

# PDA Letter

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[www.pda.org/pdaletter](http://www.pda.org/pdaletter)

July/August 2012



## Industry Comes Clean at Annual Meeting

28

6 Latest TR Helps Industry Validate Analytical Methods

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48 The Evolving Role of ICH



Brochure now  
available!  
Download at  
[www.pda.org/ICHQ10](http://www.pda.org/ICHQ10)

*The Parenteral Drug Association presents...*

# Responsibilities of Executive Management (Operations and Quality) – Implementing the Principles of ICH Q10: 2012 PDA/FDA Pharmaceutical Quality Systems Workshop

*Business and Regulatory Expectations*

**September 12-13, 2012**

Baltimore Marriott Waterfront Hotel | Baltimore, Maryland

*“The commitment to quality may cost more, but it manages the risk of even more costly failures. I think only until the business side becomes convinced of this equation and how it parses out that we are going to get substantial progress. Both FDA and industry need to take additional steps. You can expect from us a renewed effort over the next several years in this area to move many of the issues brought up in this talk forward to get us to the desired state.”*

**Woodcock Criticizes Industry on Quality Management, FDA WebView**

The principles of ICH Q10 can improve business performance and productivity through enhanced quality and compliance. Success relies on a multi-functional team. Realizing the full business value of ICH Q10 requires close collaboration between the development, manufacturing and quality teams.

Ensure your executive operation teams are also present to hear from experts in the application of ICH Q10. Take this unique opportunity for your stake-holders to have a seat at this important table. Explore the rapidly changing expectations around quality, as seen by industry leaders and key FDA personnel.

#### Some confirmed speakers are:

- **Richard Friedman**, Associate Director, OMPQ, CDER, FDA
- **Neil Wilkinson**, Senior Partner, NSF-DBA
- **Steven Lynn**, Office Director (*acting*), OMPQ, CDER, FDA
- **Robert Sausville**, Director, Division of Case Management, CBER, FDA
- **Anders Vinther**, PhD, Vice President, Quality Biologics Operating Unit, Global Quality, Roche
- **Ronald Stellon**, Vice President, Quality Assurance, AstraZeneca



Visit [www.pda.org/ICHQ10](http://www.pda.org/ICHQ10)  
for more information and to register.





Register By  
**September 7th**  
and Save Up  
to \$200!



*The Parenteral Drug Association presents the...*

# PDA Biennial Training Conference

*From Training to Learning – Improving  
Performance in a Regulated Environment*

**October 8-9, 2012**

Hyatt Regency Bethesda | Bethesda, Maryland

The *PDA Biennial Training Conference* has been designed to provide participants with innovative knowledge, skills and proven tools to increase employee performance within a regulated environment. Created for anyone with training responsibilities in the bio/pharmaceutical industry, this conference will provide the most current information needed to strengthen your training expertise.

PDA is offering you **the** best training conference in the industry and sessions include:

- A MUST ATTEND Opening plenary session:
  - **Vaccine Academy Training:** Learn how a company's Vaccine Sterile Manufacturing division is leveraging learning to build capability and become a high performance organization
- 27 Concurrent sessions broken down into three topic structures:
  - From Training Programs to Learning Programs
  - Training System Effectiveness
  - From Theory to Practice
- Round table sessions devoted to current training issues:
  - What to Do When Training is NOT the Solution
  - What to Do When an Employee Passes Their Initial Assessment, But Does Not Apply the Knowledge/Skills on the Job
  - Use of Job Aids (Paper and Electronic)
- Closing plenary session on **Regulatory Training Expectations**. Hear directly from the regulators on what they want to see when they visit your organization
- And much more

PDA's Training and Research Institute will be hosting three training courses following the *PDA Biennial Training Conference* on October 10-11.



Visit [www.pda.org/biennial2012](http://www.pda.org/biennial2012)  
for more information and to register

**Exhibition: October 8-9 | Courses: October 10-11**

## Cover



### 28 Industry Comes Clean at PDA Annual Meeting

Cleaning: It happens in every manufacturing plant, storage facility and anywhere else a drug product is processed, stored, etc., and it is a vital part of the manufacture of quality, safe products. Whether for a facility, equipment or instruments, cleaning seems like a rather straightforward proposition; yet, there is a lot of science associated with a high-quality cleaning program.

*Cover Art Photographed by Katja Yount, courtesy of Training and Research Institute's Facility*

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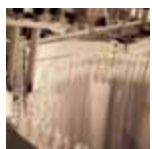
### 36 10 Lessons from 2012 PDA Sterile Technology Conference

Bioburden and ongoing regulatory problems in the manufacture of sterile products are just two of the major issues discussed at the *2012 PDA Innovation & Best Practices on Sterile Technology Conference*. For those who missed it, the cochairs have highlighted the top 10 lessons they learned during the event.



### 38 Current Sterile and Lyo Issues Discussed at Joint IG Session

Interest in the unique requirements for aseptic processing of lyophilized products is heightening with the number of new therapeutics increasing on the market, including many new biopharmaceuticals such as monoclonal antibodies.



### 44 Ensuring a Quality Culture

Pharmaceutical companies can boast about their ability to manufacture products of the highest quality; yet, pressure is mounting on firms to improve their quality culture.

## PDA's MISSION

To develop scientifically sound, practical technical information and resources to advance science and regulation for the pharmaceutical and biopharmaceutical industry through the expertise of our global membership

## PDA's VISION

To be the foremost global provider of science, technology, and regulatory information and education for the pharmaceutical and biopharmaceutical community



Connecting People, Science and Regulation®

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## Latest TR Helps Industry Validate Analytical Methods

Similar to the manufacturing process, an analytical method can also be considered a process. The validation strategy for analytical methods could therefore conceptually follow those of Process Validation. As such, Analytical Method Validation (AMV) can be defined as the collection and evaluation of data from the analytical method development stage throughout routine QC testing which establishes scientific evidence that an analytical method is capable of consistently delivering accurate and reliable results.

*PDA Technical Report No. 57: Analytical Method Validation* provides practical

and strategic guidance to efficiently use historical data and knowledge to design suitable risk-based AMV studies and to set appropriate protocol acceptance criteria. The document provides an illustrated map of the typical method lifecycle steps prior, during, and beyond the AMV studies to help users visualize their AMV program. The typical sequence of all pre-validation, validation, and post-validation steps is reflected in the sequence of sections in the technical report.

Technical Report No. 57 provides risk-based guidance for the validating methods following their development or

qualification. It also contains risk-based guidance for other, related method lifecycle steps, such as Analytical Method Transfer (AMT).

The guidance provided builds upon the International Conference on Harmonization (ICH) Q2 (R1) guidelines and includes additional considerations for analytical platform technology (APT) methods as well as the impact of stakeholder considerations, and essentially all modern quality expectations as recommended in the ICH Q8 (R2), Q9, and Q10 guidelines. 🍷

### PDA Analytical Method Validation And Transfer For Biotechnology Products Task Force Members

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store.pda.org

## Coming Soon! PDA's Latest Technical Report on Controlled Distribution

*PDA Technical Report No. 58: Risk Management for Temperature-Controlled Distribution* will be available in August. Check the *PDA Letter* and the PDA Bookstore for more information. 🍷



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## Over 30 U.S. FDA Officials to Speak

Over thirty officials from the U.S. FDA have confirmed that they will be speaking at the 21st consecutive PDA/FDA Joint Regulatory Conference.

Throughout the event, mid-level officials will provide updates on the current efforts impacting the development of global regulatory strategies in Baltimore, Md.

Later at the conference, compliance directors will provide their perspective on current “hot topics” in the compliance and enforcement areas. Significant FDA 483 observations and other regulatory actions will be covered.

Agency leaders from CBER, CDER, CDRH, CVM and ORA will also speak about their Center’s current and future initiatives at the final plenary session. For more information or to register for the event, visit [www.pda.org/pdafda2012](http://www.pda.org/pdafda2012). 🌐



## Special Offer for the Quality Systems Workshop!

To make sure you bring your operations personnel to the 2012 PDA/FDA Pharmaceutical Quality Systems Workshop, we are extending a special registration discount of 20% to those in operations.

Please note that those in quality will pay full price for the Workshop.

Visit [www.pda.org/ICHQ10](http://www.pda.org/ICHQ10) to register today! 🌐



The Parenteral Drug Association presents...

# PDA Europe Conference Parenterals 2012

Due to the fact that parenterals are gaining ever more importance, the 2012 conference will address the following topics:

- Technology updates, innovations in equipment and process technology
- Production environments and their control
- Facilities design and production planning
- Impact of recent regulatory guidances
- Component related quality impacts, testing and inspection
- Regulatory expectations and trends

6-7 November 2012

Hesperia Tower Hotel  
Barcelona | Spain



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<https://europe.pda.org/Parenterals2012>

# Help Improve the Integrity of the Supply Chain

Bethesda, Md. • November 13-14 • [www.pda.org/supplychain2012](http://www.pda.org/supplychain2012)

## 2012 Program Planning Committee

The program planning committee would like to invite you to attend the *2012 PDA/FDA Pharmaceutical Supply Chain Conference* from November 13-14 in Bethesda, Md.

Improving the integrity of the entire supply chain for pharmaceutical ingredients and finished products ultimately helps ensure the quality and safety of medicines for patients. Globalization of pharmaceutical manufacturing and distribution is bringing manufacturers and suppliers

to public forums such as these to discuss how to manage emerging concerns including illegal acts such as counterfeiting, diversion and intentional adulteration. Globalization is also prompting legislators and regulators to seek enhancement to existing standards and practices for improved supplier quality management, manufacturing and distribution. Regulators are also developing

cooperative approaches to share information and the burden of oversight.

Management of today's globalized supply chains by manufacturers requires a greater volume of knowledge about suppliers, careful consideration of a multitude of factors and a variety of science- and risk-based approaches. There

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### *Cooperative efforts and innovation within industry and regulatory agencies aiming to enhance oversight and the integrity of pharmaceutical supply chains are starting to come to fruition*

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is a great deal of information to manage and a need for timely sharing of newly acquired knowledge about emerging risks in the global pharmaceutical supply chain.

Cooperative efforts and innovation within industry and regulatory agencies aiming to enhance oversight and the integrity of pharmaceutical supply chains


are starting to come to fruition. Building on earlier PDA-cosponsored conferences and workshops, the *2012 PDA/FDA Pharmaceutical Supply Chain Conference* will provide a forum for presentations by industry experts as well as group discussions that will foster implementation of innovative ideas that will enhance supply chain integrity

to protect patients from potentially unsafe or ineffective medicines.

This conference will provide participants the opportunity to:

- Hear from senior personnel from the U.S. FDA and other regulatory agencies
- Share improvements in programs for supplier management and new technology
- Identify any barriers and associated actions to enable implementation of feasible solutions
- Learn about proven monitoring and testing methods as preventive measures
- Benchmark systems with leading pharmaceutical companies

We encourage you to attend this conference to help in the development of initiatives to ensure the integrity of the global pharmaceutical supply chain.

To learn more or to register, visit [www.pda.org/supplychain2012](http://www.pda.org/supplychain2012). 

On November 12, TRI will hold a course about developing a robust supplier management process. The course will

- Identify the primary steps in the supplier management process
- Apply the use of risk management tools in supplier management
- Identify critical elements to evaluate during on-site supplier audits
- Describe key metrics to use for supplier monitoring
- Develop an action plan to either enhance the supplier management process at their company

## New Members: Learn about PDA Over Breakfast

What are you doing on Monday, September 10 at 7:00–8:00 A.M.? If you are a new member who has joined PDA on or after April 1, you should attend the new member breakfast!

Held on-site at the *2012 PDA/FDA Joint Regulatory Conference*, the breakfast will give you an opportunity to learn more about PDA and a chance to meet PDA board members including the Chair of the Board, **Anders Vinther**, PhD, VP, Quality, Genentech. Other new members and PDA staff will be on hand as well.

You must be a full conference attendee and RSVP by August 15 to attend.

For more information and to RSVP, please contact **Hassana Howe**, Director, Membership & Chapters, at [howe@pda.org](mailto:howe@pda.org) or 301-656-5900 x 119. ☎



## Join Us at the PDA/FDA Gala and Networking Reception

We know how important it is to network, and we've made time for you at the *2012 PDA/FDA Joint Regulatory Conference* to talk to and meet friends, industry members and regulators! Join us at the networking reception on September 10 and the gala reception on September 11. To learn more and to register, visit [www.pda.org/pdafda2012](http://www.pda.org/pdafda2012). ☎

*The Parenteral Drug Association presents the...*

## PDA/FDA Vaccines Conference

*Challenges and Opportunities  
for Providing Vaccines to the World*

**December 3-4, 2012** | Bethesda North Marriott Hotel | Bethesda, Maryland  
**Exhibition: December 3-4** | **Courses: December 5-6**

Advances in science and technology are leading to research and development of a wide array of new vaccines and novel manufacturing approaches that may result in new and advanced tools for the prevention of emerging infectious diseases.

The *PDA/FDA Vaccines Conference* will provide a forum for discussion of many important vaccine development, manufacturing and regulatory issues.

Hear these regulatory experts from the FDA present on the following:

- Arifa Khan, PhD, Senior Investigator, *CBER, FDA: Regulatory Perspective on Adventitious Agent Testing*
- Konstantin Chumakov, PhD, Associate Director for Research, *CBER, FDA: Regulatory Perspectives on Analytical Changes*
- Vladimir Chizhivkov, Chemist, *CBER, FDA: Rapid Mycoplasma Detection Methods*
- Marion Gruber, PhD, Director, *OVR, CBER, FDA: US Regulatory Challenges*



Register Before  
**September 21st** –  
The Largest  
Registration  
Savings Deadline!



Agenda just released! Visit [www.pda.org/vaccines](http://www.pda.org/vaccines) for more information.



# Your "Secret Weapon" in the battle for compliance

## USE YOUR "SECRET WEAPON" TO LEARN:

- How to avoid criminal 'Park Doctrine' liability if your company cuts corners on quality
- How to make sure recalls don't cause shortages of your drug products
- How to win FDA approval for big changes like single-use systems
- How to protect your supply chain from high rollers in procurement
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## Faces and Places: Workshop with PIC/S



(l-r) Harald Scheidecker, Boehringer Ingelheim; Gabriele Gori, NoVartis Vaccines & Diagnostics; Douglas Kovacs, U.S. FDA



(l-r) Harald Scheidecker, Boehringer Ingelheim; Georg Rössling, PDA; Boon Meow Hoe, HSA; Hans Smallembroek, Health Care Inspectorate; Stephan Rönninger, F. Hoffman-La Roche



(l-r) Boon Meow Hoe, HSA; Georges France, Novartis; Jacques Morénas, ANSM; Stephan Rönninger, F. Hoffmann-La Roche; Steven Mendivil, Amgen; Ilisa Bernstein, U.S. FDA; Tor Gråberg, MPA Sweden; Carmelo Rosa, U.S. FDA

May 9–10, 2012



(l-r) Georg Rössling, PDA; Richard Johnson, PDA; Harald Scheidecker, Boehringer Ingelheim Pharma



(top l-r) Jiri Holy, ISCVBM Czech Republic; Steven Mendivil, Amgen; Jacques Morenas, ANSM; Tor Gråberg, MPA Sweden; Georges France, Novartis

(middle l-r) Sandra Schröder, F. Hoffmann-La Roche; Carmelo Rosa, U.S. FDA; Gabriele Gori, Novartis; Harald Scheidecker, Boehringer Ingelheim Pharma; Georg Rössling, PDA

(bottom l-r) Stephanie Reid, Health Canada; Jette Christensen, Novo Nordisk; Boon Meow Hoe, HSA; Stephan Rönninger, F. Hoffmann-La Roche; Douglas Kovacs, U.S. FDA



(l-r) Rich Levy, PDA; Jette Christensen, Novo Nordisk



## Faces and Places: Glass Quality Conference

June 4–5, 2012

### Development Considerations/Glass



(l-r) Cristophe Wagner, SGD; Nicholas DeBello, Wheaton Industries; Robert Langer, MIT; Christopher Weikart, SiO<sub>2</sub> Medical Products; Dan Haines, Schott; Ron Iacocca, Eli Lilly

### Pharmaceutical Packaging in Glass



(l-r) Dave Machak, American Glass Research; Roger Asselta, Genesis Packaging Technology; William Bogle, Genesis Packaging; John G. Shabushnig, Pfizer

### Distribution/Packaging/Transportation



(l-r) Shana Whitmore, Amgen; Bryan Williams, Lansmont Corporation; Stanley Hall, Pfizer

### Monitoring Customer Feedback & Other Factors to Consider in Glass Defect Prevention



(l-r) Catherine Gould, U.S. FDA; Maria Linzmayer, Merck; Jim J. Janimak, GlaxoSmithKline; Krista Liotta, Merck

### What Are We Going To Do To Make It Better?



(l-r) Shana Whitmore, Amgen; Diane Paskiet, West Pharmaceutical Services; Roger Asselta, Genesis Packaging Technology; Mihaela Simianu, Eli Lilly; Richard Johnson, PDA; Juan Cerdan-Diaz, Nipro Glass Americas; Thomas Schoenknecht, Schott; Milind Ganjawala, U.S. FDA; Steven Wolfgang, U.S. FDA



## Faces and Places: PDA/FDA Virus and TSE Safety Conference

### Regulatory Update: Biopharmaceuticals



(l-r) Marc Martin, ANSM; Kurt Brorson, U.S. FDA; Yashurio Kishioka, PMDA; Jeffrey Skene, Health Canada

### QbD Type Clearance Studies – Role & Structure of Risk Assessments and Design of Experiment Studies



(l-r) Lisa Connell Crowley, Amgen; Rachel Specht Genentech; Dayue Chen, Eli Lilly

### Current Clearance Technologies



(l-r) Dominick Vacante, Johnson & Johnson; Judy Glynn, Pfizer; Hannelore Willkommen, Regulatory Affairs & Biological Safety Consulting; Olga Galperina, Human Genome Sciences

June 15-17, 2012

### Assessing Virus Clearance of Specific Unit Operations



(l-r) Qi Chen, Genentech; Herb Lutz, EMD Millipore; Kurt Brorson, U.S. FDA; Jeffrey Ucran, Acceleron Pharma

### Current Clearance Technologies



(l-r) Hannelore Willkommen, Regulatory Affairs & Biological Safety Consulting; Houman Dehghani, Amgen; Albrecht Groener, CSL Behring; Min Zhang, Genentech

### Risk Mitigation Strategies – Raw Materials



(l-r) Brian Hubbard, Amgen; Jack Ragheb, U.S. FDA; Tara Tagmyer, Merck; Lilly Kong, PrimeraDx; Rebecca Sheets, NIH



(l-r) Thomas R. Kreil, Baxter BioScience; Roger Hart, Amgen; Raymond Nims, RMC Pharmaceutical Solutions; Rosemary Versteegen, International Serum Industry Association



Register Before  
**September 3rd**  
and Save  
Up to \$400!

*The Parenteral Drug Association presents the...*

# 2012 Pharmaceutical Cold Chain & Good Distribution Practice Conference

*Temperature Controlled Supply Chain –  
A Global Partnership*

**November 15-16, 2012**

Bethesda North Marriott Hotel | Bethesda, Maryland

As the cold chain industry becomes progressively complex and increasingly subject to global scrutiny, the urgency to remain competitive and compliant in global markets is contingent upon a cooperative initiative for well-developed Good Distribution Practices (GDP).

In its seventh consecutive year, the 2012 *Pharmaceutical Cold Chain & Good Distribution Practice Conference* will focus on the various challenges, solutions and case studies regarding integrated supply chain management and GDP.

#### Plenary sessions include:

- Opening plenary session:  
**Pharmacopeial Updates:** An overview of the various activities and projects by the USP will be presented
- Update on Global Comparisons of Cold Chain/GDP Regulations
- Supply Chain Integrity and Security
- Migration from Cold Chain to Temperature Controlled Good Distribution Practice
- The Role of Good Distribution Practice in Supply Chain Management: Regulatory and Industry Perspectives
- Regulatory and Industry Consensus on Data-Driven Approaches to Ensure the Quality of Pharmaceuticals in Distribution
- Pharmaceutical Supply Chain Temperature Controlled Solutions – Case Studies

There will also be a Pharmaceutical Cold Chain Interest Group session where attendees are invited to learn and contribute to the global activities of the PCCIG.

Agenda just released! Available at [www.pda.org/coldchain2012](http://www.pda.org/coldchain2012)



Visit [www.pda.org/coldchain2012](http://www.pda.org/coldchain2012)  
for more information and to register

Exhibition: November 15-16 | Course: November 12

# Please Welcome the Following Industry

**Luis Alves**, Bristol-Myers Squibb

**Shane Anderson**, Gerresheimer

**Howard Anderson**, U.S. FDA

**Sandra Anderson**, REXAM Healthcare

**Clementina Anyakora**, Uchechukwu NAFDAC

**Hana Artin**, MacroGenics

**Godfrey Aschmann**, Nipro Glass Americas

**Jayson Babler**, Boston Scientific

**Anja Bagger**, Novo Nordisk

**Helena Baiao**, Infarmed

**Arash Barghian**

**Joanne Beck**, Shire

**Sabine Behnert**, Novartis

**Brian Bell**, Bristol-Myers Squibb

**Ilisa Bernstein**, U.S. FDA

**Ana Boban**, Agency Medicinal Products and Medical Devices

**Pam Bobbette**, Cangene BioPharma

**Susanne BoeHansen**, Novo Nordisk

**Duane Bonam**, Amgen

**Jerry Booth**, Merck

**Lucie Bouchoud**, Geneva University Hospitals

**Beth Brescia**, EMD Millipore

**Ethan Brookes**, Lonza

**Andrea Calandrino**, Luitpold Pharmaceuticals

**Christel Calmelly**, GlaxoSmithKline

**Alessandra Carpenedo**, DOC

**Jeffrey Carpenter**, Jubilant HollisterStier

**Tomas Carrasquillo**, McNeil Consumer Healthcare

**Marie Carrette**, Merck

**Cortney Caudill**, Samsung Biologics

**Martin Ceiler**, Gambro

**Olivier Cheylat**, Merck

**Giwon Cho**, Korean FDA

**Jennifer Clark**, Commissioning Agents

**Anne Collins**, Hospira

**Yvonne Concannon**, Mylan

**Bridgette Cornwell**, Hospira

**Andrew Cotter**, Mylan

**Melissa Crabb**, Afton Scientific

**Stephanie Croft**, World Health Organization

**Asha Cyriac**, Hospira

**Deborah Czarnecki**, FMC

**Francois Daguanel**, Sanofi-Pasteur

**David Danelson**, Biovalidation Association

**Pankaj Dave**, Emcure Pharmaceuticals

**William Dawes**, Lantheus Medical Imaging

**Alice Dayoub**, Celgene

**Rui de Sousa**, Stematters

**Christopher DeMerlis**, Colorcon

**Massimo Denti**, Biologici Italia Laboratories

**Reprints Desk**, Reprints Desk

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**Nick Dyar**, Eisai Machinery

**Thomas Evans**, Expression Systems

**Theodora Ezie Nkechinyere**, NAFDAC

**Theresa Farrell**, Fenwal

**Unine Felix**, Department of Health

**Adam Fenimore**, Alkermes

**Michael Ferguson**, Envirotainer

**Derek Fitzgerald**, New Zealand Medicines and Medical Devices Safety Authority

**Theresa Flores**, Mylan

**Michael Foy**, Bayer Healthcare

**Sarah Francis**, Genzyme

**Sabine Frantz**, Novartis

**Greta Franzoso**, Stevanato Group

**Sandra Freigang**, Boehringer Ingelheim Pharma

**Jens Fricke**, Leo Pharma

**Karin Froidbise**, AFMPS

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**Kihlon Golden**, Portola Pharmaceuticals

**Ronaldo Gomes**, ANVISA

**Joey Gouws**, Medicines Control Council

**Tomasz Grabowski**, Zaklady Farmaceutyczne Polpharma

**Suzan Hadorn**, PIC/S

**Stanley Hall**, Pfizer

**Jeffrey Hancock**, Novartis

**Nani Handayani**, National Agency of Drug & Food Control

**Shinichi Hashimoto**, Taikisha

**Anna Hayes**, Anew Optics

**Antje Heidemann**, Parexel International

**Violet Helfen**, Fresenius Kabi

**Masaya Hizaki**, Sawai Pharmaceutical

**Brenda Holman**, U.S. FDA

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**Eric Strickland**, GE

*Continued at bottom of page 18*



## 2011 Honor Awards Recipients

The PDA Honor Awards are bestowed on members who provide exceptional leadership and service to the Association and have been awarded at the Annual Meeting since 1958. The 2011 award winners were announced at the *2012 Annual Meeting* in April, and they will be highlighted in each *PDA Letter* until next year's event. This month we highlight the PDA Honorary Membership and the Frederick J. Carleton Award.



### Honorary Membership

This is PDA's most prestigious award, conferring lifetime membership benefits to the recipient. The award has usually been given in recognition of very long service, of a very significant nature, to PDA. The award requires unanimous approval of the PDA Board of Directors, and honorary members are not eligible for other awards in the same year.

This year's recipient is **James Agalloco**. He has been a member since 1972 and the past PDA President from 1988-89. He is a TRI instructor, SAB Member, cochair of the Production & Engineering Interest Group, cochair of the Isolator Validation Task Force as well as a member of the Cleaning Validation Task Force and Solid Dosage Validation Task Force.

He is also a founding member, active speaker and contributor to the PDA Metro chapter.



### Frederick J. Carleton Award

Presented as a tribute to lifetime contributor, past President, past Executive Director, and Honorary Member Frederick J. Carleton, this award is designated for past or present Board members.

This year's recipient is **Kathleen Greene**. She is a former Board member (2002-2007), who is currently the cochair for the Quality Requirements for the Extemporaneous Preparation of Clinical Trial Materials Task Force. She is also serving on the 2012 PDA/FDA Joint Regulatory Conference Planning Committee.

Welcome New Members continued from page 17

## Please Welcome the Following Industry Leaders to the PDA Community

**Se-Eun Suh**, Korean FDA

**Yukihito Sumino**, Shionogi

**AMIT Swain**, Ranbaxy

**Alexander Szivak**, BASG/AGES

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# James Cooper Celebrates 40 Years of PDA Membership

Endotoxin guru **James Cooper**, PharmD, has recently celebrated his fortieth year as a PDA member.



Cooper became serendipitously involved with PDA after contacting **Gordon Personeus** in 1970 for help with his thesis, which compared the new LAL (*Limulus* amoebocyte lysate) and rabbit pyrogen tests for endotoxins.

After Gordon brought this work to the PDA's attention, **Fred Carleton** arranged for Cooper to present his research results at a PDA conference; he subsequently became Cooper's mentor. Cooper also served on PDA's Board of Directors from 1983-85.

Cooper said that he has retained his membership, in part, because PDA "has been effective in advancing change in Federal policy." Cooper told the *PDA Letter* that in 1981 the U.S. FDA had proposed guidelines for determining endotoxins with the LAL Test. Cooper, **Mike Upjohn**, **Jim Agalloco** and others found the endotoxin limit in the draft guideline to be unacceptable and sent in comments to the FDA that were backed up with scientific data. The Agency, according to Cooper, revised the draft guide to the specifications that PDA had sent in.

Another reason Cooper gave for his long-term membership was his involvement with PDA's Training and Research Institute. An instructor for 27 years, Cooper along with Mike Korczynski designed the endotoxin section of the course to meet students' new and existing needs. Cooper said that out of all his PDA volunteer experiences, he has enjoyed interacting with students during the aseptic processing course the most.

Cooper said that PDA became his professional home and principal source of information. He plans to continue teaching, giving presentations and working on technical reports for the next forty years. He enjoys volunteering at the state and Federal level to promote management programs that assure a sustainable stock of horseshoe crabs in the Atlantic Ocean. He enjoys skiing and attending story-telling festivals with Frances, his wife of 50 years.

## About the Expert

**James Cooper**, PharmD, is an innovator of the bacterial endotoxins test for parenteral products. His publications span the history of LAL technology. He founded Endosafe Inc. in 1987, an LAL production unit, which is now part of Charles River Laboratories. Following retirement in 2001, he consults on depyrogenation, BET methods, endotoxin issues and root-cause investigations. He teaches the endotoxin component for PDA and U.S. FDA courses. 🍷



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- Quality and Regulatory Job Market Outlook 2012
- R – Evolving Expectations for Biosimilars
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PDA Interest Groups function as vehicles and resources for the individual PDA member to develop and make an impact on his or her scientific, technological, regulatory or training area of interest. IG's operate in both Europe and the United States to better serve the specific needs of members in those regions. Please go to [www.pda.org/interestgroups](http://www.pda.org/interestgroups) for more information.

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# Strategies to Enhance Communication Skills

**Joelle K. Jay, PhD, Pillar Consulting**

One of the biggest challenges managers face is communication. And yet, communication is also one of the most critical aspects of leadership. Without good communication, managers can fail to gain commitment from employees, fail to achieve business goals and fail to develop rapport with the people on their team. In short, they can fail as leaders no matter how good their intentions may be.

Sound scary? It can be, especially for first-time managers. Front-line employees simply don't need the same level of communication skills as leaders do. But when employees rise to leadership positions, they must learn to connect with a greater number of people more effectively to get the job done.

Managers can enhance their communication skills with commitment and practice using a few key strategies that will help determine what, when and how to communicate effectively.

## 1 Listening

The most effective leaders know when to stop talking and start listening. This is especially important in three particular situations:

- When emotions are high
- In team situations
- When employees are sharing ideas

First, listening is crucial when emotions are high. Extreme emotions, such as anger, resentment and excitement, warrant attention from a personal and a business standpoint. On a personal level, people

feel acknowledged when others validate their feelings. Managers who ignore feelings can create distance between themselves and their employees, eroding the relationship and ultimately affecting the working environment.

From a business perspective, emotions can also interfere with clear thinking. Allowing employees to address their emotions helps them move beyond the situation at hand in an effective way and get back to business. Managers can develop stronger relationships with their employees while enhancing productivity simply by listening to their employees when emotions are high.

The second most important time to listen is in team situations. Team environments can involve multiple personalities, complex dynamics and competing agendas. By listening carefully, managers can ensure that everyone is working toward the same goal. Listening also helps managers identify and address conflicts early as well as to facilitate healthy-working relationships among team members.

Third, listening is vital when employees are sharing ideas. When managers stop listening to ideas, employees stop offering them. That means managers are essentially cut off from the creativity and expertise of the people on their team, and leadership becomes an illusion.

In these and almost any situation, the advantages of listening make it worth doing well. The basic fundamentals of good listening include the following:

- Attending closely to what's being said, not to what you want to say next.
- Allowing others to finish speaking before taking a turn.
- Repeating back what you've heard to give the speaker the opportunity to clarify the message.

With these fundamentals, managers can clearly communicate that they care about what the speaker is saying and want to help.

## 2 Facilitating

Facilitating communication is more than just listening, and it is more than leading a conversation. Good facilitation is a continuous cycle of three steps:

- Hearing what is said
- Integrating it into the topic at hand
- Saying something to move the conversation forward

For example, imagine a manager facilitating a meeting in which she and her team are developing goals for the coming year. The conversation might sound something like this:

**Manager:** As we develop our goals for next year, it's important that we hear from everyone in the department. What are your ideas?

**Employee 1:** I think it's important that we get productivity up. I notice we have a pretty relaxed pace around here, and it gets frustrating when some people are working hard and others seem to be contributing less than others.

**Manager:** Okay, so we need improved productivity. What would that look like as a goal?

**Employee 2:** Actually, I think it's more a matter of setting a higher sales goal than improving productivity in the office. We don't just need to be busier. We need to get better results.

**Manager:** I see. So the idea is that we should set higher sales goals for everyone, which would consequently address the productivity issue. Is that right?

**Employees:** Yes.

Notice in this exchange that the manager took the time to repeat what she heard so that the employees could verify its accuracy. She also integrated each comment into the topic at hand—tying the first employee's frustration with productivity to the task (goal-setting) and connecting the second employee's point about sales to the topic on the table (productivity). Even though her employees were giving all of the input, the manager stayed focused on the task of preparing goals and led all comments in that direction.

### 3 Questioning

Many leaders need information but aren't sure how to get it. Similarly, their employees may have information, but don't know how to impart it. Managers can open the lines of communication by asking good questions. Note that different kinds of questions yield different kinds of results. Here is a short primer on questioning:

- **Closed questions:** They elicit yes/no answers. These are beneficial when a manager simply needs to check the status of an issue. Has the report been completed? Do you know what to do? Can you get that to me by Friday? These are examples of closed questions that are perfectly appropriate in the right situations.

- **Open questions:** They elicit longer responses. They are useful almost any time a manager wants more than a yes/no answer—for instance, when seeking input from others, looking for information about a particular topic or exploring a problem. What do you think would be

the best way to go about this? How are you doing on that project? What went wrong? These kinds of questions give others the chance to give all of the information they have and to avoid the innumerable consequences that can come when leaders make assumptions without becoming well-informed.

- **Personal questions:** They have a special role in leadership. Inappropriate personal questions can alienate employees. Asking direct reports if they are dating anyone or why they haven't bought a house can be perceived as prying, even if the questions are well-intended. Appropriate personal questions, however, can create a sense of camaraderie between employee and boss. Asking whether employees had a nice weekend, inquiring about their families or following up on common interests all help people connect on a personal level. That relationship leads to a greater commitment as well as a more pleasant environment.

### 4 Using Discretion

Knowing when not to speak as a leader is just as important as speaking. Managers must understand that the moment they don a new title, they become a leader—one that others look to for guidance, direction and even protection. Good leaders adopt a policy of discretion, if not confidentiality, with their employees. Only then can they develop the trust that is so vital to productivity.

Confidential situations may arise in a number of areas, personal and professional. Here are some topics that may warrant discretion:

- An employee is having a direct conflict with another employee.
- An employee is concerned about another employee's conduct.
- An employee's performance has dropped substantially.
- An employee has a health issue or personal problem.
- An employee wants genuine advice on how to excel, but doesn't want to be seen as cozing up to the boss.

In any of these cases, the employee is facing circumstances that affect him person-

ally and could affect business if not addressed effectively. A manager who invites a confidential conversation could help the employee discuss the situation openly and develop strategies to handle it well. But a manager whose trustworthiness is questionable will undoubtedly scare away any hope for a candid discussion. The consequences could have a bearing on the employee's ability to perform at his best.

How do managers communicate that they can be trusted? One approach is to tell employees directly that you are always available for private conversations when needed. Managers who do this further assure employees who come to them that the conversation will be kept confidential. Then managers keep that promise. In the end, actions speak louder than words. When managers talk behind their employees' backs, gossip or show favoritism of any kind, employees doubt their discretion and opt to keep their thoughts to themselves. The lines of communication shut down, to the potential detriment of the team.

### 5 Directing

Notice that directing comes last on the list of communication strategies. It may not be the least important, but it is definitely one to use less often. Many managers direct their employees because they believe it's the only way to get things done. It is not. The other forms of communication discussed above—listening, facilitating, questioning, using discretion—can all get employees working more productively in a spirit of cooperation and in a friendlier environment than directing.

But, directing has its place; directing means to give directions clearly and unequivocally, so people know exactly what to do and when. It is best used in times of confusion or when efficiency is the most important goal. Although it can be effective, directing also can lead to complacency on the part of employees who may adopt an "I just do what they tell me" attitude. Use it sparingly.

### Benefits to Communication

Communication takes effort. But it is

*Continued at bottom of page 26*





## Meeting Preview

### Interest Group and Advisory Board Meeting Schedule

The business of the Association will be conducted, as always, at the Annual meeting.

Below is a schedule of the Science advisory board, committee and interest group meetings that will take place.

**Note:** All interest group meetings are open to meeting registrants; all other ancillary meetings are by invitation only. (For Regulatory Affairs ancillary meetings, see the Regulatory Snapshot, p. 46).

#### Sunday, September 9

1:00 p.m. – 5:00 p.m.

Process Validation and Verification (Committee Invitation Only)

#### Monday, September 10, 2012

12:15 p.m. – 1:15 p.m.

Science Advisory Board Meeting (Invitation only)

4:45 p.m. – 6:00 p.m.

Process Validation	Visual Inspection of Parenterals
--------------------	----------------------------------

#### Tuesday, September 11

12:15 p.m. – 1:15 p.m.

Biotechnology Advisory Board (Invitation only)

#### Wednesday, September 12

12:30 p.m. – 5:00 p.m.

Prefilled Syringe Task Force (Task Force Invitation Only)

#### Thursday, September 13

8:00 a.m. – 5:00 p.m.

Prefilled Syringe Task Force (Task Force Invitation Only)

8:00 a.m. – 12:00 p.m.

PCMO<sup>SM</sup> Team 2.1 Knowledge Management (Committee Invitation Only)

4:45 p.m. – 6:15 p.m.

Prefilled Syringes	Facilities & Engineering
Packaging Science	Pharmaceutical Water Systems
Sterile Processing Parenteral Drug Manufacturing/Lyophilization	

## Journal Preview

### Submit Your Research to the Journal to be Published

The July/August PDA *Journal of Pharmaceutical Science and Technology* includes a good follow-up to **Janet Woodcock's** May/June Commentary, featured in the June *PDA Letter's* "Journal POV." The Review article, by **Chan Lai Wah**, et al., takes a look at raising the QA bar for sterile drugs. The issue also features two articles that should capture the interest of microbiologists. Editor **Govind Rao** addresses social media with his thought-provoking commentary, "Do you 'like' us?"

#### Editorial

Govind Rao, "Do you "like" us?"

#### Review

Chan Lai Wah, et al. "Toward Higher QA: From Parametric Release of Sterile Parenteral Products to PAT for Other Pharmaceutical Dosage Forms"

#### Research

Dennis Jenke, et al., "Evaluation of the General Solution Compatibility of Polymer Materials Used in Medical Devices such as Syringes"

Aymen S. Yassin, et al., "The Application of Uniplex, Duplex, and Multiplex PCR for the Absence of Specified Microorganism Testing of Pharmaceutical Excipients and Drug Products"

Madhusudan Rao Yamsani, et al., "Design and Characterization of Atenolol Transdermal Therapeutic Systems: Enhancement of Permeability via Iontophoresis"

Ismail Uysal, et al. "Effects of Radio Frequency Identification- Related Radiation on In Vitro Biologics"

Gerhard Haake, et al. "The Importance of Accurate Microorganism Identification in Microbial Challenge Tests of Membrane Filters. Part II. The Comparison of *Hydrogenophaga pseudoflava* ATCC 33668 and *Curvibacter* sp. ATCC 700892 by Microbial Challenge Tests with Membrane Filters"

#### Technology/Application

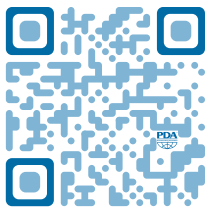
Volker Sigwarth, et al. "A Potent and Safe H<sub>2</sub>O<sub>2</sub> Fumigation Approach" 



## Journal *POV*

### A Look Back: Globalization of Public Health Standards

*In this Journal POV, we look back to the first issue of 1998, which contained the Keynote remarks of the U.S. FDA's Sharon Smith Holston at the September 1997 PDA/FDA Joint Regulatory Conference. It is interesting to see that after more than a decade, FDA is still working hard to ensure the quality and safety of foreign sources of material and products. The following is an excerpt of her remarks; for the full Commentary article, go to [journal.pda.org](http://journal.pda.org) and look up the Jan/Feb 1998 issue in the "Past Issues" archive.*



We've had an exceptionally good year also overseas, where our activities are guided by the spirit of cooperation and workload sharing that, as most of you know, we embraced in recent years in order to contribute to globalization of the highest public health standards and secure greater consumer protection at lower cost to taxpayers.

In June, our government and the European Union completed an unprecedented Mutual Recognition Agreement, or MRA, whose negotiation was greatly assisted by hardworking staff from many components of the U.S. FDA. When fully implemented, the agreement will allow FDA and its EU counterparts to exchange reports on inspections of pharmaceutical and medical device facilities that export products to our respective countries. Currently, we're conducting 200 overseas inspections each year, while the Europeans are similarly inspecting exporting facilities in the United States.

If, at the end of a three-year confidence-building transition period, we and the European Union are satisfied that our inspection processes and culture are equivalent, each party will be able to carry out the other's inspections for compliance with the respective Good Manufacturing Practices and quality system requirements, and thus save considerable resources we now have to spend on overseas travel. Both we and our counterparts can find plenty of use for those funds in other, higher risk areas.

Another provision of the Mutual Recognition Agreement allows for the review of medical devices by third parties in the United States and European Union. This accord broke new ground by clearing the way—under clearly specified conditions—for authorized European organizations, both governmental and private, to review low- and medium-risk premarket notifications called 510(k)s against U.S. requirements and submit the reviews to FDA for final action. Similar reviews could be carried out by FDA, or accredited third parties in this country, for the European regulatory authorities in ac-

*Continued at top of page 26*

## Tech Trends

### Taking an Absolute Approach to Improve Environmental Sustainability

Emily Hough, PDA

Many pharmaceutical companies are now wondering what they can do to keep improving environmental sustainability within their firm after the “easy to implement” items such as solar panels and single use systems have been implemented.

AstraZeneca might have found the answer by focusing on total environmental sustainability by looking at lowering API emissions to packaging and transportation materials.

Last year, AstraZeneca's worldwide sites looked at their emissions and compared them to the firm's environmental quality standard concepts, which take into account indirect exposure of potential consumers such as fish-eating mammals and humans, as well as primary producers (e.g., algae) and primary and secondary consumers (e.g., invertebrates and fish). All but two sites met the standard. Corrective actions were taken, and all sites now meet the firm's internal standard. The firm also started to share its environmental quality standard concepts with its key outsourced manufacturing partners. This enabled suppliers to perform risk assessments and manage any emissions of the APIs they manufacture or formulate on AstraZeneca's behalf. This allows AstraZeneca to better understand and manage its manufacturing global footprint.

According to the firm's website, “Our work to reduce our carbon footprint and our use of natural resources brings benefit for the environment and for our business because of the associated cost efficiencies. Similarly, our efforts to minimize the waste we produce includes making improvements to our production processes which can also boost manufacturing efficiency.”

The firm is additionally concentrating on finding and developing a drug compound that reaches the environment in a relatively unchanged active form to improve future product pipeline. By working with computer and laboratory-based tools, AstraZeneca can assess potential hazards and risks to the environment, which in turn will impact decision making about candidate drug selection. AstraZeneca's environmental risk management plans accompany all new medicines through their lifecycle, enabling all available environmental data to be taken into account at key decision points.

The firm has also implemented an API manufacturing process, called the “SHE Triggers' model, which identifies potential safety, health and environmental problems. At the earliest possible stage, issues affecting those areas are designed around. The firm has applied the model to its primary and secondary manufacturing processes as well as its pharmaceutical products, including the environmental assessment of packaging and devices. Where it can, AstraZeneca is looking to change

*Continued at middle of page 26*

*Journal POV continued from page 25*

cordance with their criteria.

Because of its novelty and potential importance, we will test this system—which parallels our own domestic pilot program for selected medical devices—very carefully. We will be preparing written guidance to help assure review consistency for medical devices both here and in Europe. After the three-year transition period, we must reach consensus on which European notified bodies have demonstrated proficiency in conducting product reviews consistent with our standards. And of course, we will continue to make the final decisions on all regulatory issues involving public health protection in this country.

The MRAs were not easy to conclude, because they were part of other complex foreign trade issues, and involved commercial interests advanced by the

Transatlantic Business Dialogue, which includes 250 top business executives in this country and in Europe. But the fact that the negotiations succeeded testifies to our commitment to cooperation with the business community, as well as our foreign counterparts.

In July, this cooperation again proved itself in the highly productive fourth meeting of the International Conference on Harmonisation, whose members are the regulatory authorities and pharmaceutical associations in Europe, Japan and the United States. In its relatively brief existence, ICH agreed on 44 state-of-the-art, harmonized guidelines for drug development and registration. A recent survey of 72 pharmaceutical companies in the United States, Europe and Japan showed that some of these tripartite documents are being utilized by as many as nine out of ten respondents.

The conference also reported agreement on a new medical dictionary that provides common terminology for regulatory authorities to use in communicating with their counterparts on safety issues. Most encouraging of all, the ICH members agreed to the new and challenging goal of harmonizing the format and content of documents for new product applications, and on increasing the participation in their work by associations representing manufacturers of over-the-counter drugs and generics.

Work sharing across international boundaries, and by governments and private enterprise—a strategy to which our agency looks for part of the answer to our growing responsibilities without a corresponding increase in resources—last year demonstrated remarkable vitality and great potential. 🌐

*Tech Trends continued from page 25*

the way it transports products and intermediates around the world by replacing traditional wooden pallets with lighter

pallets made from corrugated cardboard. Transporting these lighter pallets by road, air and sea will reduce the amount

of fuel required and thus reduce the CO2 generated by these activities. 🌐

*Tools For Success continued from page 23*

effort well-spent given the benefits—a more pleasant, more productive work setting in which everyone feels valued, ideas are shared openly and relationships are characterized by trust.

**One last tip:** When you practice good communication, notice the effect. The

results that come from communicating wisely will be the proof that communication really is the key to good management.

This article was originally published in *HR Magazine* in January 2005.

### About the Author

**Joelle K. Jay**, PhD, president, Pillar Consulting,

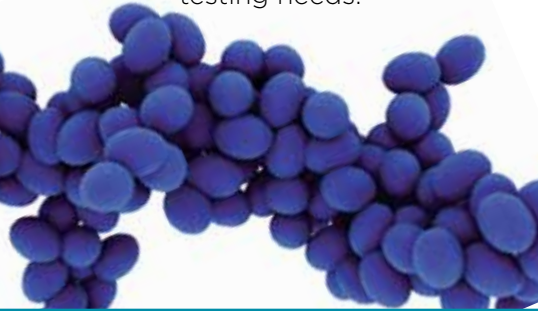
helps leaders achieve top performance and business results. Her clients include presidents, vice presidents and C-level executives in Fortune 500 companies. Joelle is the author of *The Inner Edge: The 10 Practices of Personal Leadership*. To find out how Joelle can help you reach the next level, visit: [www.TheInnerEdge.com](http://www.TheInnerEdge.com). 🌐

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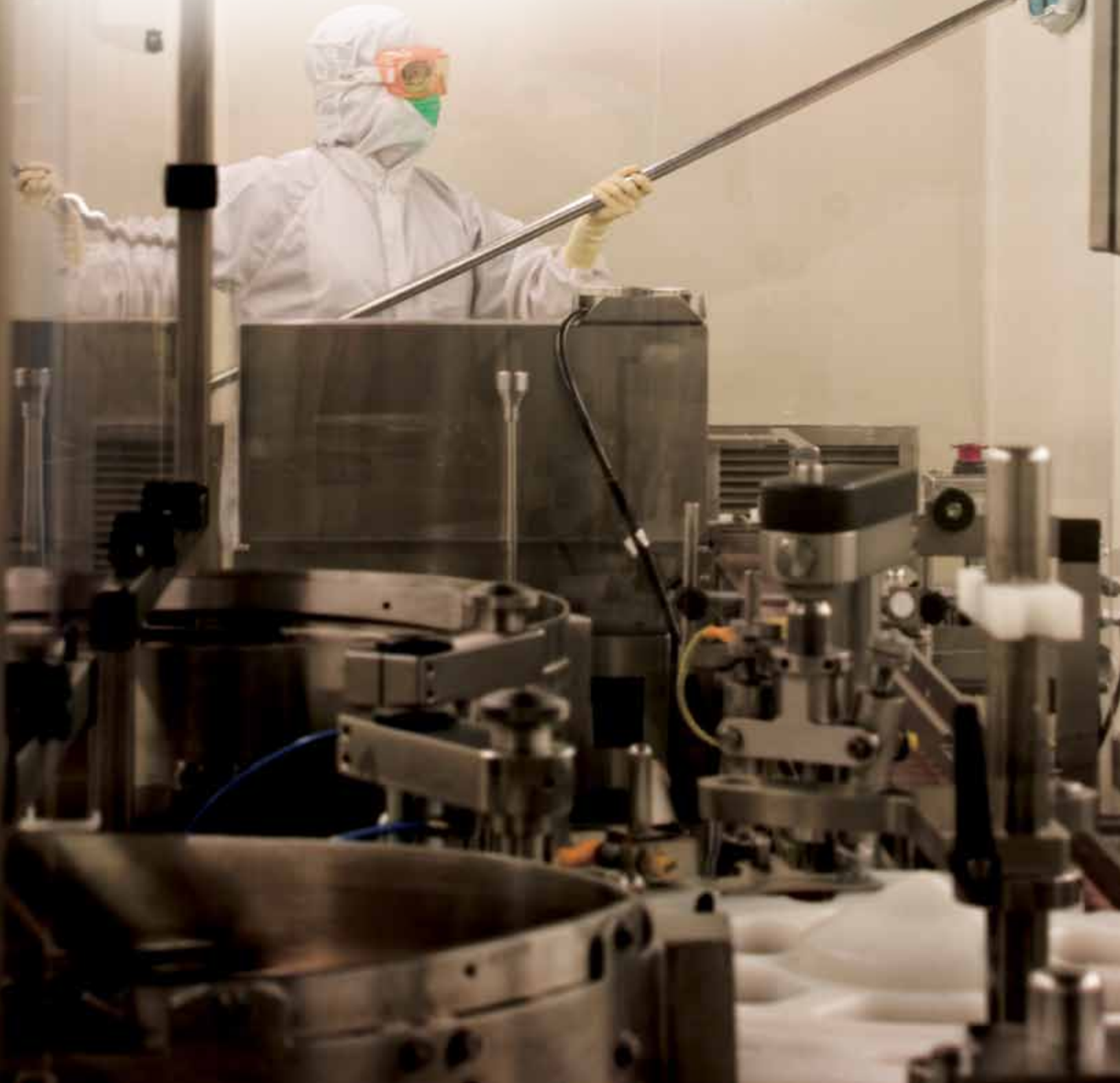
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# Industry Comes Clean at PDA Annual Meeting

Tenacious residues, disposable systems among various cleaning-related topics addressed



**Cleaning:** It happens in every manufacturing plant, storage facility and anywhere else a drug product is processed, stored, etc., and it is a vital part of the manufacture of quality, safe products. Whether for a facility, equipment or instruments, cleaning seems like a rather straightforward proposition; yet, there is a lot of science associated with a high-quality cleaning program.

Breakdowns in cleaning procedures can pose hazards to patients, so great emphasis needs to be placed on developing, designing and controlling a cleaning program.

When cleaning fails, the results can be startling. Earlier this year, reports surfaced regarding findings of bacterial contamination of a pharmacy dispensing robot at Wake Forest Baptist Medical Center. The case demonstrates the importance of a sound cleaning practices at all levels of drug manufacturing and distribution. The hospital found that the *Bacillus cereus* contamination uncovered in samples of an intravenous drug could be traced to the dispensing robot. Further investigation implicated the source of contamination on the machine as the washing station and associated tubing. The washing station is an area outside the sterile environment for which the hospital had no formal cleaning and maintenance procedure. No patients were harmed.

When it comes to equipment cleaning, manufacturers of biopharmaceutical products face many questions and various technology choices for their programs. For instance, how can a cleaning program effectively remove tenacious residues that form at the air-liquid interface of a bioreactor? Can single-use, or disposable, systems help reduce cleaning

## The tenacious residues form on production bioreactors at the air-liquid interface (ALI)

steps and costs? If so, are they safe to use for all product types? How can cross-contamination of products be prevented at multiproduct facilities?

The 2012 PDA Annual Meeting included a number of presentations that dealt with these and other questions.

### Cleaning the Air-Liquid Interface

A presentation called “Cleaning Validation Challenges for Bioprocesses: Strategies for Eliminating Tenacious Residues” by Amgen’s **Rizwan Sharnez**, Principal Engineer, offered a look at the problems caused by such residues and some practical solutions. Sharnez spoke in a session on “Process Control/Validation” in the “Control Strategies for Biopharmaceutical” track of the Annual Meeting.

Sharnez told attendees that tenacious residues form on production bioreactors at the air-liquid interface (ALI). He attributed the formation of tenacious residues at the ALI in bioreactors to the push for higher yields, which results in higher cell densities, longer processing times, more antifoam and higher protein concentrations. He showed photos of a residue on the interior of a 3L bioreactor which had formed following 14 days of processing prior to and following rinsing. He also showed photos of a pilot plant bioreactor both before and after cleaning in place. Both sets of photos demonstrated the inability of the cleaning procedures to remove the residue.

Sharnez explained that the residue at the ALI presents the “greatest cleaning challenge,” and showed through more photos how a 1% alkaline cleaner can effectively clean a coupon spotted with bulk soil, but not effectively clean a sub-

mergible coupon suspended at the ALI. Besides the cell debris and media, the residues in the bioreactor can also contain “complex insoluble organic molecules, including antifoam, silicates, slip agents, hydrocarbons, and polymers.” Because of their tendency to be highly hydrophobic and buoyant, they “gravitate to the ALI,” forming the tenacious residue.

Sharnez reported that peroxide-based cleaners (PBCs) can effectively remove or reduce these residues. In addition, PBCs can “work synergistically with alkaline cleaners.” He discussed the details of a small-scale model Amgen used to evaluate the cleanability of PBCs in combination with an alkaline cleaner (AC). The result showed that the PBC with AC was effective in cleaning 316L stainless steel coupons spiked with solutions of polyvinyl chloride, slip agents and silicates (at 70 deg C for 10 minutes) These residues could not be cleaned effectively with AC alone.

The PBC/AC combo was also effective in cleaning the following submerged parts and coupons that were not cleaned with AC alone: end caps and baffles

### Article Scrubbed Down

- Residues formed in bioreactors after lengthy processing times are difficult to clean with alkaline cleaners alone; adding PBCs can help
- Single Use Technologies have gone large scale at Shire and Grifols
- Vendor selection and relationships are critical to ensuring successful single use implementation

from bioreactors, and coupons suspended at the ALI.

Sharnez also presented results showing the effectiveness of PBC/AC sprayed manually post-clean-in-place (1% PBC + 1% AC; 70 deg C at 60 min).

Validating the combo involved determining safe rinsing levels for the PBC. Sharnez advised using toxicology data to set acceptance limits. Companies might also have to demonstrate that residual hydrogen peroxide does not adversely impact product quality attributes. He also touched upon the analytical and engineering challenges Amgen tackled to move forward with this new cleaning solution.

Sharnez's presentation provided a glimpse into the various challenges that manufacturers constantly face in managing effective cleaning programs. Of course, one way to deal with these challenges is to simply eliminate as much cleaning as possible. Disposable systems have been helping firms do just that, though not without presenting challenges of their own.

#### Single Use Shot Heard 'Round the World

Such systems are growing more popular each year among biopharmaceutical manufacturers, as demonstrated by two

## Residue After Alkaline-Only Treatment & After Alkaline + Peroxide



From Rizwan Sharnez's presentation "Cleaning Validation Challenges for Bioprocesses: Strategies for Eliminating Tenacious Residues"

case studies presented at the PDA Annual Meeting and the Single-Use Systems workshop that followed.

Shire Human Genetic Therapies newest facility in Lexington, Mass., has gained plenty of attention for the extensive application of single-use technologies throughout the biological operation, including the use of large-scale bioreactors utilizing 2000L disposable bags. The facility, dubbed "Atlas," received the prestigious ISPE, INTERPHEX, *Pharmaceutical Processing* 2011 Facility of the Year Honorable Mention and LEED certification in 2012.

**[Editor's Note:** Shire's Atlas facility was highlighted in the *Science Snapshot: Technology Trend* in the April 2012 issue, p. 21.]

The new operation incorporates 100% single use technology for a number of operations and partial single use technologies for others, according to Shire Manufacturing Director – Upstream Operations **Chuck Hart** in his presentation, "Application of Single Use Technology at Large Scale."

Hart's instructive discussion of implementation challenges with respect to process, logistics, design and other challenges was nearly overshadowed by the impressive results and unique implementation solution he also shared.

The benefits included:

- Reduction in facility size (only 200,000 ft<sup>2</sup> housing multiproduct upstream and downstream operations for two simultaneous production runs; 38% reduction in footprint)
- Reduction in initial capital cost
- Significant reduction in water and chemical use
  - No need for CIP/WFI flushes for Single Use Components
  - 87% reduction in water use
  - 95% reduction in chemical use
- Significant reduction in plant steam and clean steam use
- Significant reduction in equipment turnaround times
  - No need for Product Changeover

### Materials Clearance for Disposables Flow-Control Tubing Clamp

#### Risk-Based Approach to Materials Clearance

- Potential product contact surface was measured for a minimum batch size
  - Based on intended use, calculated results would be acceptable
- Identified that a clamp entering product is low risk due to external nature of use
- Clamp was approved for use without additional testing
  - *Non-Product Contact Material Safety Risk Assessment Form*

#### Benefits to Risk-Based Approach

- Avoid additional testing
- Avoid starting the selection process over
- Identify results representative of actual use
- Reduce time to implementation

Low Risk

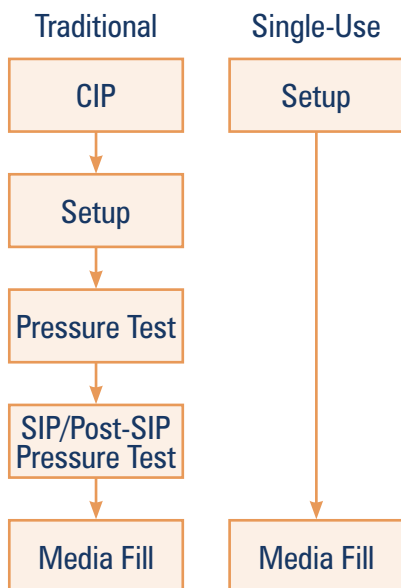
- ✓ Manufacturing Risk Assessment
- ✓ Quality Approval

From Claire Frazier's presentation "Case Study: Implementation of Disposable Systems for Buffer Delivery"



## Bioreactor Setup Differences

### Sequence of Operations— Shire's Atlas Facility



From Chuck Hart's presentation "Application of Single Use Technology at Large Scale"

(Multi-Product)

- Quicker decontamination process

### Performance Testing Done in "Sandbox"

Functional performance testing at scale was conducted with full controls in place at a fully automated, off-site location the Shire referred to as "Sandbox."

Sandbox was staffed by Shire's engineering and operations staff and possessed full batch capabilities using water and trace buffers for pH simulation. This enabled Shire to make some difficult decisions up front, including tube lengths and bag design.

In addition, the firm uncovered and resolved process issues early. Hart noted that over 2000 automation issues were remedied because of Sandbox. All draft procedures and batch records were examined at Sandbox, resulting in a shake-down that eliminated costly errors and inefficiencies from the final process line. Sandbox also afforded Shire the opportunity to provide months of hands on training on actual equipment, which was important so operators could familiarize

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themselves with the single use technology and automated systems.

Shire started designing the facility in 2007 and completed it by 2010. In November 2011, the firm filed applications with the U.S. FDA and the EU EMA for the production of VPRIV® (velaglucerase alfa) in Atlas. EU approval was awarded this past February.

For the less ambitious, there is always the option of adding single use systems to one component of a process to help reduce some of the cleaning burden.

Grifols' **Claire Frazier**, Technical Operations Support, presented "Case Study: Implementation of Disposable Systems for Buffer Delivery." The project involved both small volume buffer addi-

## Cleaning Failures Affect Quality, Cost and Speed

From Rizwan Sharnez's presentation, "Cleaning Validation Challenges for Bioprocesses: Strategies for Eliminating Tenacious Residues"

### Compliance: Regulatory Expectations

- Equipment should be "Visually Clean"
- Effect of residue on product quality and cell growth should be investigated

### Speed and Cost: Impact of a Cleaning Failure

- Lower run rate
- Intrusive manual cleaning is undesirable
  - Unsafe
  - Surface damage and rouge
  - Cleanability issues can be exacerbated
- Resources are strained
  - Equipment inspection and sampling
  - Additional cleaning and CIP skid time
  - Investigations

tions (25L) and large volume (35-200L).

Frazier's case study included details on disposable product selection and materials clearance for disposables. For the latter, she noted that materials for product contact must be approved based on the U.S. Pharmacopeia's requirements for extractables and leachables. Vendor data may be used in replacement or in conjunction with on-site testing.

Frazier added that the "Materials Clearance file" for each product material should be updated to include potential contact solution (chemicals, buffers, intermediate products) and contact product part number and description. Single-use bags, tubing sets and even the flow-control tubing clamp were evaluated.

Frazier went on to describe how her firm worked to customize the disposable bags and tubing, a critical aspect of the Shire project as well.

### Work Well with Single Use Vendors

The Grifols and Shire projects shared several key elements, if not scale. These included careful disposable product and vendor selection, materials clearance and customization.

In the end, both presentations highlighted the importance of developing strong working relationships with vendors following a careful vetting process.

Whether manufacturers of biopharmaceutical products are content with their current cleaning practices with traditional stainless steel facilities or want to employ single use systems, it is clear that the 2012 PDA Annual Meeting provided enough information to help clean up their decision making process.

Apple iPhone, IPAD and IPOD Touch users, as well as Android system users, can go to the respective App stores to download the PDA Annual Meeting App to view these and other presentations until the end of September 2012.

### Disposable Facility: Single Use Technology at 400 Shire Way

Shire Human Genetic Therapies has implemented single use technology throughout operations at its year-old facility in Lexington, Mass. The following are the specific process that possess either 100% or partial single use capabilities:

#### 100% Single Use Technology

- Cell Initiation and Expansion
- Production (Perfusion via Centrifugation)
- Harvest and Clarification
- Unpurified Bulk and Drug Substance Fill

#### Partial Single Use Technology

- Recovery Operations (Chromatography and UF)
- Purification Operations
- Media and Buffer Makeup and Hold

## About the Experts

**Dr. Rizwan Sharnez** is Principal Engineer at Amgen, Colorado. Previously he was with Merck and BioSeparations. His responsibilities at Amgen include cleaning characterization, CIP cycle development, process development and technology transfer. He has 28 peer-reviewed publications and 8 patents, and has given over 30 presentations at professional conferences.



**Chuck Hart** has been with the Operations group at Shire HGT for 3 years. Since 2010, he has served as the Director of Upstream Operations, responsible for managing all Cell Culture and Media Prep Operations at the new state-of-the-art manufacturing facility at 400 Shire Way in Lexington, Massachusetts. Prior to joining Shire HGT, Mr. Hart has had increasing roles of responsibility in Upstream and Downstream Operations at GSK, Wyeth, Amgen, and ImClone, with a previous role of Associate Director of Downstream Operations at ImClone.



**Claire Frazier** has been with Grifols Inc since 2006 in the Research and Development group supporting Technical Operations. At Grifols, she has been involved in new product process development during toxicological and clinical phases. She is currently responsible for providing engineering and developmental support to manufacturing operations, with a focus on implementation of new or modified systems for improved process yield, purity, control and operation. 🇺🇸



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# 2012 PDA UPCOMING EVENTS

## JULY EVENTS

**30-3**

### Quality Systems for Aseptic Processing

Bethesda, Maryland

[www.pda.org/qualitysystems2012](http://www.pda.org/qualitysystems2012)



## AUGUST EVENTS

**20-24**

### Aseptic Processing Training Program – Session 4 Week 1

(Week 2: September 10-14)

Bethesda, Maryland **SOLD OUT**

[www.pda.org/2012aseptic](http://www.pda.org/2012aseptic)

**27-31**

### Filtration Week

- Filters and Filtration in the Biopharmaceutical Industry – Basics Course (August 27-28)
- Filters and Filtration in the Biopharmaceutical Industry – Advanced Course (August 29-31)

Bethesda, Maryland

[www.pda.org/filtrationweek](http://www.pda.org/filtrationweek)

**29-30**

### Fundamentals of an Environmental Monitoring Program

Bethesda, Maryland

[www.pda.org/environmental2012](http://www.pda.org/environmental2012)



## SEPTEMBER

**10-14**

### 2012 PDA FDA Joint Regulatory Conference and Course Series

Baltimore, Maryland

[www.pda.org/pdafda2012](http://www.pda.org/pdafda2012)

**12-13**

### 2012 PDA ICHQ10 Workshop: Expectations of Operations & Executive Management

Baltimore, Maryland

[www.pda.org/ICHQ10](http://www.pda.org/ICHQ10)

**18-19**

### Pharmaceutical Freeze Drying Technology

Ljubljana, Slovenia

<https://europe.pda.org/FreezeDrying2012>



[www.pda.org](http://www.pda.org)



For an updated PDA calendar of events please visit  
[www.pda.org/calendar](http://www.pda.org/calendar).



*Save these dates!*

## EVENTS

## OCTOBER EVENTS

**20**

### ICH Q9: Application of a Risk-based Approach

Ljubljana, Slovenia

<https://europe.pda.org/Riskbased2012>

**20-21**

### Development of a Freeze Drying Process Training Course

Ljubljana, Slovenia

<https://europe.pda.org/TCFreezeDrying2012>

**25-26**

### Visual Inspection Forum

Berlin, Germany

<https://europe.pda.org/VisInsp2012>

**27-28**

### An Introduction to Visual Inspection

Berlin, Germany

<https://europe.pda.org/TCVisInsp2012>

**2-4**

### Developing a Moist Heat Sterilization Program within FDA Requirements

Bethesda, Maryland

[www.pda.org/moistheat2012](http://www.pda.org/moistheat2012)

**8-11**

### PDA Biennial Training Conference and Course Series

Bethesda, Maryland

[www.pda.org/biennial2012](http://www.pda.org/biennial2012)

**9-10**

### Developing and Validating a Contamination Control, Cleaning and Disinfection Program

Bethesda, Maryland

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**9-10**

### Pharmaceutical Cold Chain Management & Good Distribution Practice

Berlin, Germany

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**11-12**

### PDA Good Temperature-Controlled Management Practices

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**15-19**

### The Universe of Pre-filled Syringes & Injection Devices and Course Series

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### Aseptic Processing Training Program – Session 5 Week 1

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**22-26**

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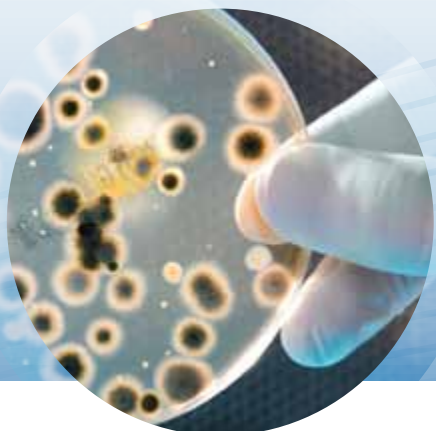
[www.pda.org/microbiology2012](http://www.pda.org/microbiology2012)

**30-1**

### Validation of Biotechnology-related Cleaning Processes

Bethesda, Maryland

[www.pda.org/biotechnology2012](http://www.pda.org/biotechnology2012)



# 10 Lessons from 2012 PDA Sterile Technology Conference

Bioburden and ongoing regulatory problems in the manufacture of sterile products are just two of the major issues discussed at the *2012 PDA Innovation & Best Practices on Sterile Technology Conference*. For those who missed it, the cochairs have highlighted the top 10 lessons they learned during the event:


1. Biofilm bioburden presents unique issues. It has been a major source of contamination in sterile product manufacturing operations. It requires rigorous and specialized remediation efforts for aqueous operations. Offline modeling technologies were discussed that can be utilized to develop effective cleaning regimes and more effective methods for prevention and removal of biofilm (*Look for an upcoming PDA technical report on Biofilm and Bioburden*).
2. Companies continue to be the subject to regulatory observations for the validation of sterile product manufacture and ongoing control of aseptic processes. In order to ensure expedient approval of regulatory submissions and especially those involving unique and new products and approaches, the U.S. FDA endorses a proactive approach of dialog prior to submission including teleconferences and face-to-face meetings.
3. There have been significant advances in radiation sterilization, irradiator design, dose measurement designs and cycle development of lower dose sterilization. These have been used successfully to minimize degradation effects for drugs

making radiation feasible. This suggests greater usage for API and other product and component sterilization options for pharmaceuticals, biopharmaceuticals and API's processes.

4. Steam-in-Place systems are becoming more common place as a means to sterilize complex product contact lines as companies increase the use of in line filter sterilization, isolators and RABS for filling sterile products (*Look for an upcoming PDA technical report on Steam in Place*).
5. Nitrogen dioxide has the benefit of compartmentalized designs and reduced residual issues. Thus providing nitrogen dioxide with significant potential for sterile component packaging surface sterilization.
6. Aseptic process simulations alone do not validate the aseptic process, but when designed and performed properly, they remain an important part of an overall aseptic validation program, confirming the effectiveness of the process (See PDA *Technical Report No. 22 (Revised 2011), Process Simulation for Aseptically Filled Products*.)
7. The use of multi-departmental, integrated user teams, including vendors, suppliers and engineering is an effective way to recognize and meet production and regulatory requirements of a modern sterile drug manufacturing facility. Automation, modeling and modular design can enhance the utility of the modern sterile drug manufacturing facility.
8. Quality risk management control strategies are effective decision making tools in the design of sterile



product manufacturing lines and facilities. Implementation of quality risk management as an enabler requires understanding the details of the process and product impact to optimize the integration in the quality system.

9. It is essential that the  $F_{\text{BIO}}$  concept be used to provide the most accurate interpretation of biological indicator inactivation results. Also,  $F_{\text{PHY}}$  and  $F_{\text{BIO}}$  should be used in a complementary approach to ensure the most robust moist heat sterilization program.
10. Alternatives to an overkill design approach, such as the product-specific approach (See PDA *Technical Report No. 1 (Revised 2007), Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Qualification and Ongoing Control*), are considered to be far superior to aseptic processing due to the lower risks of non-sterility with terminal sterilization processes. For the product specific approach, a biological indicator is selected based upon the population and moist heat resistance characteristics of the product bioburden. 







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# Current Sterile and Lyo Issues Discussed at Joint IG Session

Richard Johnson, PDA; Ken Muhvich, Micro-Reliance; Edward Tidswell, Baxter Healthcare; Edward H. Trappler, Lyophilization Technology

Interest in the unique requirements for aseptic processing of lyophilized products is heightening with the number of new therapeutics increasing on the market, including many new biopharmaceuticals such as monoclonal antibodies. Many issues arise when manufacturing lyophilized products, including the elusive problem of stopper “pop-up” and process simulation media fills.

To meet the growing demand for information on issues like these, PDA's Sterile Processing/Parenteral Drug Manufacturing Interest Group and Lyophilization Interest Group will hold a combined session at the upcoming *2012 PDA/FDA Joint Regulatory Conference* in September. All interested conference attendees are invited to discuss any topics relating to sterile processing and lyophilization.

This will mark the fifth occasion when the two groups have merged sessions in order to spark dialogue on this increasingly important area. The prior sessions successfully brought together subject-matter experts and others interested in the fields of aseptic processing and lyophilization; conversation at each session was engaging and productive.

Like the previous four, the upcoming joint-IG session will be an open forum in which participants will drive the discussion by recommending topics and then voting on which hold the most interest. From there, discussion will start with the topics receiving the most votes. In the past, topic polling revealed surprisingly common concerns and apparent industry trends that bridged the four prior meeting sessions.

It cannot be overstated that attendee participation will be key to the success of the session. The previous sessions have been valuable in that they have represented a forum for sharing information and providing individuals' perspectives.



## Variation Primary Concern in 2009

The first combined Sterile Processing and Lyophilization Interest Group session was scheduled during the *2009 PDA Annual Meeting*. Attendee polling narrowed a list of seven initial topics down to the following four:

- Vial-to-vial variation (specifically for residual moisture)
- Incomplete stoppering
- Lyophilizer equipment equivalence
- Conditions necessary for transfer, loading and unloading a lyophilizer

The high level of interest and extent of the lively discussion resulted in the session being focused on the two most popular topics: variation within a batch and incomplete stoppering.

Attendees raised concern about residual moisture during the discussion of vial-to-vial variation. Residual moisture is the only truly quantitative measurement of a critical quality attribute common to lyophilized preparations. A survey of the group revealed residual moisture ranges from as low as 0.5% to as high as 5%.

It was well recognized by the group that results can be strongly influenced by the variation in the test method, particularly when a product has a very low total dry weight and very low residual moisture content. One third of the participants agreed there should be a minimum and maximum moisture content defined in the product specification.

Factors suggested among the group to have a significant influence in batch uniformity were

- Lyophilization process
- Equipment performance
- Container/closure
- Formulation

Much of the discussions focused on the potential contribution of moisture to the dried product evolving from the stopper, particularly during long-term storage. Discussions moved onto addressing an appropriate number of containers to sample, with the only consensus being the number of samples should be dependent upon the actual product and batch size.

Annex 1 (1) and a recent PIC/s publication (2) of the accepted interpretation

of Annex 1 caused the focus to shift to incomplete stoppering. As it applies to both liquid and lyophilized product presentations, this was indeed a fitting topic for the combined interest group session. There was a large consensus that “incomplete stoppering” or a “gap” was observed between the vial and the matching flat finish on the stopper upon unloading the lyophilizer and when vials were transferred to the capping operation. This of course drove the discussions to how much, if any amount, of a gap would be acceptable. There were concerns expressed for container/closure integrity, ingress of air into the product and the resulting level of sterility assurance when any “pop-up” of the stopper would occur. The opportunity for “pop-up” exists during the interval between when the stopper is fully inserted into the vial and the overseal is crimped. For liquid products, the interval is admittedly short as the time between the stoppering station and crimping operation is extremely short.

In discussing this interval for lyophilized products, it was clear that the time duration was significantly varied. The shortest duration was described as the time required to unload the lyophilizer, transfer each tray of product to the capping machine and crimp the overseal on each vial. Allowing the shelves to rest on the vials in the stoppering position, by continually placing pressure on the stopper would prevent “pop-up” in the interim between stoppering and unloading. Raising all the lyophilizer shelves after stoppering would provide the longest time. In the case of operations with automated unloading systems, it was recognized the time interval between stoppering and capping would depend upon the approach to the material handling. No actual time intervals for this step between stoppering in the lyophilizer and crimping the vials were disclosed.

Discussions also revolved around air and moisture infiltration into lyophilized products and concerns about long term product stability. Factors contributing to stopper “pop-up” listed by the group, included:

- Level of siliconization
- The presence of a coating on the stopper
- Method of handling
- The propensity to stick to the underside of the lyophilizer shelves during stopper insertion

There was also a shared experience of the stopper acting like a suction cup, when stoppering the vials “under vacuum” at a low chamber pressure and leaving the shelves resting on the stoppered vials, the vacuum would break when the chamber pressure returned to one atmosphere. It was suggested that this would cause the stoppers to become concave due to the pressure differences between the inside of the vial having a low pressure and the environment at one atmosphere creating a “suction cup” effect between the concave stopper and underside of the lyophilizer shelf. Upon raising the shelves to unload the lyophilizer, the stoppers would stick and the vials

## The high level of interest and extent of the lively discussion resulted in the session being focused on the two most popular topics: variation within a batch and incomplete stoppering.

would be suspended from the underside of the shelf above the product. Another reported cause suggested was the stoppers being “sticky” and upon stoppering, the stoppers would adhere to the shelves when the shelves were raised. Both cases would contribute to the potential of the stoppers backing out of the vial neck, causing a gap.

Excessive levels of silicone on the stopper was identified as causing the stoppers to be more slippery and back out of the vial neck after stoppering, causing the “pop-up,” which occurs after the stoppers are fully inserted into the vial in the lyophilizer and while the vials are unloaded. Dimensional differences between the outside diameter of the stopper being larger and the inside diameter for the vial opening being smaller were

thought to be a cause of “pop-up.”

Single vent stoppers, often called an “Igloo” stopper, appear to have the greatest incidence of difficulties, particularly 13 mm stoppers. The “pop-up” appears to often occur in the region of the vent. The discussions provided a number of potential factors to consider for the incidence of the potential for a gap between the vial and the stopper flange. No good explanation was available as to why there would be a correlation or a root cause.

How much of a gap between the vial land and stopper flange was permissible was also discussed. Though opinions of what amount of a gap would be acceptable varied, there was consensus that there was no scientific rationale or regulatory guidance for any specific dimension.

There was a general consensus that the environment needs to be ISO 4.8/Class 100/Grade A for loading the lyophilizer, as the stoppers are only partially inserted and the vials are considered to be an

open container. It was clear and everyone agreed that the EU perspective is needed on transferring product and completing the capping under an ISO 4.8/Class 100/Grade A air supply because of the opportunity for raised stoppers.

The success of this first combined group session sparked agreement that a follow-up session would should be held later that year at the 2009 the PDA/FDA meeting in September.

### Second Joint Session at PDA/FDA

The decision to hold a second meeting proved a good one, as attendance was strong and the discussion was robust.

The group of participants identified a list of topics similar to that agreed on at the PDA Annual Meeting earlier that year.

Detecting raised stoppers was the “hot”



## There was a resounding unity among the session participants that a good scientific rationale is needed to provide guidance to the industry

topic. Participants also sought dialogue on process simulation media fills (PSMF).

In the respective order of popularity and interest level indicated by the poll of the group, the topics discussed were:

- Detecting raised stoppers
- Invalidating a PSMF
- Steps in conducting a PSMF
- Glass vials imperfections
- Use of buffers during lyophilizer qualification
- Air quality during lyophilizer loading
- Lyophilizer comparability
- Use of PSMF for container/closure integrity for product under “high vacuum”
- Loading pattern when conducting PSMF

The group readily acknowledged that the issue of raised stoppers was included in Annex 1, though they reiterated the concerns expressed during the inaugural meeting that there is no complete understanding of the root cause or scientific rationale for the incidence of raised stoppers.

There was a wide agreement during the previous IG session that the incidence of raised stoppers was a container/closure issue; though no one could suggest any scientific rationale, quantitative measure or even an acceptable allowance. In a whisper that gained the attention of a loud shout, one participant shared their understanding that some companies were using 1mm as an allowable gap, though the “whisperer,” nor anyone in the group was aware of any studies or supporting data in the literature for any specific gap that would be allowable.

The predominate opinion throughout the group was that this or any value should be challenged and verified in a controlled study. Anything short of a well designed and controlled study would be

simply conjecture and a “hand waving” treatment of such important concerns.

When discussions went on to monitoring “pop-up,” six of the companies represented at the interest group session reported having raised stopper detection capability installed or installation of the capability planned for their facilities. Discussions progressed to considerations around container/closure compatibility. It was suggested that relative dimensions of the vial and stopper and the allowable variations in those dimensions may be correlated to the incidence and extent of “pop-up.” The level of siliconization and the propensity of stoppers sticking to the underside of the shelves were also discussed as causing raised stoppers.

With a focus on considering how a raised stopper would impact product quality, the group tackled the question of suitable measuring techniques.

Raised stopper detectors just prior to the capping operation appeared to be the solution of choice among a resounding number of participants, though there was a long pause in the discussions when proceeding to discussions on how much the stopper can be lifted off the land portion of the vial finish was asked. PDA *Technical Report No. 43, Identification and Classification on Nonconformities in Molded and Tubular Glass Containers for Pharmaceutical Manufacturing* and ISO documents 8362 and 8871 were suggested to the group as references for some of the associated topics discussed during the session. Head space analysis was another method that was thought of, though it was recognized that the technique may suggest an adequate insertion or loss of integrity when the vials were sealed in an environment at a reduced pressure.

When polled about the appropriate chamber pressure when stoppering the vials, the group was split between: “full

vacuum” or “partial vacuum.” A small fraction indicated they stoppered product in the lyophilizer consisting of a nitrogen environment at atmospheric pressure. All in the group indicated that stoppering was conducted with the presence of compendia grade (BP, EP, JP, NF) nitrogen.

A closely related topic in the general area of lyophilized product sterility assurance was aspects of conducting (process simulation media fills). It is well recognized that conducting a PSMF is of critical importance, knowing lyophilized products have no microbiological preservative and are not currently terminally sterilized. With the extensive discussions on raised stoppers, container/closure integrity and stopper “pop-up,” there was little time left to discuss approaches to conducting a PSMF.

### The 2010 Joint-IG Sessions

The IGs agreed to hold a third joint session at the 2010 Annual Meeting, and attendance at the session again was strong.

As during previous sessions, raised stoppers were at the top of the list of interest. Approximately 25% of the companies represented at the session had some way of performing stopper “pop-up” detection in their operations and an additional 17% were considering implementing the capabilities in routine manufacturing.

There was prominent consensus that the product should be under ISO 4.8/Class 100/Grade A air supply if there was a raised stopper.

Questions arose about when sealing of the product should occur. Some were adamant about the seal occurring when the stopper is “in place” in the lyophilizer, while others assumed a vial is sealed only when the aluminum overseal is crimped. There were more questions than consensus on when a raised stopper was a problem. An example of a question raised at that session was: Is 0.5 mm the threshold or was 1mm? There was a resounding unity among the session participants that a good scientific rationale is needed to provide guidance to the industry. ➤

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Also of significant interest was future capability of nondestructive testing for finished products. When proposed, it may have been a participant's notion of an instrumental method for 100% inspection of lyophilized product.

Discussions progressed onto approaches and considerations in developing a rationale for setting an appropriate residual moisture specification. The general consensus was that there is a need to establish a moisture specification specifically suited for the product based on data gathered through stability studies during development. These studies should encompass stability testing of drug product prepared at different levels of residual moisture.

Three key points were made during the discussions:

- Chemical potential drives the reaction
- The molar concentration relative to the drug substance should be considered

## Considerations of a dedicated, single product operation as well as a multiproduct facility were pointed out as factors in justifying sterilization of the lyophilizer in preparation for each batch

- There is a need to quantify and well characterize the hydrolysis degradants

Tighter specifications for low dry weight drug product and evaluation of the uniformity of residual moisture throughout the batch were also pointed out as key considerations during the session.

At the fourth joint-IG session at the *2010 PDA/FDA Joint Regulatory Conference*, discussion of aseptic processing was prominent. Next in order of interest came, sterilization of the lyophilizer and environmental monitoring. Topics that were brought up for discussion in order of interest were:

- Sterilization of the lyophilizer after each batch
- EM around the lyophilizer (of equal interest to sterilization)

- Alternatives for HEPA (transfer) carts
- Use of QbD for Lyophilization process development
- Conducting a PSMF for Sterile API manufacturing
- Time, temperature or pressure driven cycles
- Statistical Techniques for product and process development and manufacturing

Considerations of a dedicated, single product operation as well as a multiproduct facility were pointed out as factors in justifying sterilization of the lyophilizer in preparation for each batch. The overwhelming consensus was that the safest approach would be to sterilize the lyophilizer in preparation for making each batch. This would minimize losses if there was a failure in processing or a sterility assurance concern.

Conditions within the lyophilizer were also discussed. Participants were split regarding the claim that the lyophilizer

interior is a product contact surface; a number of respondents agreed, though many hesitated and did not agree. However, when asked if the interior of the lyophilizer should be treated like a product contact surface, about three-quarters of the participants concurred.

Regarding cleaning, the majority agreed that the lyophilizer is rinsed with water; no one indicated their companies use any type of detergent, and nearly half the group indicated that purified water was used. Since the quality of purified water has the same quality requirements as water for injection, with the exception of a higher allowable microbial content, and since the lyophilizer is subsequently sterilized, the general consensus was that purified water would be acceptable.

All agreed for the need of loading the

lyophilizer within an aseptic environment being ISO 4.8/Class 100/Grade A. Discussions then proceeded to environmental monitoring. Likewise, all agreed the level of monitoring for loading operations should be the same as for the filling operations. Some companies were including occasional monitoring for anaerobes as it was pointed out that sparging the product with nitrogen creates an anaerobic environment and warrants such monitoring. None of the participants indicated they monitored for anaerobes routinely, though a small fraction of participants indicated that they monitored for anaerobes periodically.

Automated and manual loading of product in the lyophilizer was also a point of discussion. Use of transfer carts for transporting product from a distant filling line to the lyophilizer was indicated to be a surprisingly common practice, reflected by half the participants indicating such carts were being used at their facility. Another surprise was that all conducted routine sanitization, while few indicated they conducted routine cleaning and even fewer conducted environmental monitoring for the cart interior. An alarming experience was described where the control and level of sterility assurance actually decreased with use of transfer carts. In the circumstance referenced, the historical manufacturing experience demonstrated that direct transfer from the fill line to the lyophilizer under ISO 4.8/Class 100/Class A conditions was demonstrated to be a suitable method and provided a high level of sterility assurance. Upon implementing the use of transfer carts there was a decreased level of sterility assurance, resulting in discarding multiple batches due to questions of sterility or sterility issues.

The level of participation and active discussions consumed the allotted time in the program and the discussions continued. Nearly everyone stayed well beyond the scheduled end of the session. With the extent of discussions during the session, there was little time to go on to the other topics of interest. As usual, there

*Continued on bottom of page 47*



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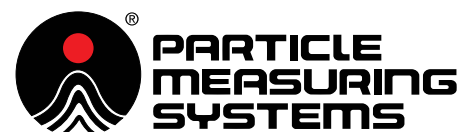
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## Ensuring a Quality Culture

Emily Hough, PDA

Pharmaceutical companies can boast about their ability to manufacture products of the highest quality; yet, pressure is mounting on firms to improve their quality culture.

In recent years, the U.S. FDA has increased its scrutiny on pharma companies. In fact, **Janet Woodcock**, MD, Director, Center for Drug Evaluation and Research, U.S. FDA, wrote about how reliable drug quality is an unresolved problem in the May/June issue of the *PDA Journal of Pharmaceutical Science and Technology*. In her article, Woodcock points out that the U.S. FDA continues to see major problems in pharmaceutical manufacturing quality in all sectors. She later mentions that while “the FDA continues to respond to poor manufacturing practices via compliance and enforcement actions, clearly the responsibility for maintaining quality rests squarely with the manufacturers themselves.”

Lately, even investors have started to place the quality culture of pharma companies under a microscope. A federal court ruled recently that a pharma company can be sued based on misleading statements about compliance with U.S. quality-control regulations.

For these reasons, the upcoming session of the *2012 PDA/FDA Joint Regulatory Conference* called “Changing the Quality Culture” (Monday, September 10 at 10:45 a.m.-12:15 p.m.) could not be more timely.

The *PDA Letter* recently asked the expert speakers of the session about what a good global quality culture means to them and how it should be built.

According to **Greg Guyer**, PhD, Senior Vice President, Global Quality, Merck Sharp & Dohme, a quality culture depends on how much each employee pays attention to the quality of materials and detail that is going into all aspects of manufacturing and packaging. It is important, Guyer said, that this attention doesn't stop until the drug product has been received. He said, “The culture is what drives you to want to continuously improve the overall quality of the products put on the market.”

While it doesn't take long to build a quality culture, he said, it takes a long time to build a good one. It is important to ensure that the quality of the material that is delivered to India is the same as is delivered to the United States or to Brazil. To guarantee the same level of quality in all products, Guyer said, regulatory expectations must be followed at all plants. This means all employees need to know and be trained on the regulations. It is imperative, he said, to have a quality management system in place where updates and improvements are systematically made across the entire network.

**Anthony Mire-Sluis**, Vice President, Corporate, Product and Device Quality, Amgen, agreed, saying “An appropriately designed quality management system should ensure an efficient, compliant, yet risk-based approach to product de-

velopment, manufacture and distribution that drives continuous improvement and individual accountability.”

He said that appropriate systems can help provide mechanisms to ensure quality through procedures, appropriate oversight, metrics and continuous improvement. To ensure that quality is a key component of the firm, it is important that the top officials of the company all the way through to the people on the manufacturing floor, including contractors, distributors and even suppliers buy into the concept.

To assess the business case for quality in the industry, **G.K. Raju**, PhD, CEO, Light Pharma, worked with others in 2011 to develop a survey that was sent out to a large number of companies. According to Raju, a significant observation was that companies believed they were already seeing benefits like cost savings and reduction in investigations and deviations that could be attributed to ICH Q8, Q9 and Q10. In his view “quality is free” and a primary takeaway from the survey was that “quality failures can be very expensive and that a culture of prevention was needed.” Also, metrics such as the cost of poor quality can help make the business case for quality.

### About the Experts

**Greg Guyer**, PhD, Sr. Vice President, Global Quality, Merck, is responsible for overseeing all Quality Operations, Quality Assurance, CMC & Research and Commercialization Quality. He joined the company in 1994 as a Senior Director, Worldwide Regulatory CMC, Merck Research

*Continued on page 54*



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## Meeting Preview

### Interest Group and Advisory Board Meeting Schedule

The business of the Association will be conducted, as always, at the Annual meeting.

Below is a schedule of the Regulatory advisory board, committee and interest group meetings that will take place.

**Note:** All interest group meetings are open to meeting registrants; all other ancillary meetings are by invitation only. (For the Science ancillary meetings, see the Science Snapshot, p. 24).

#### Sunday, September 9

11:00 a.m. – 4:00 p.m.

Regulatory Affairs and Quality Advisory Board (Committee Invitation Only)

#### Tuesday, September 11

4:45 p.m. – 6:15 p.m.

GMP Links to Pharmacovigilance

Management on Outsourced Operations

#### Monday, September 10

4:45 p.m. – 6:00 p.m.

Clinical Trial Materials

Quality Systems

Pharmacopeial

Quality Risk Management

## Task Force Corner

### Mapping Global GMP Sterile Manufacture Guidances and Regulations

How many times have you asked the question, “How does this GMP guidance from the United States compare to that similar guidance given by the EU?” Our members have been asking this, so recently the GMP Sterile Processing Guideline Gap Analysis Task Force was formed to evaluate how best to answer questions like this.

The task force will develop a technical report which will compare and contrast several “sterile” or aseptic regulatory guidance documents in order to identify both similarities and differences between the documents. The analysis is intended to encourage regulatory and industry alignment and harmonization between any areas of major differences identified by the team.

Rapid progress is being made, according to co-leaders **Jette Christensen**, Aseptic Scientific Director, Aseptic Production, Novo Nordisk, and **Bob Darius**, Regional Director Quality Unit, Quality, GlaxoSmithKline Vaccines. Christensen stated that while the group might be small, “All of the members have been very engaged and committed to completing the project.” Darius agreed, adding that the five-member task force was intentionally kept small and includes a variety of experience in order to complete this comparative analysis of the guidelines.

Darius said that one of the challenges encountered by the team was to determine how deeply to evaluate and compare each of the guidances due to the variability in size and level of description/expectations in each document. There may be potential areas of interpretation and the team is working to deliver a product which is consistently analyzed and would be of value to both industry and regulatory bodies.

The following guidances will be included in this analysis:

- *Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*, FDA September 2004
- Volume 4 *Good Manufacturing Practice (GMP) Guidelines, Annex 1: Manufacture of Sterile Medicinal Products*, March 2009/2010
- PI 032-2: *PIC/S recommendation: GMP Annex 1 revision 2008, Interpretation of most important changes for the Manufacture of Sterile Medicinal Products*, January 8, 2010
- PI 007-6: *PIC/S recommendation on the Validation of Aseptic Processes*, January 1, 2011
- WHO technical report series 957, Annex 4: *WHO good manufacturing practice for sterile pharmaceutical products*, 2010

After completion of the analysis, the team will compare the requirements from each guidance and highlight both areas of difference and similarity. This information will be used to develop a survey for industry asking for examples on how these differences in regulatory expectations have been met by different companies. The success of this survey will depend on the support and response of

industry, so the task force looks forward to your active contributions and participation. They expect that the “blinded” survey results will demonstrate that there are multiple approaches to achieve the same results. This insight will be extremely valuable to both industry and regulatory bodies and could encourage harmonization or greater understanding of aseptic practices.

According to Christensen, the big challenge after the assessment is completed will be developing a good design for the technical report so that it is user friendly. “So far we are mapping the requirements in the five documents in an Excel sheet, but transferring it in a readable and easy way might be a challenge,” she said.

The bottom line, Darius said, is industry should be accountable for determining what aspects are scientifically relevant to their own processes and product. It has been surprising to learn that this type of detailed analysis of the full guidances has not been completed previously, since the

goal of industry is to find areas of commonality so that both industry and regulators can focus on the truly important aspects of aseptic processing.

Christensen believes the reaction from the regulatory agencies and the industry will be positive. The technical report will give the industry and regulatory agencies “a good tool where similarities and differences can easily be seen, and it will be easier working on harmonization which both parties are interested in.”

At the end of the project, the task force will cover both the areas of similarities and differences between these five guidance documents, but will not attempt to propose recommendations on how to technically manage any differences noted. The survey responses will be intended to highlight actual practices throughout industry which have been used successfully to achieve sterility assurance through aseptic practice.

### About the Experts

**Jette Christensen**, Aseptic Scientific Direc-

tor, Novo Nordisk, works within the Diabetes Finish Product section. She is responsible for sites located in Denmark, France, the United States, Brazil and China and has a global view on the manufacturing processes, authority requirements and culture. Jette has been an active PDA member since 1998 and has been involved in several activities. Currently Jette is member of PDA Science Advisory Board and Board of Directors.



**Bob Darius**, Director, Global Quality Unit, North American and German Operations, GlaxoSmith-Kline Biologicals, is responsible for the Quality Unit functions at four manufacturing locations in North America and Germany. He provides oversight of Quality Assurance, Quality Control and Validation functions for vaccines and adjuvant production facilities. Bob is also a Cochair of the Gap Analysis TF and a member of the PDA Letter Editorial Committee. 🇺🇸



## GMP Sterile Processing Guideline Gap Analysis Task Force Members

**Jette Christensen**, Novo Nordisk, Cochair  
**Bob Darius**, GSK, Cochair

**Joachim Del Boca**, Vetter Pharma-Fertigung  
**Friedrich Haefele**, Boehringer-Ingelheim

**Julia Lukas**, Merck

*Discuss Aseptic Processing and Lyophil continued from page 42*

were many more topics of interest for which there was simply no time left for the additional topics to be discussed.

A great deal of credit and gratitude goes to the participants. of the combined IG sessions. Without their participation, there would only be a quiet, empty room.

The leaders of the Aseptic Processing Interest Group and the Lyophilization Interest Group hope to replicate the energy we found in the first four joint-IG sessions. See you in September!

### References

1. EEC “Guide to Good Manufacturing Practice for Medicinal Products” Annex

1, Manufacture of Sterile Medicinal Products, European Medicines Agency, 2008.

2. PIC/S “GMP Annex 1 Revision 2008, Interpretation of Most Important Changes for the Manufacture of Sterile Medicinal Products”, Pharmaceutical Inspection Convention, Pharmaceutical Inspection Co-operation Scheme, January 2010. 🇺🇸



## The Evolving Role of ICH

**[Editor's Note:** The following is a modified excerpt from a presentation **Justina Molzon**, Associate Center Director, for International Programs, U.S. FDA, gave on May 14 at the U.S. FDA and Pharmaceutical Research and Manufacturers of America's International Conference on Harmonisation (ICH) regional public meeting. Her talk covered ICH's evolving global role.]

What we are going to do today is talk about ICH as it sort of has evolved since 1990, when it was created. And, it has really sort of evolved in outreach and inclusion of other countries and interested parties. Modification to the ICH process has occurred since its inception in terms of expanding the participants, in terms of industry representatives in countries, outreach that we're doing and efforts to be transparent. And this sort of represents the continuum of accomplishments. So ICH was unique when it was created in 1990 because it was an agreement between the EU, Japan and the United States to harmonize technical requirements for registration of pharmaceuticals for human use. And the reason it was unique, it was a joint effort by regulators and associated trade associations.

In 1990, we did not have very good relationships with our industry colleagues at that time. We have had a major shift in thinking. And, a lot of it, I think, is the fact that we have worked with our industry colleagues in ICH and work towards common technical requirements. Industry is well-suited in taking part in ICH because regulators don't submit applications to one another. It's only our industry colleagues that can tell us where areas of disharmony exist. So they're the ones that generally put forth the topics for the technical discussions.

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*We have recently expanded participation to the Eastern African Community to join the Global Cooperation Group after they expressed an interest*

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The ICH process is very similar to our good guidance practice, which became a regulation in September of 2000. We start the topic with a concept paper that is now posted on the website so others who don't participate in ICH know concept papers that have been put forward. And then an expert working group is appointed. And that group works towards building scientific consensus. When there is an

agreed-upon draft text at step two, the working group signs that off. It sort of freezes the document so it can go out for comment according to each of the ICH regions' regulatory processes. So for us, it gets posted in the *Federal Register* and is out for comment. Those comments are collected. And the working group determines the ones that are appropriate to include and which ones might change language in the document so far. That is then set forward, which is the final document, which is signed off by the expert working group and the Steering Committee. And then at step five, it is implemented into the ICH region according to their rules and regulations. So, once again, for the United States that is good guidance practices. ICH since it started in 1990, which is basically before the wide use of the internet, used to hold a series of conferences. And these rotated through the ICH countries.

We as regulators did not want to switch our submission format, because we thought it would be disruptive to our process. So we asked industry to propose a feasibility study so that they could convince us that this needed to be done. So, as a result of that, they found out that it could take up to ten months for a company to take the information from an NDA, take it apart and put it back together for an EU MA part of the application. And it could take up to fifty people to do that. So that was the tremendous amount of effort for just rearranging bits of paper. So the goal of decreasing staff in the amount of time needed to do this we thought would be helpful because if you could decrease the amount of time, you can actually get patient medications much faster.

At first, all of the effort in ICH was towards developing ICH guidelines. And that was to help industry have a harmonized approach on the specific topic. Then we put all of those building blocks and information together and created this common technical document. And that really helped in the review process. And so we're on the review side of the information flow at this point because I think we are still trying better ways to review based on the CTD format and especially the eCTD. So the eCTD really helped because it led to standardized reviewer templates, which meant the review was a lot easier. It also promoted e-submission and e-review tools, which would make a reviewer's job much easier than trying to find this jacket in this room or document room and waiting to get it delivered when it had actually been sent somewhere else. And I just think it is a much more efficient process. ➤



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There is a considerable similarity between ICH guidance to industry and what we consider good review practices. Because ICH Regions have harmonized much of the information submitted for marketing authorization, there is great benefit from working together and utilizing one another's efforts. So the CTD/eCTD has actually changed ICH, because we now have this common regulatory platform. And this promoted modification of the ICH process in terms of expanded participation, which included outreach to other countries and increased transparency. In terms of expanded participation, early in the ICH effort, we realized that the generic and over the counter industry had to be included in ICH. It could not have a two-tiered quality system. You couldn't have one set of quality standards for NDAs and another one for generics or over-the-counter.

In November of 2003—so this was after the CTD was signed off in November of 2000—harmonization initiatives were invited to the Osaka meeting, ICH-6, to discuss their inclusion in the Global Cooperation Group, which was an outreach entity of ICH, to try and get information about ICH out more widely. And at that time, the Asian Pacific Economic Cooperation Group, the Association of Southeast Asian Nations, the Gulf Cooperation Council, Pan-American Network for Drug Regulatory Harmonization, which is basically the Western Hemisphere; and, the Southern African Development Community were invited to participate in ICH meetings. We felt that we would have an opportunity to learn from these other harmonization initiatives on how they function. And they might also learn from us so we could try and figure out how we could work together in harmonizing basically the same information that would be requested for registration.

In May of 2005, because we had many requests to join and invite organizations to join ICH, we had to come up with a definition that would sort of define how you would be able to participate in ICH. Why should you be able to participate in ICH? And, we determined that an interested party was one that was regulated by or regulates by ICH guidelines. So if you are a regulator and you have implemented ICH guidelines, you are actively using them in your regulatory process, you could request to be a part of ICH. If you were required to follow ICH guidelines, you should be part of ICH. You should be part of the discussion, because you would be a stakeholder because you would have to meet those requirements. So, we invited these parties to participate in the expert working group discussions as of May of 2005. In November of 2005, we also invited those regional harmonization initiatives to participate in the expert working group. So they would sit there and observe the groups to observe the different types of discussions and also the ICH harmonization process. One of the most important expansions occurred in 2006, where the Steering Committee decided that we would need to start collaborating with standards development organizations, such as HL7 and ISO, to take advantage of their open, consensus-based processes in the development of electronic standards associated with the eCTD. It was becoming quite apparent that the working group could not do this on their own. They needed outside expertise. And I think that has helped progress the messaging standards that have been developed in a much more rapid fashion.

In June of 2008, a regulators' forum was created to allow other individual countries to participate. We have included individual countries, such as India, China, Brazil and other countries interested in implementing ICH guidelines. We also, in November of 2010, expanded the expert working groups to include participation of the regional organization initiatives, drug regulatory authorities or department of health in ICH working groups if they wanted to participate. And they had to go through an evaluation process to show that they were able to support their participation in the expert working groups, that the experts possessed appropriate knowledge, that they were committed to participating in all of the discussions over the topic life cycle. So we didn't want people to start and then stop and drop out. You had to agree to participate in the entire process and also that they would pay their own way to the meeting and also had to let us know ahead of time that they were coming.

So, to date, China, Republic of Korea, and Singapore have participated in our meetings. This started in our ICH meetings held in Cincinnati in June of 2011. And 15 technical experts have actually been nominated to participate in the various expert working groups. So this is tremendous in terms of the number of people that have expressed interest. So China would like to participate in some quality topics, safety topics, and multidisciplinary topics, Chinese Taipei, also in a quality and efficacy topic; Korea, quality, safety, and efficacy; and also Singapore. So these experts actually participated in the individual expert working groups this past November in Spain.

Most notably, when E2C, revision number 2, reached step two of the ICH process in February, it was the first time that two non-ICH experts, one from Chinese Taipei and one from Singapore, signed off on a document in recognition of their contribution. So this was a major step towards including other countries in the development of ICH guidelines.

We have recently expanded participation to the Eastern African Community to join the Global Cooperation Group after they expressed an interest. And this is very important because the Eastern African Community just went through an amazing process to focus on harmonization throughout that region. And this was just a couple of months ago that this—there was a large meeting

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to explain the process they went through. And it was sort of the inauguration of the harmonization initiative. So given the global environment and the continued success and relevance of ICH, it is going to depend a lot on broader use of ICH guidelines and standards by other industry representatives other than the ICH region and also countries from outside the original ICH region. So expansion of ICH represents a natural evolution and changing world reality. Expanded participation in ICH is expected to benefit industry, regulators, and patients and will hopefully promote faster access to innovative medicines.

There is a decision to publish the summary of Steering Committee actions and decisions, a summarized report, on the ICH website. This helps people that can't attend the meetings to know what went on. We have been doing that since 2005. We also post concept papers and business plans. And this provided for earlier notice of topics because prior to posting the concept papers and business plans, you wouldn't know that a topic was being discussed in ICH until step two was reached and the documents were posted for comment. There is a standing section on the ICH web. Anyone can comment on ICH guidelines. And the web specifically says, "If you want to help shape the ICH guidelines, by responding to one of our consultations, your contribution will then be considered by the relevant ICH working group" with links to draft guidelines and Q&A documents. So for the United States, we publish things in the *Federal Register* so that people know that these documents are available. And comments come in through the regulatory authorities: European Union, Japan, and the United States. But anyone that wants to can comment on these documents. And we take those comments into account.

For the tenth anniversary of ICH in 2000, **Caroline Nutley Loew** from PhRMA wrote a document, a brochure, to distribute at the meeting called "Value and Benefits: The Value and Benefits of ICH to Industry." On the occasion of the 20th anniversary in 2010, the regulatory authorities of ICH got together and wrote "The Value and Benefits of ICH to Drug Regulatory Authorities - Advancing Harmonization for Better Health." That document for the 20th anniversary was actually translated by the Safe Food and Drug Administration of China. And they distributed it to all of their regulators in the SFDA. I think that shows a major expansion of ICH guidelines and their use more globally.

**[Editor's Note:** FDA holds these public meetings in advance of ICH meetings in order to solicit public input and to ensure transparency.]



## 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 [www.pda.org/regulatorynews](http://www.pda.org/regulatorynews).

### North America

#### U.S. FDA Publishes Proposed Rule on Unique Device Identification Systems

The U.S. FDA has published a proposed rule on unique device identification systems.

Under the terms of the proposed rule, FDA would establish a system which would require the label of a medical device and device packages to include a unique device identifier except where the rule provides for alternative placement of the unique device identifier or provides an exception for a particular device or type of device. Each unique device identifier would have to be provided in a plain text version and in a form that uses automatic identification and data capture technology.

The rule would require the submission of information concerning each device to a database that FDA intends to make public, to ensure that the unique device identifier can be used to adequately identify the device through its distribution and use.

Comments should be submitted by November 7.

### Europe

#### New EU Pharmacovigilance Legislation

New EU pharmacovigilance legislation has come into operation.

Comprised of Directive 2010/84/EU and Regulation (EU) No 1235/2010, highlights of the new legislation include:

- Establishment of the Pharmacovigilance Risk Assessment Committee
- Clarification of the roles and responsibilities

- Engagement of more stakeholders in the process
- Improved collection of key information on medicines
- More transparency
- Better communication

#### EMA Publishes Guideline on Biotech-Derived Proteins for Biological Medicinal Products

The European Medicines Agency has released a guideline on similar biological medicinal products containing biotechnology-derived proteins as an active substance.

The guideline explains the quality requirements for a biological medicinal product claiming to be similar to another one already marketed.

The guideline also addresses the requirements regarding manufacturing processes, the comparability exercise for quality, considering the choice of reference medicinal product, analytical methods, physicochemical characterization, biological activity, purity and quality attributes for relevant specifications of the similar biological medicinal product.

Once finalized, this guideline will replace the *Guideline On Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins As Active Substance: Quality Issues* that was issued in 2005.

Consultation ends on November 30.

#### EMA Publishes Revised Guideline on Quality of Biosimilar Medicines

The European Medicines Agency has revised a 2006 guideline on the quality of biosimilar medicines.

The revised guideline describes how pharmaceutical companies should address the

#### Key Regulatory Dates Comments Due

**November 7** — U.S. FDA's Proposed Rule on Unique Device Identification Systems

**November 30** — EMA's Guideline on Biotech-Derived Proteins for Biological Medicinal Products

EMA's Revised Guideline on Quality of Biosimilar Medicines

EMA's Recombinant Production Quality Guide


quality aspects of biosimilar medicines and explains the requirements for the manufacture and comparability testing for biological medicines claiming to be similar to another medicine already on the market.

The guideline is open for consultation until November 30.

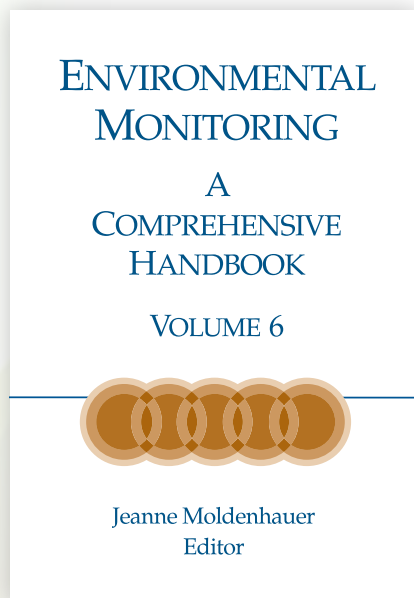
#### EMA Adapts Recombinant Production Quality Guide to Include Transgenic Animal Systems

The European Medicines Agency has posted a guideline that has adapted existing quality guidance for other recombinant production systems to transgenic animal systems.

The *Guideline on Quality of Biological Active Substances Produced by Transgene Expression in Animals* focuses on the quality issues including the selection, generation and control of the production animals and evaluation of freedom from adventitious agents.

The guideline is open for consultation until November 30. 

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# Senior Management Support of ICH Q10 Essential for Compliance

Baltimore, Md. • September 12-13 • [www.pda.org/ICHQ10](http://www.pda.org/ICHQ10)

Ronald Branning, Genzyme

Senior management needs to understand that ICH Q10 provides the framework for the creation of an efficient and robust production quality system that meets regulators compliance expectations around the world. It is also the basis for the fastest and least expensive path for product development and approval by the regulatory authorities.

Modern regulatory requirements beginning with the 1906 Pure Food and Drug Act through the 1962 Drug and 1976

Medical Device GMP regulations have been promulgated to enhance public health and safety. In addition, a number of guidance documents such as those for water systems, process validation and computerized systems have been widely used to clarify the regulations and the meaning of “current” in CGMPs. One of the more significant guidance documents is the CDHRH quality system for devices, the model for FDA’s quality systems inspections and the forerunner of the ICH Q10 Pharmaceutical Quality System guideline.

As regulations and guidance have matured, regulators’ inspection approaches have become more sophisticated. The regulators’ expectation is that there is a

quality system in place with oversight of all production and quality operations. The increasing number of quality system observations, particularly by FDA, has led to a growing number of regulatory enforcement actions in recent years particularly warning letters and consent decrees. The solution to regulators’ concerns about quality system failures is a

robust process


Product descriptions that are constructed as a product that make their way through the development process are the basis for designed experiments. These help to confirm the critical aspects of the product, process, maximize productivity

and provide evidence for regulatory filings, which is essential for speed to market.

Senior management’s understanding of ICH Q10 and support for the imple-

mentation of production quality systems is essential for compliance. Quality systems underpin a climate of learning and continuous improvement that ensures a sustainable quality culture, rapid product development, robust processes, safe and effective products and more certain regulatory approval of products developed within the quality system structure.

Join us in Baltimore, Md. from September 12-13 for our *Responsibilities of Executive Management (Operations and Quality) – Implementing the Principles of ICH Q10 2012 PDA / FDA Pharmaceutical Quality Systems Workshop*.

To learn more or to register, visit [www.pda.org/ICHQ10](http://www.pda.org/ICHQ10) . 

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## *Senior management’s understanding of ICH Q10 and support for the implementation of production quality systems is essential for compliance*

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successful implementation of ICH Q10 that results in a comprehensive, integrated production quality system.

The production quality system is not just a “quality system”; it integrates all the engineering, maintenance, supply chain, manufacturing, packaging, quality and other activities required by a firm to reliably produce safe and effective products.

The heart of the quality system is the product description consisting of

1. A process map
2. Definition of product critical quality attributes
3. Identification of critical process parameters that impact product quality
4. Process monitoring and quality con-

*How to Ensure Quality continued from page 44*


Laboratories. Prior to joining Merck, Greg served in varied capacities over ten years at the U.S. FDA in the Center for Drug Evaluation & Research and also in the Center for Veterinary Medicine.

**Anthony Mire-Sluis**, PhD, Vice President, Corporate, Product and Device Quality, Amgen, was previously Principal Advisor, Regulatory Science and Review, Office of Biotechnology Products, CDER and Head of Analytical Sciences and Standards, Office of the Director, CBER, U.S. FDA. He is the Chairman of the IABS

Biotherapeutics Committee, Vice Chairman of the USP Biologicals Characterization Expert Committee, an expert for the International Committee for Harmonization and on the board of the Journal of Immunological Methods.

**G.K. Raju**, PhD, Chairman and CEO, Light Pharma, has expertise in defining the strate-



gic role of pharmaceutical development and manufacturing and enabling its performance with the pharmaceutical and biotechnology industry. His work focuses on pharmaceutical process innovation and addresses issues of manufacturing science, regulatory compliance, six sigma, operational excellence, systems dynamics, organizational learning, process analytical technology, on-line sensors, economic modeling, data analysis, pattern recognition and knowledge based systems. 



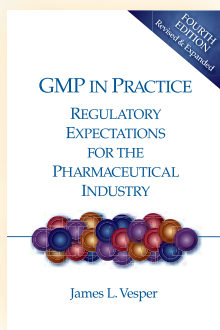


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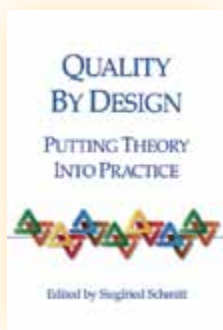
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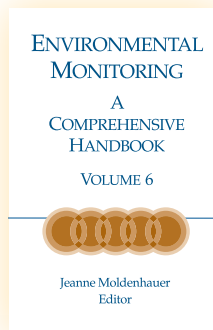
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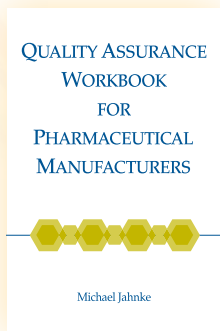
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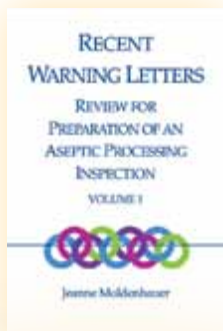
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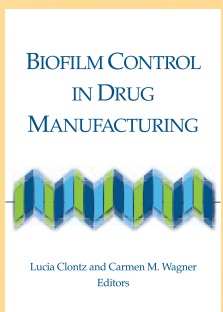


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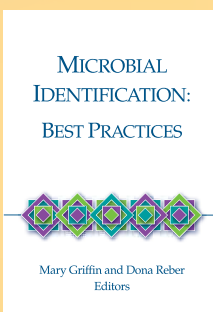
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- 100% controls - a fad or the future?
- Dual cartridges - a dosage form with a bright future in freeze drying?
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- Is there a need for a PDA Technical Report on Lyophilization?

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# Robust Quality Systems Further Company Goals

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Cochairs Steve Mendivil, Amgen and Susan Schniepp, OSO BioPharmaceuticals Manufacturing

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The 2012 Planning Committee has worked hard over the last year to offer attendees new and exciting topics that help make this meeting one of PDA's best. In joint collaboration with the FDA, the committee has designed the contents of the program to reflect how a robust quality system can enhance business goals and objectives.

The conference will start with a presentation from the Office of the Commissioner and **Steven Solomon**, Associate Director, Global Operations and Policy, Office of Regulatory Affairs, U.S. FDA. Solomon will give a presentation on global regulatory operations as they relate to the supply chain. The second plenary session will focus on the changing quality of culture. **Greg Guyer**, Senior Vice President, Global Quality at Merck, Sharp & Dohme, **Anthony Mire-Sluis**, Vice President, Corporate, Product and Device Quality, Amgen and **G.K. Raju**, CEO, Light Pharma, will speak about the importance of quality at all levels of an organization, how it is defined by patient needs and the global regulatory environment. **[Editor's Note:** See related article on 44.]

The third plenary will focus on the emerging discipline of contract manufacturing organizations from the various viewpoints of the contract giver, the

contract provider and an independent third party. **EJ Brandreth**, Vice President, Quality and Regulatory, Althea and **Christopher Masterson**, Senior Director of Quality, Cubist Pharmaceuticals are confirmed to speak about the dynamics and challenges of managing CMO relationships. The conference will end with a panel of FDA experts providing insight on upcoming Center Initiatives. FDA representatives from The Center for Biologics Evaluation and Research, The Center for Drug Evaluation and Research, Center for Devices and Radiological Health, Center for Veterinary Medicine and Office of Regulatory Affairs are confirmed to partici-

ence attendees will hear about regulatory submissions and meetings, drug safety, user fees and regulatory process from approval to inspectional readiness.

The *Innovation and Science* track will focus on future trends in the pharmaceutical industry with compelling session titles such as manufacturing in the future, cell therapy innovations and emerging API regulations.

There will also be eight breakfast sessions offered during the conference on a variety of topics, including a review of the January 2011 of the revised U.S. FDA Process Validation Guidance. Twelve interest groups—three of which are new—will also meet at the conference. The Pharmacopeial Interest Group will discuss the activities and initiatives of the United States, Japanese and European Pharmaco-

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pate in the closing session.

The conference will be organized into a series of concurrent sessions divided into three tracks:

- *Quality and Compliance*
- *Product Development*
- *Submissions, Innovation and Science*


The sessions offered in these tracks will build on the plenary talks by providing practical applications and case studies.

The *Quality and Compliance* track will focus on the positive impact a functioning and sustainable quality system has on the business needs of a company. There will be talks on quality systems, quality risk management implementation, quality agreements and investigations. The *Product Development and Submissions* track will focus on regulatory concerns associated with product development. Confer-

ence attendees will hear about regulatory submissions and meetings, drug safety, user fees and regulatory process from approval to inspectional readiness. The *Innovation and Science* track will focus on future trends in the pharmaceutical industry with compelling session titles such as manufacturing in the future, cell therapy innovations and emerging API regulations. There will also be eight breakfast sessions offered during the conference on a variety of topics, including a review of the January 2011 of the revised U.S. FDA Process Validation Guidance. Twelve interest groups—three of which are new—will also meet at the conference. The Pharmacopeial Interest Group will discuss the activities and initiatives of the United States, Japanese and European Pharmaco-

peias, the Management of Outsourced Operations interest group, which will open up dialog between attendees on how to manage contract operations, and the GMP Links to Pharmacovigilance interest group, which will focus on discussions revolving around safety concerns associated with particulate matter in parenterals and data mining techniques and the utility in product quality issues.

Immediately following the *Conference*, PDA's Training and Research Institute will host six courses on September 13-14.

Please join us and bring your colleagues to Baltimore for another exceptional PDA/FDA Joint Regulatory Conference and courses. We look forward to seeing you. For more information on the conference, courses and to register, visit [www.pda.org/pdafda2012](http://www.pda.org/pdafda2012). 





Register Before  
**August 31, 2012**  
to Receive the Largest  
Savings Deadline for  
This Event!

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# PDA/FDA Pharmaceutical Supply Chain Conference

*Global Supply Chain Integrity – A Shared Responsibility*

**November 13-14, 2012**

Bethesda North Marriott Hotel | Bethesda, Maryland

Improving the integrity of the entire supply chain for pharmaceutical ingredients and finished products ultimately helps ensure the quality and safety of medicines for patients. Globalization of pharmaceutical manufacturing and distribution is bringing manufacturers and suppliers to public forums such as these to discuss how to manage emerging concerns including illegal acts such as counterfeiting, diversion and intentional adulteration.

At the *PDA/FDA Pharmaceutical Supply Chain Conference* participants will hear regulators as well as industry experts present on an array of topics addressing practices and approaches to be considered to ensure the integrity and quality of the global supply chain.

Regulatory speakers confirmed to moderate and/or speak at this meeting include:

- **Lieutenant Commander Eleni Anagnostiadis**, Pharmacist, Consumer Safety Officer, *CDER, FDA*
- **Ilisa Bernstein**, PharmD, JD, Acting Director, Office of Compliance, *CDER, FDA*
- **Frederick Fricke, Jr.**, Director, Forensic Chemistry Center, *ORA, FDA*
- **Gregg Goneconto**, Special Agent, Office of Criminal Investigations, *FDA*
- **Gerald Heddell**, Director, Inspection Enforcement & Standards Division, *MHRA*
- **Captain Valerie Jensen**, Associate Director, Drug Shortage Program, *CDER, FDA*
- **Commander Connie Jung**, PhD, Acting Associate Director for Policy and Communications, Office of Drug Security, Integrity and Recalls, *FDA*
- **Nancy Kennedy**, Special Agent, Senior Operations Manager – Drug Investigations, Office of Criminal Investigations, *FDA*
- **S. Leigh Verbois**, PhD, Acting Deputy Director, Division of Supply Chain Integrity, Office of Drug Security, Integrity and Recalls, *CDER, FDA*
- **Steven Wolfgang**, PhD, Acting Associate Director, Risk Science, Intelligence and Prioritization, *CDER, FDA*

Immediately before the conference, PDA's Training and Research Institute (PDA TRI) will be hosting a course, *Developing a Robust Supplier Management Process*, onsite on November 12.



Visit [www.pda.org/supplychain2012](http://www.pda.org/supplychain2012)  
for more information and to register.

**Exhibition: November 13-14 | Course: November 12**

# Whose Learning is it Anyway?

Bethesda, Md. • October 8-11 • [www.pda.org/biennial2012](http://www.pda.org/biennial2012)

Conference Committee Member Kristina R. Barkhouser, Excelen Performance

Is it time for your annual compliance training? Do you ever wonder who *really* cares?

Regulators care that you've provided *it*. The U.S. FDA 21 CFR §211.25 states that training should be given "*with sufficient frequency to assure that employees remain familiar with cGMP requirements applicable to them.*"

Your quality department cares that *they* can demonstrate to the regulators that the training was delivered.

Your managers care that *they* can demonstrate to your quality department that training was delivered.

Your training department would like to deliver something meaningful to trainees, but is often up to managers to come up with a "one size fits all" training session for hundreds or thousands of people to ensure minimal interruption to the business. So, with these varied interests in the delivery of compliance training, whose learning is it anyway?

Have you ever wondered what the employees really care about and for whom the training should actually be designed? In a culture where tracking training and proving that it is *delivered* is very familiar, we would likely find our efforts a huge waste of time, if we actually measured the return on investment. The intent of the

training regulations is not just that employees "*remain familiar*" with requirements, but rather that they *apply* the learning to their daily lives and operate in a state of compliance. The preamble to the FDA regulations state: "*The Commissioner intends that training be meaningful to the employee, not a formalistic but useless exercise to satisfy a regulation.*"

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## *It's imperative that we begin to think of the real customer when it comes to delivering compliance training*

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Therefore, it's imperative that we begin to think of the real customer when it comes to delivering compliance training. Are you measuring whether or not the training was actually meaningful? If your training isn't making a difference in the attitudes, skills or knowledge level of employees, then you're simply wasting your time and money on a "*formalistic, useless exercise to satisfy a regulation.*"

Training can be designed and delivered in a way that engages employees, helping them take ownership of the learning and apply it to their work! A key to improving performance is driving ownership of learning to the trainees. When training is done properly, organizational effectiveness and business results are typically enhanced. Leading training profession-

als in the industry know how to accomplish and measure this and would love to share these insights with you!

The theme of this year's PDA Biennial Training Conference is *From Training to Learning – Improving Performance in a Regulated Environment*. This year's conference will offer a wealth of information

to help trainers and managers in regulated industries provide useful training tips and techniques.

The conference offers three main tracks of concurrent sessions in the areas of:

- *From Training Programs to Learning Programs*
- *Training System Effectiveness*
- *From Theory to Practice*

Join us at this year's conference in Bethesda, Md. October 8-9 and learn from leading industry practitioners in the craft of compliance training, learning and workplace performance. This is an outstanding opportunity to explore innovative techniques for improving performance in a regulated environment.

Immediately following the conference, PDA's Training and Research Institute will be hosting three courses from October 10-11.

To learn more about the conference, courses or to register, visit [www.pda.org/biennial2012](http://www.pda.org/biennial2012). ☺

# Join Us at the Annual Microbiology Conference

Bethesda, Md. • October 22-26 • [www.pda.org/microbiology2012](http://www.pda.org/microbiology2012)

Planning committee member Osama (Sam) Elrashidy, Bayer Healthcare

It has been seven years since our first PDA microbiology conference and each one has been better than the last. This year's conference is scheduled from October 22-24 in Bethesda, Md. and will discuss many of the topics that microbiologist and regulators face day-after-day to ensure the safety of products before they reach end users.

The PDA annual global conference on pharmaceutical microbiology is one of the only places where pharmaceutical and industrial microbiologists get together from all over the world to learn from each other and exchange valuable experience and knowledge.

This conference will cover:

- Role of microbiology
- Contamination control

- Risk management in manufacturing
- Requirements in maintaining sterility of products and services
- Strategies for maintaining a non-sterile manufacturing environment

The knowledge gained at this conference will help attendees save time and resources as well as to ensure the safety and efficacy of pharma and biopharma products.

This year, experts in the microbiology field will share with us their visions and expertise, suppliers will introduce their latest equipment and devices that will help us in our daily activities and scientists will present their latest research findings. On the first day of the conference, **Matthew Arduino**, Dr. PH, Lead Microbiologist, Chief Clinical and

Environmental Microbiology Branch, Centers for Disease Control and Prevention, will kick off the conference with a detailed account of outbreaks he has dealt with at the CDC over the last 25 years. On day two, a keynote presentation by **Anders Vinther**, PhD, Vice President, Roche Quality Biologics Operating Unit, Genentech, will cover approaches taken to enhance detection and prevention of bacterial contamination.

This year we are also adding a very interesting new session that answers questions related to applying the appropriate mathematical principles to the compendial testing methods. Be sure to check out the "Do the Math" session on day two of the conference. Our popular sessions on regulatory and USP updates, urban myths and future leaders will also

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## 2012 PDA/FDA Joint Regulatory Conference & TRI Courses

*Compliance through Quality Systems: Implementing & Advancing a Sustainable Global Quality Culture*

September 10-12, 2012 | Baltimore Marriott Waterfront Hotel | Baltimore, Maryland

In conjunction with the 2012 PDA/FDA Joint Regulatory Conference & TRI Courses, the PDA Training and Research Institute (PDA TRI) is offering six stand-alone courses related to the latest concepts, newly-enacted regulations and updated processes in the pharmaceutical and biopharmaceutical industries.

- Biopharmaceutical QA/QC for Senior Management | September 13
- Preparing for Regulatory Inspections for the FDA and EMA | September 13-14
- Application of a Quality Systems Approach to Pharmaceutical CGMPs | September 13-14
- Application of Phase-Appropriate GMP to the Development of Protein Bulk Drug Substances – *New Course* | September 14
- Development of Qualification and Validation Protocols – A Risk Management Approach | September 14
- Good Distribution Practices for the Pharmaceutical Supply Chain – *New Course* | September 14



For details and to register, visit [www.pda.org/pdafda2012](http://www.pda.org/pdafda2012)

Exhibition: September 10-11 | Post-Conference Workshop: September 12-13 | Courses: September 13-14



be held throughout the conference.

Additionally, sessions will be covering the following topics:

- Advances in microbiological control during pharmaceutical manufacturing
- Preparing the QC micro workforce of the future

- Real time microbial detection and quality control
- Control of product package integrity and seal quality
- Biofilms, biotechnology and hold time

Join us at our meeting and expand and share your knowledge and expertise with many pharmaceutical and industrial mi-

crobiologists from all over the world.

Immediately following the conference, PDA's Training and Research Institute will be hosting five courses from October 25-26.

For details on the conference, courses or to register, please visit [www.pda.org/microbiology2012](http://www.pda.org/microbiology2012). 🍷

## Thermal Protection Significant Tenet to Conference

Berlin, Germany • October 9-12 • [europe.pda.org/ColdChain2012](http://europe.pda.org/ColdChain2012)

Erik J. van Asselt, PhD, PCCIG EU Branch Leader and Rafik H. Bishara, PhD, PCCIG USA Branch Leader

If you are a patient and obtain medication from your physician, pharmacist or care taker, you hope that that product helps you to recover as soon as possible. If you use a pharmaceutical temperature sensitive product, you expect that all supply chain stakeholders take care of their responsibility to provide optimal thermal protection to the product during manufacturing, storage and distribution--any failure might impact your health and recovery. In the upcoming *Pharmaceutical Cold Chain Management & Good Distribution Practices* conference and training course in Berlin from October 9-12, thermal protection and supply chain integrity are the two central themes.

Active and passive systems such as temperature-controlled trucks and thermal packouts are currently well-established thermal protection practices. These systems maintain cold chain products within the required shipping temperature range. However, new regulations are appearing, which compel manufacturers and wholesalers to apply thermal protection to room temperature pharmaceutical products as well. This

change in mindset impacts distribution practices worldwide and drives companies to search for new thermal protective solutions, temperature monitors as well as to apply additional risk management principles. In the upcoming conference, these aspects will be presented by various speakers from the pharmaceutical indus-

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*For the third time, the successful "PDA Good Temperature-Controlled Management Practices" course will be held from October 11-12*

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try, suppliers and regulators.

In Europe and in the United States, new regulations are in development regarding pharmaceutical supply chain integrity. The aim is to minimize supply chain risks to medicines from the sourcing of pharmaceutical raw materials up to delivery to the patient. During this time, the product quality, safety and efficacy should be maintained by preventing product adulteration, counterfeiting, theft and diversion; however, the complex global supply chain for pharmaceuticals, cost pressures and the presence of

bad actors make this an intricate quest. But, effective supplier partnerships, quality management systems and track & trace tools reduce the supply chain risk. These aspects and others will be further explained by several experienced speakers during our conference.

For the third time, the successful "PDA Good Temperature-Controlled Management Practices" course will be held from October 11-12 following the conference. Participants will get insight into the global GDP regulation, PDA Cold Chain Interest Group Technical Reports, cold chain risk management, development and qualification of active and passive systems as well as temperature monitoring and data analysis. In this interactive course, trainees will have the opportunity to learn the best cold chain practices from international field experts.

On behalf of the PDA Europe and Program Planning Committee, we encourage and welcome you to sign up for this event. This will be your next step to learn and contribute to how to provide effective medicines to patients worldwide.

See you in Berlin in October. 🍷

# Innovation is Key at Prefilled Conference

Las Vegas, Nev. • October 15-17 • [www.pda.org/prefilled2012](http://www.pda.org/prefilled2012)

Yu Hu, PhD, Eli Lilly & Company

As we approach this year's *Universe of Pre-Filled Syringes and Injection Devices* meeting, we look forward to welcoming you to Las Vegas, Nev. October 15–19.

Since the introduction of the annual PDA meeting focusing on prefilled syringes and associated injection devices, we have seen a significant growth in this type of packaging and delivery system. It has long been acknowledged that prefilled syringes offer significant benefits to both the user and drug manufacturer. With the growth of therapies aimed at chronic conditions such as Rheumatoid Arthritis, Multiple Sclerosis and other autoimmune diseases, the preferred packaging and delivery system has become the prefilled syringe in combination with an autoinjector. This trend is set to continue and drive future innovation.

It is rare to see a segment of the industry where so many factors have an influence, and create challenges/opportunities for all involved. These include:

- Growth in specific-market segments, increasing competitive pressures and the ongoing need for lifecycle management
- Regulatory trends, increased scrutiny by regulatory agencies and drive towards improved quality
- Continuing innovation from packaging and delivery system suppliers
- Increasing requirements for pharmaceutical and biotech companies and a market that is often sensitive to change
- Patients, family members and caregivers assuming more responsibility for treatment, including more injectable therapies

To address challenges we are facing, it is crucial to continue on the path of innovation as we have been on for many

years. This comprehensive program is intended to integrate the unmet market needs and bring it all together for tomorrow's success, and we have been de-

challenge and demand new approaches from manufacturers such as combination products and human factors.

- A first look at how a design of experi-

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*This is an excellent opportunity to interact with peers and industry experts in this growing field, and we look forward to welcoming you to Las Vegas, Nev.!*

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lighted with the support from presenters, exhibitors, sponsors and participants from very diverse industry, academic and regulatory backgrounds.

Consider just a few of the many sessions to be held over this exciting 2 ½ day conference:

- A keynote will provide attendees with the opportunity of what it is like to be a patient struggling from a chronic disease and how using the tools of our industry have greatly affected the quality of their life.
- A number of compelling revelations of new methods and techniques from the "front lines," which will show you how to increase patient compliance and safety in difficult to treat patients.
- Novel technologies that are helping to meet the needs of the market by improving administration, compliance, safety, costs and accuracy through the use of a novel integrated approach to prefilled syringes and injection devices.
- Discussions and new advances in material construction, manufacturing processes, and other improvements that ensure a dynamic future for the drug delivery arena in the future.
- A series of presentations on new and challenging guidelines from myriad of regulatory agencies that continue to


ments are being used to gain a deeper understanding and offer optimal formulations and delivery systems for complex combinations of formulation parameters with differing syringe configurations.

- Emerging market assessments that will provide you with unique insights on regulatory, technical and scientific challenges in a dynamic world followed by a panel of industry and regulatory experts.

This is an excellent opportunity to interact with peers and industry experts in this growing field, and we look forward to welcoming you to Las Vegas, Nev. Whether you are new to the field or an industry veteran, you will take away practical knowledge to put immediately into use as well as meet new colleagues and contacts. We invite you to participate in the *2012 PDA Universe of Pre-Filled Syringes and Injection Devices*, October 15-17, in Las Vegas, Nev.

Immediately following the conference, PDA TRI will be hosting three courses from October 18-19.

Please visit [www.pda.org/prefilled2012](http://www.pda.org/prefilled2012) for more information about the conference, TRI courses or to register.

We hope to see you soon! 

*The Parenteral Drug Association presents...*



# 2012 PDA

# Visual Inspection Forum

See the Highlights:

- **Recent compendial and regulatory activities**
  - Regulatory inspection trends
  - What's new from the pharmacopoe and health authorities
- **New inspection technologies**
  - Particles
  - Protein aggregates
  - Freeze dried products
  - Automated integrity and leak testing
- **Special considerations for the inspection of biopharmaceuticals**
  - Monoclonal antibodies
  - Freeze dried products and liquids in pre-filled syringes
- **Preparation and use of standards and defect sets**
- **Classification of defects and preparation of defect libraries**
- **Qualification of manual and validation of automated inspection systems**

**Training Course**  
An Introduction on  
Visual Inspection -  
Make sure your  
seat!

You will have a plenty of case studies,  
networking and discussion opportunities.  
Don't miss the two-day hands-on  
training course!

## 25-28 September 2012

RAMADA Hotel Berlin-Alexanderplatz  
Berlin | Germany

CONFERENCE 25-26 Sep | EXHIBITION 25-26 Sep | TRAINING COURSE 27-28 Sep



<https://europe.pda.org/VisInsp2012>





## Two New Courses Offered at PDA/FDA

Baltimore, Md. • September 14 • [www.pda.org/pdafda2012](http://www.pda.org/pdafda2012)

Stephanie Ko, PDA

This September, the Training and Research Institute will be presenting two new courses on September 14 in conjunction with the *2012 PDA/FDA Joint Regulatory Conference* in Baltimore, Md.

What is unique about these courses? They are exclusive, offered only by PDA. They are also based on PDA's very own technical reports and PCMO<sup>SM</sup> (Paradigm Change in Manufacturing Operations) documents, reflecting industry best practices.

"Application of Phase-Appropriate GMP to the Development of Protein Bulk Drug Substances," will be taught by **John Geigert**, PhD, RAC, President, Bio-Pharmaceutical Quality Solutions. This is a can't-miss course based on the manufacturer's need to implement a pharmaceutical quality system that ensures the safety and quality of products intended for use in clinical trials and provides the basis for subsequent assurance of the equivalence of products used in trials to products submitted for marketing approval. Participants will be able to discuss current CGMP principles important for manufacturing pre-marketing therapeutic bulk protein and be given an introduction to a phase-appropriate approach to the implementation of CGMP. This phase-appropriate approach enables sponsors to supply safe clinical materials for studies in humans while maintaining manufacturing flexibility at non-commercial scales and during scale up and process transfer to

commercial facilities.

Examples will be provided of approaches towards CGMP compliance during clinical studies. Through lecture and discussion, an overview will be presented of the expectations across regulatory authorities as products proceed from the discovery/R&D stage through completion of phase 3 clinical trials. At the completion of this course, attendees will have an understanding of the importance and underlying principles for a phase-appropriate approach to CGMPs to the development of protein bulk drug substances.

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*Get the most out of your trip by attending the conference and a training course—you won't be disappointed!*

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"Good Distribution Practices for the Pharmaceutical Supply Chain" will be taught by **Karl Kussow**, Manager, Quality and Validation, FedEx Custom Critical. This course was developed in response to a new regulatory guidance that requires the temperature sensitivity of all shipments to be defined and the distribution methods to be qualified. Shipping and storage methods must also be qualified and appropriately controlled and/or monitored to prove the product was not harmed by the ambient environment. Specifically, this means that shipments that have historically been distributed in the "ambient" environment may soon be required to have temperature controls or monitoring applied. The increase in costs associated with this added control or monitoring is

a large concern; therefore, companies are making it a priority to create strategies that reduce the financial impact of these new GDP expectations.

Participants will be thoroughly engaged through lecture, discussion, case studies and exercises, where they will learn the tough choices involved in meeting the expectations of good distribution practice on a global scale. Students will understand the risks and opportunities associated with shipment of temperature sensitive products. Upon completion of the course,

participants will be able to describe strategy options for implementing practices that meet GDP guidelines and explain the pros and cons associated with the strategies available for their individual products.

Students will receive copies of PDA *Technical Report No. 46, Last Mile: Guidance for Good Distribution Practices for Pharmaceutical Products to the End User*, and PDA *Technical Report No. 52, Guidance for Good Distribution Practices for the Pharmaceutical Supply Chain*.

This is your opportunity! Become a more valuable professional with new tools and knowledge that can be applied immediately when you return to your job. In addition, this is your chance to network with others and meet the experts in the field. Get the most out of your trip by attending the conference *and a training course—you won't be disappointed!*

Please go to [www.pda.org/pdafda2012](http://www.pda.org/pdafda2012) for a list of other training courses offered throughout the year. 🌐



The 2012  
Aseptic Processing  
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Visit [www.pda.org/aseptic](http://www.pda.org/aseptic)  
to sign up to receive  
an email notice when  
registration opens for the  
next session.

## Parenteral Drug Association Training and Research Institute (PDA TRI)

### Upcoming Laboratory and Classroom Training for Pharmaceutical and Biopharmaceutical Professionals

#### September 2012

**2012 PDA FDA Joint Regulatory  
Conference Course Series**  
September 13-14 | Baltimore Marriott  
Waterfront Hotel in Baltimore, Maryland  
[www.pda.org/pdafdacourses2012](http://www.pda.org/pdafdacourses2012)

- Biopharmaceutical QA/QC for Senior Management | September 13
- Quality Management Best Practices: Real World Approaches to Meeting the Expectations of Q10 and Case Studies in Quality Management Failure | September 13
- Application of a Quality Systems Approach to Pharmaceutical CGMPs | September 13-14
- Preparing for Regulatory Inspections for the FDA and EMA | September 13-14
- Application of Phase-Appropriate GMP to the Development of Protein Bulk Drug Substances | September 14 - **New Course**
- Development of Qualification and Validation Protocols - A Risk Management Approach | September 14
- Good Distribution Practices for the Pharmaceutical Supply Chain | September 14 - **New Course**

#### October 2012

 **Developing a Moist Heat Sterilization Program within FDA Requirements**  
October 2-4 | Bethesda, Maryland  
[www.pda.org/moistheat2012](http://www.pda.org/moistheat2012)

 **Developing and Validating a Contamination Control, Cleaning and Disinfection Program for Controlled Environments**  
October 9-10 | Bethesda, Maryland  
[www.pda.org/contamination2012](http://www.pda.org/contamination2012)

**2012 PDA Biennial Training  
Conference Course Series**  
October 10-11 | Hyatt Regency in  
Bethesda, Maryland  
[www.pda.org/biennialcourses2012](http://www.pda.org/biennialcourses2012)

- Qualifying Your SMEs as Trainers | October 10
- Learning, Knowledge Management and Impact: Moving from Theory to Practice | October 10-11 - **New Course**
- FDA Inspection Readiness for a Training Systems Audit | October 11

**The Universe of Pre-filled Syringes and  
Injection Devices Course Series**  
October 18-19 | Red Rock Resort and Spa  
in Las Vegas, Nevada  
[www.pda.org/prefilledcourses2012](http://www.pda.org/prefilledcourses2012)

- Combination Products: Principles, Regulations, Current Issues and Solutions | October 18
- Technical Development of Pre-filled Syringes, Autoinjectors and Injection Pens | October 18
- Syringes and Elastomers: Understanding the Effects on Quality and Demonstrating the Production Process, Influences and Needs | October 19

**PDA's 7th Annual Global Conference  
on Pharmaceutical Microbiology  
Course Series**  
October 25-26 | Bethesda North  
Marriott Hotel in Bethesda, Maryland  
[www.pda.org/microcourses2012](http://www.pda.org/microcourses2012)

- Alternative Methods for Mycoplasma Testing | October 25 - **New Course**
- Biofilms | October 25 - **New Course**
- Evaluation, Validation and Implementation of New Microbiological Testing Methods | October 25 - **New Course**
- Microbiological Issues in Non-Sterile Manufacturing | October 26
- Investigating Microbial Data Deviations | October 26 - **New Course**



**Validation of Biotechnology-Related  
Cleaning Processes**  
October 30-November 1 | Bethesda, Maryland  
[www.pda.org/biotechnology2012](http://www.pda.org/biotechnology2012)

#### November 2012



**Steam in Place**  
November 2 | Bethesda, Maryland  
[www.pda.org/steam2012](http://www.pda.org/steam2012)

**2012 PDA FDA Pharmaceutical Supply  
Chain Conference Course Series**  
November 12 | Bethesda, Maryland  
[www.pda.org/supplychaincourses2012](http://www.pda.org/supplychaincourses2012)

- Developing a Robust Supplier Management Process | November 12



**DoE Basics for Validation  
by Design**  
November 13-14 | Bethesda, Maryland  
[www.pda.org/doe2012](http://www.pda.org/doe2012)



**Single-Use Systems for  
Manufacturing of Parenteral  
Products - **New Course****  
November 14-15 | Bethesda, Maryland  
[www.pda.org/suscourse2012](http://www.pda.org/suscourse2012)



**Qualification of Pharmaceutical  
Systems - **New Course****  
November 27-29 | Bethesda, Maryland  
[www.pda.org/pharmasystems2012](http://www.pda.org/pharmasystems2012)

**For more information  
on these and other  
upcoming PDA TRI  
courses please visit  
[www.pda.org/course](http://www.pda.org/course)**



Laboratory Courses



The PDA Training and Research Institute is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education.

## Editor's Message

### PDA/FDA and Sterile Processing

It would be remiss of me to write about the July/August *PDA Letter* without first mentioning the great design work of PDA's **Katja Yount**, Publication Design Specialist. **Walter Morris**, Director of Publishing, PDA, came up with the idea of a "faux" cover that would allow us to illustrate the articles we are publishing to promote the upcoming PDA/FDA Joint Regulatory Conference, but would also allow us to highlight articles related to sterile processing, our theme for the issue's feature stories. Katja took the idea and designed the great cover that displays a globalized supply chain route.

For actual cover, Katja photographed "cleanroom technician" **Stephanie Ko**, Senior Manager, Lecture Education, in PDA's TRI facility demonstrating how to sanitize a cleanroom with a mop.

This issue also includes a "lessons learned" article from the cochairs of the *2012 PDA Innovation & Best Practices on Sterile Technology Conference*. Two articles highlighting the upcoming PDA/FDA meeting in September are also in this issue (see pages 38 and 44).

Be sure to check out the Faces and Places section. We have included pictures from the PDA/PIC/S workshop, Glass Quality Conference and PDA/FDA Virus and TSE Safety Conference.

### Goodbye... Hello

For almost five years, I've had the pleasure of working on the *PDA Letter* and sharing my challenges and triumphs with Walt and Katja. We've commiserated with each other when we needed to work late at the office to finish an issue of the Letter or computers shut down when an important story was being written or designed (and not yet saved!).

As a part of the Letter staff, I've had a chance to meet and work with numerous members who were part of committees, interest groups, task forces and advisory boards. I've also worked very closely with the *PDA Letter* Editorial Committee. This group of men and women works tirelessly to help us vet articles of interest and relevance to the membership.

While my time with the Letter has been very fun and educational, I recently decided to move to the Marketing department at PDA to broaden my skill set.

I would like to thank everyone who has helped me and encouraged me in the last few years—I would list names, but I fear the list is too lengthy to include in this space. But, please know that I really appreciate all the help, kind words and constructive feedback that has been directed my way and hope that it continues in my new role.

Please know that only my title will change—I will still be only a phone call or email away. ☺

**Emily Hough**

# PDA Letter

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*Subscriptions are not available.*

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The Parenteral Drug Association presents the...

# The Universe of Pre-filled Syringes and Injection Devices

*Integrating the Unmet Market Needs:  
Bringing it All Together for Tomorrow's Success*

**October 15-17, 2012**

Red Rock Resort and Spa | Las Vegas, Nevada

Register before  
**August 3rd**  
and Save up  
to \$400

Our industry is entering a challenging phase for the next decade. Costs and regulatory demands exert downward pressure on our ability to introduce devices that are safe and effective. To address challenges we are facing, it is crucial to continue on the path of innovation as we have been on for many years.

The *Universe of Pre-filled Syringes & Injection Devices* will bring together industry and regulatory experts to share their experiences, new developments, regulatory considerations, challenges and industry trends in this exciting area.

**Highlights of this meeting include:**

- Opening Keynote Address by **W. Bradley Fain, PhD**, Georgia Tech Research Institute (Sponsored by West Pharmaceuticals) on **Addressing the Needs of the Patient**
- Numerous plenary, concurrent, interest group and breakfast sessions
- Closing plenary session on **Global Market Assessments and Panel Discussion** featuring:
  - **Brigitte Reutter-Haerle**, Vetter Pharma International
  - **Ian Thompson**, Ypsomed
  - **Sheldon Moberg**, Amgen, Inc.
- **Kingman Ng, PhD**, Novartis Vaccines & Diagnostics
- **Thomas Schoenknecht, PhD**, SCHOTT
- **Klaus Schreiber**, Robert Bosch
- **FDA Representatives Invited**

Immediately following the conference, PDA's Training and Research Institute (PDA TRI) will be hosting three courses onsite October 18-19.



Visit **[www.pda.org/prefilled2012](http://www.pda.org/prefilled2012)**  
for more information and to register.

**Exhibition: October 15-16 | Courses: October 18-19**



The Parenteral Drug Association presents the...

Register for the  
2012 PDA/FDA Joint  
Regulatory Conference  
Before July 16, 2012 –  
the Largest Registration  
Discount!

# 2012 PDA/FDA Joint Regulatory Conference

*Compliance through Quality Systems: Implementing  
& Advancing a Sustainable Global Quality Culture*

**September 10-12, 2012**

Baltimore Marriott Waterfront Hotel | Baltimore, Maryland



The 2012 Planning Committee would like to welcome you to the 2012 PDA/FDA Joint Regulatory Conference. New and exciting topics make this meeting one of the best in the industry and we have an impressive line-up to share.

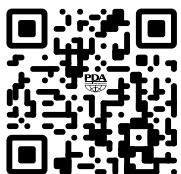
In joint collaboration with the FDA, the committee has designed this program to reflect how a robust quality system can enhance business goals and objectives. The conference will jump start with a presentation from the **Office of the Commissioner** and **Steven Solomon**, Associate Director for Global Operations and Policy with FDA's Office of Regulatory Affairs who will speak on *The Global Regulatory Operations as it Relates to the Supply Chain*. The conference will conclude with a panel of FDA experts providing insight into upcoming Center Initiatives.

In between the opening and the closing sessions, the conference will offer three great plenary sessions:

- The first plenary is titled **Changing the Quality Culture**. Our confirmed speakers are ready to talk about the importance of quality at all levels of an organization and how it is defined by patient needs and the global regulatory environment
- The second plenary will focus on Contract Manufacturing Organizations (CMO). Contract Manufacturing is an emerging discipline in the pharmaceutical industry and this session is designed to offer perspectives on CMOs from various points of view: the contract giver, the contract provider and an independent third party
- The last plenary session, on Wednesday morning, will feature an update from the Compliance Directors of each Center of the FDA – a can't miss session!

Immediately following the conference:

- On September 12-13, the *Responsibilities of Executive Management (Operations and Quality) – Implementing the Principles of ICH Q10: 2012 PDA/FDA Pharmaceutical Quality Systems Workshop* will be hosted
- PDA's Training and Research Institute (PDA TRI) will be hosting seven stand-alone training courses on-site on September 13-14.



Visit [www.pda.org/pdafda2012](http://www.pda.org/pdafda2012) for more information.

**Exhibition: September 10-11**  
**Post-Conference Workshop: September 12-13**  
**Courses: September 13-14**