

People

Science

Regulation

# PDA Letter

Volume XLVIII • Issue #2

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

February 2012



## The USP Issue

**10** Nominate a BoD  
Candidate

**40** Challenges of EU  
GMPs

**56** TRI Aseptic Course  
Goes the Distance

Register  
by March 6th  
and Save Up to \$200!

The Parenteral Drug Association presents...



# 2012 PDA ANNUAL MEETING

*Manufacturing Innovation: Achieving Excellence in Sterile  
and Emerging Biopharmaceutical Technology*

**April 16-18, 2012**

JW MARRIOTT DESERT RIDGE RESORT • PHOENIX, ARIZONA

We are facing extremely tough conditions and challenges within our industry, not only due to our economic pressures and mergers/acquisitions, but a globalization factor that is expanding at a rate that was hard to imagine decades earlier.

For our current processes, in order to remain competitive, we need to implement a continuous improvement concept. This needs to go well beyond quality implications and include all aspects of our operations, business and scientific decision making.

The *PDA Annual Meeting* will provide discussions and ideas on how to implement these concepts and verify their effectiveness with top industry personnel and scientists in order to shape the future of our business.

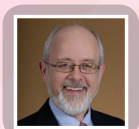
## Just Announced:

PDA Chair, **Anders Vinther**, PhD, Vice President, Quality Biologics, *Genentech*, to speak on a novel bacterial contaminant in CHO cell culture processes that has implications for the biotech industry at large.

## Leading the discussion, keynote speakers:



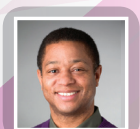
**David Shanahan**,  
President, *Mary Crowley  
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President, CEO and  
Founder, *Gradalis*



**David Urdal**, Chief  
Scientific Officer,  
*Dendreon*



**Andy Hopkins**, Sterile  
Products Inspector,  
*MHRA*



**Ted Love**, MD, Executive  
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**Matt Croughan**, Professor,  
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of Applied Life Sciences*



**Emily Shacter**, PhD,  
Chief, Laboratory of  
Biochemistry, *CDER, FDA*

- **John E. Butler**, PhD, Global Project Leader, *Bayer Innovation*
- **Tom Finn**, CMC Reviewer, *CBER, FDA*
- **Stephan Krause**, PhD, Principal Scientist/Associate Director, *Medimmune*
- **Stephen Brown**, PhD, Chief Technology Officer, *Vivalis*
- **Barbara Potts**, PhD, Principal, *Potts and Nelson*
- **And many more -**  
[www.pdaannualmeeting.org/speakerbios](http://www.pdaannualmeeting.org/speakerbios)
- **Michael Wiebe**, PhD, President, *Quantum Consulting, LLC*



[www.pda.org/annual2012](http://www.pda.org/annual2012)

EXHIBITION: April 16-17 | CAREER FAIR: April 16-17  
POST-CONFERENCE WORKSHOP: April 18-19 | COURSES: April 19-20



*The Parenteral Drug Association presents...*

# 2012 PDA Europe Workshop

# Quality by Design

## The Role of Analytical Science in Implementing QbD

*– Technical and Regulatory Aspects*

### See the Highlights:

- Setting the Scene – Goals & Introduction
- Regulatory Positions (EMA/FDA) – two presentations
  - Differences between agencies, challenges, common views, etc.
  - EMA and FDA representatives should work together on presentations in order to make them complementary not repetitive
- Pharmacopoeial Positions (EDQM, USP)
  - EDQM and USP representatives should work together on presentations in order to make them complementary not repetitive
- Industry Position



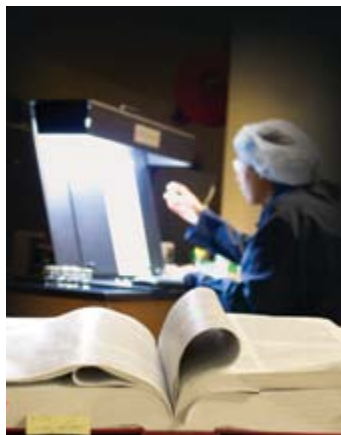
**6-7 March 2012**

**Hilton Hotel Liverpool  
United Kingdom**

**WORKSHOP 6-7 March | EXHIBITION 6-7 March**

<https://europe.pda.org/QbD2012>

## Cover



Cover Art Illustrated by Katja Yount

### 26 Lack of Compendia Harmony for Visible Particles Causing Confusion

The major compendia have harmonized the testing methodology and acceptance criteria for subvisible particles; however, the absence of a harmonized guidance for visible particles has led to confusion in the global industry.

### 30 The Importance of Commenting on Public Standards

To ensure items being introduced by USP are appropriate, industry must take the time to participate in the USP commenting process.

### 34 USP Updates Given at PDA's 2011 Micro. Conference

During last year's PDA Micro meeting, the USP stated that they were going to update/revise the existing USP 1223 informational chapter and provide additional guidance with respect to the use of alternative micro methods.

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- 56 TRI Takes Aseptic Processing Course to the Next Level

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It is anticipated that further discussions among the constituencies, with focus on control strategy, should lead to the final version of ICH Q 11(Step 4) before the end of the 2nd quarter in 2012.



### 38 Audit Program Part of FDA Pathway for Global Product Safety

The Center for Devices and Radiological Health (CDRH) and the Center for Biologics Evaluation and Research (CBER) are testing a Pilot Multi-Purpose Audit Program in 2012 and 2013 that will allow medical device companies under their jurisdiction to voluntarily submit certain audits and receive Agency inspection relief for one year.

#### 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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PDA President Richard Johnson

## PDA to Expand Global Reach in 2012

I am pleased to report that 2011 was a very successful year for your Association. With the help of countless volunteers and our hardworking staff, PDA delivered outstanding conferences and training, enhanced member benefits, and continued development of industry-leading technical reports and regulatory comments. All of this activity was guided by your input and the PDA 2010-2015 Strategic Plan (published in the January 2011 *PDA Letter*). We will continue executing against this strategic plan in 2012.

I would like to highlight a few elements of the plan for this year:

1. Focus resources to continue delivering outstanding technical reports, including:

- New Aseptic Processing Survey 2012
- Risk Management for Temperature-Controlled Distribution
- PDA *Technical Report No. 30, Parametric Release of Pharmaceuticals Terminally Sterilized by Moist Heat*

- TBA—Detection and Mitigation of 2,4,6-Tribromoanisole and 2,4,6-Trichloroanisole Taints and Odors in the Pharmaceutical and Consumer Healthcare Industries
- PDA *Technical Report No. 13: Fundamentals of a Microbiological Environmental Monitoring Program*
- PDA *Technical Report No. 3: Validation of Dry Heat Processes Used for Sterilization and Depyrogenation*
- The first of our Paradigm Change in Manufacturing Operations (PCMO<sup>SM</sup>) technical guidances:
  - Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations (R01)
  - Application of Phase-Appropriate CGMP and Quality Systems to the Development of Protein Bulk Drug Substance (or API) (L05)
  - PDA *Technical Report No. 29 (Revision)—Points to Consider for Cleaning Validation (P02)*
  - Process Validation and Verification: A Lifecycle Approach (P01)
- And several others

2. Continue Signature meetings, such as:

- 66<sup>th</sup> PDA Annual Meeting in Phoenix, Ariz.
- 21<sup>st</sup> Annual PDA/FDA Joint Regulatory Conference in Baltimore, Md.
- 9<sup>th</sup> Pre-filled Syringe Conference in Las Vegas, Nev.
- Microbiology Conferences in both the United States and in Europe
- Parenterals Meeting in Berlin, Germany
- PDA/PIC/S Workshop in Geneva, Switzerland

3. Explore newer topics to help our community meet new challenges, such as:

- 2<sup>nd</sup> Glass Quality Conference
- Single Use System Workshop
- ATMP Focused meetings in Europe and in the United States

4. Expand our training activities in the United States and around the world, with more than 50 courses, including:

- Enhancements to our premier Aseptic Processing Courses
- Reprocessing of Biopharmaceuticals
- Recommended Practices for Manual Aseptic Processes
- Implementation of Quality Risk Management for Commercial Pharmaceutical and Biotechnology Manufacturing Operations
- Identification and Classification of Nonconformities in Molded and Tubular Glass Containers for Pharmaceutical Manufacturing
- Preparation of Virus Spikes Used for Virus Clearance Studies based on PDA's TR-47
- Virus Filtration
- Steam Sterilizers—Getting it Right from the Beginning
- Validation of Dry Heat Sterilization Processes based on PDA's TR-3
- Fundamentals of an Environmental Monitoring Program based on PDA's TR-13
- Good Distribution Practices for the Pharmaceutical Supply Chain
- Alternative Methods for Mycoplasma Testing
- Biofilms
- Validation of Biotechnology-Related Cleaning Processes
- And many others

*continued at bottom of page 8*

2012 PDA Europe  
Pharmaceutical Freeze Drying Technology  
18-19 September 2012 | Ljubljana | Slovenia



## Call for Papers and Posters

We would like to invite you to submit a paper or poster abstract for presentation at the **2012 PDA Europe Conference on Pharmaceutical Freeze Drying Technology** in Ljubljana, Slovenia on 18-19 September 2012. Paper abstracts and posters must be non-commercial in nature, describing new developments or work that significantly contributes to the body of knowledge relating to Pharmaceutical Freeze Drying.

Topic areas of interest include but are not limited to the following:

Papers on manufacturing, quality, non-clinical and clinical challenges in each topic area as well as case studies are particularly desired.

### 1. Technologies Topics

- Machines and equipment
- IPCs, test methods
- Container, components, devices
- Handling of freeze dried products

### 2. Device and Application Systems

### 3. Development

- Formulation issues
- Freeze dry cycle development
- Freeze drying of biotech, potent drugs
- Controlled nucleation
- Recent development, especially for biotech products

### 4. Manufacturing

- Qualification, validation
- VHP Sterilization
- Technology transfer
- New manufacturing concepts
- Case studies
- CMO - Technology Transfer
- Maintenance Issues: Leak Testing
- Cleaning Validation

### 5. Quality & Compliance

- QbD, DoE
- PAT
- Media fill strategies
- Regulatory issues, process optimization

Commercial abstracts for papers or posters will only be reviewed for eventual poster presentations. All submitted abstracts will be reviewed by the Program Committee for acceptance. Upon review by the Program Committee, PDA Europe will advise each submitter of the status of the paper for presentation in writing. PDA Europe will provide one complimentary registration per podium presentation. Additional presenters and poster presenters are required to pay appropriate conference registration fees.

### Submissions received must include the following information:

- |   |  |
|---|--|
| - Title                                     | - Phone number                                   |
| - Presenter                                 | - Fax number                                     |
| - Presenter's biography (approx. 100 words) | - E-mail address of the presenter                |
| - Additional authors                        | - Key objectives of your topic                   |
| - Full mailing address                      | - 2-3 paragraph abstract, summarizing your topic |

### All submitted abstracts will be reviewed by the Program Committee for acceptance.

Upon review by the Program Committee, the PDA will advise each submitter of the status of the paper for presentation in writing.

Please send your abstract and required information to Ailyn Kandora (PDA Europe) at [kandora@pda.org](mailto:kandora@pda.org).

**If you have any questions, please do not hesitate to contact us.**

### Attention Exhibitors

PDA is seeking vendors who provide excellent products/services in support of this conference. Space is limited and is on a first-come, first-serve basis. To reserve your space, please contact Creixell Espilla-Gilart at [espilla@pda.org](mailto:espilla@pda.org) or via telephone +49 33056 23 77 14.

**Deadlines** Abstracts of papers for presentation: 29 February 2012  
Poster abstracts: 31 August 2012



PDA Chair Anders Vinther

## 2012 Looks Bright at PDA

Welcome to 2012. At PDA, we are in the process of finalizing goals for this year. I am really excited about all the great plans we have in place that focus on our mission of *Connecting People, Science and Regulation*<sup>SM</sup>.

2011 was a fabulous year in which PDA published a high number of new technical reports, sponsored great conferences that covered both our signature meetings and new emerging topics, offered state-of-the-art training courses, and developed many opportunities for interaction with our members. 2011 was a year where we delivered on a lot of our strategic plan elements, including stabilizing our overall organization and financial capabilities. This will allow us to continue a strong growth in PDA over the next years.

I want to thank PDA President, **Richard Johnson** and the entire staff for all their hard work and dedication in 2011. I would also like to thank **Maik Jornitz** for his vision and leadership

as Chairman of the Board in 2010-2011 and the Board of Directors for leading the Association and setting its direction. A special thanks goes to outgoing PDA Board members **Amy Scott-Billman** and **John Shabushnig** for their contributions through the years. Of course, much of what we do at PDA would not be possible without our volunteers; so I want to thank everyone who has attended meetings, spoke at conferences, wrote technical reports, worked on advisory boards, interest groups, task forces, etc., and in so many other ways contributed in making PDA the most exciting Association in our industry. This work benefits all PDA members, the industry, health authorities and, ultimately, the patients that benefit from the medicines that are developed and produced.

At this time, I would also like to welcome new Board members **Ursula Busse** and **John Finkbohner** and all of the volunteers who have started to take a more active role at PDA.

In 2012, we will continue with our many signature conferences and add new “hot topic” conferences. I am very excited to inform you that we are offering a conference in conjunction with PIC/S later this year. We will also offer a number of state-of-the-art training courses, with an increasingly unique curriculum; publish a large number of technical reports; expand our activities globally; increase chapter and headquarter interactions; and, further integrate our various activities to ensure we are meeting the mission and vision of PDA.

I am really excited to serve as PDA's Chairman of the Board and spend the next two years working with the staff, the Board, the health authorities, vendors and all of our members. I encourage you to stay engaged or start getting engaged in volunteer work in 2012.

I look forward to any feedback and great ideas to keep PDA a leading global provider of science, technology and regulatory information. Happy New Year to all of you. 🍷

### *President's Message continued from page 6*

5. Expand our global reach and work effectively with global regulatory authorities to enhance pharmaceutical science and advance health of patients, by:
  - Providing science and technology based input on regulations and guidelines related to PDA strategic areas, utilizing PDA's volunteer and membership base
  - Bringing sound scientific and technical information to the regulatory process, maintaining valuable and effective relationships with global regulators, and educating members on current expectations
  - Engaging with regulatory agencies for the development and adoption of PDA technical reports.
6. Manage your Association's resources by establishing a five-year rolling financial and marketing plan to sustain and balance major activities. Leverage staff and volunteer resources by aligning programs, technical reports and other PDA activities

2012 promises to be another busy year of *Connecting People, Science and Regulation*<sup>SM</sup>, but none of it will happen without the support and volunteer efforts that make these activities so valuable. If you would like to volunteer in a task force, interest group or a committee, visit [www.pda.org/volunteer](http://www.pda.org/volunteer).

Please email us or stop by and let us know how we are doing. Remember, this is *your* Association. Our doors are always open, and we would love to hear from you. 🍷



Save \$150 when you register for this workshop and the 2012 PDA Annual Meeting!



**New Speaker Just Announced:**  
Ingrid Markovic, PhD, Expert Review Scientist, CDER, FDA (via teleconference) to discuss Extractables & Leachables.

*The Parenteral Drug Association presents the...*

# PDA Single Use Systems Workshop

*Knowledge Enables Implementation - A Consensus Approach*

**April 18-19, 2012**

JW Marriott Desert Ridge Resort | Phoenix, Arizona



The PDA Single Use Systems Task Force is completing a Technical Report on the design and implementation of Single Use Systems (SUS). The *PDA Single Use Systems Workshop* will showcase and encourage the philosophies championed in the technical report and will offer a different approach, presenting science and risk-based concepts which are flexible and can be applied in many different situations and organizations.

Single-use systems offer unique challenges for both Sr. Management and the shop floor technician. This workshop will help all organizational levels understand the right questions to ask to overcome SUS challenges and ensure the right decisions are made.

**Closing Plenary Session Speaker:**  
**Tor Graberg**, Chair of PIC/s and Head of Inspection, *Medical Products Agency* to speak on **Regulatory Issues Related to Single Use Systems!**

Plenary sessions at this year's meeting include:

- Technical Report (TR) Overview
- Section 6 Part 1 - Qualification
- Section 4 - Technology
- Section 7 - Implementation
- Section 5 - Business Drivers
- Regulatory Issues Related to Single Use Systems



Visit [www.pda.org/singleuse2012](http://www.pda.org/singleuse2012) for more information.

## New Participation Opportunity: Nominate a BoD Candidate

PDA's Board of Directors has adopted a new open nomination process for Board of Director/Executive Committee elections, starting with the 2012 BoD election later this year.

Previously, the nominating committee (comprised of the members of the Executive Committee) nominated PDA members for the elections. Seeking to expand individual member contribution to the Association and empower members, the Board is now opening up the nominating process.

Open nominations will also help ensure that the Board and Executive Committee is truly representative of PDA's increasingly diverse and international membership. This point was stressed by Nominating Committee Chair (and Immediate Past Chair of PDA) **Maik Jornitz**.

PDA members are encouraged to nominate their colleagues within the Association for the Board elections. Only members in good standing can nominate (that is, their membership is current). The PDA Nominating Committee will consider all nominations, but certain minimum standards will apply for nominees to appear on the final ballot, including: **1)** status of membership; **2)** level of activity within PDA; **3)** volunteer history; and **4)** length of membership.

To nominate, send an email to: [nominate@pda.org](mailto:nominate@pda.org)

Nominations for the 2012 BoD elections will be accepted through May 31<sup>st</sup> 2012. 🗓️

Nominations for the 2012 BoD elections will be accepted through May 31<sup>st</sup> 2012.

To nominate, send an email to: [nominate@pda.org](mailto:nominate@pda.org)

*The Parenteral Drug Association presents...*

## PDA Chemistry Manufacturing & Controls (CMC) Workshop

*Implementing Quality by Design Principles in Vaccine Development: A-Vax Case Study*

**May 14, 2012** | Hyatt Regency Bethesda | Bethesda, Maryland



Immediately before the *PDA/FDA Virus and TSE Safety Conference* PDA will host a pre-conference workshop to facilitate discussion of concepts captured in the A-Vax case study (*public availability scheduled for early 2012*) within the vaccine industry and regulatory health authorities.

The case study, conducted by five vaccine manufacturers (GSK, MedImmune, Merck, Pfizer, and Sanofi Pasteur), illustrates how Quality by Design (QbD) can be applied to vaccine development. The study provides opportunities to discuss novel ideas that might help improve the overall process for developing and manufacturing vaccines. The focus of presentations will be the exploration of tools and frameworks to enable ICH Q8, Q9, and Q11 implementation strategies in vaccine development.



Register for both the CMC Workshop and the *PDA/FDA Virus and TSE Safety Conference* and save \$150 on your registration!

Visit [www.pda.org/cmc2012](http://www.pda.org/cmc2012) for more information and to register.



## On the forefront - Mab developments in Europe

# Emerging Trends for Therapeutic Monoclonal Antibodies and Related Products

*Considerations for Quality Attributes throughout the Development Continuum and Registration*

### Session 1: Development for biological IMPs

- What is the appropriate level of quality detail needed for biological IMP dossiers?
- Are acceptance criteria and details for in-process control required for early stages?
- How can an IMP dossier be built based on QbD principles?
- Degree of characterization of IMPs in early drug development?
- To what extent can shelf life dating be based on supportive data?

### Session 2: Molecular Approaches to Optimization

- Can certain routine testing be eliminated based on molecule optimization strategies?
- Is it possible to optimize a monoclonal antibody drug substance to the point of having no critical quality attributes related to its molecular properties?
- How should molecule design features be communicated in the market application?
- What are the expectations for in vitro bioassays when more than one cell-killing target is involved?

### Session 3: Late-stage Process Development

- How is process parameter criticality assessed and confirmed?
- How much can we rely on prior knowledge to support process characterization?
- What are the most frequent questions health authorities ask regarding the control strategy. What are the major missing elements in the dossier?
- What information on the control strategy needs to be provided during an inspection? How far back into process development does the inspector look?

### Session 4: Development, Regulatory and Future

- What are Molecular particulars and how are they characterized?
- How do we characterize the starting material used to manufacture the Antibody Drug Conjugate (ADC)?
- What are the test methods used to investigate and quality control ADC and multifunctional antibodies?
- How do we characterize the linker-quality, its mechanism in-vivo and the relevant data requirements?
- What are the unique dossier structure and data requirements for ADC and multifunctional antibodies?

### Workshop Co-Chairs:

Steffen Gross, *Paul-Ehrlich-Institut, Germany*

Michael DeFelippis, *Eli Lilly*

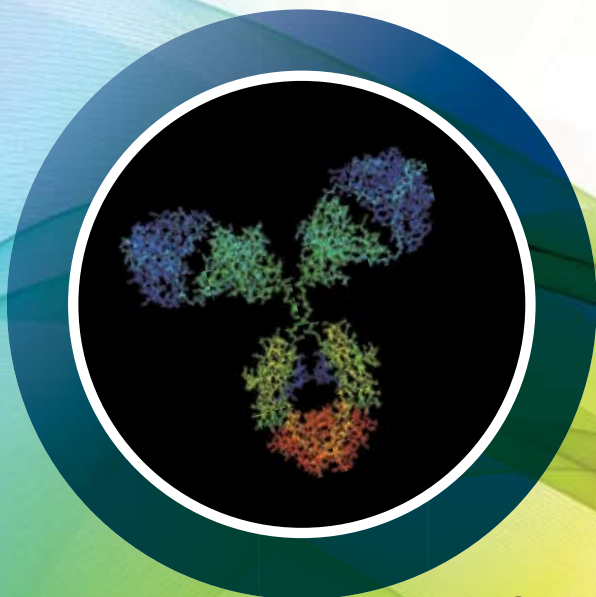
**12-13 June 2012**

Hotel NH Danube City  
Vienna | Austria

Register by  
20 April 2012  
and SAVE!

**WORKSHOP 12-13 June | EXHIBITION 12-13 June**

<https://europe.pda.org/Monoclonal2012>





## Volunteer

### Thomas Pamukcoglu, Director of Quality, SAFC



**PDA Join Date:** 1994

**Interesting fact about yourself:** I'm really not that interesting, although my passion is in parenting three young boys.

**Why did you join PDA?** I originally joined to learn more about technical issues and to build my general level of understanding of the complex parenteral manufacturing process.

**Of your PDA volunteer experiences, which have you enjoyed the most?** I've gotten the most satisfaction from forming PDA's new Missouri Valley Chapter and bringing all that PDA has to offer closer to home.

**How has volunteering in PDA benefited you professionally?** I've made a lot of great contacts who I have turned to periodically to bounce ideas off and solicit alternative perspectives. The professional networking available through PDA is critical when building a broad-based experience portfolio to leverage in our industry.

**Which PDA conference/training course is your favorite?** The FDA/PDA Conference is my favorite. The dynamic that exists between regulator and industry representative is excellent!

**What would you say to somebody considering PDA membership?** Join! You really can't afford not to. 🌐

This  
Conference  
is Back by  
Popular  
Demand!



*The Parenteral Drug Association presents the...*

## PDA/FDA Glass Quality Conference

June 4-5, 2012 | Renaissance Downtown Hotel | Washington, D.C.

In the recent past there have been several recalls and increasing concerns about pharmaceutical glass packaging, both with regard to defects and/or incompatibilities with finished product over the shelf life.

As a follow up to the sold out 2011 PDA/FDA Glass Quality Conference, speakers will present answers to some of the more complex questions posed at last year's meeting.

Pharmaceutical manufacturers, regulators, and glass suppliers all share a common goal of assuring the highest quality products (including packaging) for patients. This meeting will discuss these issues; best practice to preventing and/or detecting at risk glass packaging; and review current expectations to ensure that recalls are avoided and container closure integrity is assured.

PDA's Training and Research Institute will be hosting two training courses following 2012 PDA/FDA Glass Quality Conference.

[www.pda.org/glass2012](http://www.pda.org/glass2012)

Conference: June 4-5 | Exhibition: June 4-5 | Courses: June 6-7



Register Before  
**March 23rd** –  
The Largest  
Registration Savings  
Deadline!



## 2010 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 2010 award winners were announced at the *2011 Annual Meeting* in April and they have been highlighted in each *PDA Letter* since. This month we recognize the recipients of the Gordon Personeus Award, the Frederick Carleton Award, and the President's Award.

### Gordon Personeus Award

The Gordon Personeus Award is intended to honor a PDA member for his or her long-term acts or contributions that are of noteworthy or special importance to PDA.



This year's recipient is **Ed Trappler**, President, Lyophilization Technology. Ed joined PDA in 1984 and has been actively involved in the Association. Ed currently teaches at the PDA-TRI, heads the Lyophilization Interest Group and chaired the inaugural Pharmaceutical Freeze Drying Workshop in San Diego in November 2010.

### Frederick J. Carleton Award

The Frederick J. Carleton Award is presented to a past or present Board member whose services on the Board are determined by his/her peers as worthy of such recognition.



This year's recipient is **Bob Dana**, Senior Vice President, Regulatory Affairs and Training and Research Institute, PDA, who was on PDA's Board of Directors from 2001-2004. Bob is currently responsible for the planning, operation and administration of PDA's educational programs as well as the identification and pursuit of global regulatory affairs opportunities for PDA.

### PDA President Award

PDA's President Award recognizes PDA staff members, other than Senior Staff, whose exemplary performance has contributed to PDA's success during the previous year. This year's recipients are **Leon Lewis, Sr.** Manager of Programs and Meetings, and **Dirk Stelling**, Manager Finance and Controlling.



#### Leon Lewis

Combining his previous experiences in program development, project management and meeting coordination, Leon made numerous major strides at PDA. Over the course of his career at PDA, Leon has maintained an excellent record of being prepared to handle increasing responsibilities.



#### Dirk Stelling

Responsible for accounting, controlling and several other administrative duties at PDA's Berlin office, Dirk is additionally accountable for the development of PDA Europe's website.

# PDA/FDA Adventitious Agents and Novel Cell Substrates Conference

November  
2-4, 2011

## Opening Keynote/Adventitious Agent Testing and Emerging Methods Part I



(l-r) Houman Dehghani, Amgen; Kathryn King, U.S. FDA; Michael Wiebe, Quantum Consulting; Arifa Khan, U.S. FDA; Johannes Löwer, International Alliance for Biological Standardization

## Technologies and Application to Evaluation of Biological Materials Part I



(l-r) James Gilbert, Biogen Idec; David Onions, BioReliance

## Day 2 Keynote Presentation



(l-r) Marcie McClure, Montana State University; Anthony Lubiniecki, Johnson & Johnson

## Insect, Avian and Mammalian Cell Substrates Part I



(l-r) Pawan Jain, U.S. FDA; Jonathan Stoye, MRC National Institute for Medical Research; Celine Breda, Vivalis

## Insect, Avian and Mammalian Cell Substrates Part II



(l-r) George Rohmann, Oregon State University; Jane Halpern, Novavax

### Expert Panel Discussion



(back l-r) Amy Rosenberg, U.S. FDA; David Onions, BioReliance; David Munroe, SAIC; Johannes Löwer, International Alliance for Biological Standardization; Phil Krause, U.S. FDA; Anthony Lubiniecki, Johnson & Johnson; Kathryn King, U.S. FDA; Arifa Khan, U.S. FDA  
 (front l-r) Vidadi Yusibov, USA Center for Molecular Biotechnology; Michael Wiebe, Quantum Consulting; Rosemary Versteegen, International Serum Industry Association; Tara Tagmyer, Merck; Tom Slezak, Lawrence Livermore National Laboratories; Ranga Sampath, Abbott-Ibis Biosciences; George Rohmann, Oregon State University; Mark Plavsic, Genzyme; Marcie McClure, Montana State University; Qi Chen, Genentech

### Poster Exhibit



# Please Welcome the Following Industry

- Frank Amato**, Hospira
- Philip Anderson**, Abbott Laboratories
- Yosita Anggraeni**, National Agency of Drug & Food Control
- Firoz Antia**, Palatin Technologies
- Adam Antoine**, Eli Lilly
- Angela Armani**, Novartis
- Tanya Arp-Nielsen**, Leo-Pharma
- Ernst Aschwanden**, Ypsomed
- Christophe Aubert**, Aubert Biomedical Consulting
- Charles Baechler**, Kloeckner Pentaplast Schweiz
- Nicole Barber**, Genentech
- James Barry**, Pall
- Rush Bartlett**, LyoGO
- Iran Bateman**, The Tech Group
- Jean-Francois Bauer**, Mikron
- Ulrike Bauer**, Ypsomed
- Stefan Bauer**, Schott
- Michael Becher**, R+E Automationstechnik
- Tony Bedford**, Cambridge Consultants
- Mohamed Belkacem**, GlaxoSmithKline
- Henrik Bengtsson**, Novo Nordisk
- Charles Bennett**, Pfizer
- Corrie Bennison**, Battelle Memorial Institute
- Irmhild Bernhard**, Boehringer Ingelheim Pharma
- Stefan Bernsau**, Harro Hoeffliger
- Sunil Bhamare**, Methapharm
- Torsten Bisschop**, Merck Millipore
- Carla Blackadder**, Genentech
- Bettine Boltres**, Schott
- Nicolas Bourges**, Sanofi Chimie
- Jean-Francois Brac**, Becton Dickinson
- Christa Brandt**, Hoffmann Neopac
- Dominik Braun**, Friedrich Sanner
- Ros Brehm**, Health Protection Agency
- Stuart Breslin**, Eli Lilly
- Brant Bulgarelli**, Laureate Biopharma
- Kirsten Bundgaard-Nielsen**, Novo Nordisk
- Bart Burgess**, West Pharmaceutical Services
- Patrick Campbell**, The Technology Partnership
- Ian Campbell**, Bespak
- Francois Capitaine**, Technoflex
- Charles Carey**, Pfizer
- Pierre Carlotti**, Aptar Pharma
- Jose Castro-Pagan**, Ben Venue Laboratories
- Eric Chanie**, Merck Serono
- Shou-Bai Chao**, MedImmune
- Paul Chen**, Biogen Idec
- Dean Cirotta**, EAS Consulting Group
- Marie-Noel Cochet**, Sanofi Chemistry
- Laura Corral-Cardenas**, Boehringer Ingelheim
- Michele Coulaloglou**, Lachman Consultants
- Avery Coyle**, Merck Millipore
- Desireemae Crisolo**, Genentech
- Raymond Cuany**, Coplax
- Mikkel Dührkop**, Nordic
- Amanda Davis**, Becton Dickinson
- Lawrence Davis**, Baxter Healthcare
- Ian Davison**, Health Protection Agency
- Michael de Goeje**, IDA foundation
- Danielle Debonnaire**, Merck Chimie
- Eberhard Dengler**, Schoettli
- Kimberly Dezura**, Merck
- Ann Dodds-Frerichs**, Biogen Idec
- Barbara Domanska**, UCB
- Angie Drakulich**, Advanstar Communications
- Ralph Duerr**, Schott
- Sabine Dufner**, Novartis
- Luis Alejandro Eslava**, Catalent Pharma Solutions
- Chris Evans**, West Pharmaceutical Services
- Michael Exner**, CSL Behring
- Fabio Fais**, Crucell
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- Christine Farrance**, Accugenix
- Sherry Fedorko**, Unilife Medical Solutions
- Martin Fies**, Cilag
- Gaetano Fiorentino**, Italfarmaco
- Dena Flamm**, Bosch
- Thomas Fontaine**, Covidien
- Nicole Fontourcy**, Pall
- Adam Fowler**, Santarus
- Smitha Francis**, Baxter Healthcare
- Betsy Fritschel**, Johnson & Johnson
- Ruth Frommherz**, Sandoz
- Elisabetta Fustella**, IBSA
- Frederic Gabriel**, Haselmeier
- Maxime Gaillot**, F. Hoffmann - La Roche
- Jeffrey Gaspar**, Weiler Engineering
- Martin Gastens**, Abbott
- Andrea Gatti**, Italfarmaco
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- Jeff Henderson**, Vetter Pharma
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- Claudia Holarek**, AGES PharmMed
- Jakob Hoppe**, Novo Nordisk



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**Stephan Horst**, Boehringer Ingelheim

**Gabriela Huber**, Novartis Pharma

**Dirk Hueber**, F. Hoffmann - La Roche

**Gildas Huet**, Laboratoire Aguettant

**Carl Humbles**, Health Protection Agency

**Ronald Imhoff**, Janssen Biologics

**Chiaki Inaba**, Kyowa Hakko Kirin

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**Markus Keller**, F. Hoffmann - La Roche

**Serge Kemps**, Datwyler Pharma Packaging

**Inbal Keret**, Av Tech Improvements

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**Alexandra Kirchner**, Cilag

**Murakami Koichi**, Becton Dickinson

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**Alexa Konstantinos**, Battelle Memorial Institute

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**Juergen Kossinna**, Novartis Pharma

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**Juan López**, S.A.I.C.

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**Carole Langlois**, Sartorius Stedim Biotech

**Angelique Lanier**, Vivalis

**Paul Le Brun**, Central Hospital Pharmacy

**Stephanie Lemoult**, Nycomed

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**David Saldana**, Merck

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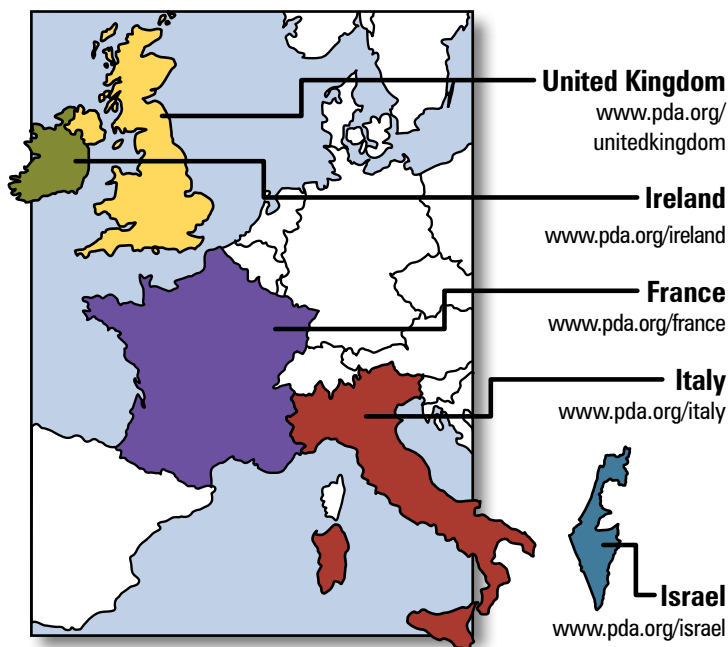
**Ferdinand Westhoff**, Bayer

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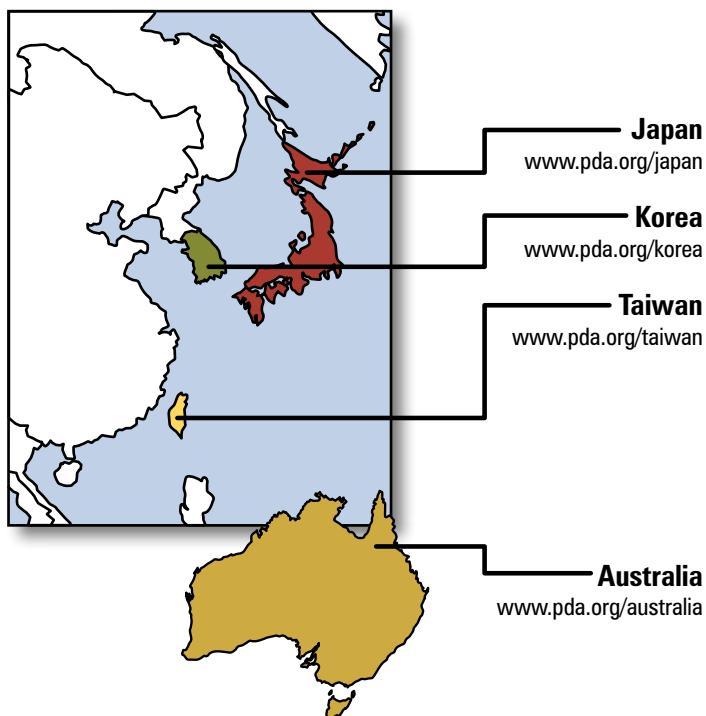
# PDA Chapters

The following are PDA's Chapters, organized by the regions of the world in which they are located. For more information on the Chapters, including their leaders and upcoming events, go to their websites which are listed below.

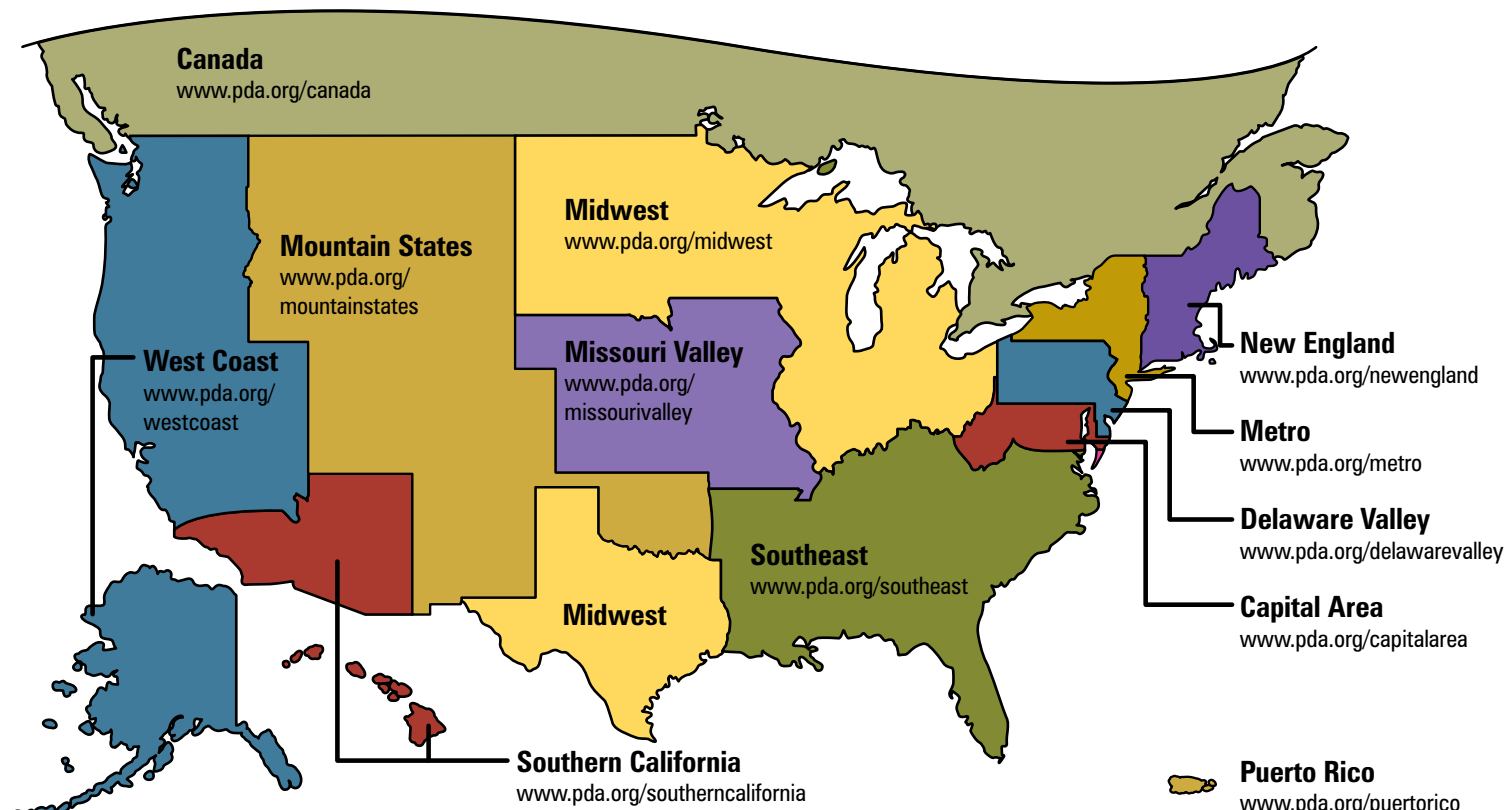
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## Change Your Management Mindset

Jean Kelley

Whether you're in a new leadership position due to a promotion or being newly hired, you may have to learn to think in a new way. To be successful, you need to shift your mindset so you can focus on the new requirements and outcomes you're being held accountable for. In other words, you need to let go of many tasks that have made you successful thus far and focus on what your team can deliver. If you don't, you won't make the leap into your new position successfully.

Unfortunately, many people don't transition into leadership roles well. Why? Sometimes they simply don't know what's expected of them. Communication is poor in many companies, and few people receive detailed instructions on how to lead and what competencies it takes to lead. So while someone may get a new title, they have no idea what to actually do in this new role. As such, they face ambiguity every day. Other times people are moving from a technical role into a leadership role, and they don't want to let go of their spreadsheets, maps, or other technical responsibilities. They enjoy the details of the work and aren't ready to delegate those details to others. They claim that it will take them longer to teach someone than to actually do the work themselves.

However, when you're living with daily ambiguity or not delegating the details, you quickly become overworked and overstressed. That's why you need to shift your mindset, let go of who you were or what you did, and make the leap into your new leadership role. The following tips will help you do that successfully.

### Learn the Differences Between Supervisory Management and Leadership

The management job involves planning, organizing, directing, and controlling, and a good manager knows how to do all of that. Leadership takes all that plus vision, passion, and influence. However, many managers fail when they move into a leadership role because they don't know how to shift those responsibilities into a leadership position. They can't totally let go of those detail-oriented things because they're still accountable for them, just in a different way.

Realize that some people are great leaders while they are still supervisors and managers, while others are chosen for leadership because of their superb technical skills and critical thinking abil-

ity. If you are the latter, the climb for you is steeper.

So the first step is to find out what you're being paid for and what, specifically, is required of you in this new position. A good question to ask is, "What am I getting paid for?" or "What do I need to be doing that I'm not doing now?"

One way to develop a strategic and leadership-oriented way of thinking is to start reading the "Harvard Business Journal" every month. Very soon you will know how CEOs from around the world and in various industries think. Additionally, stay away from industry specific journals, because you're probably an expert in that area already. Rather, read about different companies and how they attained success. Autobiographies of famous leaders are good sources too.

Ultimately, a leader is paid for thinking strategically and for making sure plans is executed. A supervisor is paid for participating in getting those things done. So while you may not individually be responsible for all the details any longer, don't fool yourself; you can't drop the details. You need to be checking them since you're still accountable for them in some form. Inspect what you expect.

### Rebrand Yourself

Unless you are new at a company you already have a reputation. A reputation is what you have; a brand is what you want to be known for. Rebranding takes work.

When you're in a leadership role, however, you must know what your reputation is, and you must make a conscious decision on what you want to be in terms of your brand. The best way to uncover this information is to ask people, "What do others think of me?" As you do this, don't waste time asking your friends and family. They'll be more concerned with sparing your feelings than giving you honest feedback. Rather, ask co-workers, upper management, past managers, and anyone else whom you believe would give you thoughtful insight. Yes, it takes boldness and humility to do this, but it's information that can guide your future career.

Once you receive the feedback, analyze it. Is it accurate? Are the answers in line with what you thought about yourself? Do you like the feedback? Using the replies you received from people,

decide where you need to make changes in your approach and what you want to be known for in the company. Then take the steps to be the type of leader you want to be.

#### Start Building Social Capital Right Away

Leaders have willing followers. A good leader knows how to get things done without formally delegated authority. A superb leader has built social capital and knows how to spend it. Social capital is about doing appropriate things to help others do their job. Can you offer assistance on a project or give people needed information? If so, and if you offer it, then you're building social capital.

One of the ways to get social capital is during meetings with your new executive peer group. Keep notes on every peer. Write down everything you learn about them. And if you learn something new in a meeting, go back immediately and write it down. It's not possible to remember all of this. As the old adage says, "The palest ink is better than the best memory." To be a successful leader, you have to learn about your new peers,

and you have to learn the functions of their areas and how their function is tied to what you do. And yes, it is tied; otherwise you wouldn't be on the executive team.

Social capital is something you can spend, but you can't spend it if you don't have it. Therefore, always offer to help your peers. If there's something you're specifically good at, and you know how to get some information that they mentioned in a meeting or in passing, say, "I can help you with that!" That will build social capital.

There are a lot of studies on reciprocity, and reciprocity is done in every culture in the world. You give somebody something; they give something back to you. That's just the way the world works. So if you haven't done anything for anyone, then you don't have any chips to cash in when you need something. Then, when you're up at eight o'clock one night at the office and you need something from another department, if you don't have that social capital built, it's going to be really hard to call them at eight or nine

at night and ask them to come back up and help you.

#### Make the Switch Today

Moving into a leadership position is both exciting and challenging. You begin to stretch to reach new levels of achievement while letting go of tasks that brought you to your current level of success. It's a time to reinvent yourself with a new peer group while perhaps transitioning into a new persona for those you've worked with for years. By all accounts, it's a time for change and personal and professional growth. Make the most of this time and transition wisely, as doing so will reap the greatest rewards for both you and your company.

#### About the Author

**Jean Kelley**, author and entrepreneur, is the managing director of Jean Kelley Leadership Alliance whose faculty and Trainers have helped more than 750,000 leaders and high potentials up their game at work in the US and in Canada. For information on keynotes, in-house programs, or customized training, email [jkelly@jeankelley.com](mailto:jkelly@jeankelley.com) or go to [www.jeankelley.com](http://www.jeankelley.com). 🍷

### Latest Hot-Job Postings

For a complete list of all job postings, please visit [www.pda.org/careers](http://www.pda.org/careers).

**Gilead Sciences**, Foster City, Calif.  
Manager, QA Compliance Audits

**Gilead Sciences**, Oceanside, Calif.  
Associate Director, Quality Assurance

**Pall**, Ann Arbor, Mich.  
Microbiology Laboratory Manager  
(Scientific & Laboratory Services)

**Pall**, Port Washington, N.Y.  
Associate Scientist III

#### Welcome New Members continued from page 18

**Priscilla White**, Infinity Pharmaceuticals

**John Wichelt**, Grand River Aseptic Manufacturing

**Urs Widmer**, Confinis

**Florian Wildenhahn**, F. Hoffman-La Roche

**Ann Williams**, AP Pharma

**Matt Williams**, Cambridge Design Partnership

**Gene Wloch**, Abbott

**Erin Wong**, Baxter

**Markus Wyss**, Datwyler Pharma Packaging Group

**Frank Yeschanin**, Lantheus Medical Imaging

**Matthew Young**, Oval Medical Technologies

**Reiner Zeidler**, TeamTechnik Maschinen und Anlagen

**Reinhold Zimmermann**, West Pharmaceutical Services

**Andreas Zurflueh**, Ypsomed

## Interest Group *Corner*

### Pharmaceutical Water Systems IG Plans to Revitalize Group

Pharmaceutical Water Systems Interest Group (PWSIG) co-leaders **Phil DeSantis** and **Bill Collentro** spoke to the *PDA Letter* about their plans to visit PDA chapters in 2012 in order to publicize issues with water systems and, hopefully, increase participation in the PWSIG. The 2012 goal, according to the two leaders, is to reenergize the group. A key component of this effort will be the PWSIG gatherings at both the *2012 PDA Annual Meeting* in Phoenix, Ariz., April 18-19 and *PDA's 7th Annual Global Conference on Pharmaceutical Microbiology* in Bethesda, Md., Oct. 22-24.

Phil and Bill bring a broad perspective to the PWSIG, as Phil comes to it from a drug manufacturer's perspective and Bill from a supplying vendor. They spoke with PDA about issues the PWSIG needs to address and their goals to reenergize the group.

Phil, recently retired Senior Director, Engineering Compliance and Validation, Merck, told the Letter that water treatment methodology is one major difference between the European Union and the United States with respect to water for injection expectations; the European Union requires distillation and the United States does not. There are ongoing discussions in industry about influencing the European Union to change its water for injection regulation.

Bill, Sr. Consultant, Concordia ValSource, said that another problem for manufacturers occur when municipal treatment plants in the United States change the water disinfectant agents without notifying the appropriate individuals at a pharmaceutical company. This is unsafe as the pharmaceutical company is then ill-equipped to remove any the disinfecting agent and associated byproducts from the water. Also, the addition of sequestering agents, such as poly and/or ortho phosphates, to water by municipalities can produce colloids of material, such as iron, not removed by water multimedia filtration or water softening.

Phil said that when systems are designed for companies, they are most often designed with data that has been gathered on incoming water, which is usually relatively limited. "This is a problem that many people are unaware of. Ignorance of these kinds of things can get people into serious trouble. We want to make our colleagues aware of these issues and develop relationships with their water companies to insure that these problems are known and controlled."

*continued at top of page 24*

## Task Force *Corner*

### Manufacture of Investigational Drug Products Task Force to Publish Technical Report in 2012

The PDA GMP Points to Consider for Manufacture of Investigational Drug Products Task Force has hit its stride in 2012, as the team works to help bring a clearer understanding of the issues surrounding this area to industry.

The task force is set to submit a technical report for PDA review and hopes to publish the document later this year, according to chair **Karen Ginsbury**. The *PDA Letter's* **Emily Hough** talked to Karen about the task force and the upcoming technical report.

**PDA Letter:** What are some of the hot topics facing the task force in the United States? In Europe?

**Ginsbury:** One of the biggest challenges is the difference in approach between the United States regulators and the European Union regulators in the field of GMPs for IMPs—that's GMP for investigational medicinal products.

In the United States, there is an exemption from GMP requirements (21CFR parts 210 and 211) in the manufacture of clinical trials material for phase 1 GMPs. Of course, that isn't totally true. All drug products manufactured for administration to humans must comply with the requirements for the Federal Food Drug and Cosmetic Act, which states that a drug is considered to be adulterated if it was not manufactured in compliance with GMPs. The paradox is primarily for phase 1 drugs where there is a specific exemption from 21 CFR part 211 GMPs for finished pharmaceuticals for phase 1 manufacture. However, the U.S. FDA Guidance on GMPs for phase 1 manufacture is rather general and open to interpretation.

In the European Union, the approach is to apply all of the GMPs and then add Annex 13 specifically points for IMPs. That means that the nine main parts regarding the quality management system, personnel, facilities and equipment, documentation, production, etc., are applied in full unless you can justify doing less. On top of that, you need to implement Annex 13 which has specific requirements pertaining to IDP.

Another challenge is that the European Union regulators perform mandatory inspection of sites manufacturing IMPs; whereas, FDA essentially does not inspect clinical manufacturing sites, although they are of course allowed to do so, on a "for cause" basis.

*continued at bottom of page 24*

## Journal *POV*

### Viral Safety in the 21<sup>st</sup> Century

Kurt Brorson, U.S. FDA and Hannelore Willkommen, RBS Consulting

**[Editor's Note:** This is from the January/February issue of the *PDA Journal of Pharmaceutical Science and Technology*.]

Freedom from viral contaminants is a paramount concern for recombinant biopharmaceuticals and plasma-derived medicinal products. Viral safety is achieved by a rigorous program of cell bank and source material testing in conjunction with a demonstration that product purification is capable of removing or inactivating viruses. Bioprocessing consists of sequential unit operations that capture and/or purify cell culture derived protein products. These operations, or steps, in many cases focus primarily on removal of product and process impurities while maintaining acceptable yield, but viral clearance can occur as a secondary outcome. Others are specifically introduced to the manufacturing scheme for removal (filters) or inactivation (low pH incubation, solvent/detergent treatment) of viruses.

There is a worldwide regulatory and industry recognition that challenges, gaps and opportunities exist for improvement of viral clearance technology. The 2009 (Indianapolis, Ind.) and 2011 (South San Francisco, Calif.) Viral Clearance Symposia were held to interactively discuss methods for virus removal and inactivation during biopharmaceutical manufacture. A series of lessons learned and next steps were identified at these meetings. A white paper summarizing the 2009 meeting was published in *Developments in Biologicals*, Vol 133, in 2010. A white paper for the 2011 meeting is being drafted.

PDA has been very active in the area of advancing viral clearance technology as well as educating members regarding regulatory approaches and technical issues surrounding viral safety. Examples include the recently published technical reports such as PDA TR No. 41, *Virus Retentive Filtration* and PDA TR No. 47, *Preparation of Virus Spikes Used for Virus Clearance Studies*. These technical reports not only educate readers regarding these highly complex technical areas, but they also define best practices. For example, TR-41 contains the first-ever test methods to classify virus retentive filters into “large virus retentive filters” and “small virus retentive filters.”

The 2012 PDA/FDA Virus and TSE Safety Conference will be held on May 15–17<sup>th</sup> in Bethesda, Md. and represents another opportunity to discuss the topic of viral safety for biopharmaceutical and plasma derived products. The conference will bring together all levels of industry and regulatory professionals to network and benefit from a program that demystifies the underlying science of virus safety and seek to address issues that our industry faces on a daily basis. 🌐

## Journal *Preview*

### Advancing Viral Clearance Technology

In the January/February issue of the *PDA Journal of Pharmaceutical Science and Technology*, Kurt Brorson, U.S. FDA, and Hannelore Willkommen, RBS Consulting, wrote about how PDA has been active in the area of advancing viral clearance technology with two of its technical reports. Four research articles as well as two technology/applications and two commentaries also make up the issue.

#### *Editorial*

Kurt Brorson, Hannelore Willkommen, “Viral Safety in the 21<sup>st</sup> Century”

#### *Research*

Christopher D. Mensch, Harrison B. Davis, “Inhibition of Tungsten-Induced Protein Aggregation by Cetyl Trimethyl Ammonium Bromide”

Dengfeng Liu, et al., “Interactions between Therapeutic Proteins and Acrylic Acid Leachable”

Abdel Naser Zaid, et al., “Evaluation of the Discrepancy between the European Pharmacopoeia Test and an Adopted United States Pharmacopoeia Test Regarding the Weight Uniformity of Scored Tablet Halves: Is Harmonization Required?”

Srividya Ramreddy, et al., “Formulation and Pharmacokinetics of Diclofenac Lipid Nanoemulsions for Parenteral Application”

#### *Technology/Application*

Luis Jimenez et al., “Validation of the BacT/ALERT® 3D System for Rapid Sterility Testing of Biopharmaceutical Samples”

Ernest J. Chow et al., “Effects of Subzero Temperature Exposure and Supercooling on Glass Vial Breakage: Risk Management and Other Applications in Cold Chain Distribution”

#### *Commentary*

Dennis Jenke, “Essential Aspects in Assessing the Safety Impact of Interactions between a Drug Product and Its Associated Manufacturing System”

H. Gregg Claycamp, “Probability Concepts in Quality Risk Management” 🌐

*Interest Group Corner continued from page 22*

To learn more about the Pharmaceutical Water Systems Interest Group or to volunteer, email **Iris Rice** at [rice@pda.org](mailto:rice@pda.org)

Rouging is another concern both experts feel needs attention. While rouging rarely contaminates the water in a pharmaceutical plant and tends to be a stable film, it can cause problems. Bill mentioned that rouging in ozonated purified water systems may be extensive, requiring annually derouging and re-passivation.

Regulatory agencies are now beginning to look for programs that periodically monitor the concentration of stainless steel corrosion products. Phil stated that more companies are beginning to put preventative programs in place.

Both leaders told the Letter that expertise in water purification is harder to find and pharmaceutical manufacturers do not have as much access to that kind

of knowledge anymore. They both hope that their IG can give companies an opportunity to learn about the issues and a chance to share experiences.

### About the Experts

**Phil DeSantis** is a pharmaceutical consultant, recently retired as Senior Director, Engineering Compliance for Global Engineering Service at Merck (formerly Schering-Plough) located in Whitehouse Station, NJ. His responsibilities included development, implementation and support of standards and practices for all facility and equipment-related capital projects and site operations. He is on the PDA Scientific Advisory Board and is active in ISPE. He has been as a frequent lecturer for both



organizations. He has published or contributed to several articles and books in the area of validation and pharmaceutical engineering. In addition, Phil has lectured on "Steam and Dry Heat Sterilization" as part of the U.S. FDA's field investigator training program.

### William V. Collentro

is Senior Consultant at Concordia-ValSource. His career spans over forty years in the area of water treatment and purification, principally for the life sciences. In addition to being an Adjunct Professor at Stevens Institute of Technology, Bill is an instructor for the Parenteral Drug Association's Training and Research Institute where he was awarded the James P. Agalloco Award for Excellence in Training in 1998. He has authored a text, *Pharmaceutical Water, System Design, Operation and Validation*, as well as chapters for other texts on pharmaceutical water, over 150 articles and presentations. 

*Task Force Corner continued from page 22*

**PDA Letter:** How is your task force addressing those issues?

**Ginsbury:** We are working on a "GMP Points to Consider" technical report for the Manufacture of Investigational Drug Products. The report is essentially written and has ten chapters.

The chapters focus on:

- Quality Management Systems
- Facilities and Equipment
- Materials Management
- Production
- Quality Control

- Packaging and Distribution

There is a special mention of interactive voice based recognition systems used to help track randomized and blinded clinical trials material. **[Editor's Note:** In 2009 the PDA/ISPE Expiry Date Task Force published a white paper on the "Use of Interactive Voice Response or Web Systems to Manage IMP Retest Dates."]

The report is undergoing final editing before being put out for peer review by PDA members. Peer review is important to ensure that we are addressing the right

issues. Anyone interested in doing that, please email **Iris Rice** at [rice@pda.org](mailto:rice@pda.org). I will make sure that those who reply receive access to the document.

**PDA Letter:** What are your next steps?

**Ginsbury:** We must keep the dialogue going. The issues are so numerous, and PDA members have so much collective knowledge that sharing is critical. This, to me, is what PDA does best, and I am sure there will continue to be numerous forums where these discussions are held. One of the challenges we had with regard to the practice of validating

### Members of the Task Force

**Carina Sonnega**, Biotechnology Consulting

**Volker Eck**, Eck Pharmaceutical Consulting

**Joachim Leube**, Crucell Holland

**Bob Dana**, PDA

**Ailsa Searles**, Pfizer

**Barabar Zinck**, Zinck Consulting

**Barbara Unger**, Amgen

**Mickaela Blake**, Merck

**Sue Mann**, Sue Mann Consultancy

**Vince Mathews**, Eli Lilly

**Didier Hallard**, Prosensa Therapeutics

**Amnon Eylath**, Ariad Pharmaceuticals

**Tom Thorpe**, Afton Scientific Corp.

**Richard Funnell**, MHRA

**Mark Glass**, Microchem Laboratories

**Musetta Hanson**

**Chris Cullen**, Irish Medicines Board

**Bronwyn Philips**, Ret. MHRA

**Monica Caphart**, U.S. FDA



filters used for sterile filtration of aseptic product in early phase studies. In order to benchmark, PDA conducted a survey, and we were quite surprised that over 50% of respondents said they validated filters in early phase studies. When we went into the details, however, we found that the interpretation of “validation” was extremely liberal; in most cases it was just performing pre- and post-use integrity tests. So we went to the regulators. We were told by MHRA that the default position should be to perform formal validation studies. A company could then use a risk assessment to consider whether the investigational product in question falls within a matrix of similar products already validated for that particular filter e.g., similar viscosity, pH and surface activity. If there is, there may be a scientific rationale that can be documented for not performing product specific validation. We have incorporated this approach into the TR.

**PDA Letter:** Is there anyone you would like to recognize?

**Ginsbury:** Thanks to a very devoted team of individuals this project is nearing completion. There are some members of the team who must get a special mention—in the early stages of the project **Carina Sonnega** and **Volker Eck** pretty much kept it moving. Thanks to **Bob Dana** for taking over the project when Volker left PDA, although he is still active on the team. **Joachim Leube** has been and remains a mainstay, **Sue Mann**, our QP, has kept us on track, and **Bronwyn Philips** was really involved. Since her retirement, her spot has been reassigned to **Richard Funnel**, who is waiting for us to bring him in to look at the final edited draft.

**Barbara Zinck** should get a gold medal, because she dug this document out of the mud during the last few weeks and got it going once again. When we reach the finish line, I have to say it will be Barbara who helped us over.

## About the Expert

**Karen Ginsbury**, President, PCI Pharmaceutical Consulting, is the Leader of the Investigational Medicinal Products taskforce. Karen is a long standing PDA member and volunteer, Past President of



PDA's Israel Chapter. She currently serves on PDA's Regulatory and Quality Affairs Advisory Board. 🇺🇸

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# Lack of Compendia Harmony for Visible Particles Causing Confusion

Dan Berdovich, Micro Measurement Laboratories and James Melchore, Melchore Consulting



The major compendia require sterile injectable and ophthalmic drugs to be prepared in a manner that is designed to exclude particulate matter (1-4). In the United States, this requirement is satisfied by testing for subvisible particles in the laboratory (USP Chapters <788> and <789>) and 100% inspection of all containers for the presence of visible particles (USP Chapter <1>).

For subvisible particles, there is harmonization across the major pharmacopeia. For visible particle inspection (aka, "visual inspection"), harmony does not exist, and this is causing confusion in the industry.

## Background

Inspection for visible particles is performed in the operations area using one of three methods. Manual inspection is based on human visual acuity, the ability of the inspector to distinguish between conforming and nonconforming containers and remove nonconforming units. Semi-automated inspection is a variation of manual inspection, in which a roller conveyor handles and presents the containers to the human inspector. Fully automated inspection systems perform handling, inspection and rejection of defective containers. All inspection methods must meet the compendial requirement for sterile drug product to be “essentially free” of visible particulates.

Given the random occurrence of particles within the batch, visual detection of a particle in an individual container is probabilistic. The probability of detection for a specific particle is affected by many variables that include product attributes, container size and shape, particle composition and size, and inspection capability. The challenge set is a useful tool to assess the particle detection in product, and it may also be used to evaluate detection of container/closure defects. While the importance of a well-designed challenge set is not always recognized or understood, it serves as the cornerstone for qualification and/or validation of all inspection methods. This article is intended to provide useful information for the design, composition and use of container challenge sets for particulate inspection studies.

Inspection of product in the operations area is primarily focused on container/closure defects and particulate matter in product. Both type defects present potential harm to the patient; the circumstances surrounding their detection and rejection, however, are very different. Most container/closure defects are easier to detect than particulate matter in product and guidance provided by PDA and the U.S. FDA has enabled companies to create clearly defined acceptance criteria and disposition for each type container/closure defect (5-7).

## Harmony and Disharmony

The major compendia have harmonized the testing methodology and acceptance criteria for subvisible particles (1-4), however, the absence of a harmonized guidance for visible particles has led to confusion in the global industry.

Harmonization for subvisible particulate matter has been in place since 2007, with USP <788>, USP <789>, which describes two different methods, light obscuration and microscopic membrane. Recommendations and guidelines are described in USP Chapter <1788>, which describes equipment qualification and sample preparation methods. Unlike subvisible particulate matter testing, visual inspection of containers is probabilistic. Regardless of the method performed, it requires a human baseline to connect any method to human vision, which is probabilistic.

The wording in the major compendia for visual inspection, however, varies. At best, the pharmacopeias share only the vague expectation for injectable and ophthalmic products to be “essentially free” of visible particulate matter. This expectation is based on human visual acuity, which is subjective and can be affected by many variables.

Many questions and issues arise in discussions about the various uses of challenge sets and even more confusion exists as to what particles should be included. Also, there is a good deal of disagreement on how these sets should be utilized for qualification and training of inspectors, as well as validation and qualification of automated systems. What uses are served best by challenge sets that include real rejects and which uses can be better served with challenge sets that contain spherical particle standards? Which challenge sets must be NIST traceable? Should the challenge set contain only absolute rejects and blanks? How many reject level containers, how many blanks. Should there be “grey zone” containers? Many of the answers to these questions are further complicated by the attributes of the container as well as the formulation, es-

pecially for many biologics. What constitutes a suitable challenge set? Particle size which might be suitable for clear vials will not be the same as those for amber vials or ampoules or even syringes or administration bags. Packaging technology is moving forward and new containers are being considered that reduce cost and allow improved administration. New (often complex) formulations are being introduced along with very small volume containers for ophthalmics. Some products are viscous.

In the search for a quantitative approach to validation, much attention has been given to particle size as the criterion that contributes to particle detection, but studies show that other particle attributes including shape, composition, reflectivity, color, contrast, density and particle behavior (such as during spinning and inspection) must also be considered.

Because of the considerable differences between products, packages and formulation attributes, there are many issues that regulatory agencies will need to deal with if specifications are going to be adopted for the industry as a whole. The authors would like to suggest that the regulatory bodies consider an interim means to reduce and/or eliminate much of the current confusion through two key areas:

- 1) Introduce a high-level (guidance) document containing recommendations that affect key areas of the inspection process
- 2) Provide guidelines for the design and uses of challenge sets for visual inspection of most products. This would provide the manufacturer of

### Article at a Glance

- Major compendia share only vague expectations for injectable and ophthalmic products to be “essentially free” of visible particulate matter
- Absence of harmonized guidance for visual particles is leading to confusion in the industry

# The authors would like to suggest that the regulatory bodies consider an interim means to reduce and/or eliminate much of the current confusion

each product/package to develop the information and practices under this framework.

**[Authors' Note:** In the absence of a harmonized guidance, we are preparing a review article which is based on published studies and experience gained in the design and use of challenge sets for particulate matter studies. We believe this article will shed some light on many issues in the inspection process. It describes differences in various challenge sets as well as their use as a means to achieve better agreement and harmonization in visual inspection. The manuscript is currently going through the peer review process for the *PDA Journal of Pharmaceutical Science and Technology*, though there is no guarantee as of yet that it will be published in that Journal.]

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## About the Authors

**Dan Berdovich** started Micro Measurement Laboratories (MMLabs) in February of 1998 to expand his focus on particulate matter testing and particle size analysis by offering his experience through contract testing. Today, the lab provides several analytical and problem solving services, using a wide variety of the latest, state of the art, instrumental, microscopic and imaging techniques. Dan has over 20 years experience in, and a reputation for, solving particle-related problems found in formulations, ingredients, medical devices as well as many types of package components. He has developed and validated hundreds of methods and assisted manufacturers in regulatory submissions related to dozens of particle related issues.

**James Melchore Jr.** is the Principal Consultant for Melchore Consulting. He has over 30 years experience in pharmaceutical/biotechnology operations and has specialized in validation and training in the areas of inspection and cleaning methodologies. He offers evaluation of existing inspection programs, corrective actions, creating new programs and writing supporting documentation to include protocols, reports, SOPs and Validation Master Plans. Prior to consulting, he was an associate director of validation/process engineering for Enzon Pharmaceuticals Inc. Prior to that, he was the director of technical operations for Bracco diagnostics. From 1971 through 1997, he worked for big pharma, first for Novartis (1971-1986), then with Bristol-Myers Squibb (1986-1997). ☞

## PDA's 2011 Visual Inspection Forum

As a member of the USP Visual Inspection of Parenterals Expert Panel, **John Shabushnig**, PhD, Sr. Manager/Team Leader, Quality System & Technical Services, Pfizer, gave an update about USP's activities at PDA's 2011 Visual Inspection Forum in October 2011.

Shabushnig spoke at length about USP chapters that detail visual inspections and particulate matter. He specifically mentioned sub-visible particle counting chapters: USP 34: <788> Particulate Matter in Injections; USP 34: <789> Particulate Matter in Ophthalmic Solutions; and, USP <1788> Determination of Particulate Matter. He also addressed draft sub-visible particle chapters on injectable protein therapeutic products <787> and <1787>.

**Dan Berdovich** and **James Melchore** also presented during a session of the Forum on Good Practices in Manual Inspection.

PDFs from each presentation as well as all session recordings from the forum can be bought for \$199 with web code: VIF-P1-11. To buy presentations from the Visual Inspection Forum, visit [tinyurl.com/88uxvbk](http://tinyurl.com/88uxvbk).



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# The Importance of Commenting on Public Standards

Sue Schniepp, OSO Biopharmaceutical and Janeen Skutnik-Wilkinson, Pfizer

The standards that the United States Pharmacopeia (USP) develops are enforceable by the U.S. FDA and are relied upon in more than 130 countries. While these standards have helped ensure public health throughout the world, recently the USP has published some general information chapters that have generated, according to some, an unnecessary strain on pharma's resources. In addition, USP has proposed chapters that duplicate existing regulations/guidance and some USP chapters that go beyond USP's scope.

These issues being introduced by USP prompted the formation of the Pharmacopeial Interest Group and will require the immediate attention of its members. The Interest Group will focus on compendial issues impacting our industry. The purpose of the group is to serve as the liaison between the Regulatory Affairs/Quality Advisory Board (RAQAB) and pharmacopoeias. The Pharmacopeial Interest Group will focus mainly on the major pharmacopoeias of the world: USP, Ph Eur, JP, Indian Pharmacopoeia, Chinese Pharmacopoeia, Brazil Pharmacopoeia.

Specifically, the group is charged with:

1. Monitoring compendial activities and publications and provide periodic reports to RAQAB
2. Preparing position papers on compendial initiatives and proposals not being addressed by other PDA Committees
3. Representing PDA at the USP Stakeholders Forum
4. Proactively identify compendial topics and advocate PDA's position

It is scheduled to meet for the first time at PDA's Annual Meeting in Phoenix, Ariz.

On January 4, USP announced that

it was seeking feedback on a proposed general information chapter, entitled, USP General Chapter <1083> *Good Distribution Practices—Supply Chain Integrity*. According to USP, the new proposed standard will not be mandatory. In addition, there have been recent proposals for new general chapters covering the spectroscopic techniques of mid-Infrared (<854> and <1854>), UV/Visible (<857> and <1857>) and Atomic Absorption (<852> and <1852>). These new General Chapters are proposed to collectively replace <851> Spectropho-


**It is important for industry to make sure the items being introduced by USP are appropriate or even if it is appropriate for USP to make standard-setting processes for these types of issues**

tometry and Light-Scattering. The USP has also proposed new requirements for instrument qualification and procedure validation/verification and is in the process of revising the Heavy Metals chapters to utilize inductively coupled plasma technology\*, not commonly used by industry for QC release.

With all these changes affecting broad scope procedures and methodology, it is important for industry to make sure the items being introduced by USP are appropriate or even if it is appropriate for USP to make standard-setting processes for these types of issues. It is also important to question if this is the purpose or mandate of a pharmacopeial today.

USP has introduced the Medicines Compendia which is intended for use by healthcare practitioners outside the United States. According to the USP website, the rationale for establishing this new compendium is because *public standards are critically important,*

*especially where regulatory and compendial resources are constrained or absent. The USP Medicines Compendium (MC) represents a novel approach to bring good public standards—monographs with reference materials—into the public domain as early as possible after access in a national market. Reliance on these standards can occur at the time of approval through regulatory decision-making and allows marketplace surveillance by manufacturers, purchasers, and the regulatory authority itself. Without the public monograph, some regulatory agencies may need to conduct the same kind of review that is accomplished independently by the USP Council of Experts. The MC thus reinforces the use of good quality standards by ethical manufacturers and can conserve scarce regulatory resources. The MC can become one of a series of safety nets that help combat counterfeit and substandard medicines.*

 This is an analytical technique used for the detection of trace metals in environmental samples. The primary goal of ICP is to get elements to emit characteristic wavelength specific light which can then be measured.

Though the USP *Medicines Compendium* Frequently Asked Questions says that *standards in the MC are developed in an open, transparent process that seeks public comment—similar to the well-established process by which USP's other compendial standards are developed,*" the USP website says: *USP MC standards are reviewed and approved by Expert Committees of USP's Council of Experts. These Expert Committees follow all applicable rules and procedures of the Council of Experts, although the process may differ from that for other USP compendium.*

In our opinion, this seems like the Medicines Compendia is opening the door

to bypass the comment process and set standards without the input of industry and proper review.

The rules and procedures of the current Council of Experts in section 7.02 states *accelerated revision processes are used to make revisions to the USP-NF official more quickly than through USP's standard revision process when necessary to correct errors, address patient safety issues, or resolve compliance issues. Such accelerated revisions, which include Interim Revision Announcements, Revision Bulletins and Errata, do not always require notice and comment and allow for a revision to become official prior to the next USP-NF or Supplement. Accelerated revisions may be used only in the circumstances described in USP's Guideline on the Use of Accelerated Processes for Revisions to the USP-NF, which is posted on USP's website.*

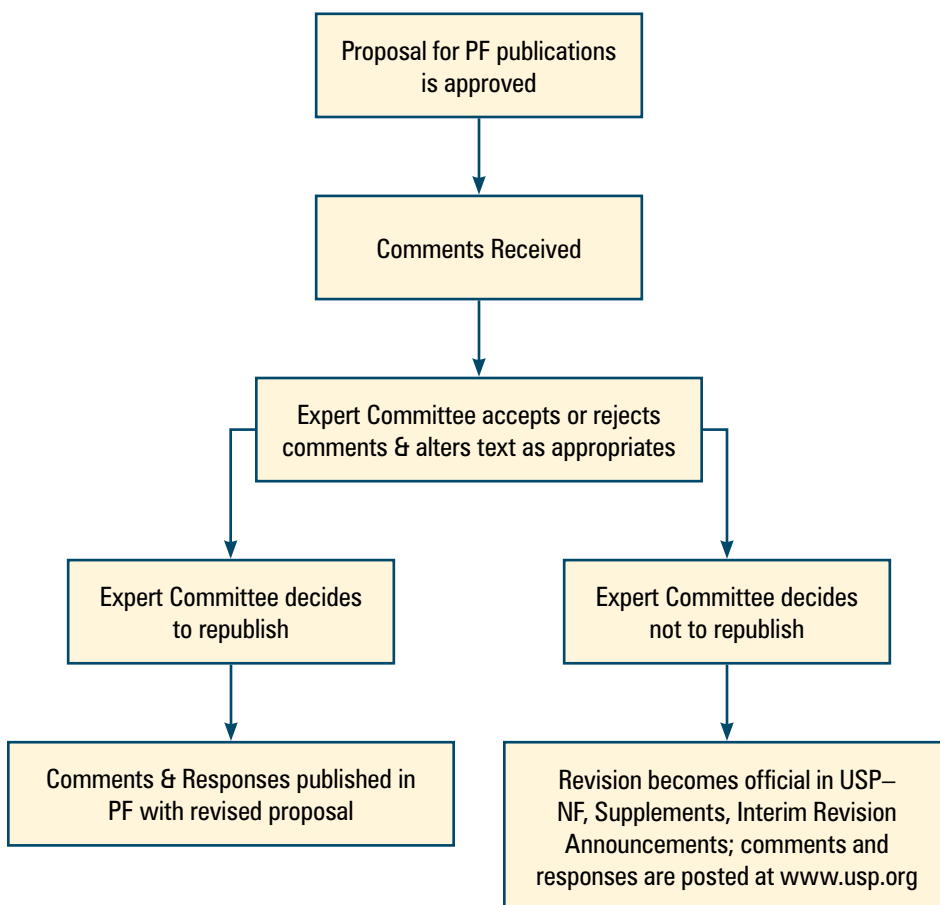
It goes on to say: *all proposals for revisions to the USP-NF\* shall, at the direction of either an Expert Committee, or the Scientific Liaison (following notice to the appro-*

*priate Expert Committee), be published in the Pharmacopeial Forum (PF) for public review and comment. Unless otherwise determined by USP, a proposal that includes the use of a new USP Reference Standard shall not be scheduled for publication in PF until a suitable reference standard bulk candidate has been received by USP.*

However, in the case of monographs for the Medicines Compendia, it says, *except in rare cases where the MC Expert Committee(s) determine that a new or revised standard should be made available immediately because of an urgent public health need, all proposals to revise the MC shall be published in draft on the MC web site, and provide an adequate period for public review and comment.*

The United States Pharmacopeia–National Formulary (USP–NF) is a book of public pharmacopeial standards. It contains standards for medicines, dosage forms, drug substances, excipients, medical devices, and dietary supplements.

### USP Public Review and Comment Process



To ensure an active voice in the USP process, industry must take the time to participate in the USP commenting process. The public review and comment process starts with a proposed change to an existing standard or introduction of a new standard and ends when that standard is officially adopted. Often this change is intended to improve the official criterion or procedure.

To understand the importance for the need to comment, we should look back to the changes and implementation made to the residual solvents requirements. The origin of the residual solvent requirement can be traced back to 1988 when USP proposed a general test chapter for organic volatile impurities (OVI), ultimately adopted in 1990.

In 1997, ICH finalized document Q3C, titled, *Impurities: Guideline for Residual Solvents Applicable to New Drug Substances, Excipients and Products*. The European Pharmacopoeia (Ph. Eur.) subsequently adopted this guideline in 2000. In 2003, the USP published a proposal in the *PF* to revise the chapter on OVIs and align it with the ICH and Ph. Eur. documents. The official adoption date for this revision was to be April 1, 2004, and the proposed revision that would include a line item for residual solvent testing in every monograph, was discussed at the USP Annual Scientific and Stakeholder Forum meetings held in September 2004.

The feedback provided at these two venues prompted a major revision and ultimate delay in the adoption of the standard. Industry publicly commented that the inclusion of this requirement in all monographs would result in unnecessary testing. The rationale for this state-

#### Article at a Glance

- The public review process is an important mechanism for USP
- Industry should participate in the public commenting process to assure the adopted standard is suitable and appropriate

ment was based on the premises that: 1) If a monograph calls for a test, then a result or value must be generated and 2) excipients, drug substances or dosage forms that do not use residual solvents during the synthesis or formulation processes would not need to be tested. Based on the public feedback, USP revised their initial proposal and formed a project team that would meet and make recommendations on how this new proposed standard should be adopted.

It is important to keep in mind that the USP requirement is not limited to new drug substances, excipients or products but encompasses previously approved items. This distinction is critical, because it meant that previously unknown information would need to be collected, investigated and assessed for approved marketed products. Since many of these products were developed before the ICH requirement was adopted, much of the information required to meet the new USP requirement was unknown. The USP understood this argument presented by industry and began working with the pharmaceutical community to develop education and training programs that would help industry implement the requirement with limited disruption. This collaborative effort culminated with the adoption of the standard in the *USP-NF*

on July 1, 2008 with little or no comment from industry. This is not to imply there were not issues after the standard finally became official. However, the remaining issues are more about the applicability of the standard and not about the content.

The public review process is an important mechanism for USP in obtaining necessary feedback from the industry regarding changes to the official standard-setting processes. It is important for industry to be aware of and participate in the process to assure the standard ultimately adopted is suitable and appropriate. As mentioned earlier, there are a number of broad scope issues currently under revision and adoption in the USP.

The lessons learned from the residual solvents case are meant to provoke industry into actively participating in the standard-setting process by reviewing and commenting on the proposed revisions to ensure they meet the needs of the industry. There are a number of ways industry may comment on proposed changes in the USP. These include commenting as an individual, as part of a company or as a member of a trade organization.

The timeliness of the formation of the interest group in light of current devel-

opments at USP will offer PDA members a vehicle for commenting on concerns regarding apparent deviation from a pharmacopoeial mandate and entry into areas where there are already sufficient resources and noted authorities acting and writing guidance for industry.

### About the Authors

**Susan Schniepp** is the Vice President of Quality for OSO BioPharmaceuticals Manufacturing, a contract manufacturing organization for sterile injectables. She has 30 years of industry experience in quality control and quality assurance. During her career, she has had responsibilities for complaints, labeling, investigations, compendial affairs and other quality systems. Sue is also a member of Regulatory Affairs/Quality Advisory Board, the *PDA Letter* Editorial Committee and has presented at many PDA venues.



**Janeen Skutnik-Wilkinson** is the Director of Quality Policy at Pfizer. She is the past chair of IPEC Americas and has been involved in IPEC as Chair of the Compendial Review committee from 1998-2007. She has given many presentations on excipients in various countries over the past decade and a half. Janeen has also been the chair of PhRMA's Compendial Liaison Committee since 1998 and was the Topic Leader for ICH Q4B on Pharmacopoeial Interchangeability. She has been a member of PDA for many years and a speaker at several PDA meetings and conferences both in the USA and Europe. Janeen is also a member of the Regulatory Affairs/Quality Advisory Board and the *PDA Letter* Editorial Committee. 

Please consider joining us at the *PDA 2012 Annual Meeting* and engage in a discussion on compendial issues. For more information about the pharmacopoeial interest group or to volunteer, contact **Iris Rice** at [rice@pda.org](mailto:rice@pda.org).



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# USP Updates Given at PDA's 2011 Micro. Conference

Michael J. Miller, PhD, Microbiology Consultants

*Long-time PDA volunteer Dr. Michael J. Miller maintains a blog for his firm's website: [rapidmicromethods.com](http://rapidmicromethods.com). Miller routinely blogs about various topics of interest from the RMM community. This year, he covered a session about the USP's update on Rapid Micro Methods and Chapter <1223> from the PDA 6<sup>th</sup> Annual Pharmaceutical Microbiology Conference, and has graciously allowed us to share some of his posts in the PDA Letter. Go to his website to read his other blog posts from the meeting.*

## USP <1223>, the informational chapter that provides guidance on validating alternative or rapid methods, is under revision

During last year's PDA Micro meeting, the USP stated that they were going to update/revise the existing USP 1223 informational chapter and provide additional guidance with respect to the use of alternative micro methods. First, we must be reminded that the use of RMMs as a replacement for existing methods is nothing new, as the USP provides guid-

ance on the validation of alternative methods. More importantly, USP micro methods are intended to be referee tests (i.e., adjudicative) for the analysis of monograph products and compendial articles, and they were not intended to be QC release assays or in-process tests. Actually, USP referee tests were not intended to be used as QC assays without modification, and this modification is the responsibility of the method user.

USP <1223>, the informational chap-

ter that provides guidance on validating alternative or rapid methods, is under revision. Some of the changes from the current version may include enhanced guidance on method selection and qualification, and more specific content than what is currently provided. Additionally, the committee is concerned that RMM implementation is being held up because

users are too concerned at arriving at a perfect definition of method equivalence. Therefore, we may see some changes in how the USP recommends how to determine whether an alternative method is as good (or better) than a compendial method that is current in use.

Next, the expert committee is now exploring the development of a new referee sterility test; however, the referee method cannot be sourced from a single, patented technology. The committee will initially will focus on biologics (cytotherapy/regenerative medicine products) and radiopharmaceuticals. And they will get support from the USP biologics committee as well as scientists from CBER (please see my August blog posts for additional guidance from the FDA on the use of RMMs for sterility testing).

Finally, the committee plans on providing validation-useful information for the development and validation of HPLC methods for antibiotic assays for products where micro methods are still being employed.

### About the Author

**Michael J. Miller, PhD**, is President of Microbiology Consultants, LLC and is an internationally recognized microbiology consultant. He is a subject matter expert in pharmaceutical microbiology and cutting-edge rapid microbiological methods and new technologies and the editor of the popular, three-volume PDA/DHI book, *Encyclopedia of Rapid Microbiological Methods*, available at [www.pda.org/bookstore](http://www.pda.org/bookstore). He has held numerous technical, consulting, management and senior leadership roles within Research and Development, Manufacturing, Quality Assurance and Business Development at renowned companies such as Johnson & Johnson, Eli Lilly and Company and Bausch & Lomb. 



**Radhakrishna Tirumalai**, USP (left) and **James Akers**, Akers Kennedy & Associates (right) both provided updates to the USP Microbiology Expert Committee activities.

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# Progress of the Quality Topics at the ICH Meeting in Seville

Stephan Rönninger, F. Hoffmann-La Roche supported by Jim Lyda, PDA and Steve Mendivil, Amgen

The International Conference on Harmonisation (ICH) Steering Committee and its working groups met in Seville, Spain from November 5-10, 2011.

ICH is a project representing three major drug development markets as well as regulators and delegates from industry pharmaceutical innovator trade associations. Delegates from the United States include the U.S. FDA and Pharmaceutical Research and Manufacturers of America (PhRMA); from Europe, the European Commission (EU), the European Medicines Agency (EMA) and the European Federation of Pharmaceutical Industries and Associations (EFPIA) are represented; and, from Japan, members from the Ministry of Health, Labour and Welfare (MHLW), Pharmaceuticals Medical Devices Agency (PMDA), and the Japan Pharmaceutical Manufacturers Association (JPMA) are in attendance. Observers also participate from Health Canada, the European Free Trade Association (usually represented by Swissmedic) and the World Health Organization (WHO).

On occasion, representatives from other interested authorities e.g., China, Chinese Taipei and India, have participated. Other interested parties from industry include the World Self-Medication Industry (WSMI) and the International Generic Pharmaceutical Alliance (IGPA). If biotech operations are focused on, delegates from the European Biopharmaceutical Enterprises (EBE) or the Biotechnology Industry Organisation (US-BIO) are invited by the ICH Steering Committee to send representatives as an interested party.

## Global Outreach Activities

The ICH Global Cooperation Group (GCG) is a subgroup of the ICH Steering Committee and is composed of representatives from each of the parties at the ICH Steering Committee, plus the observers (WHO, Health Canada and EFTA) and International Federation of Pharmaceutical Manufacturers &

Associations (IFPMA). The members of the Regional Harmonisation Initiative, (RHI) also participate, namely:

- Asia-Pacific Economic Cooperation (APEC)
- The Association of Southeast Asian Nations (ASEAN)
- East African Community (EAC)
- Golf Corporation Council (GCC)
- Pan American Network for Drug Regulatory Harmonization (PANDRH)
- The Southern African Development Community (SADC)

The Drug Regulatory Authorities and Departments of Health from Australia, Brazil, China, Chinese Taipei, India, Republic of Korea, Russia and Singapore are also members.

The ICH GCG welcomed, for the first time at this meeting, representatives of the East African Community, a regional harmonisation initiative composed of Burundi, Kenya, Rwanda, Tanzania and Uganda. The Global Cooperation Groups intention is to support the implementation of the ICH guidelines outside the ICH regions. They also sponsor trainings in their respective area of responsibility ([www.ich.org/trainings/ich-trainings.html](http://www.ich.org/trainings/ich-trainings.html)).

## Heavy Metal Impurities (ICH Q3D)

During the ICH meeting in Seville, the Expert Working Group (EWG) completed a pre-step 2 ICH Q3D draft document that will be circulated to the ICH parties for informal feedback through February 2012. The major progress in developing the pre-step 2 draft included an agreement on the permissible daily exposure values for all metal impurities listed in the guideline for the oral, parenteral and inhalation routes of administration. A new risk-based control strategy section provides several alternatives to traditional testing including an example specific to biotechnology products illustrating overall reduced risk to contamination by metal impurities. No

major issues are anticipated that will prevent the EWG from reaching consensus (Step 2) in June 2012. A public consultation will follow by publishing this draft document for comments by the U.S. FDA, EMA and PMDA. PDA may collect comments and provide feedback to the EWG at that time.

## "Genotoxic impurities" ( ICH M7)

The ICH meeting in Seville was quite a successful one for the ICH M7 Expert Working Group. The first internal draft on M7, *Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk*, was finalized for initial review with the ICH constituencies (step 1 document). These comments will be consolidated at the next ICH meeting. A document for public comments might be available at the end of 2012.

## Development and Manufacturing of APIs (ICH Q11)

After the public consultation phase, this EWG made good progress managing the 1,300 comments received from the three regions. The discussions focused on updating the chapters on:

- Introduction and scope
- Manufacturing process development
- Description of manufacturing process and controls
- Selection of starting materials
- Control strategy including upstream controls
- Process validation/evaluation and the option for continuous process verification

There were also discussions on submission of information on the section about the common technical document as well as change management activities during the commercial and product discontinuation phase. It is anticipated that further discussions among the constituencies, with focus on control strategy, should lead to the final version of this ICH guidance document (step 4 of the ICH

procedure) before the end of the 2<sup>nd</sup> quarter in 2012. At that point it will be published for implementation by the three ICH regions.

#### Quality Implementation Working Group (Q-IWG)

The original remit of the Q-IWG was to provide considerations on implementing the final ICH guidance of Pharmaceutical Development (ICH Q8 R2), Quality Risk Management (ICH Q9) and Pharmaceutical Quality Systems (ICH Q10). In parallel, the ICH guidance on Development and Manufacturing of APIs (ICH Q11) was developed. The ICH Q-IWG ensured consistency in the messages provided.

The Q-IWG completed three more documents on points to consider. In Seville, the points to consider documents addressed the open questions from the 2010 training workshops performed in the three ICH regions (Tallinn, Washington D.C. and Tokyo) and more recently in Canada (Ottawa) and South Korea (Seoul). These documents address process validation/process verification, role of modeling in QbD, and design space. Combined with previously released question and answer documents and training materials, these documents provide a complete set of support guidances for implementation of the modern paradigm on development and manufacturing of pharmaceuticals in the twenty first century.

The new QbD points to consider document covers considerations and categorizations on the role of models in QbD which are used by industry in development. Suggestions for model validation and model verification are included in the document as well as answers to what has to be documented in regulatory submissions.

The document on design space describes in more detail the development and verification of design space during scale-up. Also, more details are provided on how to document the design space in a regulatory submission. The document ends with remarks on the lifecycle management of a design space.

The last points to consider document focuses on process validation and continuous process verification. General considerations were followed by a discussion of continuous process verification; this is the ICH term used for an enhanced approach of process validation during development and/or manufacturing. Please note that FDA uses "continued process verification" as a term describing the 3<sup>rd</sup> lifecycle stage in the process validation guidance. The suggested relationship to the requirements concluded the topic in the ICH document.

At this meeting, the ICH Q-IWG finalized their tasks according to the concept paper. A summary of the deliverables and achievements was provided to the GCG at ICH. These deliverables are published with the quality guidelines at the ICH homepage. They can be found at the ICH homepage at [tinyurl.com/6uq67jm](http://tinyurl.com/6uq67jm). To open the the folder on Q8/Q9/Q10 implementation and find answers to questions raised during the workshop and training breakouts on the training program and points to consider documents, open either the Q8,

*continued at bottom of page 48*

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# Audit Program Part of FDA Pathway for Global Product Safety

Voluntary ISO audit submission can net a medical device plant a one-year GMP inspection “pass”

Emily Hough and Walter Morris, PDA

The Center for Devices and Radiological Health (CDRH) and the Center for Biologics Evaluation and Research (CBER) are testing a Pilot Multi-Purpose Audit Program in 2012 and 2013 that will allow medical device companies under their jurisdiction to voluntarily submit certain audits and receive Agency inspection relief for one year.

The policy was announced in *Draft Guidance for Industry, Third Parties and FDA Staff Medical Device ISO 13485:2003 Voluntary Audit Report Submission Program*, issued by CDRH/CBER in May 2010, and was discussed in a session of the 2011 PDA/FDA Joint Regulatory Conference.

FDA’s goal is to leverage regulatory audits/for risk-based planning of FDA inspections. This is an important prong of a four-pronged approach outlined in a 2011 FDA “special report” called *Pathway to Global Product Safety and Quality*. During the opening session of the ‘11 PDA/FDA conference, **Deborah Autor**, who was on the report drafting team, said, “We really pushed ourselves hard to step back and think about what we needed to do to take a quantum leap forward to

really deal with the challenges of globalization, not just for today, but ten years down the road. Even if we were to catch up to today, by the time we got there, the world would have changed. We had to recognize that we can’t do it alone.” Autor is the Deputy Commissioner for Global Regulatory, Operations and Policy, U.S. Food and Drug Administration.

The fourth prong delves into partnering with “public and private third parties,” Autor said. “We need to think about the leverage models we can use so that we can have enough information that we need to have about all these facilities, all these products and all these supply chains all around the world, which are many and very disperse. We anticipate they will be even more so, ten years from now.”

FDA is accepting risk by this strategy, but sees no other choice. “If something goes wrong, and I’ve relied on my counterpart, I can see folks in this country saying, ‘How come you weren’t there? How come you didn’t go to this facility and the EU did?’”

The reality is, she said, FDA does not “have enough resources to be every-

where and if I choose to go everywhere that the EU went, just because I’m worried, for example, that something might go wrong and I might have to account for the fact that I relied on someone else and I choose to do duplicative work, then there is a lot of work that I cannot do.”

Ultimately, Autor said, FDA must “leverage and be effective and efficient so that we are treating like risks in equivalent ways, regardless of where they are located. We need to figure out how to get there. That is the challenge at FDA. That is the big picture and that is where we are going.”

Later during the conference, **Kimberly Trautman**, Expert on Medical Device Quality Systems, CDRH, U.S. FDA, said that the pilot program would apply to companies that receive and choose to share with FDA audit reports from accredited third parties that adhere to ISO 13485:2003, *Medical devices—Quality Management Systems—Requirements for Regulatory Purposes*. FDA is recognizing third-party auditors accredited by fellow Global Harmonization Task Force member regulatory authorities:

- Canada’s Medical Devices Conformity Assessment System
- Australia’s Therapeutic Good Administration
- European Union Notified Body Accreditation System
- Japan’s Medical Device Ministry of Health, Labour and Welfare

The Global Harmonization Task Force was conceived in 1992 in an effort to achieve greater uniformity between national medical device regulatory systems.

If the information contained in the audit meets the needs of the FDA compliance program, the Agency will give that firm a bye on inspections for a year. However, firms need to submit the report to FDA within 90 days of the close of the audit and must include all reports

## Four Prongs to FDA’s Product Safety/Quality Pathway

FDA is developing an international operating model (1) that relies on enhanced intelligence, information sharing, data-driven risk analytics, and the smart allocation of resources through partnerships. The new approach rests on four core building blocks:

- 1) FDA, in close partnership with its foreign counterparts, will assemble global coalitions of regulators dedicated to building and strengthening the product safety net around the world.
- 2) With these coalitions, FDA intends to develop a global data information system and network in which regulators worldwide can regularly and proactively share real-time information and resources across markets.
- 3) FDA will continue to expand its capabilities in intelligence gathering and use, with an increased focus on risk analytics and thoroughly modernized IT capabilities.
- 4) FDA will effectively allocate agency resources based on risk, leveraging the combined efforts of government, industry, and public- and private-sector third parties.

### References

1. “Pathway to Global Product Safety and Quality,” U.S. FDA, July 7, 2011, [www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/GlobalProductPathway/UCM262528.pdf](http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/GlobalProductPathway/UCM262528.pdf)

of ISO 13485 audits that were issued during the preceding 2-year period.

Once the Agency receives the report, the CDRH's Office of Compliance Field Operations Branch will ask the Office of Regulatory Affairs (ORA) to not inspect the firm for 30 days. During this time, CDRH/OC will review the audit report per Compliance Program 7382.845. By the end of the 30 days, CDRH/OC will notify both the firm and the Office of Regulatory Affairs of the result, which could be for the District Office to proceed with the routine GMP inspection or remove the firm/facility from the workplan for one year.

Trautman stressed that the pilot program does not preclude FDA from conducting PMA preapproval inspections or for-cause inspections.

During the next two years, the FDA will determine if the policy is viable. FDA is also "figuring out how many times a firm can sign up [for the program]," according to Trautman.

In the course of her presentation, Trautman gave examples of past FDA information-sharing pilot programs. In 2008, FDA implemented a multi-purpose audit pilot program with Health Canada. Manufacturers who participated in the program had the opportunity to be assessed by a qualified auditing organization that met the regulatory requirements of both the United States and Canada. In 2009, the Agency initiated the Third-party (Accredited Persons) Inspection Program. Trautman said that this program hasn't been utilized very much as "instead of waiting for FDA to come in for free, now somebody would have to pay [the accredited persons]."

**[Editor's note:** The U.S. FDA and the European Medicines Agency announced in December that they are formally adopting the information sharing procedure tested during an "EMA/FDA Joint Inspection Pilot Program." This program related to GMP inspections of drug product facilities. See related story, p. 46.]

**Carmelo Rosa**, Supervisory Consumer Safety, CDER, U.S. FDA, agreed that inter-regulatory communication and in-

formation sharing with other regulatory authorities is necessary to inspect the more than 3,000 domestic and foreign registered drug manufacturing firms.

"It's not possible for the FDA to inspect the world as much as we would like to. We need to share information."

In April 2011, he said that the European Directorate for the Quality of Medicines (EDQM) placed a firm under an import alert. After FDA talked to the EDQM inspectors, FDA was able to place its own alert on the company without manually inspecting it.

Rosa said that many of the items that firms are being cited for are not new. "Things that we found 5-10 years ago are the same things we are finding in our inspections now," he said. Some of the most important issues that were cited related to inadequate laboratory controls, lack of procedures and QA systems, he said.

Another important issue was related to vendor qualification. Rosa said that that firms are still being cited because of poor or inadequate qualification programs. He shared a 2011 warning letter where the FDA cited a firm with a failure to investigate complaints about oversulfated chondroitin sulfate in its product. The firm also failed to extend the investigation to other lots that used the same crude lot and failed to conduct an audit on its vendor that could have possibly caught the problem.

Rosa said that the Agency is looking to see what the possible cause could be for the repeating deviations. In the meantime, he said that the FDA is working with other agencies to identify compliance issues and collaborating with industry to resolve them.

**Diane Alexander**, Chief, Biological Drug and Device Compliance Branch, CBER, U.S. FDA, had an interesting admission at the conference. She said there is not a trend in the deficiencies in the untitled and warning letters that CBER sends out. However, Alexander noted that in FY 10 the citations that were issued were "unique" to those that had been listed in the past.

The deviations were:

- 211.192 – "You failed to thoroughly investigate..."
- 211.113(b) – "Your firm failed to establish and follow procedures designed to prevent microbial contamination..."
- 211.94(a) – "You failed to assure that drug product containers or closures are not reactive..."
- 600.14 – "You failed to report biological product deviations..."
- 600.12 – "You failed to inform FDA about each change..."

Alexander also identified the top six citations for biological drug intermediates and substances in FY10. Citations were related to: investigations, production and process controls, control of microbiological contamination, equipment cleaning and maintenance, laboratory controls, and control of components.

Alexander reminded the audience that FDA expects voluntary compliance from the industry when significant deficiencies or problems are identified. She said that if voluntary compliance is not achieved, FDA will ensure compliance by issuing a notice of intent to revoke a license or, in the case of domestic firms, a firm injunction.

## About the Experts

**Kimberly A. Trautman** is the U.S. FDA's Expert on Medical Device GMPs and Quality Systems. She reviews inspection reports of foreign and domestic medical device manufacturers to identify violations of the GMP requirements and provides GMP guidance to FDA field investigators and the medical device industry. Kimberly also provides GMP expertise to CDRH for various legal actions and regulatory reviews.

**Carmelo Rosa** is a member of the foreign drug inspection cadre. He has conducted many inspections of complex pharmaceutical inspections and other commodities regulated by the FDA that have resulted in significant regulatory actions initiated by the FDA. He currently serves as the Director for the Division of International Drug Quality.



*continued at bottom of page 56*

## Regulatory Authority *Update*

### Challenges with the Maintenance of EU GMPs

**Karen Ginsbury, PCI Pharmaceutical Consulting; Stephan Rönninger, F. Hoffmann-La Roche; Georg Rössling, PDA, with support from Jim Lyda, PDA**

On November 23, 2011 a PDA delegation had the honor to participate in the Interested Parties meeting of the EU inspectorates hosted by the European Medicines Agency (EMA) at their headquarters in London.

The interested parties invited included:

- European Self-Medication Industry (AESGP)
- Active Pharmaceutical Ingredient Conference (APIC)
- European Federation of Pharmaceutical Industry and Associations (EFPIA)
- European Generic Medicines Association (EGA)
- European Industry Pharmacists Group (EIPG)
- European QP Association, Animal Health Industry Associations (IFAH-Europe)
- International Society of Pharmaceutical Engineers (ISPE)

The meeting had a packed agenda with presentation of an update on the current status of the Inspector's Working Group (IWG) 2011 work plan followed by a series of presentations from industry representatives led by PDA.

**David Cockburn**, Head, Manufacturing and Quality Compliance, EMA and chair of GMP/GDP Inspectors Working Group, described what had been achieved by the GMP/GDP Inspectors Working Group (IWG) in 2011, and **Dimitrios Catsoulacos**, Scientific Administrator, Manufacturing and Quality Compliance, EMA, gave a sneak preview of next year's work plan which will be published in early 2012. The major topics included are:

- The maintenance of the EU-GMPs to implement principles from ICH Q8, Q9 and Q10
- Implementation of the falsified medicines legislation
- Assisting the European Commission in standards for third country assessment
- Developing a Good Distribution Practice guide for APIs
- Creating a guidance on a risk assessment on GMP for excipients and new or updated community procedures as needed

Also, the following EU-GMP requirements are being worked on currently:

- In Chapters 1 and 2 on "Quality Management System" and "Personnel," the chapters will be revised to integrate concepts and terminology of ICH Q10
- For Chapters 3 and 5 on dedicated facilities, a revised strategy including toxicological evaluation and a concept paper released by Safety Working Party (SWP) will be used
- In Chapter 5, traceability of supply chain will be revised to be in line with the falsified medicines legislation and control of starting materials
- In Chapter 6, there will be an ongoing revision to update the text to reflect analytical methods transfer current practices
- In Chapter 7, there will be a revision in line with ICH Q10. Also, there will be an expanded scope to include all outsourced operations
- In Chapter 8, a concept paper on product shortages will be revised to align text with the falsified medicines legislation
- Annex 2 will include GMP for biologic products
- Annex 15 will be considered and link to the QWP guideline on process validation
- Annex 16 will reflect changes to the GMP guide and global pharmaceutical environment as well as integrating requirements of the falsified medicines legislation
- Annex 17 will be considered and link to the QWP guideline on parametric release and real time release testing (RTRT)
- Good Distribution Practice requirements for APIs and drug products are being developed

#### EU GMPs

At the meeting, PDA presented concerns with recent revisions to the EudraLex Vol. 4 (EU GMPs). Members had identified a changed environment as drivers for updates to most parts of the GMPs and the GDP regulations. The drivers include: legislation e.g., the falsified medicines directive; ICH Q8, Q9 and Q10 integration; harmonization activities with PIC/s and the unclear status of Part 3 of the EU-GMPs. The problems that members had noted, included:



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- Case studies and validation of environmental monitoring
- Aseptic processing, process simulations and the use of isolators for sterile product manufacturing
- Microbial identification
- New technologies and rapid microbiological methods
- The very popular Ask the Regulators open panel discussion

- Lack of consistency between chapters. For example, Quality risk management is mentioned in Chapter 1 for drug product only. Annex 1 traditionally required QRM for environmental monitoring only; whereas, it has far wider applicability in aseptic processing. The status and content of Part III of the GMPs is unclear as it presently includes the site master file and ICH Q9 and Q10. In fact, if the website is accessed, and the ICH Q9 or Q10 files are clicked, the link connects to all of the ICH quality guides. This raises a question as to whether all of the ICH quality guides are now within the scope of the GMP guidance
- Inconsistent terminology. For example, Chapter 1 adopts the term quality management system; whereas, ICH Q10 uses the term “pharmaceutical quality system.” In other places (particularly the proposed GDP draft), the terms quality unit, quality assurance, quality system and quality control are all found. The glossary does not undergo revision as individual chapters are updated
- Lack of a holistic approach. For example, Different competent authorities have different risk tolerance levels as evidenced in the pre-filter integrity test issue and in the approach to the need (or not) for dedicated manufacturing facilities and application of risk management principles. Annexes may give different messages or be updated independently of, and not necessarily in line with, chapters discussing the same topics. For example, Chapter 1 discusses QP responsibilities for batch release as does Annex 13, “Investigational Medicinal Products,” and Annex 16 (currently under revision with a concept paper issued) on QP certification of batches. Another aspect is that portions of the ICH guidances are imported “as is” rather than adopting the principles and appending the guidance which is intended to be voluntary rather than mandatory. This can be found in the concept of lifecycle product management in Chapters 1 and 2 and RTRT. The addition of these principles have an influence on the process of parametric release and therefore influence the requirements explained in Annex 17

PDA's presentation wrapped up with some thoughts to move forward. It focused on the need for training involving some industry representatives and incorporating ICH principles rather than “bits” of text. The presentation ended with a question as to whether it might not be an opportune time for an overhaul of the GMPs into a format similar to that of Part 2: “Basic Requirements for Active Substances used as Starting Materials.”

EMA responded that the GMPs were essentially already one document and that industry already had some say in the updates through the commenting process. EMA mentioned that it is constantly considering how to improve and better understand industry concerns before or after issuing a concept paper while at the same time maintaining a clear line between regulator and industry. ➤

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EMA noted that they had talked about improving the consultation process by reaching out more to industry than they are currently doing. It was suggested by APIC that when there is a hot topic there should be an informal way to get contacts from regulators and industry to have a dialogue whereby an ad hoc task force brings outcomes back to each side. EMA said it would think about it, but noted that meeting with a limited/selected number of organizations is problematic.

The second topic addressed the revision of the QP requirements (Annex 16) and focused on what the QP's role is within the quality management system and the level of data that a QP could rely on if a company follows an ICH Q10 type quality system. A discussion followed addressing topics such as personal knowledge and role of QP in releasing batches with associated deviations. It was generally felt that there should be a statement that when the QP signs a QP declaration it does not mean the QP has to perform all the duties personally, but could rely on the companies QMS. The European QP Association representative indicated that their preference (also mentioned by PDA) was that Annex 16 should focus on batch certification/release, and other duties of the QP would be addressed elsewhere in the GMPs, if at all. It was their opinion that if a QP was assigned a lot of other tasks, this would corrupt their ability to focus on batch release. EMA responded by reiterating that there is no intention of adding new tasks for the QP.

#### Dedicated Facilities

The topic on dedicated facilities was a key item for all of the participating interested parties. The Safety Working Party (SWP) released a concept paper in October 2011, which was open for comments through January 2012, regarding the use of toxicological assessments. APIC pointed out that while they fully support the SWP paper, risk assessments are needed not just for cleaning acceptance criteria, but also for the cleaning procedures themselves. EFPIA made the point that industry should be advised earlier rather than later of the intended decisions, because when making decisions about facility planning they are presently trying to second guess what's going to be allowed. Industry is requesting a clear guidance now, rather than waiting for the toxicological position and then

waiting for the actual guidance to come out. ISPE pointed to the Risk-MaPP which had been agreed on as an acceptable concept. PDA mentioned that during an inspection performed on behalf of EMA in the United States, two different inspectorates participated and couldn't agree amongst themselves if the Risk-MaPP position was an acceptable approach. This was addressed as a major finding. GMP inspectors have a clear view on revision of Chapter 5 and have agreed on its text. They have identified other sections in the GMP where it is necessary to update the document according to what is seen on a dedicated facility or not. EMA is waiting for the SWP results. The revision to the guidance will come out after the SWP results are in. However, the EMA noted that the SWP input is only part of the coming guidance.

#### Falsified Medicines Legislation

Position papers were submitted by EFPIA regarding the falsified medicines legislation. EFPIA pointed out that six months into implementation, there were provisions which followed on one from another. For example, delegated acts through 2014 impact safety features activity, which is coming out later in 2017. Several provisions are to be implemented from January 2013 including GDP for APIs and GMP for APIs, import, export, registration of brokers and importation process will come out in July 2013. There is a lot of work to do, and industry will need clarity on harmonized implementation.

EFPIA identified priorities for clarification in the position papers and hope they will be considered when drafting on importation from 3<sup>rd</sup> countries authorities, GMP of APIs, QP role and traceability, GMP for excipients, and audit of suppliers. GDPs are already sufficiently addressed in ICH Q7 so that isn't high priority. Most important is importation. If industry representatives are in contact with 3<sup>rd</sup> country authorities, the legislation will rely on cooperation. Mechanisms must be in place by mid-2013 for these provisions to work. EMA requested industry to reach out to suppliers and manufacturers to clarify what is expected of them. A brief discussion was held on the QP declaration template for APIs GMP conformance. It was generally agreed that the standard of QP declarations received was poor, but that the proposed template was overly burdensome.

#### Improving Cooperation

In summary, a packed agenda was covered. EMA pointed out that from PDA input to this meeting appears to be a common theme and industry should let the regulators know what the concrete expectations are. In order to try to maintain manufacturing in Europe, industry and regulators have an interest to retain creditability and need to work together. EMA would welcome any ideas for improving the cooperation between industry and regulators without any conflict of interest. It should be possible to always reach a conclusion that best serves the patient. ☺

The PDA delegation would like to thank the task force that put together this presentation on behalf of the Regulatory Affairs and Quality Advisory Board:

**Robert Counce**, Hospira, Australia

**Steven Mendivil**, Amgen, USA

**Sue Schniepp**, Oso Bio, USA

**Jim Lyda**, PDA, Europe



# The Universe of Pre-filled Syringes and Injection Devices

October 15-17, 2012 | Red Rock Resort and Spa | Las Vegas, Nevada

## CALL FOR ABSTRACTS /CASE STUDIES

The 2012 Pre-filled Syringe Program Planning Committee invites you to submit a scientific abstract for presentation at PDA's 2012 Universe of Pre-filled Syringes and Injection Devices. The theme of this year's conference is: ***Integrating the Unmet Market Needs: Bringing it All Together for Tomorrow's Success.***

Suggested topics include, but are not limited to:

- **Advances in Primary Container/ Prefilled Syringe Technology:**
  - Analytical Characterization Methods
  - Quality Improvements
  - Protein/Syringe Interactions
  - New Materials/Injector Technologies
  - Multiple Chamber Injector
  - Safety Devices
  - Autoinjectors and Add-ons
- **Factors Influencing the Selection and Development of Delivery Devices:**
  - Human Factors
  - End User Needs and Perspectives
  - Interaction between Device and Syringe
  - Regulatory Filing Process
  - Impact of Drug Characteristics
- **Case Studies: Market and Regulatory**
  - Global Market Trends
    - Asia Market
    - Europe Market
    - Latin America Market
    - North America Market
  - Regulatory and Clinical Strategies
  - Combination Products
- **Case Studies: Manufacturing**
  - Vial to Pre-filled Syringe Conversion
  - Integration of PAT and Q8
  - Manufacturing Technologies Based on Disposable Processing Units
  - Material Selection
  - Stability Study Strategies
  - Aseptic Processing and Final Packaging Best Practices
  - Tech Transfer Best Practices
  - Contract Manufacturing Best Practices
  - Clinical Trails with Prefilled Syringes
  - Release Testing
    - Incoming Components
  - Microbial Control
  - Quality Agreements

**Abstracts must be received by March 30, 2012 for consideration.**  
Please visit [www.pda.org/prefilled2012](http://www.pda.org/prefilled2012) to submit your abstract.

Case studies are particularly desired. Commercial abstracts featuring promotion of products and services will not be considered. After June 1, 2012, you will be advised in writing of the status of your abstract. PDA will provide one complimentary registration per podium presentation. Additional presenters and all poster presenters are required to pay appropriate conference registration fees. All presenters are responsible for their own travel and lodging, with the exception of health authority speakers.

### QUESTIONS?

Contact PDA:  
**Leon D. Lewis**  
Manager  
Programs and Web Seminars  
Tel: +1 (301) 656-5900 ext. 149  
Fax: +1 (301) 986-0296  
Email: [lewis@pda.org](mailto:lewis@pda.org)

### ALL ABSTRACTS WILL BE REVIEWED

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

### ATTENTION EXHIBITORS

PDA is seeking vendors who provide excellent products/services in support of this conference. Space is limited and is on a first-come, first-service basis. To reserve your space, please contact David Hall at [hall@pda.org](mailto:hall@pda.org) or +1 (301) 656-5900 ext.160.

[www.pda.org/prefilled2012](http://www.pda.org/prefilled2012)

# PDA Suggests Less Prescription in Media Fills Guidance

*For the comments grid, visit [www.pda.org/regulatorycomments](http://www.pda.org/regulatorycomments)*



December 23, 2011

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, rm. 1061  
Rockville, MD 20852

RE: Draft Guidance entitled “Media Fills for Validation of Aseptic Preparations for Positron Emission Tomography (PET) Drugs”;  
Docket No. FDA-2011-D-0691

Dear Sir/Madam:

PDA is pleased to offer comments on the draft guidance entitled “Media Fills for Validation of Aseptic Preparations for Positron Emission Tomography (PET) Drugs”. PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by a committee of experts with experience in the manufacture of Positron Emission Tomography Drugs, as well as manufacturing and validation of aseptically processed drug substance and drug products. The committee included members representing our Regulatory Affairs and Quality and Science Advisory Boards. PDA appreciates the opportunity to offer comments and wishes to thank FDA for the opportunity to do so.

In general, our reviewers found this to be a document which will have utility for the manufacturers of PET Drugs and will provide needed guidance to them in the conduct of aseptic processing simulation studies. PDA believes that the principles contained in this draft guidance should be consistent with other FDA documents which address the conduct of aseptic processing simulation studies, as well as other industry documents and practices addressing the subject. To that end, we have made some suggestions in the accompanying table which we believe will further strengthen the draft guidance, bring it into alignment with these other documents and practices and increase the utility to the manufacturers of PET drug products.

We would be pleased to offer our expertise in a meeting with FDA to provide clarification of our comments. Should you wish to pursue that opportunity, or if there are any other questions, please do not hesitate to contact me.

Sincerely,

Richard V. Levy, Ph.D.  
Senior Vice President, Scientific & Regulatory Affairs, PDA

CC: Richard M. Johnson, PDA

Robert L. Dana, PDA

## PDA Commenting Task Force

**Bob Dana**, PDA (Task Force Chair)

**Hal Baseman**, ValSource

**Walter Henkels**, ConcordiaValSource

**Mike Long**, ValSource

**Russ Madsen**, The Williamsburg Group

**Ken Muhvich**, Micro-Reliance

**Barbara Zinck**, Zinck Consulting

# PDA Requests Addition to GDP Guideline

For the comments grid, visit [www.pda.org/regulatorycomments](http://www.pda.org/regulatorycomments)



31 December 2011

European Commission  
Pharmaceuticals Unit  
Brussels  
SANCO-gmp@ec.europa.eu

European Medicines Agency (EMA)  
Inspections Sector  
London  
ADM-GMDP@ema.europa.eu

Reference: *Commission Guidelines on Good Distribution Practice of Medicinal Products for Human Use, Brussels, SANCO/C8/AM/lan D(2010) 380358, 15 July 2011.*

To: Responsible Person: European Commission, Pharm. Unit

To: Responsible Person: EMEA Inspections Sector

PDA is pleased to have the opportunity to comment on the revised Guideline on Good Distribution Practice. Attached you will find our general and specific comments in the standard EMA comment matrix. Our general comments include:

**Scope of the guideline:** We recommend addition of a Scope section giving information on the types of products and the responsibilities of persons covered by the guideline (Comment 1).

**Risk based concepts:** We recommend the guideline embody risk-based thinking and decision making which will allow flexibility and validated solutions to transport issues (Comments 2-3).

**Definitions & terminology:** We recommend use of existing definitions consistent with ICH and/or other sources, and a review/deletion of qualifiers such as 'any' and 'all' on a case-by-case basis (Comments 4 & 6).

**Consultation and deadline for coming into operation:** Considering the magnitude of this revision we recommend consideration of a second round of consultation and an extension of the 'coming into operation' deadline to at least 18 months (Comment 5).

**Industry technical resources:** In support of the revision process we are sharing with the Commission and the drafting group copies of four PDA Technical Reports (Nos. 39, 46, 52 & 53) which are directly related to GDP technical issues. They will be sent to the EC and EMA contacts under separate email cover (Comment 7).

Please contact me, or James Lyda of the PDA staff ([lyda@pda.org](mailto:lyda@pda.org)), if you have any questions.

With very best regards,

Georg Roessling, Ph.D.  
Senior VP, PDA Europe

[Roessling@pda.org](mailto:Roessling@pda.org)

cc: S. Rönninger, S. Schniepp, R. Levy, J. Lyda, R. Dana

## PDA Commenting Task Force

**Jim Lyda**, PDA (Task Force Co-chair)

**Paul Ellis**, GlaxoSmithKline

**Sue Schniepp**, OSO Biopharmaceutical

**Barbara Jentges**, PHACT (Task Force Co-chair)

**Karen Ginsbury**, PCI Pharmaceutical Consulting

**David Ulrich**, Abbott Laboratories

**Erik van Asselt**, Merck Sharp & Dohme

**Steve Mendivil**, Amgen

**Rafik Bishara**

**Siegfried Schmitt**, Parexel

# U.S. FDA and EMA Now Relying on Each Other

Walter Morris, PDA

The U.S. FDA and the European Medicines Agency announced in December that they are formally adopting the information sharing procedure tested during an “EMA/FDA Joint Inspection Pilot Program.” This program is related to GMP inspections of drug product facilities.

Below is the full text of their December 5, 2011 announcement.

**[Editor’s Note:** For background on the pilot program, see “EMA/FDA Joint Inspections to Continue Following Pilot,” in the October 2011 *PDA Letter*, p. 34., it was reported that the EMA had completed joint inspection programs for Good Clinical Practices and APIs.]



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

5 December 2011

## Enhancing GMP Inspection Cooperation between EMA and FDA Moving from confidence-building to reliance upon

### 1. Background

Many demands are placed on the resources of the EEA and FDA GMP inspectorates. With the globalisation of the manufacture of medicines, it is increasingly evident that sharing of resources by authorities is necessary and in the best interest of public health.

FDA and the European Regulatory Network, recognising the need for cooperation on inspections, have explored options to increase information sharing and ultimately rely upon that information to meet inspectional obligations. These include confidentiality arrangements and participation in joint inspection and information-sharing projects.

Authorities from both regions have recognised the potential resource efficiencies to be gained from progression beyond existing collaborative projects towards reliance on each others inspection outcomes. It has been noted that a large number of inspections are being carried out by FDA in EU and vice versa, and that in the face of the globalisation of manufacture and shift of manufacturing base away from Europe and USA, a change may be justified. Since EMA is responsible for requesting many EEA inspections in USA, it has been asked to take a lead on the EU side in exploring how this change could come about.

Both sides see this progression as an important next step, and FDA believes that using EMA as a central contact point in relation to GMP inspections for both centrally and nationally authorised products is critical.

Finally, such a change would not only enable better use of inspection resources, but also provide some relief to manufacturers, who direct substantial resources to host inspections.

## 2. Proposed Strategy

A strategy has been developed that will allow some inspections on each others' territories to be deferred or waived completely based on a number of considerations. The strategy is applicable to GMP inspections related to manufacturing sites located in USA and EEA involving products for both human and veterinary use.

The general approach will utilise information exchange for sites. It will primarily focus on sites which are already known to each authority and already have a history of satisfactory GMP compliance following previous inspections by EEA authorities in the case of sites in USA and by FDA in the case of sites in EEA.

The most likely impact will consequently be in the area of routine post-authorisation/surveillance inspections. Pre-authorisation/pre-approval inspections will continue largely unchanged, as by definition the sites are unknown or a specific inspection trigger has been identified. Exceptions nevertheless may be made on a case-by-case basis.

The following considerations will be taken into account:

- As mentioned above, the inspection history of the site.
- The nature of the product.
- Quality defects associated with the site.
- Variations or significant changes since the last inspection.
- Outstanding inspection follow up.
- Whether there is an urgent public health need to expedite regulatory decision-making e.g., product shortage.

Waiving inspections connected to the centrally authorised products will be proposed by EMA but the final decision will rest with the Supervisory Authority.

## 3. Next Steps

EMA plans to start this initiative for inspections planned for adoption by CHMP/CVMP from January 2012.

FDA also plans to start to implement this initiative in January 2012.

Member States have been encouraged to develop similar approaches for inspections to be performed in USA that are not directly coordinated by EMA. In some cases, this will require the establishment of bilateral confidentiality arrangements with FDA.

The EMA/FDA joint inspection pilot project for dosage forms will continue as it remains important to maintain mutual confidence and build further mutual understanding of GMP inspection approaches.

Both parties will keep track of the number of inspections deferred or waived, and any other information that both parties agree upon. After a period of 3 years, the approach should be reviewed and further extension considered.

## 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 Completes Recommendations for User Fee Programs

The U.S. FDA announced that it has completed its recommendations for three user fee programs. The programs include the fifth authorization of the Prescription Drug User Fee Act (PDUFA), and new user fee programs for human generic drugs and biosimilar biological products.

The recommendations were transmitted to Congress on January 13.

#### U.S. FDA Issues Report on Improving Guidance Document Development

The U.S. FDA has issued a report on some of FDA's best practices and makes recommendations on improving guidance document development.

The report, entitled, *Food and Drug Administration Report on Good Guidance Practices: Improving Efficiency and Transparency* was prepared in response to one of the action items associated with FDA's

transparency initiative.

Comments are requested by February 28.

### Europe

#### Danish Medicines Agency Clarifies Active Substance Master File Process

The Danish Medicines Agency has released a document on its website clarifying the process of updating an active substance master file (ASMF) for marketing authorization holders (MAH).

For example, the document specifies that the active substance manufacturer is required to inform the MAH when changes are made to the applicants' part and/or the restricted part of the ASMF. The MAH is responsible for applying for these changes in order for them to be implemented in the marketing authorization.

#### TGA Requests Comments on Streamlined Submission Process as Part of Revision to Prescription Medicines Regulation

Australia's Therapeutic Goods Adminis-

### Key Regulatory Dates Comments Due:

**February 28 — U.S. FDA Issues Report on Improving Guidance Document Development**

tration (TGA) is asking for comments on its streamlined submission process project, which will improve submission quality and provide predictable timeframes for the evaluation and registration of prescription medicines in Australia.

Some of the key differences between the streamlined submission and the previous process can be found in the pre-submission phase, submission quality and in the submissions themselves.

The project is part of the business process reforms program the TGA is undertaking to regulate prescription medicines in Australia. 🇺🇸

### Progress of the Quality Topics at the ICH Seville Meeting continued from page 37

Q9 or Q10 folders.

There are no further formal activities planned by the Q-IWG. However the GCG may ask former members to support an ICH sponsored training in emerging markets.

#### Manufacturing Practice of APIs (ICH Q7)

Activities related to this 10 year old ICH guideline were discussed briefly by the ICH Steering Committee. It has been suggested to set up a process to assess the currency of this guideline. This might result in an ICH Q7 Implementation Working Group (IWG) to potentially start after ICH Q11 is finished. The deliverable of such an ICH Q7-IWG might be a Q&A document.

#### Futher Activities

The *Pharmaceutical Development* (ICH Q8), *Development and Manufacturing of Drug Substance* (ICH Q11), *Quality Risk Management* (ICH Q9) and *Pharmaceutical Quality Systems* (ICH Q10), which support the ICH quality vision of 2003: "Develop a harmonised pharmaceutical quality system applicable across the life cycle of the product emphasizing an integrated approach to quality risk management and science," will be further developed by the approval of the ICH Q11 guidance which is expected soon. Further activities will lead to the benefits of the implementation of the ICH paradigm for building-in quality and creating more efficient regulatory processes.

### About the Author

Dr. -Ing **Stephan Rönninger** is the Head of External Relations Europe/Japan at F. Hoffmann-La Roche based in Basel, Switzerland.



He is responsible for collaboration, information management and commenting regarding Quality Management, Good Manufacturing and Distribution Practice topics. He acts as the Chair and the European Regional Leader of the Regulatory Affairs and Quality Advisory Board for PDA and is one of the founders and co-chairs of the Paradigm Change in Manufacturing Operations. 🇺🇸



Register before  
**March 2, 2012** –  
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registration savings  
deadline for this  
event!



# PDA/FDA Virus and TSE Safety Conference

*Proactive Approaches to Mitigate Virus & TSE Risk*

**May 15-17, 2012**

Hyatt Regency Bethesda | Bethesda, Maryland

## Agenda Now Posted Online!

Freedom from viral contaminants is a paramount concern for recombinant biopharmaceuticals and plasma-derived medicinal products. Viral safety is achieved by a rigorous program of cell bank and source material testing in conjunction with a demonstration that product purification is capable of removing or inactivating viruses.

PDA has been very active in the area of advancing viral clearance technology as well as educating our industry on the regulatory approaches and technical issues surrounding viral safety. The *PDA/FDA Virus and TSE Safety Conference* represents another opportunity to discuss the topic of viral safety for biopharmaceutical and plasma derived products.

Plenary sessions at this year's conference include:

- Regulatory Update: Biopharmaceuticals
- Current Clearance Technologies
- Assessing Virus Clearance of Specific Unit Operations
- QbD Type Clearance Studies – Role and Structure of Risk Assessments and Design of Experiment Studies
- Hepatitis E Virus – A New Challenge for Human Plasma and Animal Sourced Products?
- Virus Preparations Used for Clearance Studies
- Risk Mitigation Strategies – Raw Materials
- TSE Safety of Cell Substrates
- In Vitro Cell-based Assays for TSE Infectivity

**Visit [www.pda.org/virustse2012](http://www.pda.org/virustse2012) for more information.**

**Pre-Conference Workshop: May 14 | Exhibition: May 15-16 | Courses: May 18**

**Call for Posters:** Submit an abstract/case study for poster presentation at this year's meeting. Abstracts are due **March 9, 2012!**



# Achieve Excellence: Attend the 2012 PDA Annual Meeting

Phoenix, Ariz. • April 18-20 • [www.pda.org/annual2012](http://www.pda.org/annual2012)

Committee Member Miguel Montalvo, Expert Validation Consulting

As a member of the Program Committee, I would like to invite you to attend the 2012 PDA Annual Meeting that will be held at the JW Marriott Desert Ridge Resort, Phoenix, Ariz. on April 16-18<sup>th</sup>. TRI courses will be offered from April 19-20<sup>th</sup>.

## Theme of the Conference

Our theme for this year is “*Manufacturing Innovation: Achieving Excellence in Sterile and Emerging Biopharmaceutical Technology.*”

I see this theme as having two different but related perspectives. The first viewpoint demonstrates that in order to achieve excellence

with our current processes we need to apply effective innovation and continuous improvement based on concepts such as the application of the lifecycle approach, which is the base for the new U.S. FDA viewpoint on process validation. The other outlook of our theme is more focused on emerging technologies and how to understand and implement them within our biopharmaceutical regulatory and industrial environment.

## Why it is Important to Attend

We are facing extremely tough conditions and challenges within our industry, not only due to our economic pressures and mergers/acquisitions, but a globalization factor that is expanding at a rate that was hard to imagine decades earlier. For our current processes, in order to remain competitive, we need to implement a continuous improvement concept. This needs to go well beyond quality implications and include all aspects of our operations, business and scientific decision making. The meeting will provide discussions and ideas on how to implement these concepts and how to verify their effectiveness.

In terms of new challenges and emerg-

ing technologies, our meeting will include presentations by industry experts on how to apply such processes considering all the different requirements and conditions. The goal is to provide an increasing number and better quality of therapy options to our patients at a reasonable cost, which is a daunting challenge due to the complex technologies and individualized applications involved in these processes.

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*You will not want to miss this opportunity to discuss critical topics and to share your experiences and concerns with top industry personnel and scientists in order to shape the future of our business*

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You will not want to miss this opportunity to discuss these critical topics and to share your experiences and concerns with top industry personnel and scientists in order to shape the future of our business. In addition, the meeting will provide an extremely valuable networking opportunity for experienced management personnel as well as novices to our operations and scientific functions. This is the most important PDA event of the year, and we expect a large portion of our globalized membership to be present. Come network with old friends and meet new ones.

## Main Topics Addressed

The meeting will be conducted in our traditional format with three parallel concurrent sessions with several main topics to be addressed, including:

1. Innovation and Productivity in Large Scale Manufacturing
2. Personalized Medicine/Cellular Therapeutics
3. Control Strategies for Biopharmaceuticals
4. Large Scale Production of Biopharmaceuticals

As at every Annual Meeting, our interest groups will also conduct their independent sessions to discuss the latest advances and news on each particular area with participation from industry experts in their field.

## Sunday, April 15<sup>th</sup>

In addition to the formal conference proceedings, we have put together an impressive choice of optional and fun events beginning with the 6<sup>th</sup> Annual PDA Golf

Tournament at the Wildfire Golf Club and the 6<sup>th</sup> Annual Fun Walk/Run on Sunday, April 15<sup>th</sup>. Make your conference experience a well-rounded one by taking part in

these networking activities.

## Monday, April 16<sup>th</sup>

At the Opening Plenary on April 16<sup>th</sup>, the committee is excited to present two distinguished leaders in the advancement of cancer therapy. **David Shanahan**, President, Mary Crowley Research Center and CEO and Founder, Gradalis, will provide an entrepreneurial vision for the transformation of cancer treatment through personalized medicine. Joining him will be **Ted Love**, MD, a pioneering physician/scientist in the development of cancer and cardiovascular biotechnology derived therapies. Love will use his perspectives as Executive Vice President, R&D and Technical Operations at Onyx Pharmaceuticals and a board member of the California Institute for Regenerative Medicine to present the exciting scientific opportunities ahead for innovative cellular therapies as well as the technical and regulatory challenges.

## Tuesday, April 17<sup>th</sup>

We are also including an additional breakfast session on Tuesday, April 17<sup>th</sup> for career development strategies. This session will include three perspectives on how ►



Register Before  
**April 6th**  
and Save up  
to \$400!

*The Parenteral Drug Association presents...*

# 2012 PDA Innovation & Best Practices on Sterile Technology Conference

**June 18-19, 2012** | Conrad Chicago | Chicago, Illinois

The 2012 PDA Innovation & Best Practices on Sterile Technology Conference will explore new and improve best practices on sterile technology. The meeting will provide participants with a comprehensive review of contemporary practices for the conduct of terminal sterilization and aseptic processing with special emphasis on process simulation, risk assessment/mitigation, parametric release and post-aseptic fill lethal treatments.

The conference will address topics and concerns related to aseptic processing technologies. Plenary sessions will include presentations by regulatory and industry representatives on topics such as:

- Aseptic Risk Assessment Modeling Alternatives
- Regulatory Expectations for Aseptic Processing Submissions
- Highlights of PDA's Revised TR No. 22, Process Simulation for Aseptic Processing
- PDA TR No. 30, Parametric Release of Pharmaceutical and Medical Device Products Terminally Sterilized by Moist Heat
- PDA TR No. 3, Validation of Dry Heat Processes Used for Sterilization and Depyrogenation
- Steam-In Place TR
- Preservative Systems
- Formulation Development on Safe Use
- Coverage of PDA's Position Paper on Post-Aseptic Fill Lethal Treatments
- Intervention Practices in Aseptic Processing
- Sterility by Design – The Newest Thinking in Aseptic Process Definition
- Novel Technologies
- And much more

The complete program agenda will include presentations from regulatory and industry representatives from around the world who will share recent case studies, current and future trends.

Following the conference, PDA's Training and Research Institute will be hosting courses on June 20-21, 2012.



Visit [www.pda.org/steriletechnology2012](http://www.pda.org/steriletechnology2012)  
for more information and to register.

Courses: June 20-21

to advance your career and growth opportunities within our industry with an human resources senior executive, a career strategy advisor and a senior executive recruiter.

We will also have a second plenary on the future of the biopharmaceutical industry.

### Wednesday, April 18<sup>th</sup>

Based on the success of our Fundamentals track from last year, we will conduct a three-topic “Foundations” concurrent session on the morning of Wednesday 18<sup>th</sup> to address:

1. Cleaning Validation for Biotechnology Products
2. Good Distribution Practices
3. Evaluation, Validation and Implementation of New Microbiological

### Test Methods

Later on, we will enjoy a closing plenary session with **Matt Croughan**, Professor, Keck Graduate Institute of Applied Life Sciences, who will speak about the manufacturing opportunities and challenges in the next 10-20 years. **Emily Shacter**, PhD, Chief, Laboratory of Biochemistry, CDER, U.S. FDA, will address emerging regulatory expectations in the same session.

### Thursday and Friday, April 19-20<sup>th</sup>

Immediately following the *2012 PDA Annual Meeting*, April 19<sup>th</sup> and 20<sup>th</sup>, PDA’s Training and Research Institute will be offering eight courses designed to complement what you’ve learned at the conference. The courses include: “Reprocessing of Biopharmaceuticals”

“Recommended Practices for Manual Aseptic Processes”

“Biotechnology: Overview of Principles, Tools, Processes and Products”

“Implementation of Quality Risk Management for Commercial Pharmaceutical and Biotechnology Manufacturing Operations”

“Sterile Pharmaceutical Dosage Forms”

“Process Validation and Verification: A Lifecycle Approach”

“Process Simulation Testing for Aseptically Filled Products”

“Investigating Microbiological Data Deviations”

We all look forward to seeing you in the warm, but welcoming, Phoenix, Ariz. in April. 🌴

## Best Practices Discussed at Sterile Technology Conference

Chicago, Ill. • June 18-19 • [www.pda.org/steriletechnology2012](http://www.pda.org/steriletechnology2012)

Co-chairs Joyce Bloomfield, Merck Sharp & Dohme and Michael Sadowski, Baxter Healthcare

Look no further if you are looking for a conference that will help prepare you to better understand and meet the challenges of manufacturing sterile health care products in the modern global technological and regulatory environment. On behalf of the program planning committee, we would like to invite you to attend the *2012 PDA Innovation & Best Practices on Sterile Technology Conference*, June 18–19<sup>th</sup> in Chicago, Ill.

The theme for this year’s event highlights state-of-the-art approaches that can be employed to strengthen your sterile product manufacturing operations.

We believe that you will find the *2012 PDA Innovation & Best Practices on Sterile Technology Conference* to be a unique unrivaled event! The conference will bring together all levels of industry professionals to network and benefit from a program that will explore new and improved

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*The complete program includes presentations from regulatory and industry experts from around the world who will share their expertise including panel discussions, recent case studies and current and future trends*

---

best practices on sterile technology.

This two-day conference will provide participants with a comprehensive review of contemporary practices for the conduct of

terminal sterilization and aseptic processing with special emphasis on risk assessment/mitigation, contamination control, parametric release and novel sterilization technologies. The complete program includes presentations from regulatory and industry experts from around the world

who will share their expertise including panel discussions, recent case studies and current and future trends. During the conference, PDA will host an exhibition of leading bio/pharmaceutical

companies that will showcase new technologies and trends.

We look forward seeing you June 18–19<sup>th</sup> in Chicago, Ill. 🌴

*The Parenteral Drug Association presents...*



**2012 PDA Europe**

# Advanced Therapy Medicinal Products

*Science Translating into Cures*

## **You Will Learn**

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- Risk-based approach for licensing application submission
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A large, circular inset image in the lower right quadrant shows a microscopic view of a cell or embryo. The cell is blue and translucent, with several internal structures visible. It is surrounded by a dark purple circular border. The background of the entire page features abstract, flowing blue and white lines that suggest a scientific or medical theme.

Register by  
13 April 2012  
and SAVE!

# Implementing Quality by Design in Vaccine Development

Bethesda, Md • May 14 • [www.pda.org/cmc2012](http://www.pda.org/cmc2012)

Committee chair John Finkbohner, PhD, MedImmune

PDA has partnered with a consortium of vaccine manufacturers in the presentation of a the *PDA Chemistry Manufacturing & Controls (CMC) Workshop* on May 14<sup>th</sup> to explore the implementation of Quality by Design (QbD) principles over the vaccine product lifecycle. Five vaccine manufacturers (GlaxoSmithKline, MedImmune, Merck, Pfizer and Sanofi Pasteur) have joined forces, with assistance from PricewaterhouseCoopers, in order to tackle the shared goal of preparing a case study to illustrate how QbD could be applied to vaccine development.

The intent of the workshop is to help stimulate discussion within industry as well as between industry and regulatory agencies to better comprehend and solve the challenges associated with attempting to apply QbD to vaccine develop-

ment. The case study is not intended to provide a gold standard in terms of how vaccines should be developed using QbD, but instead provide opportunities to discuss novel ideas that might help improve the overall process for developing and manufacturing vaccines.

Informal dialogue with regulatory health authorities was initiated as the consortium worked over the past year in developing the “A-Vax” case study with valuable feedback captured in the document. Not only does A-Vax build on the concepts captured in an earlier biotechnology product QbD case study\*, it also provides a venue for extending these concepts in a novel manner to vaccine products using a matrix approach.

During this workshop, four sessions are scheduled with the intent of facilitating

active discussion of concepts captured in the A-Vax case study within the vaccine industry. The focus of presentations will be on the exploration of tools and frameworks enabling ICH Q8, Q9 and Q11 implementation strategies in vaccine development through the use of a model vaccine.

The case study document and study guide will be made publicly available in early 2012 on PDA’s website.

More information on this case study can be found at: [tinyurl.com/75qrpgq](http://tinyurl.com/75qrpgq).

The workshop marks a significant opportunity to expand these critical discussions on the implementation of QbD concepts in vaccine development within the vaccine community. 🍷

## Join Us at the Single Use Workshop

Phoenix, Ariz. • April 18-19 • [www.pda.org/singleuse2012](http://www.pda.org/singleuse2012)

Chris Smalley, Merck

The PDA Single Use Systems Task Force would like to invite you to attend the *PDA Single Use Systems Workshop* planned for April 18-19<sup>th</sup> in Phoenix, Ariz., immediately following the *2012 PDA Annual Meeting*.

The Task Force has almost completed its Technical Report on the design and implementation of single-use systems (SUS) and would like to get your feedback at the event.

SUS offer unique opportunities and challenges for both management as well as the users. SUS can be the solution for many problems that facilities and processes encounter through containment, aseptic control, cross contamination and cleaning challenges. However, it is not the solution for all problems or challenges. Implementing SUS can themselves

pose challenges. We want to share with you the success stories and business cases for considering SUS as well as strategies for implementation.

The workshop will showcase and explain the philosophies championed in its Technical Report. This workshop will offer a different approach by presenting science and risk-based concepts which are flexible and can be applied in many different situations and organizations. We will discuss the following opportunities:

- Reducing upfront capital investment in fixed systems
- Flexibility within processes to adapt to changing market requirements or process modifications
- Savings in cleaning and cleaning validation

- Decrease in facility renovation and startup costs

We will discuss the challenges of identifying possible extractables and which of those may become leachables as well as the impact it might have on your product/process. We will also have presentations on how to improve the reliability and understanding of the SUS capabilities as well as disposal issues.

This workshop will raise these questions and more, but more importantly it will strive to provide answers to these questions. We invite you to this workshop to bring your questions, experiences and challenges to engage in a conversation which will be used to improve the technical report. Please join us for information crucial to professionals using or considering using SUS. 🍷



# PDA/FDA Virus and TSE Safety Conference

*Proactive Approaches to Mitigate Virus & TSE Risk*

May 15-17, 2012 | Hyatt Regency Bethesda | Bethesda, Maryland

## CALL FOR POSTERS /CASE STUDIES

The 2012 PDA/FDA Virus and TSE Safety Program Planning Committee invite you to submit a scientific abstract for posters at the PDA/FDA Virus and TSE Safety Conference. The theme of this conference is: **Proactive Approaches to Mitigate Virus and TSE Risk**. The conference will bring together all levels of industry and regulatory professionals to network and benefit from a program that demystifies the underlying science of Virus and Transmissible Spongiform Encephalopathy Safety and seek to solve the problems that our industry faces on a daily basis.

Suggested topics include, but are not limited to:

- **Current Virus Clearance Technologies, Mechanism of Action; Critical Process Parameters**
- **New Virus Clearance Methods; Novel Unit Operations**
- **Quality by Design and DoE Concepts for Virus Clearance Studies**
- **Application of the Risk Assessment Tools for the Development of an Appropriate Study Design**
- **Model Viruses Used for Virus Clearance Studies; Characterization of Virus Spikes Used for Clearance Studies**
- **Risk Mitigation Strategies for Raw Materials; Treatments to Assure Viral Safety; Inactivation of FBS or Trypsin or Other Animal Derived Raw Materials.**
- **New Viruses of Concern – How Can We be Proactive?**
- **Investigational TSE Studies, Detection Methods and Characterization of Spike preparations; comparative TSE studies (methods used for detection of TSE agents; different spike preparations).**
- **Cell Culture Techniques for Detection of TSE Agents**

**Abstracts must be received by March 9, 2012 for consideration.**

Please visit [www.pda.org/virustse2012](http://www.pda.org/virustse2012) to submit your abstract.

Case studies are particularly desired. Commercial abstracts featuring promotion of products and services will not be considered. Submitters will be advised in writing of the status of their abstract after March 23, 2012. All poster presenters are required to register for the conference at the prevailing registration fee; in addition, poster presenters are responsible for their own travel and lodging.

### QUESTIONS?

Contact PDA:

**Leon D. Lewis**

Manager

Programs and Web Seminars

Tel: +1 (301) 656-5900 ext. 149

Fax: +1 (301) 986-0296

Email: [lewis@pda.org](mailto:lewis@pda.org)

### ALL ABSTRACTS WILL BE REVIEWED

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

### ATTENTION EXHIBITORS

PDA is seeking vendors who provide excellent products/services in support of this conference. Space is limited and is on a first-come, first-service basis.

To reserve your space, please contact David Hall at [hall@pda.org](mailto:hall@pda.org) or +1 (301) 656-5900 ext.160

[www.pda.org/virustse2012](http://www.pda.org/virustse2012)

# TRI Takes Aseptic Processing Course to the Next Level

Bethesda, Md • July 30-August 3 • [www.pda.org/qualitysystems2012](http://www.pda.org/qualitysystems2012)

James Wamsley, PDA

Over 1,000 students have been through PDA's Training and Research Institute's *Aseptic Processing Training Program* to date, and for good reason; it's the most comprehensive and intense course offered in the industry. This ten-day course has given students an understanding and awareness of the entire aseptic process and the tools necessary to implement changes in the process. Based on the many testimonials received, it has been an invaluable course for anyone that has taken it. As a result, there has been a push from the industry and graduates of the *Aseptic Processing Training Program* for PDA to develop something more.

A major challenge of aseptically produced products is to ensure that product quality and patient safety are not compromised. Regulatory agencies recognize this and give significant attention to aseptic processing operations during inspections. This increased attention has been especially prevalent over the past 12 months. Recently, there have also been a number of new guidance documents and guidelines published directly related to quality and aseptic processing, which created the opportunity for PDA to develop a new course intended to take the subject of Aseptic Processing to a new level.

This past December, PDA TRI offered its first ever "Quality Systems for Aseptic Processing" course to a sold out crowd

of 15 students from the industry and the U.S. FDA. Graduates of the *Aseptic Processing Training Program* learned how to optimize their quality systems associated with aseptic processing. The course also provided students with the tools necessary to identify problems and implement change within their process and their facility.

---

## *The course offers continuity and an unparalleled experience in aseptic processing and support systems*

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**David Matsuhira**, President, Cleanroom Compliance, and **Harold Baseman**, Chief Operating Officer and Principal, ValSource, led the expert faculty in this 5-day laboratory course, covering topics such as:

- Risk Assessment and Management
- Sterility by Design
- Investigations and CAPA
- Airflow Study Design and Execution
- Effectively Implementing Change
- Microbiological Controls
- Glass Quality
- Visual Inspection and Global Regulatory Requirements
- Preparing for FDA Inspections

The students participated in a number of interactive laboratory sessions that allowed them to reinforce the lecture ma-

terial immediately in a simulated production environment.

By using key faculty members from the original PDA *Aseptic Processing Training Program*, including the two lead faculty members from that course, the course offers continuity and an unparalleled experience in aseptic processing and support systems. Collectively, the faculty has over 150 years of experience in the industry and has demonstrated their ability to transfer their knowledge in the training setting.

The course was very well received by the students who, in turn, provided PDA with invaluable feedback on how we can further improve the course in future offerings. This feedback will lead to changes in course structure and content, so the next group of students will get even more from this course. If you're one of the over 1000 *Aseptic Processing Training Program* alumni, or you already have significant experience in aseptic processing, you should register for this one and only session, July 20–August 3 before it sells out again; otherwise, you'll just have to wait until 2013 for another opportunity to take this course.

For more information on this course, please visit [www.pda.org/qualitysystems2012](http://www.pda.org/qualitysystems2012) or contact PDA's **James Wamsley**, Sr. Manager, Laboratory Education, at [wamsley@pda.org](mailto:wamsley@pda.org). ☺

### *Audit Program Part of FDA Pathway for Global Product Safety continued from page 39*

Carmelo works very closely with International Regulatory Authorities in different collaboration initiatives and is also responsible for the evaluation of all GMP inspection reports of foreign pharmaceutical manufacturers and testing facilities.

**Diane Alexander** serves as a Supervisory Consumer Safety Officer with the Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research. As a Supervisory CSO, Chief, of the Biological Drug and Device Compliance Branch, she is responsible for the review and evaluation of administrative and legal ac-

tions for biological drugs and devices regulated by CBER. ☺







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

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

### April 2012



#### An Introduction to Visual Inspection

April 3-4, 2012 | Bethesda, Maryland  
[www.pda.org/visualsession2](http://www.pda.org/visualsession2)

#### The 2012 PDA Annual Meeting Course Series

April 19-20, 2012 | Phoenix, Arizona  
[www.pdaannualmeeting.org/courses](http://www.pdaannualmeeting.org/courses)

- Reprocessing of Biopharmaceutical Products - *New Course* | April 19
- Recommended Practices for Manual Aseptic Processes - *New Course* | April 19
- Biotechnology: Overview of Principles, Tools, Processes and Products | April 19-20
- Sterile Pharmaceutical Dosage Forms | April 19-20
- Implementation of Quality Risk Management for Commercial Pharmaceutical and Biotech Manufacturing Operations - *New Course* | April 19-20
- Process Validation and Verification: A Lifecycle Approach - *New Course* | April 19-20
- Process Simulation Testing for Aseptically Filled Products - *New Course* | April 20
- Investigating Microbial Data Deviations - *New Course* | April 20

### May 2012



#### Environmental Mycology Identification Workshop

May 2-4, 2012 | Bethesda, Maryland  
[www.pda.org/mycology2012](http://www.pda.org/mycology2012)



#### 2012 Aseptic Processing Training Program - **SOLD OUT**

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

#### PDA/FDA Virus and TSE Safety Conference Course Series

May 18, 2012 | Hyatt Regency Bethesda | Bethesda, Maryland  
[www.pda.org/virustse2012](http://www.pda.org/virustse2012)



### June 2012

#### PDA/FDA Glass Quality Conference Course Series

June 6-7, 2012 | Bethesda, Maryland  
[www.pda.org/glasscourses](http://www.pda.org/glasscourses)

- Technical Report 43: Identification and Classification of Nonconformities in Molded and Tubular Glass Containers for Pharmaceutical Manufacturing | June 6
- Selection and Utilization of Glass Containers in Pharmaceutical Packaging | June 7



#### Preparation of Virus Spikes Used for Virus Clearance Studies

June 12-13, 2012 | Bethesda, Maryland  
[www.pda.org/viruspikes](http://www.pda.org/viruspikes)



#### Virus Filtration

June 14-15, 2012 | Bethesda, Maryland  
[www.pda.org/virusfiltration](http://www.pda.org/virusfiltration)



#### Basic Micro for the Pharmaceutical and Biopharmaceutical Industries

June 27-29, 2012 | Bethesda, Maryland  
[www.pda.org/basicmicro](http://www.pda.org/basicmicro)

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



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

### Empowering PDA Members

2012 will be a year of member empowerment. PDA President **Richard Johnson** and PDA's 2012-13 Chair **Anders Vinther** outline a number of initiatives PDA will pursue this year to fulfill our mission and help connect our members to each other and help engage them in regulatory processes (see President's Message and Chair's message, pp. 6-8). With respect to the business of PDA, outgoing Chair **Maik Jornitz** worked with Richard Johnson to initiate a new policy of open nominations for Board of Director and Executive Committee elections (see article, p. 10). This new policy is just another way for members to influence the direction of their Association.

A great benefit of belonging to PDA is lending your voice to a group of dedicated professionals interested in helping to shape regulatory and public policy impacting pharmaceutical manufacturing and quality control. In 2012, dedicated members **Phil DeSantis** and **Bill Colletto** will be working with PDA to revitalize the Pharmaceutical Water Systems Interest Group. In an article starting on p. 22, they note that the differences in water treatment methodology in Europe and the United States. Their goal is to get members involved in the ongoing debate about whether Europe should change its water for injection regulation.

Ongoing differences between the United States and Europe were the impetus for the formation of PDA's GMP Points to Consider for Manufacture of Investigational Drug Products Task Force. This group of dedicated volunteers is completing their work in 2012 and expects to produce their technical report on the subject (see article, starting on p. 22).

Public standards are very important in the pharmaceutical industry, so participating in the processes for each pharmacopeia is necessary. **Sue Schniepp** and **Janeen Skutnik-Wilkinson** talk about this in their article, *The Importance of Commenting on Public Standards* (starting on p. 32). In the article, they mention formation of a new PDA interest group, the Pharmacopeial Interest Group. To get an idea of the breadth of issues impacted by the U.S. Pharmacopeia alone, just look at the other two feature articles in this issue: *Lack of Compendia Harmony for Visible Particles Causing Confusion* (p. 26); and *USP Updates Given at PDA's 2011 Micro Conference* (p. 34).

Certain members are constantly engaging with regulatory bodies and are happy to share their knowledge with the membership at large. Take, for example, **Stephan Rönninger**, **Karen Ginsbury** and **Steven Mendivil**. The three of them were involved in important regulatory meetings last fall and collaborated on the following reports in this issue: *Progress of the Quality Topics at the ICH Seville Meeting* (p. 36) and *Challenges with the Maintenance of EU GMPs* (p. 40).

As you can see, PDA is already off to a great start in empowering members. It also has helped us at the *PDA Letter* put together a great issue. I hope you enjoy it.

Postscript: Due to scheduling conflicts on both ends, a *PDA Letter* interview with **James Akers** regarding revised USP General Chapter <1116> on media fills was not completed in time for this issue. Our "fourth USP feature story" will run in the next issue. ☺

# PDA Letter

The PDA Letter is published 10 times per year, exclusively for PDA members.

Subscriptions are not available.

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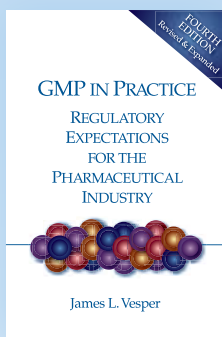
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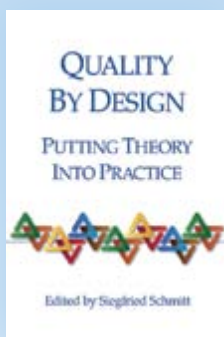
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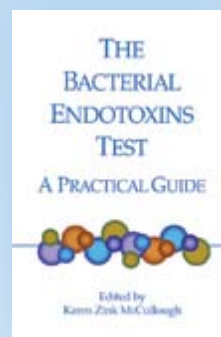
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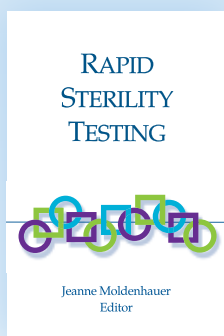
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