products, broadening the scope to include proper handling, storage and distribution as an extension of product manufacturing. The importance of good pharmaceutical cold chain management, the understanding of the complex pharmaceutical supply chain and the requirements of "Good Storage and distribution practices" (GS/DP) highlight several areas of improvement within the industry. These needs include establishing meaningful packages, temperature profiles, monitoring excursions, building good partnerships with shippers and transport service providers, and qualifying transportation routes and vehicles used, such as trucks, planes and sea containers for the temperature sensitive medicinal products in distribution.

The cost of payloads continues to rise as more and more biotech products are approved. The biotech industry has stated its vision to "personalize" treatments to the individual which may dramatically increase the need for robust cold-chain transportation in smaller shipments. Many other industries have switched from disposable products to reusable products because of the large cost savings through standardization, increased use of technology and better control of payloads.

The cold chain is now also on the verge of moving from disposable packaging to reusables. Some suppliers have set the standard for pallet-sized shipments and are routinely accepted by companies world-wide without regular requalification. The parcel-sized cold chain must also do the same by employing technology to create more robust reusable packaging that is simpler to use, by establishing a standard for size and temperature control and by protecting better from temperature excursions and physical integrity loss. Ideally what is needed is a robust, reusable temperature-critical transportation package that may be used by various logistics companies and carriers to provide end-to-end transportation solutions which are more cost effective through the reduction of engineering, qualification and product loss.

The cold chain is now also on the verge of moving from disposable packaging to reusables.

Temperature-controlled medicines require a supply chain process of planning, implementing and controlling the operations of shipping cold chain products. The most effective way to deliver the proper tools for the supply chain to facilitate the shipping process is through technology transfer. In this process, developing applications based on the results of scientific research and data is the foundation of the cold chain technology transfer and should include the following factors: design space or testing methodology; requirement documents; component qualification/characterization; design testing; thermal, physical and verification qualifications; and transportation packaging configuration.

The International Safe Transit Association (ISTA), in cooperation with the PDA Pharmaceutical cold chain Interest Group (PCCIG), has written a technical protocol for the development of temperature and humidity profiles for the cold chain transportation environment to meet qualification needs. ISTA is now in the process of planning to record the ambient temperature and humidity data that packages are exposed to during typical domestic shipments. This data will be used to create a composite profile tool that is representative of the typical conditions encountered by packages during these shipments. These profiles will be used to statistically create the exposure conditions for laboratory qualification testing of transport packaging. Monitored shipments will take place in July 2008 and January 2009, which are documented as the hottest and coldest months of the year. The data will then be analyzed and profiles will be developed by the University of Florida. The ISTA plans to incorporate the new Hot and Cold Profiles in their Test Procedure 7D *Thermal Controlled Transport Packaging for Parcel Delivery System Shipments* as the start of test standards for cold chain.

Tools for real-time monitoring of temperature and relative humidity data from multiple data recorders on any computer or across a network are available. Being able to analyze triggering events, like out-of-tolerance temperatures and humidity, helps technicians know exactly what is happening with their controlled environments, 24/7 and from any location. Users receive alarm notification on their PC, cell phone or email; use software for graphing and analyzing historical data; and create reports in compliance with 21CFR Part 11, validation and GSDP.

PDA's Technical Report No. 39 (Revised 2007), *Guidance for Temperature Controlled Medicinal Products: Maintaining the Quality of Temperature-Sensitive Medicinal Products through the*

continued on page 44

Regulatory Briefs

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

International Cooperation

U.S. and China sign an agreement about Product Safety

On Dec. 11, 2007, the U.S. Department of Health and Human Services (HHS) and the General Administration of Quality Supervision, Inspection, and Quarantine (AQSIQ) of the People's Republic of China signed two Memorandums of Agreement, one to enhance the safety of drugs and medical devices and another for the safety of food and feed.

To enhance the safety of products sold in the United States, Chinese authorities will implement two programs, both subject to an audit by the U.S. FDA. The first will require exporters to the United States to register with AQSIQ and agree to annual inspections to ensure their goods meet U.S. standards. AQSIQ will notify HHS/FDA of those that fail inspection and why. HHS/FDA will maintain an online list of registered companies. AQSIQ will also notify HHS/FDA of all companies AQSIQ suspended or that have lost their registered status. AQSIQ will implement a system to trace products from the source of production or manufacture to the point of exportation.

Second, new certification requirements will help ensure products exported from China to the United States meet U.S. standards. Once AQSIQ's Inspection Bureau confirms a shipment meets HHS/FDA requirements, it will issue a certificate that carries a unique identifying number, which AQSIQ will file with HHS/FDA.

Each party also commits to notify the other within 48 hours of the emergence of significant risks to public health related to product safety, recalls and other situations.

HHS/FDA can request a timely investigation regarding any covered product if there is reason to believe it could pose a health or safety risk.

Europe

EU Publishes Variations Guide for Comment

The Commission of the European Communities released a guidance on the variation regulations policy on Oct. 24, 2007 for public consultation. The public consultation period ends on Jan. 4, 2008. The EU intends to modify the regulatory framework covering changes to medicinal products. The purposed changes would allow a more flexible assessment for post approval changes. If approved, medicinal products would be "subject to the same criteria for the evaluation, approval and administrative handling of variations, regardless of the procedure under which those medicines have been initially authorized."

The new policy would create a more unified system of variation regulations between Member States.

United States

FDA amends 21 CFR parts 210 and 211, Withdraws 1996 Rewrite

The U.S. FDA is amending certain regulations, 21 CFR parts 210 and 211, as the first phase in an incremental approach to modifying the cGMP regulations for finished pharmaceuticals.

The regulations will be amended to modernize and clarify some of the cGMP requirements, as well as harmonize some of cGMP requirements with those of other foreign regulators and other FDA regulations.

A direct final rule is being issued because FDA expects no significant adverse comments on their proposed amendments. The rule will be effective on April 17, 2008, unless there are significant adverse comments during the comment period.

A proposed rule was also published and encompasses the same amendments. If significant adverse comments are received, the Direct Final Rule will be withdrawn, and the comments received to the Proposed Rule will be evaluated.

FDA is accepting comments on the direct final rule until Feb. 19, 2008.

In a related move, FDA withdrew the May 1996 proposed rule amending the GMP regulations for finished pharmaceuticals. A change to a more incremental rather than comprehensive approach to the revision of cGMP regulations 210 and 211 and the desire to stay consistent with changes that are occurring in other industries and countries have led to the removal of the rule.

FDA Extends CPG Expiration Date

The FDA has extended the expiration for the Compliance Policy Guide, *Sec 400.210—Radiofrequency Identification Feasibility Studies and Pilot Programs for Drugs* (RFID), to Dec. 31, 2008. The CPG will be kept in place while FDA considers the experiences of stakeholders and the Agency under the CPG. The issues raised in the CPG and section 505D of the FD&C act, which requires the development of standards for identification, validation, authentication and tracking and tracing of prescription drugs will also be regarded.

A Report on the Quality Topics from the ICH Yokohama Meeting

Landmark Pharmacopeial Harmonization Guideline Reaches ICH Step 4

Stephan Rönninger, F. Hoffmann-La Roche Ltd, with Jim Lyda, PDA

The ICH Q4B guideline, *Evaluation and Recommendation of Pharmacopoeia Text for Use in the ICH Regions,* reached Step 4 (approved as final by the Steering committee and pending regulatory implementation, Step 5). ICH Q4B makes possible regulatory acceptance of designated portions of four pharmacopeias (USP, EP, BP, JP) based on the concept of "pharmacopeial interchangeability," defined as: "Where such status is indicated, any of the official pharmacopeias from Japan, Europe or the United States can be substituted one for the other (appropriately referenced) in the ICH regions for purposes of the pharmaceutical registration/approval process. Using any of the interchangeable methods, an analyst will reach the same accept or reject decisions irrespective of which PDG pharmacopeia is used."

Parties involved in developing the Q4B guideline are the Pharmaceutical Discussion Group (PDG) and the Q4B Expert Working Group comprised of representatives from the respective regulatory bodies and industry associations: FDA and PhRMA (United States); EMEA and EFPIA (European Union); and MHLW and JPMA (Japan). Observers include the European Free Trade Association, WHO and Health Canada. Interested parties are at this time the International Generic Pharmaceutical Alliance and the World Self Medication Industry.

This report describes outcomes of the quality topics discussed at the ICH meeting in Yokohama, Japan, Oct. 29 to Nov. 1, 2007. The Yokohama ICH activities included meetings of the Expert Working Groups (EWG) and the ICH Steering Committee relating to a number of technical and quality areas. The Yokohama discussions focused on pharmacopeial harmonization (ICH Q4B and Pharmacopoeia Discussion Group), pharmaceutical development Q8(R1), and formation of a single Implementation Working Group for Q8, Q9 and Q10.

For more detailed information on the ICH process, the ICH guidelines and latest public statements, see www.ich.org.

There is recognition by most of the parties involved that harmonization of general chapters is a prerequisite for harmonization of individual monographs.

The PDG was formed in 1990 to produce harmonized pharmacopeial texts through independent public comment and consultation. The PDG reports on the status of its harmonization efforts at ICH meetings as appropriate. It consists of representatives from the European Directorate for the Quality of Medicines (which oversees the EP), the MHLW in Japan (which oversees the JP) and the U.S. Pharmacopeia (USP). The World Health Organization (WHO) participates as an observer.

There is recognition by most of the parties involved that harmonization of general chapters is a prerequisite for harmonization of individual monographs. Prioritization of this approach is necessary.

Standards considered "interchangeable" will be those that have undergone a five-step review process by the Q4B Expert Working Group per the efforts of the PDG. The process is outlined in depth on pages 2-3 of the Step 4 guideline. Just like the regular ICH guideline process, a harmonized compendial standard at Q4B Step 2 is an opportunity for public comment (managed as Step 3), and Step 4 represents approval by the ICH Steering Committee for implementation. Standards undergoing the process become annexes of the Q4B guideline.

The following standards have entered into the Q4B Expert Working Group process and are at different stages:

- Residue on Ignition/Sulphated Ash (Q4B Annex #1, Step 4)
- Extractable Volume Annex #2, Step 3)
- Particulate Contamination (Annex #3, Step 3)
- Microbiological Examination of Non-sterile Products (Annex #4, Step 1)
- Uniformity of Dosage Units (Annex #5, Step 1)

General Principles on Pharmaceutical Development

The ICH Steering committee has approved for public consultation, managed as Step 3, a new annex to ICH Q8, as a Step 2 document. The annex, Q8(R1), focuses on elements for pharmaceutical development such as target product profile, critical quality attributes, critical material attributes and process parameters. Selection of variables, unit operation, scale and equipment, proven acceptable ranges and edge of failure are key words in the design space interpretation. All knowledge should be reflected in the control strategy to be designed to consistently ensure product quality. Product lifecycle management and continual improvement are addressed and have to be reflected in the concepts of regulatory flexibility.

The main body of Q8(R1) represents basic principles and understanding which may be applied to both API

(small molecule and biotech) and drug products (solid and liquid dosage forms). Practical assistance for reviewers and industry is provided in the chapter on the Common Technical Document (CTD) as well as in the appendices covering differing approaches and illustrative examples. Quality by Design concepts enhance product and process understanding and encourage sharing knowledge with regulators. Opportunities to use risk-based thinking (link to ICH Q9) and quality systems (ICH Q10) are expressed.

There will be public consultation over the next six to nine months. The Q8 Expert Working Group will most probably reconvene at the ICH meeting, November 2008 in Brussels, to discuss the inputs received by the agencies. PDA is able to provide comments during the consultation period.

In addition, there are a number of assumptions relating to the principles of Q8, Q9 and Q10, as they are applicable to chemical and biotech drug substances. For such products the broad spectrum of techniques, processes and molecular complexities could impact implementation. These principles provide significant opportunities (and challenges) for more complex molecules and processes. The fundamentals of good product development need to be addressed, regardless of "traditional" or "new" development paradigms. The focus should be on enhancing quality and knowledge rather than using specific terminology or tools. The lack of harmonized guidance on drug substance development is still regarded as a gap. Related issues to be addressed are, for example, information that should be included in an application file or dossier and the basis for releasing a product to the market and communication.

The ICH Steering Committee is considering the development of an ICH guideline on development and manufacture of drug substances. First, a concept paper referring to Section S2 of the Common Technical Document-Quality (CTD-Q) and a business case is planned to be established by the next ICH meeting. These topics include similarities and differences in technical development between chemical and biotech drug substances, and the intention, as of now, is to include them in one document.

The ICH Steering Committee agreed to establish a single Implementation Working Group (IWG) for Q8, Q9 and Q10.

Implementation Working Group for Q8, Q9 and Q10

ICH Q8, Q9 and Q10 as strategic guidances are generating a lot of discussion for both regulators and industry. Many questions on training, interpretation and implementation surround the documents, but only opinions from individuals can be provided, as the regulatory institutions and the industry have not yet agreed on many of the answers. As such, ICH is promoting a holistic approach to facilitating a smooth and consistent implementation of the three documents at least in the three regions.

To that end, the ICH Steering Committee agreed to establish a single Implementation Working Group (IWG) for Q8, Q9 and Q10. The IWG will develop Q&A implementation guidance by responding to questions from stakeholders from industry and regulatory authorities—both inspectorates and reviewers. Other topics might be the development of strategic training material to enhance harmonized implementation is under discussion.

Some of the key technical issues for possible focus by the IWG include, for example: common interpretation of terminology, holistic approach of Q8, Q9 *and* Q10, and applicability to both reviewer and inspectorates.

The IWG will meet the first time at the next ICH meeting in June 2008. It will establish a working procedure and evaluate initial technical questions and proposed responses. In addition to exploring collaboration with nonprofit scientific organizations, the IWG may consider training and communication needs to ensure globally consistent implementation of Q8, Q9 and Q10. A key aspect of the IWG work will be fostering communication and training on-site for the implementation. This may be done by, for example, by collaboration with scientific non-profit organizations like PDA.

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downs, and "routinely disinfected" at the time of replacement of the sterile "set-ups."

- "Deep-cleaning" refers to a systematic program of disinfection using a series of disinfectants one after the other. The equipment is wiped down with one disinfectant, left for a contact time (often overnight), rinsed off with 60–70% alcohol (alcohol leaves no residues) and disinfected again with a second disinfectant, rinsed, and so on.
- "Routine disinfection" refers to wiping down the equipment with the disinfectant that is on current rotation, leaving for a contact time and rinsing off with 60–70% alcohol.
- Continuous disinfection in Grade A/B areas refers to the frequent disinfection with 60–70% alcohol by operators when running filling lines in response to their interventions into critical areas.

PDA meetings offer the best opportunities to discuss the evolution of regulations.

Jean Louis Saubion

Company: UFCH (Unité de Fabrication et de Contrôle Hospitaliers) a governmental company that specializes in small batches of parenterals for hospitals and is a subcontractor for Phase I and II batches

Title: Production and Regulatory Affairs Manager

Education: Pharmacy (University of Bordeaux), PhD in Law (University of Bordeaux II)

PDA Join Date: Early 1980's

Areas of PDA Volunteerism:
President and cofounder of the PDA France Chapter
Contributing organizer of the PDA French Chapter Annual Meeting
Co-chair of the Latin Europe Annual Meeting (PDA Italy, Spain and France Chapters)

Interesting Fact about Yourself: As the Germans say "Happy as God in France." This describes living in the Bordeaux vicinity, surrounded by famous vineyards and tremendous golf courses and located one hour away from the Atlantic beaches and two hours from Spain. It could almost be a frustrating environment considering the little amount of time I have to enjoy it all.

Of your PDA Experiences which stand out the most? Launching the PDA France Chapter in a difficult context was quite an experience. Equally rewarding is the annual organization of a joint meeting with my Spanish and Italian colleagues. We can thus assess the differences between the Latin and Anglo-Saxon cultures while trying to make the most of both approaches. Recent examples are the co-organization with the French SFSTP (Société Française des Sciences et Techniques Pharmaceutiques) of a meeting on new techniques for sterilization in 2006 and of a joint collaboration on endotoxins. This type of collaboration with local professional associations is most fruitful and rewarding for both sides.

Which Member Benefit do you most look forward to? Access to the PDA website database is one of the membership's invaluable advantages. Through PDA's worldwide community, one has contact with professionals all over the world. I will always remember a meeting in Seoul when some Korean counterparts suddenly changed their behavior when they heard I was a member of PDA and chaired the France Chapter! PDA can obviously be a password to open foreign companies' doors and half-open those of regulatory bodies. Information seems to flow freely and easily in today's world of information overload, but PDA validates information and guarantees its international recognition. Also, PDA meetings offer the best opportunities to discuss the evolution of regulations.

Which PDA Event/Training Course is your Favorite? Dozens of advertisements for professional meetings reach our mailboxes everyday, and we have to make a choice according to their efficiency and the opportunities they offer to meet regulators and get acquainted with new techniques. The PDA/EMEA Joint Regulatory Conference, organized in 2006 for the first time, was most successful. In my mind, it was an outstanding event. It should prove in the near future as useful as the joint PDA/FDA Join Regulatory Conference. It does indeed meet the needs of big pharmas and biotech start-ups.

As for training courses, whenever they deal with topical issues (e.g., pre-filled syringes in Germany last year or CGP/GMP's practices for IMP's in Paris in January) and are conducted by expert professionals and followed by meetings with the best specialists, they are always appreciated and beneficial to attendees.

How Has PDA Benefited you professionally? I have known PDA for many years through the *Journal of Pharmaceutical Science and Technology* (incidentally I have a collection of the early 1970's issues if anyone is interested). As the years went by, my expertise of parenteral manufacturing went on improving (and so did, to a lesser degree, my knowledge of English). I attended various meetings and acquired a sense of belonging to a technical and scientific community. PDA is a global community whose members come from various sectors (pharmacists, engineers, biochemists, bacteriologists, etc.) and various countries and get together almost every week through scientific committee conference calls, organized meetings or through comments on guidelines.

A recent illustration of PDA's valuable contribution to my activity took place a few months ago during an audit of my company. The interpretation of a European norm concerning sterilization was in question, so I showed and explained PDA Technical Report No.1, which had just been issued and provided the right answer, thanks to which a general agreement was easily reached.

On a personal level, I asked my childhood sweetheart, Christine, to travel with me to the 2005 PDA International Congress in Rome. Just prior to the start of the meeting, we visited the Trevi Fountain, where I got down on one knee and proposed! We are now very happily married, and, I have to say, that is a benefit that speaks for itself!

Michael J. Miller

Company: Eli Lilly and Company

Title: Senior Research Fellow, Manufacturing Science & Technology

Education: B.A. Anthropology/Sociology, Hobart College, Geneva, NY
Ph.D. Microbiology/Biochemistry, Georgia State University, Atlanta, GA

PDA Join Date: 1992

PDA Volunteerism:
Strategic Planning Committee (current)
Program Advisory Board (current)
Technical Book Advisory Board (current)
Active speaker and moderator for numerous PDA meetings
2007 Annual Meeting Program Committee Member
Program Chair for the 2007 PAT Meeting
Program Chair for the 2006 PDA Annual Meeting
Chair for the 2006 Global Conference on Pharmaceutical Microbiology Meeting
PDA-DHI author

PDA and Professional Awards Won:
2006 Distinguished Service Award, PDA
2006 Microbiologist of the Year, Institute for Validation Technology

Interesting Fact about Yourself: A number of PDA members will try to get me to talk about my karaoke singing. However, I have been playing the trombone with some of my Lilly colleagues at a few gigs in Indianapolis. More recently, I shared the stage with the Dave Koz band on his annual smooth jazz cruise in November! Pictures will be on sale at the next annual meeting!

Of your PDA experiences, which stand out the most? One of the most gratifying experiences was working with industry leaders in developing a global program for advancing the science of pharmaceutical microbiology. Microbiology is at the heart of PDA's original areas of interest, and this discipline has a significant impact on pharmaceutical manufacturing and ensures that drug products of the highest quality are available for the patient. The 2nd Annual Global Conference on Pharmaceutical Microbiology, held in October 2007, was a huge success due to the commitment and very hard work of the organizing committee and the co-chairs—many of whom are practicing microbiologists in their respective organizations. The opportunity to work with this dynamic team was a tremendous benefit of my PDA membership.

Which member benefit do you most look forward to? I routinely make use of the online Pharmaceutical Sci-Tech Discussion Group. If there is one forum where hot-topics on pharmaceutical manufacturing science and technology are discussed (and debated), this is it! Next, I look forward to reading the monthly *PDA Letter.* This publication is my jumping-off point for all things PDA, including meetings and industry topics of interest. Finally, I enjoy attending Interest Group meetings where I can focus on specific disciplines in order to find (and influence) next generation solutions for pharmaceutical manufacturing.

Which PDA event/training course is your favorite? Obviously my heart is with the Global Microbiology meeting, but I am always able to take away relevant information from the Annual Meetings and bring these back to Lilly. Because the Annual Meeting has an expanded breath of scientific, regulatory and compendia topics and offers the opportunity to liaise with other industry leaders and technical experts, this meeting is one I rarely miss.

How has PDA benefited you professionally? For the past 15 years, my involvement with the PDA has significantly strengthened my ability to directly impact the manner in which pharmaceutical products are developed and manufactured. Furthermore, the opportunity to help influence the future direction of pharmaceutical science and technology, and to actively interact with global regulators is unmatched by any other professional organization in the industry.

On a personal level, I asked my childhood sweetheart, Christine, to travel with me to the 2005 PDA International Congress in Rome. Just prior to the start of the meeting, we visited the Trevi Fountain, where I got down on one knee and proposed! We are now very happily married, and, I have to say, that is a benefit that speaks for itself!

PDA/EMEA Joint Conference: New Member Breakfast

Budapest, Hungary · February 20, 2008 · 7:00 a.m. – 8:00 a.m.

Hassana Howe, PDA

Welcome new PDA members! If you joined PDA on or after Oct. 1, 2007, you are invited to kick-start your PDA membership by attending this year's New Member Breakfast hosted on-site at the 2008 PDA/EMEA Joint Conference. This is a wonderful opportunity to learn more about PDA and meet other new PDA members, board members and staff.

Please RSVP by Feb. 11, 2008 to **Hassana Howe** at either **howe@pda.org** or +1 (301) 656-5900 ext. 119. Please direct any questions regarding the breakfast to her.

For more information about the 2008 PDA/EMEA Joint Conference please visit www.pda.org/emea2008.

PDA **Training and Research Institute**
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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 **EIGHT** industry courses:

- Problem Solving Techniques in Nonconformance Investigations – ***New Course!***
- Bioassay Development and Validation
- 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
- Process Validation for Biopharmaceuticals
- What Every Biotech Startup Needs to Know about CMC Compliance

San Francisco Training Course Series
March 10-12, 2008
Kabuki Hotel (Formerly Hotel Mayuki)
1625 Post Street
San Francisco, CA 94115 USA
Tel: +1 (415) 922-3200

Contact:
Stephanie Ko
Manager,
Lecture Education
+1 (301) 656-5900 ext. 151
www.pdatraining.org/sanfrancisco

Revitalization in Puerto Rico and Canada, and Other Chapter Tales

Henry Kwan, Ph.D., Kwan Consulting, LLC

In 2007, the 11 PDA chapters in North America hosted a record total of 43 educational and networking events for the membership. This was a special year also for PDA as we witnessed the beginning of the revitalization of the Puerto Rico and the Canadian chapters.

Under the leadership of **Manuel Melendez** and an entirely new group of volunteers, Puerto Rico put on two very well-attended dinner events in San Juan in April and July (with a scheduled November event postponed until Feb. 20, 2008). Both events involved multiple speakers with topics ranging from out-of-specifications final guidance from the U.S. FDA, process validation, to PAT applications for parenteral and solid dosage forms.

North of the border, the Canadian chapter, led by **Patrick Bronsard** and their new board, put together an all-day conference in Montreal on Feb. 18, 2008. The program included five speakers representing Health Canada and industry who shared their thoughts on new Canadian GMPs, biotech regulations in Canada, Rapid RT-PCR detection of microbial contamination, validation of temperatures in the supply chain and environmental monitoring considerations in oral solid dosage forms.

While the momentum is building within these rejuvenating chapters, maintaining the enthusiasm among the membership in these regions would be paramount to their future success. Therefore, I would like to encourage anyone interested in getting involved with these two chapters to please contact **Patrick Bronsard** in Canada (patrick.bronsard@snclavalin.com) and **Manuel Melendez** in Puerto Rico (manuelm@amgen.com). I am sure they would love to hear from you.

Autumn, A Time to Learn

Like the schools and universities across North America busily preparing for new school years each autumn, PDA chapters are typically busy in the autumn putting on events for their membership. The months of September and October last year, were no exception. I attended four of the six events and would like to share with the global PDA membership what has transpired at these chapter meetings. My intention is to provide a flavor of what some of the PDA chapters are doing to bring hot topics and expert speakers to their local membership. As you shall see, the scope of the topics is diverse and it represents many of the timely issues facing the pharmaceutical industry.

Southeast Chapter

On September 5, a near-record attendance for the Southeast chapter of over 100 people and 30 exhibitors showed up at the Sheraton Imperial Hotel in Research Triangle Park, N.C., to support the autumn exhibitor show and meeting. The all-day event included exhibits from 9 a.m. to 4 p.m. and three podium presentations. The featured speakers and their talks were:

Anthony Polletta, Talecris Biotherapeutics, Inc., "Ongoing stability programs for approved drugs"

Kathleen Wessberg, Abbott Labs, "EU directive of APIs compliance with GMPs"

Wade Speir, PA Consulting, "FDA CAPA compliant root cause investigation and documentation"

Metro Chapter

On Sept. 11, the chapter hosted a dinner meeting at the Ramada Inn in Somerset, N.J. that was attended by over fifty people. **Michael Ruberto,** PhD, *Ciba Specialty Chemicals,* gave a talk on "The polymer supply chain and the impact on extractables and leachables in pharmaceutical container closure systems." This was the fourth event of the year for the chapter with two more scheduled in 2007. At this event, the chapter raffled off one of the prizes in the form of a one-year PDA membership which was very much appreciated by those in attendance.

Delaware Valley Chapter

The fourth event of the year, titled "A Focus on EMEA Considerations and Vendor Night," was again held at

the fabulous venue of the Desmond Hotel in Malvern, Pa. on September 27. More than 200 people attended the chapter's annual vendor show where 31 exhibitors from the local area participated. At the conclusion of the vendor show (4 to 7:30 p.m.) and the buffet dinner in the exhibition hall, more than half of the attendees moved upstairs to a cozy amphitheater for the second half of the event.

Mitch Garber was able to arrange for his colleague **Roger Smith** to travel all the way from his office in Ware, UK to share his experience on the EMEA. Roger shared his extensive knowledge about the regulatory infrastructures in the EU including the PIC/S, the MHRA and the MRA. Being a certified Quality Person in the EU, he also shared with the audience the concept of the Quality Person and the important role that it plays in an EU facility.

Mountain States Chapter

In the second week of Oct., the Colorado Rockies were not the only team busy in the Denver area. On October 11, thanks to the enthusiastic group of volunteers at the PDA Mountain States chapter led by **Sara Hendricks,** more than 70 people attended the annual vendor show and dinner meeting at the chapter's favorite venue, the Radisson Hotel in Longmont, about an hour north of Denver. There were 17 exhibitors participating, including the Denver District Office of the FDA. After dinner, **Ron Branning** gave a talk entitled, "Pharmecutical Quality Systems—from QC & QA to ICH Q10." Indeed it was a great evening of networking and educational opportunities for all of us.

Teamwork

On behalf of the PDA and its members, I would like to once again acknowledge the volunteer efforts and the contributions made by all the chapter leaders as well as the guest speakers who took time out of their busy schedules to support the PDA chapters and their membership. I encourage all the PDA members to step up their efforts to contribute to the chapters—as a volunteer, a sponsor and/or a prospective speaker at chapter events. For those of you who know of any non-PDA members who have been attending the chapter events, please encourage them to become PDA members. The benefits are countless, not the least of which are the complimentary Technical Reports and the six issues of the PDA Journal of Pharmaceutical Science and Technology that have been the signature technical documents published by the PDA. I should know, having been a member for 30 years.

PDA'S Who's Who?

Ron Branning, Independent Consultant, Commissioning Agents, Inc.

Patrick Bronsard, Project Manager, SNC-Lavalin Pharma and Canadian Chapter President

Mitch Garber, Corporate Quality Manager, GlaxoSmithKline and Delaware Valley Chapter Event Coordinator

Sara Hendricks, Senior Engineer, Commissioning Agents, Inc. and Mountain States Chapter President

Manuel Melendez, Sr. Director, Quality, Amgen Manufacturing and Puerto Rico Chapter President

Anthony Polletta, Senior Operations Manager, Talecris Biotherapeutics, Inc

Michael Ruberto, PhD, Head of Regulatory Services, Ciba Specialty Chemicals

Roger Smith, Quality Manager, GlaxoSmithKline

Wade Speir, Managing Consultant, PA Consulting Group

Kathy Wessberg, Corporate Program Manager Quality Operations, Abbott Laboratories

Upcoming Chapter Events

Metro Chapter

January 24, 2008 | Bridgewater, New Jersey

Join guest speaker **Anthony Cundell**, PhD, Schering-Plough Corp., for a networking and presentation conference on the topic of "Updates on Revisions to the USP Micro Chapters."

www.pdachapters.org/metro

Ireland Chapter

February 1, 2008 | Bridgewater, New Jersey

Trends in Asectic Processing—A Risk Management Approach

www.pdachapters.org/ireland

Japan Chapter

February 1, 2008
Toyama area GMP Symposium.

February 28, 2008
Sterile Product GMP Committee Symposium

www.pda.org/japan

Canada Chapter

February 18, 2008 | Quebec, Canada

The PDA Canada Chapter is pleased to offer an exciting program once again at the PDA Canada Chapter 2008 Montreal Annual Conference. The conference will cover an array of topics, providing useful information and perspectives for and from participants across the industry.

www.pdachapters.org/canada

Puerto Rico Chapter

February 20, 2008 | San Juan, Puerto Rico

An important strategy for successful cleaning validation is the development of robust cleaning cycles. A major obstacle in implementing this strategy is that manufacturing equipment and adequate quantities of process soils are often not readily available for cycle development. Join us for this topic discussion at the upcoming educational dinner conference.

www.pdachapters.org/puertorico

Chapter Contacts

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

Asia-Pacific

Australia Chapter
Contact: Anna Corke
Email: acorke@medicaldev.com

India Chapter
Contact: Darshan Makhey, PhD
Email: dmakhey@hotmail.com

Japan Chapter
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Email: terada@phar.toho-u.ac.jp
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Korea Chapter
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Southeast Asia Chapter
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Taiwan Chapter
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Europe

Central Europe Chapter
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France Chapter
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Ireland Chapter
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Israel Chapter
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Capital Area Chapter
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Delaware Valley Chapter
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Metro Chapter
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Midwest Chapter
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Southern California Chapter
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www.pdachapters.org/southerncalifornia

West Coast Chapter
Areas Served: Northern California
Contact: John Ferreira
Email: jferreira@banzigersystems.com
www.wccpda.org

PDA Welcomes New Members

Deirdre Abelha, Catalent

Abiola Akinwunmi, Molak

Ashok Ajmani, Boehringer Ingelheim

Michael Angelastro, Dept. of Health & Human Services

Nasim Anwar, Wyeth

Assia Aqallal, Polytechnic School of Montreal

Jiichi Arai, Takeda Pharmaceutical Company Limited

Peggy Auney, sanofi pasteur

Sean Bacchus, Johnson & Johnson OMJ

Emil Baczynski, SciencePharma

Keith Bader, JM Hyde Consulting

Cherie Baker, Alkermes

Ken Baker, AdvantaPure/NewAge Ind.

Kevin Ballard, MasterControl

Fahima Benaiche, GlaxoSmithKline

Dawn Benson, Jazz Pharmaceuticals

Katherine Burri, Lonza

Grace Cao, Teva Parenteral Medicines

Oscar Casillas, Business Excellence Professional Consulting

Kelly Cloman, Pall

Christine Conley, Genzyme Corp.

Jason Cramer, Bayer HealthCare Pharmaceuticals

Mary Day, Bayer Health Care

Mathew Desmarais, Associates of Cape Cod

Felipe Diaz, Merck & Co.

Xiaogang Ding, Advanced Medical Optics

Seung-Wook Do, Huons

Larry Donnell, Human Genome Science

Tracey Downey, Roxane Laboratories

Robert Dracker, Infusacare Medical Services

Pamela Dunn, sanofi pasteur

Deirdre Dwyer, Baxter Healthcare

Michelle Ellwanger, Schott North America

Aprel Ezzell, Novo Nordisk Pharmaceutical

Joe Featherstone, Cruinn Diagnostics

Rick Floyd, Integrated Project Services

Stacey Foti, UNC-Chapel Hill

Debbi Fox, Government

Derek Freeman, DFMicro

Linus Gaarn Johansen, Pharma-Skan

Parrish Galliher, Xcellerex,

Claire Gautier, Cenexi

Ivanka Gavanski, Amylin Pharmaceuticals

Eric Golovchenko, Bristol-Myers Squibb

Amar Gor, Genzyme

Julia Goswick, Marketing General

Arun Gupta

Shozo Hayase, Taiho Pharmaceutical

Keith Helinsky, SAIC-Frederick

Elisabet Helmerson Lundahl, Carmel Pharma

Simon Hendry, ALK-Abello

Miriam Herrero, F. Hoffman-La Roche

Ji Hee Hong, Celltrion

Ballard Jamison, Drinker Biddle & Reath LLP

Dina Jarrar, Jazz Pharmaceuticals

Laura Jenkins, GlaxoSmithKline

Susanne Joergensen, Novo Nordisk

Anne Johnston, Allergan

Lorraine Kelly, Merck Sharp & Dohme

Peter Kilkenny, Wyeth

Rana Kumar, Covidien

Whitney Kutney, ValSource

Dominique Lammerant, Nextpharma Braine

Jian Lan, sanofi pasteur

Ronald LaPointe, Commissioning Agents

Laurence Le Moine, BD Becton Dickinson Medical

Anne Leonard, Baxter Healthcare

So-Yan Leung, Genentech

Aubry Liette, Scientific Affairs Pharmetics

Celine Liew, National University of Singapore

Eugene Lofton, Merck

Tyne Lomeland, Hyaluron Contract Manufacturing

Phillip Lunney, Bayer MaterialScience

Amy MacLauchlan, Millipore

Christy Madigan, Allergan

Tara Mallory, Regeneron Pharmaceuticals

Lauren Markley, Human Genome Science

Debra McCrady, Fort Dodge Animal Health

Larry McElhiney, Self Employed

Christine McGarry, Johnson & Johnson

Yolanda McLean, ImmunoGen

Paul McVeigh, PharmEng

Siamak Meskarzadeh, Bavarian Nordic

Wayne Miller, Rapid Micro

Brady Moira, Wyeth Biotech

Seamas Moneley, Allergan Pharmaceuticals

Paul Moody, Centocor

Michael Morgan, Wake Tech Community College

Pierre Muentnich, Sanofi Pasteur

Mari Murphy, Merck Sharp & Dohme

Jesper Nilsson, Knightec AB

Seik Oh, Baxter

Kolawole Oluwatoyin, University Of Witwatersand

Bismark Oteng, Human Genome Science

Susan Paulyshyn, Cangene

Keith Peacher, Amec

John Pirro, Synomics Pharma

Nicholas Pishon, Millipore

Sue Poinsett, Greer Laboratories

Leigh Pracht, NIH

Cathal Riordan, Wyeth

Erik Rippel, DHC Consultant GMBH

Alejandro Riva, Laboratorios Eticos

Kieran Ruane, Allergan Pharmaceuticals

Erika Rzomp, Bayer Healthcare

Andrew Sage, Rapid Micro Biosystem

David Sanson, Genzyme

Yoshinori Sato, Mitsubishi Space Software Co.

Torsten Schmidt-Bader, Pharmaplan

Anthony Scott, Bayer

Roland Sebbane

Anu Seth, Watson Pharmaceuticals

Frances Sharpe, Novo Nordisk

Elisabeth Soerensen, Novo Nordisk

Jan Spitael, Enzon Pharmaceuticals

William Stagner, Campbell University

Jessica Stevens, ISPE

Joseph StLaurent, Chemic Laboratories

Denise Tally, Wyeth

Vanessa Thorpe, Pfizer

Francisco Vazquez, Allergan

Brad Wagner, Alkermes

Kristian Walbum, Bavarian Nordic

Christophere Walker, URL Mutual Pharmaceutical

Clifford Wallace, Pacira Pharmaceuticals

Guangyu Wang, Schering-Plough

Jeffrey Wedeking, Amgen

Olivier Wespe, Anabiotec

Coby Wheeler, Baxter Healthcare

Patricia Whelton, Argos Therapeutics

Jane Williams, Wyeth Pharmaceuticals

John Williams, Baxter Healthcare

Carmen Xuereb, Key Pharmaceuticals

Frank Zappulla, University of Connecticut

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

PDA Parenteral Drug Association
Training and Research Institute
EDUCATION • TRAINING • APPLIED RESEARCH

Improve Your Aseptic Processes to **Ensure** Sterile Product!

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
- Develop working knowledge of component preparation and sterilization to eliminate inherent product contamination risk
- and more!

Four 10-day sessions are being held in 2008!

Session 1: January 28-F[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

CONTACT:
James Wamsley, Senior Manager, Laboratory Education | +1 (301) 656-5900 ext. 137 | wamsley@pda.org
PDA Training and Research Institute, Bethesda Towers, 4350 East West Highway, Suite 150, Bethesda, Maryland 20814 USA

Networking Near the Danube: The 2008 PDA/EMEA Joint Conference

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

Networking is an important component of your conference experience. The opportunity to interact with colleagues, industry experts and regulators is invaluable to staying current on the quickly evolving European regulatory environment. Discuss what you learn from the podium presentations with your peers; have your questions answered by the speakers; and share experiences with industry experts at the planned events.

These include:

- ***Nine networking breaks:*** Take some time out between sessions to re-fuel during coffee breaks and lunch and exchange ideas about the presentations with other attendees.
- ***Gala Dinner*** (Feb.20): This event will be held at a typical Hungarian restaurant with a wonderful view of the Danube River. Classic Hungarian favorites will be served along with an extensive selection of famous Hungarian wines.
- ***New member breakfast*** (Feb.20): If you're new to PDA, don't miss the chance to hear how your membership puts you on the cutting edge of our profession with direct access to leading decision makers, the latest technical reports and scientific information you won't find anywhere else.

And, take advantage of beautiful Budapest to network informally with new and old friends. It is a city rich in both natural and architectural beauty, as well as a fascinating history and vibrant cultural heritage. Budapest has maintained its magic and charm and is known as both the Queen of the Danube and the City of Spas. For more information on what to do in Budapest, visit www.budapestinfo.hu/en/

Expand your network, make new contacts and advance your career by taking advantage of the networking opportunities offered at this year's PDA/EMEA Joint Conference. See you in Budapest!

PDA Parenteral Drug Association — *Connecting People, Science and Regulation®*

EMEA

PDA 2008 Annual Meeting—A Networking and Educational Opportunity Not To Be Missed

Colorado Springs, Colo. • April 14-18, 2008 • www. Pda.org/annual2008

Maik Jornitz (Sartorius Stedim Biotech), Program Committee Chair, and Ian Elvins (Lonza Biologics), Program Committee Member

The time for the 2008 PDA Annual Meeting is rapidly approaching. This year, PDA has excelled again and has secured the outstanding Broadmoor resort in Colorado Springs, Colo., to cater to the needs of a wide variety of scientists and experts from the pharmaceutical and biopharmaceutical industry. The PDA 2008 Annual Meeting, from April 14–18, creates a most advantageous platform to exchange information, whether you are participating as a speaker delivering a highly qualified presentation, a member of a PDA Chapter or participant in a PDA Interest Group, an active volunteer on an advisory board or task force or just as an attendee.

This year's Program Planning Committee selected the theme "Science Driven Manufacturing–The Application of Emerging Technologies," which states our emphasis on new applications of science and technology within a highly regulated manufacturing environment.

Production process requirements within the pharmaceutical and biopharmaceutical industry are rapidly evolving. Drug entities are becoming more complex. Batch sizes are smaller, but the value of an individual batch can be worth multiple millions of dollars. Since the entities of these drug molecules are complex, purification and separation steps follow suit and are commonly hand-tailored to an individual application. Cleaning of equipment used within these processes reach new levels of complexity. These factors result in a shift of manufacturing processes to new, emerging technologies, like disposable units or processes.

In other instances, smaller batch sizes result in more multi-product manufacturing, which requires ever more stringent changeover procedures while maintaining ease of set-up and flexibility. Smaller batch size and the high value of such fluid streams will also require systems with low hold-up volumes. New drug entities define the process requirements and the equipment design needs. The PDA Annual Meeting will address such design topics and the validation requirements of such.

Another evolving factor, is the emergence of new types of contaminants. Changes in raw materials and adaptability of microorganisms create new challenges within process streams. The innovative detection methodologies needed to meet these challenges will be addressed. Additionally, the strategies and methodologies for the removal or inactivation of such contaminants will be explored.

All of the above places an ever increasing burden on QA departments in the constant struggle to ensure that control of manufacturing processes is maintained or improved despite the ever advancing levels of technological complexity. Strategies and tools to achieve this will be presented.

Most of all, our utmost focus is ultimately the patient. For this reason we will hear directly from patients whose lives have been changed by pharmaceutical products. Hearing how you and your organization contributed to their well-being or recovery creates for us the motivation to strive to investigate new routes of development, manufacturing and compliance. We all work in a unique industry where the actions of all of us directly affect patients' lives.

We would like to invite you to join us at the PDA 2008 Annual Meeting to take advantage of this unique opportunity to achieve the highest value for you and your company.

Training for Business Success: 2008 PDA Biennial Training Conference

New Orleans, La. • May 19-21, 2007 • www.pda.org/training2008

David Fant (David Fant Associates), Program Committee Chair

On behalf of the Program Planning Committee and PDA, I would like to invite you and your staff to attend the *2008 PDA Biennial Training Conference,* May 19–21, 2008, in New Orleans, La. This conference is sure to be one you won't want to miss.

Following a successful 2006 conference in Philadelphia, the Program Planning Committee began looking forward to 2008 and taking the conference back to New Orleans. We will again be having over 30 different concurrent sessions featuring topics that are designed for all levels of training individuals. These sessions, plus networking opportunities, will provide you with a forum to learn from the experiences and successes of your fellow trainers.

Our theme this year is "Focus on Performance: Partnering for Business Success." Working with this theme, **Tom Reeves,** PhD, Professor of Instructional Technology at the University of Georgia will present a plenary workshop on E-Learning. We also are fortunate to have **Kaylim Islam**, Vice President of Customer Training and Information Products for Depository Trust and Clearing Corporation, delivering the Keynote Presentation on improving an organization's performance by improving worker's performance through cost-effective training programs.

Attend the U.S. FDA sessions to get the latest news on current training issues and have your questions answered.

The conference will also feature the "Trainers' Choice Awards," where you will select the winners. It will also showcase a vendor's exhibit where you can see what is available for your use.

With a location like New Orleans, a dynamic programs by outstanding training professionals, networking opportunities galore, we have all the ingredients—except you.

We look forward to seeing you in the "Big Easy!"

Peering into the Crystal Ball: The Future of Good Cold Chain Management Practices, continued from page 30

Transportation Environment represents the industry's best practices and has received recognition from global regulators and pharmacopeial experts.

As we look towards the future of good cold chain management practices we must remember that most of the new biopharmaceutical products are extremely valuable, and are generally temperature-sensitive products. Several changes are taking places within this field. New technologies will be developed to provide better control of the cold chain products which can include packaging, transport and monitoring. However, new technologies must be cost effective and/or improve control and regulatory compliance or they will not be broadly deployed.

Tracking products are receiving more and more attention as regulatory bodies push for it and it is a tool in the product safety/anti-counterfeit arena. However, cost effective methods and global standards for how to accomplish this have not been identified and may be years away. In addition, global regulations are becoming more and more stringent regarding conditions (temperature) and it is expanding from traditional cold chain products to controlled room temperature (CRT) products as well.

The traditional supply chain is also being challenged and the method of transacting business between traditional trading partners is undergoing change as well. There will be a drive for more standards around the handling and transporting of cold chain pharmaceutical items driven by the standards community in concert with the pharmaceutical companies to establish best practices around these products. Given developing standards over time, there will be better cooperation and "partnering" around the various elements of the cold chain which includes transport companies (air, sea, and ground), packaging/container companies, monitoring companies, etc., to assist in providing true end-to-end control and visibility.

The **2008 PDA Pharmaceutical Cold Chain Management Conference and Training Course** will take place March 11-14, 2008, in Bethesda, Md. This important industry event will bring together regulators, pharmacopeial experts, academicians, the pharmaceutical and biotechnology industry, and partners and solution providers to discuss the advances that have been made in the field of good cold chain management practices, as well as the future of this industry. In addition to the two-day conference and for the first time in the United States, the PDA Training and Research Institute will host a preconference course, **Global Regulations and Standards: Influences on Cold Chain Distribution, Packaging Testing and Transport Systems,** which will be held March 11–12, at the new TRI facility in Bethesda, Md.

For more information on these events, visit www.pda.org/coldchain08.

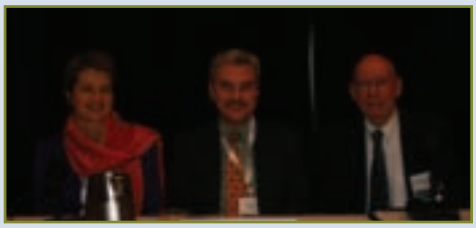
Faces and Places

2nd Annual Global Conference On Pharmaceutical Microbiology

(l-r back row) Michael Miller, Eli Lilly, Steffen Prowe, PhD, Bayer Schering Pharma, Brenda Uratani, FDA, (l-r front row) Jette Christensen, Novo Nordisk, Anthony Cundell, PhD, Schering-Plough, and Edward Balkovic, PhD, Genzyme Corp.

(l-r back row) Rich Levy, PDA; Bryan Riley, FDA; (l-r front row) Vivienne Christ, TGA; and Hanne Kristensen, Danish Medicines Agency

(l-r back row) Radhakrishna Tirumalai, USP; Anothony Cundell, Schering-Plough; (l-r front row) Jim Agalloco, Agalloco & Associates; Don Singer, GlaxoSmithKline; and Dave Porter, Vectech



(l-r) Jette Christens, Novo Nordisk, Bryan Riley, PhD, FDA, and Anthony Cundell, PhD, Schering-Plough

Quality Systems

(l-r back row) Steve Mendivil, Amgen; Zena Kaufman (l-r front row) Douglas Throckmorton, FDA; and Kim Trautman, FDA

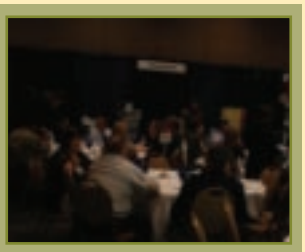
(l-r) Monica Caphart, FDA; Steve Mendivil, Amgen; Rebecca Rodriguez, FDA; and Ian Thrussel, MHRA.

(l-r) Gerry Migliaccio, Pfizer; Zena Kaufman, Abbott Laboratories; and Joe Famulare, FDA

(l-r) John O' Sullivan, Pfizer; Martin Van Trieste, Amgen; Neil Wilkinson, AstraZenca; and Gerry Lohan, Merck & Co., Inc

2007 Visual Inspection Forum

Speakers from the 2007 Visual Inspection Forum, (l-r) Albinus D'sa, FDA, Gerald Budd, Phoenix Imaging, Julius Knapp (committee), R&D Associates, Ronald Leversee, Pfizer, Michael Eakins, Eakins & Associates, Jean Pierre Cesari, Sanofi Pasteur, Deborah Shnek, Amgen, Pat Hanley, Genentech, Dan Berdocich, Micro Measurement Laboratories, Aarti Gidh, Amgen, John Shabushnig (co-chair), Pfizer, Deepak Sharma, Brightwell Technologies, Roy Cherris (committee), Bridge Associates, Rebecca Elliot, Eli Lilly, D.Scott Aldrich, Ultramikro. Those not shown are: Markus Lankers (co-chair), rap.ID, Carole Jones, FDA, Karen Bossert, Lyophilization Technology, Eugene Polini, West Pharmaceutical Services and Daniel Wildman, Wilco



Attendees of the 2007 PDA Visual Inspection Forum spent time at the Speakers Lunch talking to the speakers of their choice.

TRI TALK

Happy New Year

Gail Sherman, PDA

We had a very big year last year (in with a bang and out with a bigger bang). As you all know, TRI opened in Bethesda in July and was dedicated in September (refer to November/December issue of the Letter for photos). We began training almost immediately with the very first course in the new facility—the Mycology Identification Workshop—held in July. Our flagship Aseptic Processing course was first held in August in its new home. **Jessica Petree** left us, and **Stephanie Ko** joined our staff.

So let's move on to 2008, which shall be a very busy year indeed!

Along with our ever popular Aseptic Processing Training Program we are adding a few new lab courses, including: *Pharmaceutical Water; Contamination Control; Developing an Environmental Monitoring Program;* and *Pre-filled Syringes.* We will also for the first time, offer *An Introduction to Visual Inspection* in the TRI facility. In 2007 we offered this course in a hotel conference room.

Our lecture programs will continue to hit the road, with training in San Francisco in March, Raleigh, N.C. in June and New Brunswick, N.J. in October. We will, of course, offer training in conjunction with the PDA/EMEA Meeting in Budapest in February, the Annual Meeting in Colorado Springs, the Biennial Training Conference in New Orleans and PDA/FDA in Washington, D.C.

Classroom lecture training at TRI will open the season with TR-32, Computer Auditor Training. For the first time in the United States, we will offer training associated with PDA's Cold Chain Conferences and Technical Report. This course will focus on *Global Standards and Technical Report 39.* This training was previously held in Berlin, Germany in October and Cork, Ireland in November.

We will be working with the PDA staff in Europe throughout 2008 to develop a European training initiative. We are going to focus this training on manufacturing and production, and hope to be able to build some training around product development. We are also looking for some input from our members in Europe on your needs and wants in the area of training, so that we will be able to offer training that better meets your specific needs.

Finally, the relatively newly appointed TRI Education Advisory Committee is off and running in several areas, including a short survey on training needs that should show up in a PDA Connector shortly. Please complete this and return it to PDA, as it will allow us to anticipate and serve your needs now and in the future.

So I guess that's it for another month. Again, I wish to thank our supporters and sponsors, instructors and students and all of you who have participated in or intend to participate in a TRI event in the near future. If you haven't seen our new home, please make it a point to visit. I think you will like what you see.

Happy New Year!

Maximize Your Trip to Budapest: PDA/EMEA Joint Conference Training

Budapest, Hungary • February 18-19, 2008 • www.pdatraining.org/budapest

Tim Morris, PDA

It can be difficult to take time away from your busy schedule to attend one of PDA's many events. That is why the PDA Training and Research Institute is conducting six lecture courses preceding the 2008 PDA/EMEA Joint Conference in Budapest, Hungary, that correspond to the topics to be presented at the Conference.

If you already plan on attending the conference, consider making your trip to Budapest complete by participating in one of these outstanding educational opportunities:

- Preparing for and Passing an EU or US GMP Inspection
- Quality System Strategies for Investigational Drugs
- Risk-Based Approach and Risk Management in Pharmaceutical Manufacturing Processes
- Drug Registration in Europe – An Insightful View (New)
- ICH Q10 and its Potential Impact on the Pharmaceutical Industry (New)
- Briefing Meetings, Scientific Advice/ Protocol Assistance, and Pre-submission Meetings with EMEA — When to Do What and How to Prepare (New).

Held at the Novotel Budapest Congress & World Trade Center, this selection of courses is led by several esteemed faculty members, who have dedicated much of their career to the development of pharmaceuticals and biopharmaceuticals. This year's faculty includes **Michael H. Anisfeld,** PhD, Globepharm Consulting; **Marco Budini**, PhD, Novartis (retired); **Trevor Deeks,** PhD, Emergent BioSolutions; **Karen Ginsbury,** Pharmaceutical Consulting Israel Ltd.; and **Barbara Jentges,** PhD**,** PhACT GmbH Switzerland.

For full course descriptions and registration information visit www.pdatraining.org/budapest.

PDA Parenteral Drug Association
Training and Research Institute
EDUCATION • TRAINING • APPLIED RESEARCH

Stay on Top of the Regulatory Issues that Matter Most!

The PDA Training and Research Institute will be holding two days of lecture training preceding the **2008 PDA/EMEA Joint Regulatory Conference** in Budapest, Hungary, February 18-19, 2008. This year's training courses include:

FEBRUARY 18, 2008
New! Drug Registration in Europe – An Insightful View
New! ICH Q10 and its Potential Impact on the Pharmaceutical Industry

FEBRUARY 18-19, 2008
Preparing for and Passing an EU or US GMP Inspection
Quality System Strategies for Investigational Drugs

FEBRUARY 19, 2008
Risk-Based Approach and Risk Management in Pharmaceutical Manufacturing Processes
New! Briefing Meetings, Scientific Advice/Protocol Assistance, Pre-submission Meetings with EMEA–When to Do What and How to Prepare

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Alkotàs utca 63-67
H-1123 Budapest

"TRI-ing" Hard to Meet Your Needs

James Wamsley, PDA

Each new year brings promises of new beginnings. Whether people want to start going to the gym, improve their eating habits or to help the environment, everybody wants to do something to make the new year better than the last. In 2007, PDA TRI saw a new beginning: After ten years in Baltimore, TRI closed its doors last May only to open them again in August in Bethesda, Md. Now, we are focusing on improving how our lab and lecture courses meet the industry's needs.

PDA has always strived to offer the best training by continually updating current offerings and adding new ones. When the decision was made to consolidate PDA Headquarters and TRI into the same location, we committed to building a state-of-the-art facility that more closely approximates what our members see at their own facility. Not only did we improve the cleanroom environment, we were able to improve our capacity by adding two additional laboratories to complement out micro lab—a Biotech lab and a Clean-In-Place (CIP) lab. We are using the former for our Aseptic Processing and Cleaning Validation courses, and the latter will be used for a new course on CIP Design and Engineering. course under development. The new lecture rooms are state of the art, and students will be able to plug in their laptops and access the internet right at their classroom tables.

Now that you've heard a little about how PDA has improved the learning environment, let's dig into what we've done to improve our catalog. In 2007, PDA offered several new courses and will continue the trend in 2008.

Developing an Environmental Monitoring Program was first offered in November 2007 and is designed to help you define the key components necessary for a successful EM program. The course is held in an interactive cleanroom setting, and covers personnel monitoring, viable monitoring, non-viable monitoring and test site selection criteria. The viable monitoring section will cover several surface sampling techniques including contact plates, swab sampling, as well as active and passive air sampling.

Development of Pre-filled Syringes will make its debut in the U.S. in March 2008. The course will cover the practical aspects of developing and processing pre-filled syringes. Attention will be paid to major process steps such as siliconization, filling, stoppering and visual inspection. Also covered are in-process controls and functionality tests such as silicon oil determination and distribution in the syringe, friction force measurement and particulate determination.

Downstream Processing: Separation, Purification and Virus Removal was one of the first courses offered at the new TRI facility in August 2007 and will return for 2008. This course will provide participants with an overview of the fundamentals of downstream processing for biochemical product recovery. The primary focus is on traditional unit operations such as Crossflow Filtration Systems, while ensuring understanding of new concepts and emerging technology such as membrane chromatography and virus filtration.

Pharmaceutical Water System Microbiology is being offered for the first time in March 2008 and will focus on microbiological issues with purified water and Water for Injection (WFI) systems. Students will understand how, where and why biofilms grow in high purity water systems and the impact they can have on the functionality and quality of the system and its water. Students will also learn good sampling practices and be able to identify possible problematic practices.

Fermentation Scale-Up and Biologics Production is a new four day laboratory course scheduled for August 2008. This course is meant to teach the practical concepts that need to be applied when scaling-up. Students will also learn how and why simple microorganisms can produce complex protein products using practical terms and examples to illustrate the principles, including the actual handling of fermentors, bioreactors, filters and chromatography systems.

Above are just a sample of the new courses that are on the horizon at PDA TRI. Several others are still in development as we continue "TRI-ing" hard to meet your training needs through updated courses, new offerings and better technology. As always, if you have any suggestions on how we can improve our programs—or what we should be offering to the industry, please feel free to contact us at infotri@pda.org.

PDA Holds First Conference Co-Sponsored by USP, EP and JP

Frankfurt, Germany • April 1–2, 2008

PDA is pleased to announce its first conference on pharmacopoeial issues supported by all three of the Pharmaceutical Discusssion Group pharmacopoeias: Japan Pharmacopoeia, European Pharmacopoeia, and United States Pharmacopeia.

The conference, entitled "PDA Compendial Forum: Future Directions of the Pharmacopoeias," will cover the following areas of interest to PDA members and to all of the pharma industry:

- Status of Compendial Harmonization following ICH Yokohama
- Sterilization & Microbiology Quality
- New Technologies
- Pharmaceutical Water
- Microbiological Quality
- Chromatography & Impurities: Opportunities for Harmonization
- Scientific Challenges of Introducing New Technologies in the Compendia
- Future Directions of the Pharmacopoeias

PDA wishes to thank the members of the program committee. The EP is represented by **Peter Castle** and **Emmanuelle Charton,** both of EDQM. The JP is represented by **Tsugo Sasaki,** National Institute of Health Sciences and **Yoshikazu Sakagami,** Kinki University. **James Akers,** Akers, Kennedy and Associates and **Darrell Abernathy,** USP, represented the USP. Also on the committee were:

Janeen Skutnik, Pfizer

Costin Camarasu, Biovail

Kevin Goode, GSK

Brian Matthews, Alcon

Daikichiro Murakami, Taikisha

Sue Schniepp, Consultant

The Berlin Bear goes to Spain or Pharmaco-Diplomacy: PDA & AEFI

Georg Roessling presents the Berlin Bear to Santiago Alsina Carrera

PDA was a recent guest at the annual conference of the leading Spanish professional association for industrial pharmacists, AEFI (Asociación Espanola de Farmacéuticos de la Industria) in Tarragona, Spain. In the photo, taken during the evening open-air gala, **Georg Roessling** is congratulating AEFI President **Santiago Alsina Carrera** on the success of their conference with a presentation of the ubiquitous Berlin Bear, the signature gift of PDA Europe.

AEFI is the primary professional society in Spain with more than 2200 members. Their two-day annual conference on October 24-25 was attended by 400 participants with a wide range of topics covered. The AEFI executive committee, **Dolores Cainzos, Carmen Castanon** and Alsina Carrera, met with Roessling to discuss potential opportunities to work together. A workshop of AEFI and PDA on Annex1 is tentatively planned to take place in Madrid or Barcelona in April. More discussions on meetings and training activities are planned.

PDA Parenteral Drug Association

Web Seminars

PDA Web Seminars are a cost-effective, high-quality training option for professionals wanting to gain the latest information about bio/pharmaceutical sciences and technology—with minimal impact on your time and budget. All you need is a touch-tone telephone, computer and Internet connection to participate in a session.

www.pda.org/webseminars

Sterile Operations and GMP inspections: Highlights of 2008 EMEA Joint Conference

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

Jim Lyda, PDA

After a year of planning, the 2008 PDA/EMEA Joint Conference European GMP—Current Issues and Future Developments will showcase sessions on two core PDA topics: Sterile Operations and GMP Inspections.

On Wednesday, February 20, parallel Track 1 will cover "Sterile Operations." Leading off the discussion with be MHRA senior inspector **Paul Hargreaves,** who will discuss the content and changes in the revised EU GMP Annex 1, Manufacture of Steile Medicinal Products. Hargreaves was the leader of the EMEA inspection working group which considered all of the consultation and industry feedback regarding the Annex. Following will be a comparative presentation entitled, "Sterile Requirements Around the World," by **Nigel Halls,** formerly of GSK and an authority in sterile manufacturing. Closing the session will be a presentation on, "Sterility—What is an Acceptable Level (A risk-based view)," by **Martyn Becker,** MSD, and former inspector. The session is chaired by **Veronique Davoust,** Pfizer.

On Thursday, February 21, the extended Track 7 will cover "GMP Inspections." Leading off will be a presentation on "Inspections by EU Authorities," by **Simona Raicu** of the Romanian national authority, ANM. Raicu will discuss how EU inspections are triggered, how they are coordinated and how inspectors are selected. Immediately following will be a presentation on "How does Europe Ensure Consistent Interpretation of GMP Regulations Among the Various Inspectorates?" by **Emer Cooke,** Head of the EMEA Inspections Sector. We will then get an 'insider's look' at "Inspections up-date: Major Observation," by the well-known **Tor Graberg,** Chief Inspector of Sweden's Medical Products Agency.

After the break, we will get advice from Paul Hargreaves, one of the most senior and experienced inspectors in Europe on "The Inspectors' Expectations (The do's and don'ts during inspections)." Closing this super session will be an "Industry Perspective on Inspections," in which John Kerridge, Eli Lilly, will discuss inspection experiences and trends. The chair of this session is David Cockburn, EMEA Inspections Sector.

If you want to hear all of this in person and ask questions to these impressive panelists, then join us in Budapest.

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PDA Parenteral Drug Association

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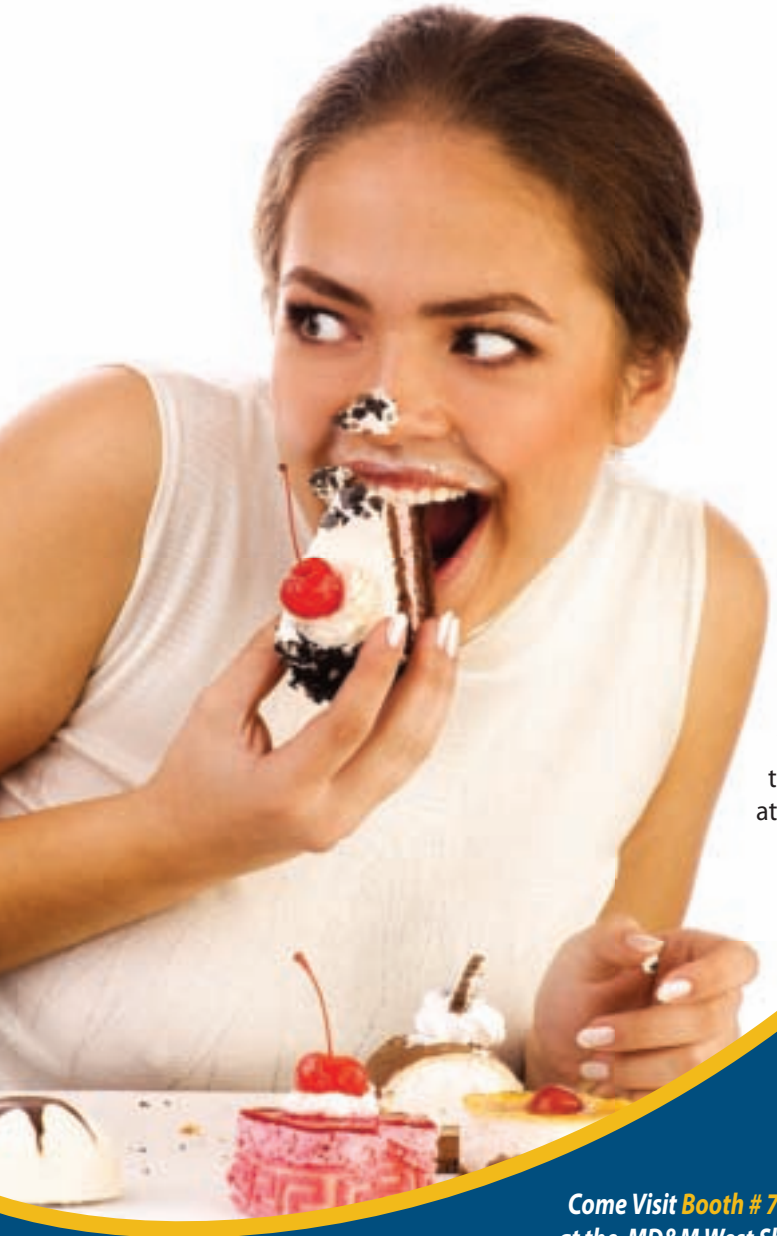
- ✓ *Regulatory Reporting*
- ✓ *Internal Audit & Observation*
- ✓ *Supplier Audit & Observation*
- ✓ *Effectiveness Check*
- ✓ *More..*



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