People • Science • Regulation

# PDA Letter

Volume XLVII • Issue #7 www.pda.org/pdaletter July/August 2011


## Preview the 20th PDA/FDA Conference

*The Parenteral Drug Association presents...*

# 2011 PDA/FDA Joint Regulatory Conference & TRI Courses

*Quality and Compliance in Today's Regulatory Enforcement Environment*

> "This conference was very useful to hear first-hand information on new initiatives...and network with colleagues."
>
> M. Crnogorac, *Genentech*

**September 19-21, 2011** | Renaissance Hotel | Washington, D.C.

**EXHIBITION:** September 19-20 | **POST CONFERENCE WORKSHOP:** September 21-22 | **COURSES:** September 22-23

Join PDA for an unparalleled conference featuring representatives from all centers of the FDA, international regulators and industry leaders to discuss the future of the global regulatory environment.

At the conclusion of the conference, two plenary sessions: Compliance Update and Center Initiatives will each feature a panel of Agency leader's from the the FDA Centers (CBER, CDER CDRH and CVM) as well as the Office of Regulatory Affairs (ORA). The following speakers will speak on one of both of these panels:

- **Ilisa Bernstein**, Deputy Director, Office of Compliance, *CDER, FDA*
- **Bernadette Dunham**, Director, *CVM, FDA*
- **Richard L. Friedman**, Associate Director, Office of Manufacturing and Product Quality (acting), *OC, CDER, FDA*
- **Christopher Joneckis**, Senior Advisor for CMC Issues, *CBER, FDA*
- **Mary Malarkey**, Director, Office of Compliance and Biologics Quality, *CBER, FDA*
- **Eric Nelson**, Director, Division of Compliance, *CVM, FDA*
- **Steve Silverman**, Director, Office of Compliance, *CDRH, FDA*
- **Howard Sklamberg**, Director, Office of Enforcement, *ORA, FDA*
- **Janet Woodcock**, Director, *CDER, FDA*

You won't find this level of direct information exchange with the FDA at any other conference!

The PDA Training and Research Institute (PDA TRI) will be hosting seven stand-alone courses on September 22-23.

In addition, PDA will be hosting a post conference workshop, the *PDA 2011 Combination Products Workshop* featuring expert speakers in the area of combination product development, testing and manufacturing. As an attendee you will hear perspectives, challenges and solutions associated with the commercialization of various types of combination products which incorporate medical devices.

**For details and to register, visit www.pda.org/pdafda2011**

SCHOTT glass made of ideas

Roche

PDA Parenteral Drug Association

Register by 12 Sept 2011 and SAVE!

*The Parenteral Drug Association presents...*

# 2011 PDA Europe

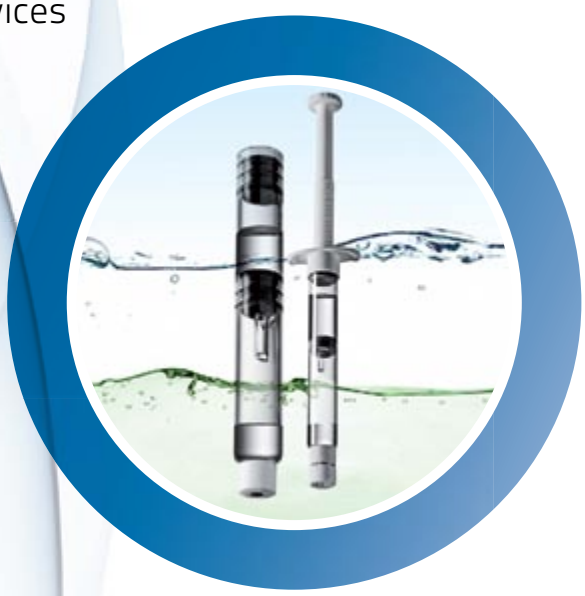
# The Universe of Pre-filled Syringes and Injection Devices

## Device Usability and Compliance

This conference gives an update on all aspects of the application of parenteral products covering a broad range of topics. PDA is seeking scientific abstracts for presentations 30 minutes in length or abstracts for posters. The theme of this year`s conference: Device Usability and Compliance. Invited Speakers will present on Technology Trends, Human Factors, Patient Compliance, Cost Benefit Studies and Health Economics.

Topics:

- Advances in Pre-filled Syringe/Injection Device Technologies
- Factors Influencing Selection of Injection Devices
- Development and Manufacturing
- Regulatory Trends and Inspection Issues



## 7-11 November 2011

**Congress Center**
**Basel, Switzerland**

**CONFERENCE** 7-11 Nov | **EXHIBITION** 7-11 Nov | **TRAINING COURSES** 10-11 Nov

https://europe.pda.org/Prefilled2011

PDA Letter

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# Cover


## 20th PDA/FDA Joint Regulatory Conference



*Cover Art Illustrated by Katja Yount*

# Departments

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## People



## Science



## Regulation



## Programs & Meetings — North America



## Programs & Meetings — Europe



## TRI — Education

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## Features

# ICH Q11 Available for Comment in All Three Regions

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

DRAFT CONSENSUS GUIDELINE

DEVELOPMENT AND MANUFACTURE OF DRUG SUBSTANCES (CHEMICAL ENTITIES AND BIOTECHNOLOGICAL/BIOLOGICAL ENTITIES)

Q11

Current Step 2 version

dated 19 May 2011

At Step 2 of the ICH Process, a consensus draft text or Guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Steering Committee to the regulatory authorities of the three ICH regions (the European Union, Japan and the USA) for internal and external consultation, according to national or regional procedures.

Cover page of Q11

In an unprecedented demonstration of urgency, the European Medicines Agency, the Japanese Ministry of Health, Labour and Welfare and the U.S. FDA have sought consultation for ICH Q11, *Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological entities)* within days of each other.

The draft guideline describes approaches to developing process and drug substance understanding and also provides guidance on what information should be provided in CTD sections 3.2.S.2.2 – 3.2.S.2.6. It provides further clarification on the principles and concepts described in ICH guidelines on *Pharmaceutical Development* (Q8), *Quality Risk Management* (Q9) and *Pharmaceutical Quality Systems* (Q10) as they pertain to the development and manufacture of drug substance.

Comments are due by September 1 to the EMA and U.S. FDA. Comments are due to the Japanese Ministry of Health, Labour and Welfare by August 15.

# Over 30 U.S. FDA Officials to Speak

Over thirty officials from the U.S. FDA have confirmed that they will be speaking at the PDA/FDA Joint Regulatory Conference in September in Washington, D.C. Throughout the meeting, mid-level officials will provide updates on the current efforts impacting the development of global regulatory strategies throughout the meeting.

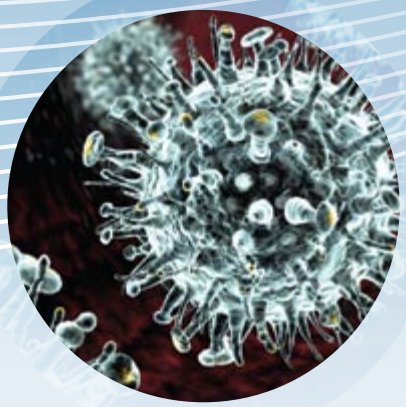
Later in the meeting, compliance directors will provide their perspective on current compliance issues affecting the manufacture; testing and distribution of biopharmaceutical products; active drug substances, drug products and medical devices; and combination products. Agency leaders from CBER, CDER, CDRH, CVM and ORA will also speak about their Center's current and future initiatives.

For more information or to register for this event, go to www.pda.org/pdafda2011.

# PDA 65th Anniversary History Book Coming Soon

PDA is preparing a book to celebrate its 65th Anniversary. From humble beginnings in New York, the Association has grown in membership and in impact. The 65th Anniversary book details the last 15 years, and incorporate two booklets developed for the 50th Anniversary in 1996.

Keep an eye out for more details in the *PDA Letter* and on the PDA website.



Register Before August 22nd - The First Registration Savings Deadline!

*The Parenteral Drug Association Presents...*

# PDA/FDA Adventitious Agents and Novel Cell Substrates: Emerging Technologies and New Challenges

**November 2-4, 2011**

**EXHIBITION:** November 2-3

Hilton Hotel | Rockville, Maryland

The *PDA/FDA Adventitious Agents and Novel Cell Substrates: Emerging Technologies and New Challenges* event will provide a forum for discussion of new adventitious detection technologies and will expand upon emerging issues related to novel cell substrates. Recent technological advances have resulted in novel virus detection methodologies and the ability to produce biological products for human use more efficiently and in a wider variety of substrates. However, alongside the benefits derived from these advances, come new challenges in ensuring biopharmaceutical product safety.

**ADVANCED NOTIFICATION** - Sign up to receive an email when more information is available about this workshop! **www.pda.org/adventitious2011**.

**For details and to register, visit**

**www.pda.org/adventitious2011**

# Two Technical Reports Expand Product Distribution Series

PDA is preparing to publish two Technical Reports to help experts responsible for drug product shipping and handling. These reports will be available for free download for 30 days to all PDA members starting sometime in July.

*Good Distribution Practices* (tentatively Technical Report No. 52) provides high-level guidance on GDPs, particularly in the areas of stability, distribution control management, performance management and supply chain partner management. The document features a Good Storage and Shipping Practices checklist that can be used immediately.

## PDA Guidance for Good Distribution Practices for the Pharmaceutical Supply Chain Task Force Members

**Maryann Gribbin,** Johnson & Johnson (co-Task Force Leader)

**David Ulrich,** Abbott Laboratories (co-Task Force Leader)

**Rafik H. Bishara,** PhD, PDA Pharmaceutical Cold Chain Interest Group Leader

**Stephanie Bradley,** Siemens Healthcare Diagnostics

**Bella R. Cohen,** PhD, Abbott Laboratories

**Emily Badraslioglu,** Department of Health and Human Services

**Larry A. Gordon,** Cold Chain Technologies

**Karl I. Kussow,** FedEx Custom Critical

**Gerry Marasigan,** SNC Lavelin Pharma

**Elaine Merritt,** Johnson & Johnson

**Arminda O. Montero,** Abbott Laboratories

**Johan Nordenberg,** Envirotainer

**Jeff Seeley,** JLS Distribution Packaging

**Elyse Smith,** Meridan Consulting

Guidance for Industry: *Stability Testing to Support Distribution of New Drug Products* (tentatively Technical Report No. 53) delves deeper into the stability studies needed to address the risks that face drug products in the distribution process.

## PDA Stability Testing to Support Distribution of New Drug Products Task Force Members

**Arminda O. Montero,** Abbott Laboratories (Task Force Co-Leader)

**Robert H. Seevers,** PhD, Eli Lilly and Company (Task Force Co-Leader)

**Rafik H. Bishara,** PhD, PDA Pharmaceutical Cold Chain Interest Group Leader

**Fabian S. de Paoli,** GlaxoSmithKline

**Maryann Gribbin,** Johnson & Johnson

**Paul Harber,** Eli Lilly and Company

**Ian G. King,** Pfizer

**David Ulrich,** Abbott Laboratories

**Erik J. van Asselt,** PhD, Merck, Sharp & Dohme

**Sally S. Wong,** Merck and Company

The PDA Pharmaceutical Cold Chain Management Interest Group is driving these reports, and anticipates producing more to cover the seven pillars of GDP:

| Stability | Distribution Control Management | Performance Management | Supplier Chain Partner Management | Qualification/ Validation | Continuous Improvement | Import/Export Compliance |
|---|---|---|---|---|---|---|
| • Storage Temperature<br>• Shipping Temperatures<br>• Stability Testing to Support Distribution | • Qualification and Training of Personnel<br>• Premises and Equipment<br>• Material Handling<br>• Storage and Inventory Control<br>• Transportation<br>• Product Disposition and Distribution<br>• Product Protection<br>• Returns Management<br>• Exception Management | • Performance Measurement and Reporting<br>• Self Inspections<br>• Management Review Meetings | • Partner Selection<br>• Quality Audit<br>• Quality Agreements<br>• Business Review Meetings | • Ambient Temperature Profiles<br>• Passive Shipping Systems<br>• Active Shipping<br>• Facility Qualification<br>• Warehouse Management System Validation<br>• Distribution Validation Master Plans | • Industry Trends<br>• Regulatory Trends<br>• Requalification | • Customs Release<br>• Documentation Control<br>• Product Tracking |

These technical reports are part of a series begun with Technical Report No. 39 (Revised 2007) on cold chain management and Technical Report No. 46 (2009) on the last mile of distribution. Both are available for purchase at the PDA Bookstore, www.pda.org/bookstore.

# GET AHEAD THE HARD WAY

If you're looking for a continuing education shortcut, you'll have to look somewhere else.

RAPS Online University is the gold standard in continuing education for healthcare products regulatory professionals, but you're going to have to work at it. In fact, RAPS Online University is everything you want in online continuing education. Except easy.

We didn't set out to make it easy. We set out to make it valuable.

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# 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 will be highlighted in each *PDA Letter* until next year's event. This month we are highlighting the James P. Agalloco Award winner.

## James P. Agalloco Award

The James P. Agalloco Award is presented annually to the PDA faculty member who exemplifies outstanding performance in education. The selection is based on student and faculty evaluations and is named for James P. Agalloco in honor of his work in developing the PDA education program.

**Art Vellutato, Jr.** is the President and CEO of Veltek Associates, Inc. (an EPA and FDA registered facility) founded in 1981. He is also the President and Senior Consultant of Aseptic Processing, Inc., the consulting division of Veltek Associates, Inc. He is a frequent industry speaker with over 50 industry publications and is one of the leading consultants in the pharmaceutical and biotechnology industry specializing in contamination control, cleaning, disinfection, gowning and environmental monitoring. He lends over 26 years of valuable experience that include his tenure as the Director of Quality Assurance at VAI for 9 years and as the Director of Manufacturing for 6 years. Art conducted cGMP training on Cleaning/Disinfection/Contamination Control/EM to FDA (CDER and CBER) in 2002 through 2009. He also conducted training for the EMA in 2004, 2006, 2007, 2009, 2010 and to the Kazakhstan (Russian) Regulatory Agency in 2005. In his tenure in the industry, he has trained over 500,000 industry professionals.

# Volunteer

## James L. Drinkwater, Process and Compliance Director, Life Sciences Bio-decontamination, Bioquell

**PDA Join Date:** UK Biological Indicators (BI) Task Force member since 2005. Full PDA member since June 2010.

**Interesting fact about yourself:** Having worked in the Pharmaceutical and Bio-Pharmaceutical industries for many years, I believe it important to "give something back" by helping share knowledge or facilitate knowledge exchange between like-minded people who have the same challenges and aims. I enjoy and actively engage in volunteering.

**Why did you join PDA?** To increase knowledge and networking opportunities as well as to increase the collaboration between PDA and the Pharmaceutical and Healthcare Sciences Society to assist harmonization of technical reports and monographs in an increasingly global and harmonized scientific, regulatory and business environment.

**Of your PDA volunteer experiences, which have you enjoyed the most?** As a member of the Biological Indicator Task force for BIs used in Gaseous Vapor Phase decontamination process qualification, I have enjoyed contributing to the recent *PDA Technical Report No. 51 Biological Indicators for Gas and Vapor-Phase Decontamination Processes: Specification, Manufacture, Control and Use*.

**How has volunteering in PDA benefited you professionally?** Volunteering has opened up contacts to members who have similar professional and scientific development aims. Contributing to the BI Task Force has helped me develop a better understanding of the science, qualification requirements and open issues that still need development and resolution.

**Which PDA conference/training course is your favorite?** The quality and diversity of presentations at the 2010 Berlin Parenterals conference together with feedback from international regulators in conference provided a high level of scientific, regulatory and business interest, which I most enjoyed.

**What would you say to somebody considering PDA membership?** Joining a scientific-based, not-for-profit organization that addresses specific process control and monitoring aspects, training, procedural and regulatory requirements together with technical reports as guidance to the developing pharmaceutical, bio-pharmaceutical and related organizations is an essential part of ongoing career development.

# Container Closure Integrity Testing Discussed at Metro Event

**Lara Soltis, Texwipe**

The PDA Metro Chapter hosted a dinner meeting on sterile product package integrity testing on May 17 that commenced with a cocktail reception.

At the Holiday Inn in Somerset, N.J., attendees were able to mingle with past and current coworkers, colleagues, PDA Metro Chapter Board and Committee Members as well as the vendors and the speaker.

**Li-Chun Tsou,** PhD, felt that the topic of container closure integrity (CCI) was so important, she drove to Central New Jersey from Pennsylvania to attend this meeting after seeing it announced in the *PDA Connector.*

**Neil Darling** mentioned that he came to the meeting as he is in the process of setting up a stability study and had some questions on container closure integrity.

Neil also explained that he's been a member of PDA for over 20 years, and he's happy to be part of the Metro Chapter. When asked why he had been a part of the PDA Metro Chapter for so long, he gleefully exclaimed, "Where else can you listen to **Jim Agalloco** speak for $49 and get dinner?!" While Jim was not a speaker of the May 17 meeting, he participated on an expert panel for the PDA Metro Chapter with **Scott Bozzone** and **Phil DeSantis** on June 8 for the *U.S. FDA's Guideline on Process Validation: General Principles and Practices—A Change in the Landscape.* Visit www.pda.org/MainMenuCatagory/Metro.aspx for more information.

After a delicious buffet dinner **Dana Morton Guazzo,** PhD, gave a presentation on "Sterile Product Package

There was superb representation from local pharma at the PDA Metro Chapter. Johnson & Johnson, Immunomedics, BristolMyers Squibb, Merck & Co., Pfizer, ImClone Systems (Eli Lilly), and GlaxoSmithKline, etc. present. SGS Life Sciences Services from Fairfield, N.J. and Seidenader Inspection Machines from Florham Park, N.J. showcased products and services pertinent to the evening's topic.

(l-r) Dana Morton Guazzo, PxPax; Nate Manco, ECO Animal Health; Bob Johnson, are all smiles following PDA Metro's Container Closure Integrity Testing Event

Integrity Testing–Current Practice, New Developments, and Common Mistakes."

Dana reviewed:

- The Quality Challenge: Are Container Closure Integrity failures really a problem?
- Common Container Closure Integrity Approaches: Do they really work?
- Test Method Selection Criteria: "What's the 'hole size' I have to detect?"
- Nondestructive Test Method Options, and Related Package Quality Test Methods
- CCI Method Validation Concept

She detailed the limitations of the commonly used dye and microbial ingress tests, and described studies on nondestructive methods like Vacuum decay, High Voltage Leak Detection and Laser Based headspaces detection.

She also described experiments that have been used to establish positive and negative leak controls and standards. Afterwards, she answered questions from the audience in order to clarify key points and expounded upon specific questions.

After the presentation, a raffle was held. **Sonia Bedi** won a PDA membership. Other attendees won door-prizes consisting of PDA Metro Chapter Day thumb drives, complete with the presentations from our successful Microbiology-themed conference held in April 2011 and some PDA tote bags.

This event would not have been successful without the PDA Metro Chapter Officers and volunteers. A special thanks to everyone who helped out!

The Metro Chapter is a very active chapter with frequent dinner seminars, full-day courses, U.S. FDA Speakers and networking opportunities.

For more information on upcoming meetings, please visit the PDA Metro Chapter site at www.tinyurl.com/3gtoj9d.

## PDA Metro Chapter Officers and Volunteers for May 17th Meeting

**Bob Johnson,** President

**Lisa Burns,** Treasurer, and Regulatory Affairs Specialist, Church & Dwight

**Lara Soltis,** Secretary, and Regional Sales Manager, Texwipe

**Leticia Quinones,** Vendor Liaison Chair, and Associate Director, Analytical R&D, Bristol Myers Squibb

**Maggie Filipowicz,** Arrangements Chair & Vendor Liasion, and Microbiologist, Dendreon

**Jim Agalloco,** Nominations Chair, and President, Agalloco & Associates

**Nate Manco,** Member-at-Large who coordinated this meeting, and Director US Manufacturing Affairs, ECO Animal Health

## PDA's Who's Who

**Jim Agalloco,** President, Agalloco & Associates

**Sonia Bedi,** PhD, Research Scientist 1, InnoPharma

**Scott Bozzone,** PhD, Sr. Mgr., Global QO Validation, Pfizer

**Neil Darling,** Associate Director, Manufacturing Technology, Technical Operations, Celgene

**Phil DeSantis,** Sr. Dir. Engineering Compliance, Global Engineering Services, Merck

**Dana Morton Guazzo,** PhD, President, RxPax

**Li-Chun Tsou,** PhD, Project Leadership, Global Pharmaceutical Commercialization Technology, Merck

## Latest Hot-Job Postings

For a complete list of all job postings, please visit www.pda.org/careers.

**New jobs posted daily to PDA's Career Center!**

**Boehringer Ingelheim,** Bedford, Ohio
Senior Process Engineer – Manufacturing Sciences and Technology

**Bristol-Myers Squibb,** Syracuse, N.Y.
Scientist (Extractables & Leachables)

**Medimmune,** Gaithersburg, Md.
Principal Scientist

**CAPS,** Irvine, Calif.
Director Quality Assurance

**Celgene,** Phoenix, Ariz.
Director, Plant Engineering

To post a job on our Career Center, please contact **Dave Hall** at hall@pda.org

# "The Gold Sheet"

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- **100% prepared for every inspection?**
- **Fully briefed on every promising new manufacturing, supply chain and documentation practice?**

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- **State-of-the-art production and quality techniques**

  You can't be everywhere around the globe, but ***"The Gold Sheet"*** can. You get reports straight from manufacturing facilities worldwide on successes and failures, so your own processes stay current and error-free.

- **Trends in quality control practices**

  It's easy to deliver headlines and soundbites. ***"The Gold Sheet"*** goes above and beyond that to uncover the trends and big picture guidance that help you be pro-active in keeping your operations fully compliant.

- **Best practices in supply chain integrity**

  With the global economy making mincemeat of supply chains, many a formerly clean operation has fallen drastically foul of FDA standards. Make sure it doesn't happen to you by reading ***"The Gold Sheet's"*** detailed reports on these issues and guidance in avoiding disaster.

- **In-depth reports on a vast range of GMP issues**

  Micro issues such as sterility, microbial controls, validation, laboratory data integrity, cross-contamination, out-of-spec (OOS) results and stability testing can be create macro problems. Let ***"The Gold Sheet"*** drill into the data and on-the-ground realities to keep these details from escaping you.

- **Drug recall and warning letter data**

  Count on ***"The Gold Sheet"*** to deliver exactly what QA/QC professionals need to know, not just general news reports aimed at executives with no quality responsibilities.

- **Early warning of new directions in FDA enforcement policy**

  ***"The Gold Sheet"*** has its ear to the ground and a large staff of reporters in the trenches around the industry who keep you one step ahead of an evolving FDA.

- **Insights from peers on ensuring quality from contract suppliers and service providers**

  Thanks to ***"The Gold Sheet's"*** global contacts, you get bulletproof guidance from the most experienced QA/QC pros in the business, making you look like a hero to your supervisor and shareholders.

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# Faces & Places: 2011 PDA/FDA Glass Quality Conference

## Introductory Overview

(l-r) David Jaworski, U.S. FDA; Joyce Bloomfield, Merck Sharp & Dohme Corp; Martin VanTrieste, Amgen

## Development Considerations

(l-r) Dan Haines, Schott; Mark Fitzgerald, Glass Tubing Americas; Juan Cerdan-Diaz, Glass Tubing Americas; Rob Swift, Amgen

## Supply of Glass

(l-r) Boris Schmid, Stevanato Group; Anthony Perry, Schott; Michael Eakins, Eakins & Associates; Theodore DeHaan, Gerresheimer; Norman K. Angel, Gerresheimer; Nicholas Debello, Wheaton Industries; Thomas Schoenknecht, Schott

## Glass Supply Control– Best Practices

(l-r) Martin VanTrieste, Amgen; Mark Paviglianiti, Merck Sharp & Dohme Corp.; Dena Flamm, Bosch; Jerry Cacia, Genentech

## Fun & Networking


Interest in the Glass Quality Conference was so strong, the room nearly cracked open

# Faces & Places: 2011 PDA/FDA Pharmacuetical Supply Chain Conference

## Supply Chain Security-A Global Initiative


(l-r) Ilisa Bernstein, U.S. FDA; Eric Berg, Amgen, Neil J. Wilkinson, David Begg Associates; Gerry Migliaccio, Pfizer

## Risk Model: Materials

(l-r) Dale Carter, J.M. Huber; John Hollenbach, Doe & Ingalls; Jared Byrne, Amgen; Steven M. Wolfgang, U.S. FDA

## Risk Model: Finish Products

(l-r) Londa Ritchey, Pfizer; Lucy Cabral, Genentech; Susan Schniepp, OSO BioPharmaceuticals Manufacturing; Kathleen Culver, U.S. FDA

## Supply Chain Tracking: Finish Products

(l-r) Connie Jung, U.S. FDA; Douglas Rich, Boehringer Ingelheim; Ashley Goldberg, Baxter Healthcare Corporation; Barrett Hightower, BSI

## Supply Chain Tracking: Materials


(l-r) Steven M. Wolfgang, U.S. FDA; Amy Mutere, Genentech; Eric Tackett, Research Organics; Londa Ritchey, Pfizer; Dwight Mutchler, Mutchler

## Solutions That You Can Use Today


(l-r) Dale Carter, J.M. Huber; David Schoneker, Colorcon; Brian Donnelly, Pfizer; Anil D. Sawant, Johnson & Johnson

# Please Welcome the Following Industry

**Haroon Akbor,** Pfizer
**Toshin Akutsu,** ENA
**Aster Amanuel,** Endo Pharmaceuticals
**Bitterlin Andreas,** BASF
**Pavel Arano Fernadez,** Probiomed
**John Arthur,** Cadence Pharmaceuticals
**Robert Atkinson,** Fresenius Medical Care
**Adria Bacon,** Gambro
**Davis Bauman,** Onyx Pharmaceuticals
**Scott Beals,** SGD
**Robert Benda,** Janssen
**Parashar Biswas,** Ranbaxy Laboratories
**Jeffrey Boyar,** Alexion Pharmaceuticals
**Rachael Brownstein,** Pfizer
**Alexander Bulloch,** Wuxi Apptec
**Maciej Cabaj,** Bioton
**Marko Cerneka,** Stevanato Group
**Hing Char,** Pharmaceutical Consulting
**Ta Kung Chen,** MedImmune
**Chirag Chodankar,** Ben Venue Laboratories
**Marisa Corso Berg,** Johnson & Johnson
**Jamie Curran,** AMRI
**Darren Curtis,** Dendreon
**Douglas Cusato,** Schott
**Samuel Dallal,** New England Student Chapter
**Diane Darlington,** North Carolina Central University
**Ireen David,** Gen-Probe
**Todd Davidson,** Catalant
**Sirisha Davuluri,** NJIT
**Janelle Derbyshire,** Qualicaps
**Ranjit Deshmukh,** MedImmune
**Mark Dickson,** Department of Health & Ageing
**Takeshi Doi,** Schott
**Steve Dombrauskas,** Celgene
**Jon Doyle,** PCI
**Uwe Drechsel,** Boehringer Ingelheim
**Timothy Dutill,** Lyophilization
**Harald Engel,** Boehringer Ingelheim
**Douglas Fenwick,** Department of Health & Ageing
**Aleksandra Ferlan,** Probiomed
**Rene Ferquin,** Sanofi Aventis
**Calvin Fok,** Genentech
**Margaret Galazka,** Bristol-Myers Squibb
**Daniel Galbraith,** BioOutsource
**Juan Gimenez,** GlaxoSmithKline
**Michael Goodman,** Quality Alliance
**Piotr Gorecki,** Bioton
**Fumio Gotsu,** Shionogi
**Kannan Govindarajan,** Navinta
**Declan Greally,** Novartis
**Heather Greiner,** Pfizer
**Andres Ernesto Guerra Pulido,** Probiomed
**Kenneth Heavner,** Banner Pharmacaps
**Sigurlina Hedinsdottir,** Sandoz
**Roger Hines,** Baxter Healthcare
**Ryan Hutchinson,** General Electric
**Shlomi Ianovitz,** Dexcel
**Luma Izzy,** Eli Lilly
**Michelle Jessen,** Micromet
**Nicolle Johnson,** Corning
**Adam Julian,** Steris
**Jinkook Jung,** Hanwha Chemical
**Elisabeth Kaszas,** Amgen
**Tom Kerkhofs,** Egemin Consulting
**Hyunseung Kim,** Baxter
**John Knighton,** Johnson & Johnson
**Michael Koby,** Eli Lilly
**Vladimir Kostyukovsky,** Novartis
**Roger Kurinsky,** Gerresheimer
**Stan Kwok,** Seattle Genetics
**Anthony Laccetti,** Shire
**Sandy Lee,** S Lee Consulting
**Yue Li,** ImClone Systems
**Lei Li,** Eli Lilly
**Wenyan Lim,** Lonza
**Chih-Yung Lin,** Yung Shin Pharm
**Daniel Littlefield,** Modality Solutions
**Fernando Lobos,** Sinergium
**Diane Lockard,** Nutramax Laboratories
**Archie Lovatt,** Vitrology
**Richard Lumb,** Hanson Wade
**Elian Magari,** Watson Laboratories
**Dan Mahan,** CDM Pharma Consulting
**Robert Mandell,** NewLink Genetics
**Uwe Marx,** Debiopharm
**Marcy Maul,** MedImmune
**Antonio Mayo,** Talecris Biotherapeutics
**Andrea McFadden,** Shire
**Lisa McNeill,** Infectious Disease Research Institute
**Lea Miller,** MedImmune


## New Member? Attend A Breakfast in Your Honor

Welcome new PDA members!

If you joined PDA on or after September 2010, you are invited to kick-start your PDA membership by attending the New Member Breakfast at the *2011 PDA/FDA Joint Regulatory Meeting* on Monday, September 19 from 7:00-8:00 a.m.

You are welcome to attend this wonderful onsite opportunity that will expose you to information about PDA as well as other new members and PDA staff, if you sign up for the full conference.

For more information and to RSVP by August 15, please contact **Hassana Howe** at +1 (301) 656-5900 ext. 119 or howe@pda.org.

# Leaders to the PDA Community

**Liibaan Moalin,** Apotex
**Bob Newton,** Abbott
**Phil Nguyen,** Gen-Probe
**Orfeo Niedermann,** Ypsomed
**Daniel O`Banks,** Pfizer
**Dennis O`Reilly,** GlaxoSmithKline
**Shane O`Connor,** Eli Lilly
**Chul Oh,** Biostream Technologies
**Kevin Olmer,** Becton Dickinson
**Daniela Ortiz,** Genzyme
**Catherine Oury,** SFSTP
**Marianne Pankratz,** Natrix Separations
**Nadia Pantuso,** Licosa
**Mathieu Petitjean,** Mednest
**David Pierce,** Mirror Metrics
**Elisabeth Piquet,** Millennium Pharmaceuticals
**Vannak Pril,** Middlesex Community College
**Dale Pulczinski,** Novo Nordisk
**Donna Radzik,** Aveo Pharmaceuticals
**Marlene Raschiatore,** Johnson & Johnson
**Swapnil Raut,** Millennium
**Ruth Reiss,** Hy Laboratories
**Paula Reynolds,** Radpharm Scientific
**Celine Rideau,** LEO Pharma
**Manfred Roether,** NNE Pharmaplan
**Patrice Romain,** Sanofi Pasteur
**Daniel Ropp,** Celgene Corporation
**Bruno Rossi,** Merck
**Guido Schenk,** Simac Masic & TSS
**Trevor Schoerie,** PharmOut
**Lars Schroder,** Novo Nordisk
**Ralph Schulze,** GEA Diessel
**Yuval Shimoni,** Bayer HealthCare
**Shailendra Singh,** Johnson & Johnson
**Renata Skros,** DPT Lakewood
**Christine Springman,** Pfizer
**Sija Stewart,** Banner Pharmacaps
**Carolyn Stockdale,** Premier-Research Group
**Aswin Sundaram,** Ben Venue Laboratories
**Steven Sutherland,** Watson Pharmaceuticals
**Elisabeth Swovick,** Bausch & Lomb
**Misty Thompson,** Bi Vetmedica
**Pierrino Torbey,** Lesirg
**Denise Trimble,** Synthes
**Sarah Tuller,** Biogen Idec
**Arun Varshneya,** Saxon Glass Technologies
**Stacey Vaughan,** Putney
**Laurence Vericel,** Sanofi Pasteur
**Eamonn Vize,** EJV Consultants
**Monique Voth,** Gambro
**Sean Walsh,** Eli Lilly
**David Weiser,** Schott
**Bill Welsh,** BTEC/NCSU
**Wally Wen,** Bachem
**Christopher Werner,** GlaxoSmithKline
**Deloris Wilson,** MacroGenics
**Tatsuro Yokoyama,** Nissan Chemical Industries

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# Be Remembered: 7 Rules to Follow When Speaking in Public

**Patricia Fripp, CSP, CPAE**

"Speak to be remembered and repeated" is the advice I give my executive speech-coaching clients. Isn't that the goal of every executive, professional speaker and sales professional—to be remembered and repeated?

However it's easier said than done.

However, here are some tips:

### 1 Speak In Short Sentences or Phrases

Edit your sentences to a nub. Jerry Seinfeld said, "I will spend an hour taking an eight word sentence and editing it down to five." In comedy, the fewer the words between the set-up and the punch word, the bigger the laugh. In business communications, change the punch word or phrase to impact phrase.

### 2 Don't Step on Your Punch Word

It should be the final word or idea in the sentence. (Yes, this works for Jerry Seinfeld and his comedian brethren, and it also works for business communicators.)

The otherwise-powerful word "today" can also be the biggest impact-diluting word in business communications if you use it wrong. For example, in the sentence, "You have to make an important decision today," your punch word should be "decision." So switch it around and change the noun "decision" to the active verb "decide." "Today, you have to *decide!*"

### 3 Perfect Your Pause

Deliver your punch word and then pause...and pause...and pause. Give your listeners time to digest what you've just said. Get comfortable with silence, and don't be tempted to rush on or fill it with "um's."

### 4 Repeat your Key Ideas More than Once

Do not be afraid of being redundant. Instead, worry that tomorrow your audience members will not remember your key ideas.

### 5 Never Read Your Speech

Remember the audience wants to hear from you. If someone is simply going to read a script or the titles off a PowerPoint slide presentation, you could have stayed home. (PowerPoint is a magnificent visual aid, but not a scripting aid.)

### 6 Use Stories. Help Your Listeners To "See" Your Words

Statistics and facts are fine, but sell your message and make yourself unforgettable by getting listeners to make the movie in their heads. For example, you might say, "Drunk driving is a bad idea. Let me share with you some statistics on the loss of control drivers experience after even one beer." Instead say, "Never, never, *never* drive drunk! Not even after one beer. I know. My friend Eliot Kramer was absolutely positive that two drinks couldn't affect his timing and judgment." (Hold up a single shoe, dangling from its shoelaces.) "Six months ago, he died." Farther on, add some statistics and then conclude with a reference to your powerful story.

### 7 Say Something Memorable

Presidents have gifted speech writers to coin ringing phrases for the history books. You can be just as memorable in your field when you think about what you want to say and why. Here's an example from the memorial for *60 Minutes'* Ed Bradley. Fellow reporter Steve Kroft said, "I learned a lot from Ed Bradley, and not just about journalism. I learned a lot about friendship, manners, clothes, wine, freshly cut flowers (which he had delivered to his office every week) and the importance of stopping and smelling them every once in awhile."

Another example, from Mike Powell when he was a senior scientist at Genentech, giving a speech to the Continental Breakfast Club: "Being a scientist is like doing a jigsaw puzzle, in a snow storm, at night, when you don't have all the pieces, or the picture you are trying to create."

Remember to try out these seven key ideas as you prepare your next presentation so your words will be remembered and repeated. Why else would you go to all that effort?

## About the Author

**Patricia Fripp** is an executive speech coach, sales presentation trainer, and keynote speaker on sales, effective presentation skills and executive communication skills. She works with companies large and small, and individuals from the C-Suite to the work floor. She builds leaders, transforms sales teams and delights audiences. She is the author of *Get What You Want!, Make It, So You Don't Have to Fake It!*, and is Past-President of the National Speakers Association. To learn more about having Patricia do her magic for you, contact her at www.Fripp.com, (415) 753-6556, or PFripp@ix.netcom.com.

Register By August 23rd and Save Up to $200!

*The Parenteral Drug Association presents...*

# 2011 PDA Visual Inspection Forum & TRI Course

## October 3-4, 2011

**EXHIBITION:** October 3-4 | **COURSE:** October 5-6
Hyatt Regency Bethesda | Bethesda, Maryland

The *2011 PDA Visual Inspection Forum & TRI Course* will provide an opportunity to present and discuss new developments in the field of visual inspection, including contributions to a basic understanding of the sampling and inspection process, practical aspects of manual and automated methods.

The forum will open with a plenary session on the medical and regulatory concerns with Particulate Matter. In addition, this session reviews the status and ongoing activities to support the USP expert panel proposed changes to Chapter ‹1› "Particulate Matter" focused on clarifying manual visual inspection parameters and the expectations of "Essentially Free" through the pharmacopeial forum process. Presentations in this session include:

- Clinical Implications of Extraneous Particulate Matter in Parenteral Products by **John Ayres**, M.D., Health Hazard Evaluation Physician, *Eli Lilly and Company*
- FDA Concerns by **Stephen Langille**, Senior Microbiology Reviewer, *CDER, FDA*
- Update from the USP Visual Inspection Expert Panel by **John G. Shabushnnig**, PhD, Senior Manager, Quality Systems and Technical Services, *Pfizer*

Immediately following the conference, the PDA Training and Research Institute (PDA TRI) will be hosting a stand-alone course, *Introduction to Visual Inspection* on October 5-6.

**For details and to register, visit**
**www.pda.org/visualinspection2011**

Photo Credits: John G. Shabushnig, Ph.D., Pfizer Quality Operations Center

# Midwest Chapter Hosts Contamination Control Conference

**Jeffrey Stockman, bioMérieux, and Jeanne Moldenhauer, Excellent Pharma Consulting**

The PDA Midwest Chapter and Baxter hosted a sold-out all-day contamination control conference and vendor exhibit on May 6. One hundred and forty industry professionals and twelve corporate sponsors from across the Midwest came to Chicago to learn from and network with many industry experts in the field of pharmaceutical microbiology.

Twelve industry experts presented topics ranging from design and operation of clean rooms, environmental monitoring program improvements, rapid identification methods, and emerging technologies in the microbiology space. (See box for more information about the speakers' talks.)

The high caliber of speakers helped make the meeting a roaring success.

Designed to give a broad sweep of major contamination control themes in today's pharmaceutical industry, the event catered to all areas of quality control and allowed the attendees to learn from industry best practices.

Additionally, the provided lunch allowed participants to network with the experts. This permitted attendees time to ask questions with the various speakers in a smaller, more intimate setting.

A six person discussion panel closed out the event where attendees were able to ask more penetrating questions pertaining to the topics discussed earlier in the day.

One attendee summarized the event as such: "This was a very impressive and educational event. It had the star power of the PDA's Annual Microbiology conference, but with the price tag and commute of a local event. Thank you!"

The PDA Midwest Chapter would again like to thank the speakers and sponsors for their continued support of the PDA's goal to connect People, Science, and Regulation.

We hope to see you out at future chapter events!

**The meeting addressed many issues in contamination control covered by world-class speakers.**

The speakers covered topics ranging from design and operation of clean rooms, environmental monitoring program improvements, rapid identification methods, and emerging technologies in the microbiology space:

- "Developing a Contamination Control Program" – **Sandy Lowery,** President, Quality Systems Consulting
- "Design and Operation of Clean Rooms" – **Douglas Bryans,** PhD, COO, Bryllan Pharmaceuticals
- "Overlooked Problems in Cleaning and Cleaning Validation" – **Paul Pluta,** PhD, Editor in Chief, *Journal of Validation Technology and Journal of GXP Compliance,* and Adjunct Professor, University of Illinois, College of Pharmacy
- "Detergent Selection Considerations" – **Mark Compo,** Director of Process Cleaning & Healthcare Divisions, Veltek Associates
- "Updating BET Procedures Maximizes Endotoxin Control" – **James Cooper,** PharmD, Endotoxin Consulting
- "Methods for Environmental Monitoring" – **Scott Sutton,** PhD, Principal, Microbiology Network
- "Addressing Microbial Contamination of Process Equipment" – **Paul Lopolito,** Specialist, Global Technical Services, Life Sciences, Steris
- "Solutions for Addressing Fungal and Bacterial Spores in Pharmaceutical, Biotech, and Medical Device Industries" – **Jim Polarine,** Technical Services Specialist, Steris
- "Emerging Technology for Fungal Contamination and Control: Natural Mold Inhibitors as Perspective Compounds for Fungal Contamination Control" – **Vladimir Podlipskiy,** PhD, Director Research & Development, Pegasus Pharmaceuticals; **Sergei Bibikov,** PhD, Senior Scientist, Pegasus Pharmaceuticals; **Brian Hubka,** VP, Business Development, Pegasus Pharmaceuticals
- "Emerging Technology: Using Maldi-TOF for Microbial Identifications" – **Gary Kruppa,** PhD, Vice President, Bruker Daltonics
- "Emerging Technology: Deciphering Species Level Spectral Uniqueness within Microorganisms" – **Andrew Bartko,** PhD, Senior Scientist, Battelle Memorial Institute
- "Avoiding Common Errors During Contamination Investigations" – **Ken Muhvich,** PhD, Principal, MicroReliance

**The PDA Midwest Chapter would like to thank the exhibitors who helped make the event possible. A special thanks to:**

| | | |
|---|---|---|
| Baxter | Brucker | BioVigilant |
| Veltek Associates | bioMérieux | Steris |
| Biotest | Hach | TSI |
| Particle Measuring Systems | Millipore | Accugenix |

*The Parenteral Drug Association presents...*

# 2011 PDA Europe Modern Biopharmaceutical Manufacturing

## Current Best Practice

The program will cover relevant updates on regulations, science and technologies used in development and manufacturing of biopharmaceutical and biotechnologically derived products.
The focus will be on these topics:

**Implementation of ICH Q8 and 9**
- QbD: From Concept to practical use
- Regulatory expectation
- Risk based approaches applied to biopharmaceutical processes

**Upstream and Downstream Processes**
- Single-use-Systems, Hybrid Systems
- How to deal with high titres in purification/alternatives to complement chromatography
- Process validation

**Extractables & leachables**
- Testing and validation strategies
- Process related E&Ls
- Primary packaging related

In addition there will be 2 one day Training Courses:
**PDA Technical Report: Single Use Technologies**
**PDA Technical Report: Cleaning Validation**

**Register by 10 Oct 2011 and SAVE!**

## 6-8 December 2011
**ENSTBB-IPB**
**Bordeaux, France**

**CONFERENCE** 6 December | **PLANT TOUR** 7 December | **EXHIBITION** 6 December | **TRAINING COURSES** 8 December

**https://europe.pda.org/BioPharma2011**

# Missouri Valley Chapter Holds First Event, Plans Second

**Thomas Pamukcoglu, SAFC Biosciences**

On Monday, April 25, the PDA Missouri Valley Chapter hosted its inaugural chapter meeting at the Kansas City Airport Hilton hotel. Following a networking/vendor reception and buffet dinner, the meeting included talks from three distinguished speakers representing industry and the U.S. FDA. The event attracted over 70 industry professionals, including many potential new PDA members and was supported by the following sponsors:

- cGMP Validation
- Regulatory Compliance Associates
- ACH Foam Technologies
- ProPharma Group

**Richard Johnson,** President, PDA, attended to help kick-off the inaugural event. Richard welcomed the new chapter into the PDA fold and gave an informative presentation on the business climate of the pharmaceutical industry and manufacturing environments as well as some insight into current industry regulatory trends.

Richard then introduced **John Thorsky** District Director, U.S. FDA, from the Kansas District Office, who provided remarks echoing many of the issues identified in Richard's presentation along with insight to the FDA's current thinking on issues and the challenges that it is facing as an agency. With the emphasis on developing core competencies, John described the requirements and challenges associated with retention of the Pharmaceutical Inspectorate. He graciously answered questions from the audience on all topics related to compliance and other topics of interest.

It is not often that one gets to ask a Director questions directly!

Following John's remarks, we were fortunate to have **Nadine Nanko,** Supervisory Investigator, U.S. FDA, who also is from the Kansas District Office. Nadine's presentation interjected some levity and also helped us to better understand the anatomy and inner workings of the District Office and the broad range of products FDA regulates.

The session opened our eyes to the types of challenges FDA is facing. Namely, more firms to inspect, rapidly changing technologies and diminishing funds. But, with consumer safety being paramount, we can expect FDA's current emphasis on compliance enforcement to continue.

With the successful completion of the first Missouri Valley Chapter event, the chapter is now planning a similar event to be held in the St Louis area. The planned date is targeted for mid-September, and the chapter is reviewing input received from the inaugural event to discuss agenda topics, identify speakers and to secure a suitable venue.

We are anxious to hear from our chapter membership about how we can make our next event even more successful!

## PDA Missouri Valley Chapter Officers

President **Thomas Pamukcoglu,** SAFC Biosciences

President-Elect **Eldon Henson,** Covidien

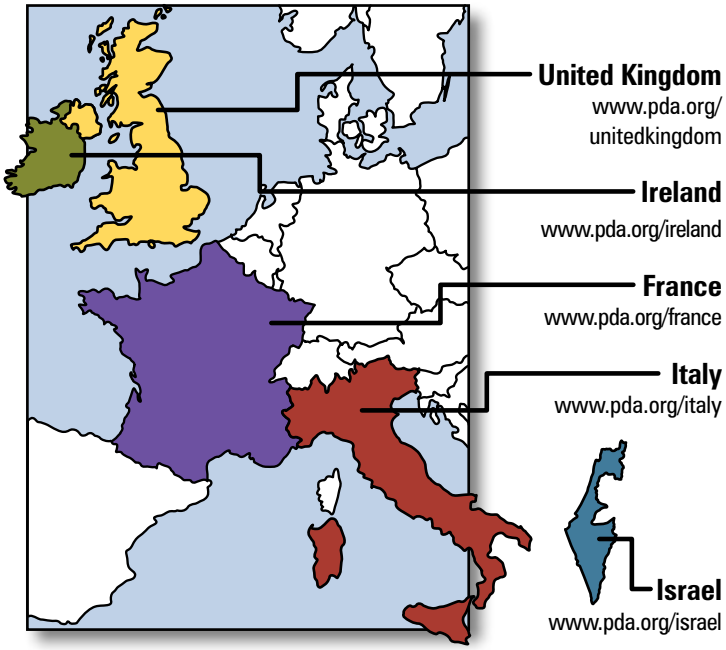
Treasurer **Keith Koehler,** Certified Energy Laboratories

Secretary **Jeff Hargroves,** ProPharma Group

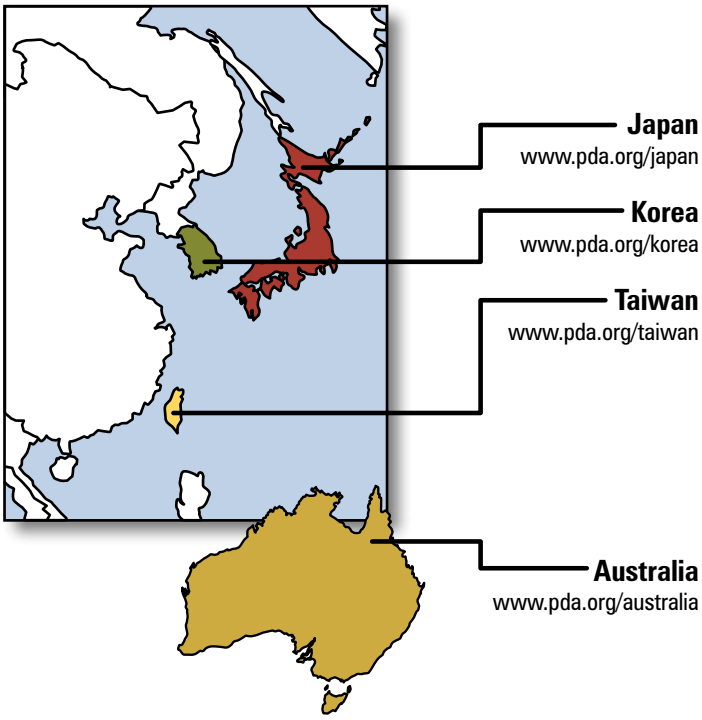
# PDA Chapters

**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.**

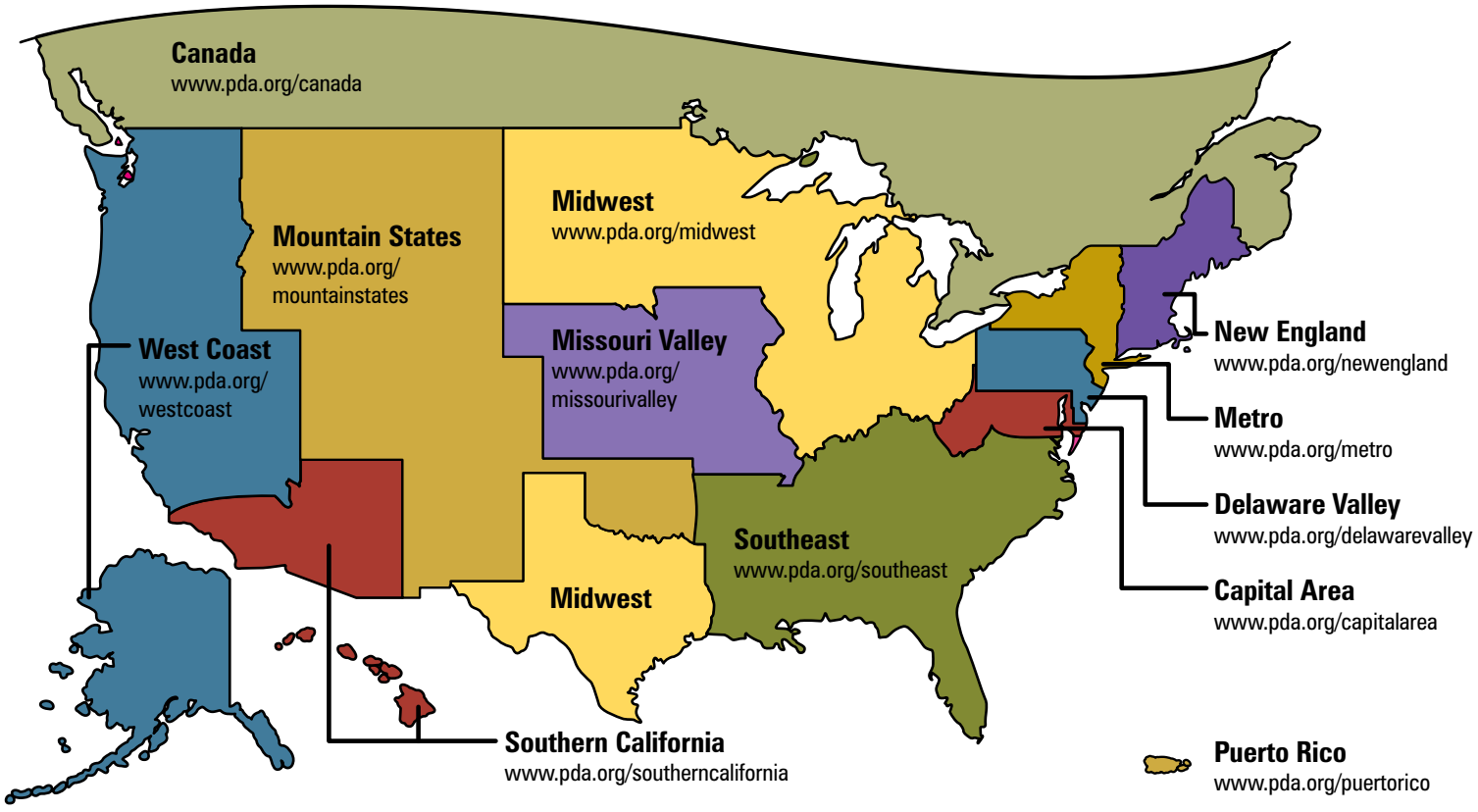
## EUROPE




## ASIA-PACIFIC




## NORTH AMERICA



snapshot

# Task Force *Corner*

## Management of Suppliers and Contractors TF to Develop ICH Q8, 9 & 10 Best Practice Document

**Amelia Mutere and Lucy Cabral, Genentech, a member of the Roche Group**

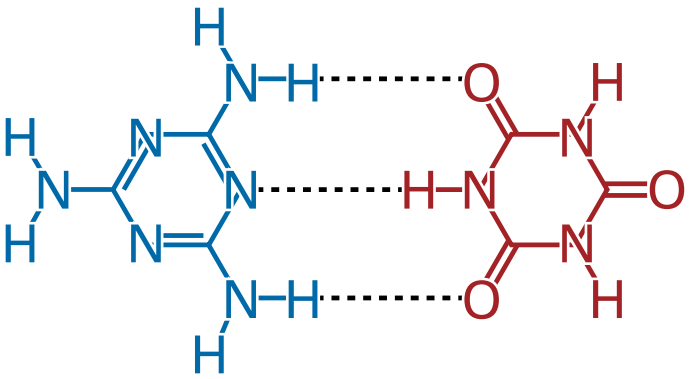
As the global world becomes smaller and more interconnected, the supply chain is increasingly under attack from natural events and counterfeiters who threaten the efficacy of the ingredients and safety to patients.

Pharmaceutical manufacturers continue to face unforeseen events to procure raw materials and managing the supply chain. Suppliers and contractors issues persist into 2011 and promise to be a focus area for pharmaceutical companies and regulatory agencies.

Japan's earthquake recovery and resulting nuclear crisis continues as shortages of electronic materials and raw materials loom. Even if suppliers can get needed raw materials out of Japan, the pharmaceutical industry is faced with whether they can use material possibly exposed to radiation at facilities and fall-out along the transport routes.

Also, in the news in 2011, sodium thiopental is no longer made in the United States. This drug is the first of three administered in lethal injections in the United States and also used in various procedures in hospitals. Hospira, the only United States-based manufacturer of sodium thiopental, says it will halt production of the chemical as a result of the Italian parliament decision invoking the European Union's ban on capital punishment. Until this decision, the manufacturer was increasing production at it plant in Liscate, Italy. Hospira will halt production at this time leaving hospitals and prisons forced to find a new source.

Reported in 2009, chemically treated wooden pallets with 2,4,6-tribromophenol can breakdown and convert to 2,4,6-tribromoanisole (TBA), which is associated with patient complaints of nausea, stomach pain, vomiting and diarrhea. Resulting in voluntary recalls of drugs, that have a musty or mildew-like odor, major pharmaceutical companies, contractors, supplier and the pharmaceutical manufacturers have to manage this risk to their raw materials in transit and in storage at their facilities for TBA. Controlling pallets at supplier, contractors, distributors, warehouses and pharmaceutical manufacturing facilities will be a challenge in the future.



Melamine-cyanuric complex

In 2008, hundreds of thousands of children in China were sickened and some babies died when certain manufacturers added-melamine to infant formula to make it appear more nutritious. The year before, melamine contaminated pet foods sickening thousands of pets, killing dozens of dogs, and forcing recalls of nearly 90 brands in the United States and Africa. and forced. Now the pharmaceutical manufacturers have to design their supplier quality programs to ensure controls are in place to test and/or ensure raw materials are not contaminated with melamine.

And of most notorious adulterations of drugs and/or food in recent times, there have been more than 80 reported deaths in the

*continued on page 26*

# Interest Group *Corner*

## Blow Fill Seal Interest Group Needs a Leader: Is it You?

The Blow Fill Seal Interest Group (BFS IG) is looking for someone to lead or co-lead the group. The BFS IG leader is responsible for planning and coordinating the meetings, providing content for the website, and coordinating BFS related activities.

The interest group works closely with the Sterile Processing Interest Group and is involved with discussions and topics related to the use of Blow Fill Seal and sterile Form Fill Seal technology. Topics include (but are not limited to) regulatory expectations, manufacturing challenges, environmental monitoring, container formation, polymer selection and handling, leak detection, product and line cleaning, sterilization, and contamination control, as well as other matters related to the use of this advanced aseptic and sterile product manufacturing technology.

The BFS IG typically holds two meetings per year—usually at PDA signature events. It also provides input and resources for PDA technical reports and activities related to BFS Technology.

For more information, contact **Iris Rice** at rice@pda.org.

## Journal *Update*

### Mobile Website, E-Letters Now Available

**Walter Morris, PDA**

In March, PDA's **Richard Levy,** Sr. VP Scientific and Regulatory Affairs, wrote of the many exciting website modifications and updates that were coming soon for the electronic *PDA Journal of Pharmaceutical Science and Technology.* As Director of Publishing, I'm proud to announce that all have been implemented.

In May, the online commenting tool, called e-Letters, went live. Now all readers—member and nonmember alike—can post comments to Journal articles. The Journal Editors will monitor the comments, but it represents a free forum for readers to interact and comment on the content of the PDA Journal.

For our globe trekkers who like to use their IPhones, Blackberries and/or Androids for business, the e-Journal will now load easily on your mobile browser with our new mobile interface, launched June 15. The website stays the same, but when accessing from your smartphone's internet browser, readers will automatically get the mobile version of the website.

Soon, authors will be able use the online submission tool, provided by HighWire Press's partner company, BenchPress, to submit articles to the Journal. This tool will make article submission a snap, and also help the editorial team manage the review process with modern information technology. The

*continued at middle of page 27*

## *Preview*

### BioAB and SAB Activities Schedule

**Washington, D.C. • September 18-22 • www.pda.org/pdafda2011**

PDA members and volunteers will dedicate some of their time at the *2011 PDA/FDA Joint Regulatory Meeting* conducting the business of the Association. The following are the times for the Science Advisory Board and Biotechnology Advisory Board meetings (closed to board members), as well as the various Interest Groups (open) and Task Force meetings (closed) under their purview.

**Sunday, September 18**

Analytical Method Development and Method Qualification for Biotechnology Products Task Force 9:00 a.m.-5:00 p.m.

**Monday, September 19**

PCMO Steering Committee 12:00 p.m.-1:30 p.m.

PCMO R01a: Quality Risk Management for Biotech Manufacturing API 12:00 p.m.-1:30 p.m.

Application of Phase Appropriate CGMP and Quality Systems to the Development of Protein Bulk Drug Substance (or API) Task Force. 12:00 p.m.-1:30 p.m.

Science Advisory Board 12:15 p.m.-2:30 p.m.

Concurrent Interest Group Sessions: 4:30 p.m.—6:00 p.m.

- Facilities and Engineering/Water Systems

*continued at top of page 27*

## Journal *Preview*

### PDA Journal July/August 2011

This issue features a give and take between a well-informed reader and a response from the author. With the electronic Journal, readers can easily link from the Letter and the author's response back to the original article! Coinciding with the theme of the July/August Letter (sterile products manufacturing/aseptic processing), several Journal Research articles take a look at issues related to glass defects, prefilled syringes, cleanroom microflora and high-purity water.

*Editorial*

Anurag Rathore, "Technology Drivers for Quality by Design (QbD) Implementation for Biopharmaceutical Products"

*Letters*

Anthony Cundell, "Letter to the Editor"

Jennifer Gray, "Letter to the Editor (Author Response)"

*Research*

Ruchi Kothari, et al., "Modes of Degradation and Impurity Characteriza-

*continued at bottom of page 27*

## Tech *Trend*

### Pharma Companies well-represented in *Newsweek*'s '10 Green Rankings

**Emily Hough, PDA**

According to *Newsweek*'s 2010 "Green Rankings," 17 pharmaceutical companies rate among the top 500 "greenest" publicly traded U.S. companies and 7 firms rate among the top 100 globally. *Newsweek* annually ranks the biggest publicly traded companies in developed and emerging world markets on their environmental footprint, policies and reputation among their peers.

Johnson & Johnson's sustainability efforts were viewed very favorably by *Newsweek*, ranking highest among companies in the pharmaceutical/biopharmaceutical business. Its fourth place finish in the U.S. rankings is notable considering that the rest of the top 10 was comprised of technology companies like Dell, IBM and Yahoo. Globally, the pharmaceutical industry is doing much better, grabbing three of the top 10 spots.

The *PDA Letter* spoke with Pfizer's **Steve Brooks,** Vice Presi-

*continued on page 28*

*Task Force Corner continued from page 24*

2,4,5 Tribromophenol→2,4,6 Tribromoanisole

United States linked to the use of contaminated heparin. Most of the deaths occurred among patients that were administrated heparin were manufactured by a Chinese facility. An investigation found some lots of heparin were contaminated with a heparin-like substance called oversulfated chondroitin sulfate or OSCS.

Due to the increase in the maturity of the supply chain on how raw materials and CMOs are managed, the pharmaceutical industry needs to change and have a transformation relationship from a transactional relationship with the raw material suppliers and CMOs. The pharmaceutical industry will be better positioned to control issues that arise and change paradigms in the globalization of suppliers and CMOs. In addition, a proactive management process will lead to better influence of legislation and the future state of supply chain management in the industry.

PDA is driving a Paradigm Change in Manufacturing Operations (PCMO[SM]) program, under the Task Force on Management of Suppliers and Contractors group. Based on open communication with regulatory agencies, it will focus on manufacturing needs to provide scientific expertise according to new paradigms and give examples on "how-to" and proposed management topics not extensively covered by other industry groups. The objectives of this program are to enable an innovative environment for continual improvement of products and systems, to apply a science-based approach, enable an increase of process robustness and knowledge, and foster relief from regulatory agency prescription.

Under the leadership of **Lucy Cabral** and **Amelia Mutere,** the Management of Suppliers and Contractors is using the Select, Implement, Manage and Decommission/Deactivate model that many pharmaceutical companies currently use. The goal of the white paper is to develop a "best practice" document to aid the pharmaceutical manufacturers in implementation of ICH Q8, Q9 and Q10. In addition, the Task Force will publish cutting edge concepts to manage suppliers and contractors to prevent the above incidents.

A focus of the white paper will be:

- Managing suppliers and contractors throughout the lifecycle
- Risk Model: A Risk Based Approach to Contractor and Supplier Management
- Current Models to Detect Material Quality Performance and Supply Chain Risks
- Supplier and contractor input
- Case Studies

In addition, this white paper will have input from suppliers, CMOs and procurement partners in the PDA membership. Risk models, Supplier/CMO meetings, and Supplier Technical Improvement Programs such as cutting edge concepts in Supplier and CMO Management will be used.

Due in December 2011, the PCMO group welcomes input from PDA members about the white paper. If you have comments or questions, please contact mutere.amelia@gene.com.

## Task Force Members

Co-Leader **Lucy Cabral,** Roche

Co-Leader **Amelia Mutere,** Genentech/Roche

**Heather Gennadios,** U.S. FDA

**Jim Ackerman,** Roche

**Eric Tackett,** Research Organics

**Eric Berg,** Amgen

**Jessica Tan,** Amgen

**Shakuntala Maharaj**

**Jo-Ann Coyne,** GlaxoSmithKline

**Rob Frankenberg,** Consultant

**Graham McCreath,** Avecia Biologics

**Markus Schneider,** Novartis Pharma

**Dave Schoneker,** Colorcon

**Rachel Humphrys,** Perrigo

**Mark Frankcom,** Consultant

## About the Authors

**Amelia Mutere** joined Genentech External Quality in 2009 as a Supplier Collaborations, Principal Technical Manager where she worked with suppliers to improve their component quality. In 2010, she moved to the Associate Director of Americas, Supplier Quality. In the coming weeks, Amy will moves onto the GMP Compliance Group in Roche. Amy has worked in the chemical and pharmaceutical area for the past 18 years as a consultant for CROs such as Ricerca and Rosetech Consulting.

**Lucy M. Cabral,** Head, Global Supplier Quality Management, and US Distribution Quality, Genentech, a member of the Roche Group, has had over seventeen years of supervisory experience at Genentech, Inc. in the Quality Assurance, Compliance, and Quality Control groups. She has extensive experience managing commercial and clinical contract manufacturers and raw material suppliers operating in the US, Europe, and Asia. Currently Lucy is the Head of Supplier Quality Management for the Roche Pharma worldwide responsible for the management of materials (chemicals and components) and is also responsible for Distribution Quality that oversees all distribution centers and third party contractors located in the US region.

*Joint Regulatory Meeting Preview continued from page 25*

- Pre-filled Syringes
- Packaging Science
- Blow-Fill-Seal/Sterile Processing
- Process Validation

**Tuesday, September 20**

TRI Committee 12:00 p.m.-1:30 p.m.

Interest Group Leaders Meeting 12:30 p.m.-2:00 p.m.

Fundamentals of Cleaning and Disinfection Programs Task Force 12:30 p.m.-2:15 p.m.

Biotechnology Advisory Board 4:00 p.m.-6:30 p.m.

Concurrent Interest Group Sessions: 4:45 p.m.—6:15 p.m.

- Combination Products
- Supply Chain Management
- Lyophilization/Visual Inspection
- Vaccines

**Wednesday, September 21**

PCMO R05: Risk Based Manufacturing, (TR44) Packaging and Labeling 12:30 p.m.-3:30 p.m.

PCMO Q02: Meeting Requirements for the Management of Suppliers and Contractors 12:30 p.m.-3:30 p.m.

Mycoplasma Task Force 12:30 p.m.-3:30 p.m.

**Thursday, September 22**

PCMO R01: Risk Based Manufacturing 8:30 a.m.-5:00 p.m.

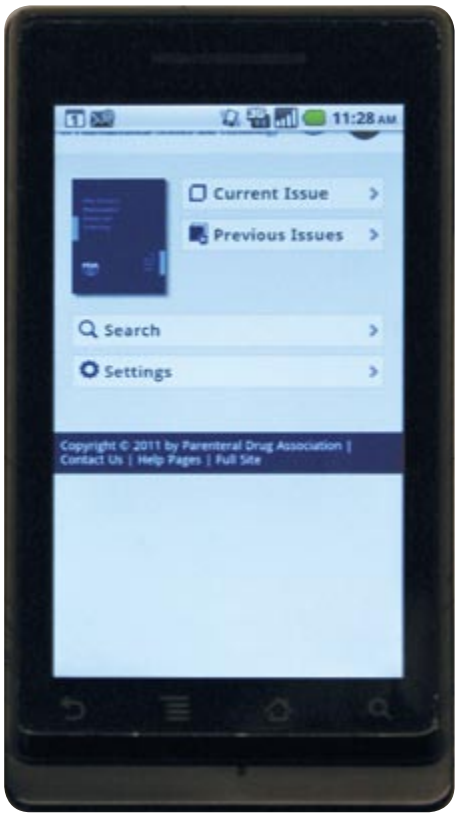
*Journal Update continued from page 25*

online submission and review tool is completed and will be available in July.

Previously, we announced the expansion of the article archives by 18 years (see the May *PDA Letter*, p. 19). The archives now include every article published in the Journal back to 1980.

I'd like to remind all members to sign up for e-Alerts and RSS feeds at the website for the *PDA Journal of Pharmaceutical Science and Technology* (journal.pda.org). These help you stay on top of the latest content.

Please send us your feedback on the Journal and these enhancements. You can contact me at morris@pda.org.




The Journal's new mobile interface makes it easy and convenient to access the website from any smartphone

*Journal Preview continued from page 25*

tion in rhPTH (1–34) during Stability Studies "

Edwin Chan, Yuh-Fun Maa, David Overcashier, Chung C. Hsu, "Investigating Liquid Leak from Pre-Filled Syringes upon Needle Shield Removal: Effect of Air Bubble Pressure"

Stefano Ceccanti, Simona Giampieri, and Susi Burgalassi, "Carrier Tests to Assess the Effective Sporicidal Concentration of a Liquid Chemical Disinfectant for a Sanitization Program"

April W. Loui, "A Method To Quantitatively Define and Assess the Risk of Cosmetic Glass Defects on Tubing Glass Vials"

Tim Sandle, "A Review of Cleanroom Microflora: Types, Trends, and Patterns"

Frank Riedewald, Edmond Byrne, and Kevin Cronin, "Comparison of Deterministic and Stochastic Simulation for Capacity Extension of High- Purity Water Delivery Systems"

***Technology/Application***

Philippe Lam and Thomas W. Patapoff, "An Improved Method for Visualizing the Morphology of Lyophilized Product Cakes"

*Tech Trend continued from page 25*

**Tables 1 & 2:** Pharmaceutical/Biopharmaceutical Companies in *Newsweek's* Green Rankings and their Rank, US and Global

| US Ranking | Company |
|---|---|
| 4 | Johnson & Johnson |
| 17 | Bristol Myers Squibb |
| 19 | Allergan |
| 21 | Pfizer |
| 42 | Abbott |
| 58 | Eli Lilly |
| 68 | Merck |
| 74 | Hospira |
| 101 | Biogen Idec |
| 102 | Life Technologies |
| 158 | Genzyme |
| 185 | Amgen |
| 351 | Gilead Sciences |
| 397 | Celgene |
| 449 | Mylan |
| 470 | Forest Laboratories |

| Global Ranking | Global Companies |
|---|---|
| 3 | Johnson & Johnson |
| 5 | GSK |
| 6 | Novartis |
| 20 | Pfizer |
| 42 | Sanofi Aventis |
| 58 | Roche |
| 59 | Bayer |

dent, Global Risk Management, Environment Health & Safety, and Business Continuity, about his firm's feelings towards the rankings. Brooks said that while "rankings and ratings definitely have merit, at the same time, our primary focus is to discover, develop and deliver new medicines to patients and customers across the globe." In 2010, Pfizer placed 20th in both the global and domestic lists.

Brooks said that the *Newsweek* ranking is just one way of assessing Pfizer's greenness and helps to identify areas for improvement. He said that Pfizer directly involves colleagues and stakeholders in improving global access to medicines, engaging in responsible business practices and enhancing environmental sustainability.

"Given *Newsweek's* broad readership, it's a good way for the public to find out what companies are doing in environmental sustainability," stated Brooks.

Brooks said that Pfizer has been committed to minimizing its environmental impact by establishing programs that drive environmental sustainability. It has also integrated those initiatives into its business to moderate consumption of resources, reduce effects on the environment, and increase energy efficiency by:

- Mitigating climate change and its impact
- Minimizing environmental footprint by advancing product stewardship across the supply chain and lifecycle
- Managing water resources in a sustainable way

To produce the "green" rankings, *Newsweek* collaborated with companies that specialize in ranking environmental performance such as:

- MSCI ESG Research
- Trucost
- CorporateRegister.com
- ASAP Media

According to *Newsweek,* "the goal was to assess each company's actual environmental footprint and management of that footprint (including policies and strategies), along with its reputation among environmental experts." To do that, *Newsweek* used three components for each company in determining their "greenness:" an Environmental impact score, Green Policies Score and Reputation Score.

**Environmental Impact Score (EIS):** Based on complied data, over 700 variables were summarized, and then considered in relation to a company's annual revenues. This was done so that companies of all sizes and industries could be compared. Four of the major elements that contribute to the overall EIS are: greenhouse gas emissions, water use (including direct, purchased and cooling), solid waste disposed and acid rain emissions.

**Green Policies Score:** This was based on an analytical assessment of a company's environmental policies and performance. It captures good use of policies, programs and initiatives, as well as challenges companies face for poor environmental performance, including community protests and sanctions, regulatory actions and lawsuits. The main elements incorporated in the Green policies score are environmental and climate change policies and performance; pollution policies and performance; product impacts; environmental stewardship and management.

**Reputation Score:** This is based on an opinion survey of corporate social responsibility professionals, academics and other environmental experts. The survey asked respondents to rate companies as "leaders" or "laggards" in key areas, such as green performance, commitment, and communications.

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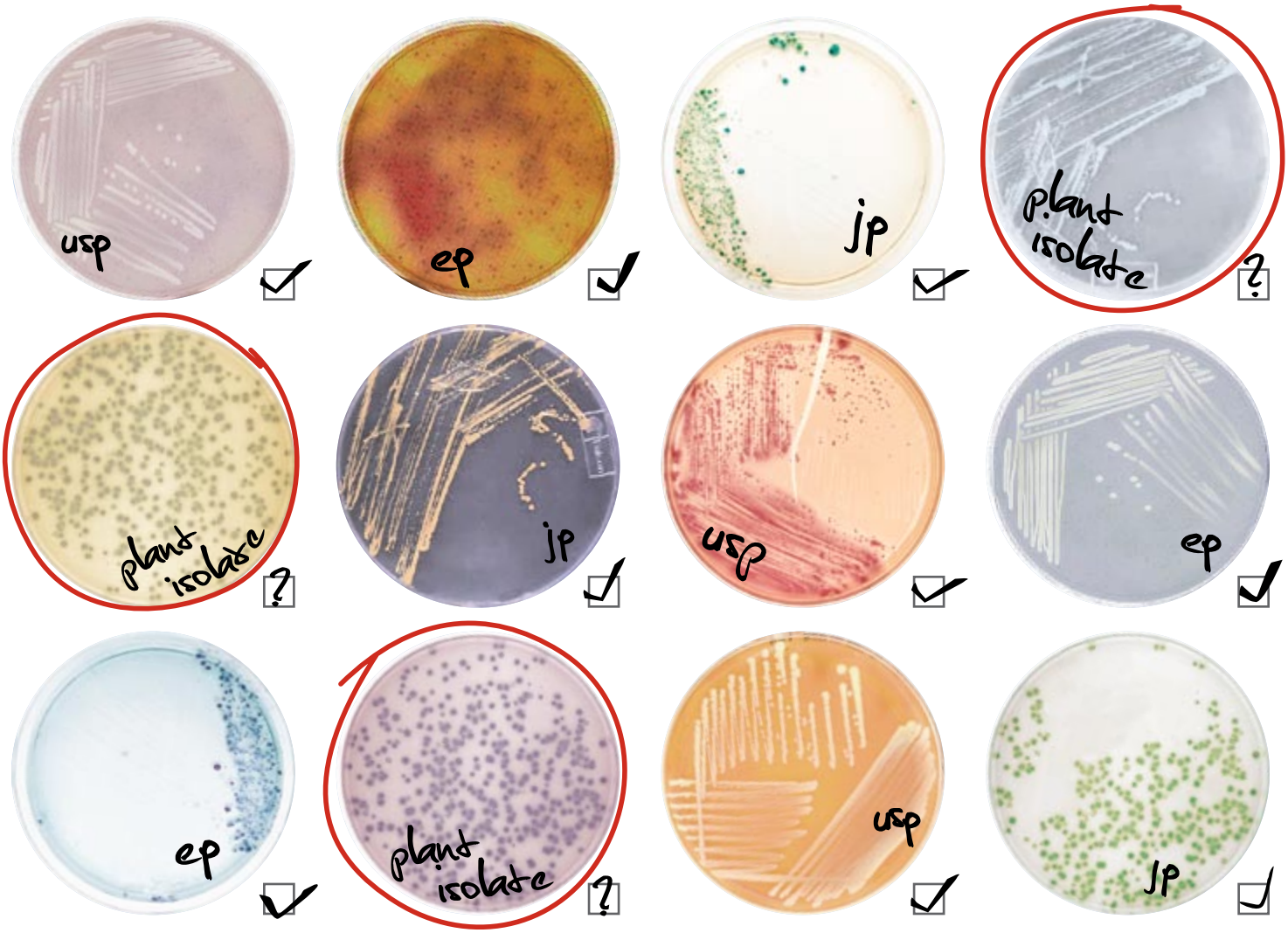
# The Value of Plant Isolates in Pharma Quality

**David Myatt, PhD and Charlotte Morgan, PhD, BTF, a bioMérieux company**




## What value are plant isolates in microbiological quality in the pharma industry?

**Increasingly, pharmaceutical companies are including their own isolates in the battery of microorganisms that they use for media growth promotion testing and validation studies. These "plant isolates" are wild-type strains isolated during environmental monitoring, sterility and bioburden testing, and routine testing for contamination or spoilage. In so doing, these companies seek best microbiology practice, but it remains somewhat controversial. Some commentators argue that compendial methods do not mandate such an approach, others challenge its scientific merit, and some query the practicality. Notwithstanding a level of public debate, many companies are implementing standard operating procedures and grappling with the practicalities of strain selection, culture maintenance that sustains the cultural characteristics of "wild" plant isolates, a degree of regulatory uncertainty and, certainly, a paucity of guidance on how to achieve the desired outcome, whether that is simply compliance or genuine commitment to more challenging tests in pharmaceutical quality management.**

### Wild-type Strains

By definition, strains found in nature. But in our context, we mean to discuss strains that are recently-isolated in a manufacturing context, either from a controlled manufacturing environment or, perhaps, a contaminant of raw materials or finished pharmaceutical product. These are strains that are not conditioned through serial subculture to growth on rich laboratory culture media and may exhibit unstable phenotypic characteristics associated with oligotrophy, desiccation or biofilm formation, namely traits that have enabled survival in harsh conditions and may not persist in strains that are serially passaged in rich culture media uncharacteristic of the environment from where they were isolated.

## Trends in Use of Wild Isolates

Let's begin by agreeing that this really isn't anything new! Authorities on quality in pharmaceutical microbiology have been suggesting the merit of including wild-type isolates in media QC testing for many years **(1, 2, 3)** and auditors now issue FDA 483 observations in relation to this expectation.**(4)** Certainly, it's become a topical matter in recent years, with periodic debate in industry discussion forums and blogging sites.**(5, 6, 7)** While perspectives on the scientific merits vary, and whether it's a function of regulatory attention or best microbiological practice, use of plant isolates (or whatever you choose to call them) is now commonplace in pharmaceutical microbiology.

One author's own insight, gleaned from many conversations with practicing pharmaceutical microbiologists, clearly indicates that many big pharma companies and smaller ones alike are implementing (or already have) the use of a few of their own isolates to complement the compendial reference strains in growth promotion testing of environmental monitoring and sterility testing media, and sometimes in validation studies for new methods such as rapid microbiological methods (RMM) for sterility assurance testing. In most cases, these labs intend to make an annual assessment of the frequency of species amongst their environmental isolates and select either the two or three with highest frequency or the highest frequency isolate from each of the Gram positive, Gram negative and fungal isolate groups. Their intention is usually articulated in terms of compliance (i.e., what auditors want) or best laboratory practice, even if they do not subscribe to the view that the use of these strains is a valuable exercise in verifying the performance of their culture media or test methods. It certainly seems that there is now a widely-perceived need for compliance here (in the absence of an FDA audit citation) given that the use of environmental isolates is strongly recommended in a number of compendial references and other authoritative documents.

It is also commonplace to see manufacturers of personal care products and nutraceuticals include extensive batteries of contaminant organisms (isolated from their raw materials or spoilage of their products) in studies to verify the efficacy of their preservative systems. Of course, conceptually, this is akin to the testing of non-sterile pharmaceuticals for objectionable organisms that often originate as contaminants in raw materials or from the manufacturing environment. Whatever the case, these practices are founded on the idea that these microorganisms are a better challenge to the microbiological method than the "standard" compendial strains.

## Applications, Regulations and Recommendations

The compendial references for sterility tests, enumeration tests, specified microorganisms, and antimicrobial effectiveness tests (USP chapters <71>, <61>, <62> and <51> respectively) and the corresponding sections of the European Pharmacopoeia do not prescribe the use of environmental or other wild isolates. However, a number of compelling recommendations in this regard are made in guidelines issued by several authorities:

- Concerning the microbiological evaluation of controlled environments, USP <1116> says "for the Growth Promotion test, representative microflora isolated from the controlled environment… may also be used to test media."
- USP <1117> concerning Microbiological Best Laboratory Practice suggests "microorganisms used in growth-promotion testing…may include representative environmental isolates (but these latter are not to be construed as compendial requirements)."
- *FDA Guidance for Industry for Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice* (September 2004) says "The QC laboratory should determine if USP indicator organisms sufficiently represent production-related isolates. Environmental monitoring and sterility test isolates can be substituted (as appropriate) or added to the growth promotion challenge."
- *FDA Guidance for Industry concerning Validation of Growth-Based Rapid Microbiological Methods for Sterility Testing of Cellular and Gene Therapy Products* (draft guidance, February 2008) suggests, in relation to selecting a panel of appropriate challenge microorganisms for validating an RMM, the inclusion of "isolates detected in starting materials, isolates detected by in-process test-

### Isolated Look at this Article

- Testing of plant isolates, or wild-type strains, is a regulatory expectation
- Arguments against such testing include practicalities related to repeatability, reproducibility in validations and cost
- The real value derives from significantly greater confidence in media, methods and systems that are validated and tested using strains that are more typical of target organisms than those referenced in compendial methods

It could be argued that the expertise and facilities needed to preserve plant isolates markedly exceeds those demanded for compendial strains

ing or during preliminary product testing, isolates detected by environmental monitoring of your manufacturing facility, [and] isolates from your production areas which represent low nutrient or high stress environments…."

- USP <1072> concerning Disinfectants and Antiseptics suggests "surface challenge tests using standard test microorganisms and microorganisms that are typical environmental isolates…."
- The Japanese Pharmacopoeia (XV, General Information section 11.4.1 concerned with Media Fill Tests) says in relation to selection of growth promotion testing organisms "one or two representative microorganisms which are frequently isolated in environmental monitoring should be used."

While none of these can be construed as a mandatory requirement, here are many calls to consider the relevance of plant isolates in growth promotion testing, validation studies and challenge testing. Presumably, this selection of references represents a much greater number of experienced individuals on expert panels who've co-authored these documents in conjunction with the regulatory agencies that have published them. So, it seems fair to say that there are widely-held views that plant isolates are relevant.

### Costs and Value

Arguments against the inclusion of plant isolates in pharmaceutical microbiology are varied and include the practicalities of standardizing such isolates for repeatability and reproducibility in validations, and the challenge of preserving these strains in a culture collection.(7) We would add to that list the considerable challenges related to expertise and specialized resources needed to manage a culture collection of plant isolates so that they're minimally compromised by subculture and preservation. This is an increasingly acute issue in pharma where everyone, including microbiological quality laboratories, is asked to do much more with much less in tougher economic times.

Experience in culture collection management and culture preservation techniques is increasingly rare when many laboratories opt to purchase strains from recognized collections or commercial suppliers. Beyond that, time and competencies needed to prepare standardized suspensions by serial dilution are also increasingly scarce. Toted up against the costs of these activities are lab space, acquisition and installation costs, qualification and validation projects, and maintenance and user training demanded by various pieces of laboratory equipment like ultra low temperature freezers, freeze-dryers, spectrophotometers and data management systems needed for a competent culture collection. There are also costs of specialized laboratory reagents and consumable items and their procurement, qualification, documentation, storage and wastage. The costs mount up dramatically. In this context, commercially-available quantitative microbiological controls produced with compendial reference strains have grown in popularity, and leading brand products are Certified Reference Materials according to ISO Guide 34 accreditation. Such products offer labs the option of "outsourcing" laborious, time-consuming, expensive and error-prone activities associated with maintaining cultures and preparing inocula for routine growth promotion tests and validations studies.

But, having outsourced these activities, those wanting to incorporate plant isolates in their testing are now challenged to reinstate skills, time and other resources needed to maintain and prepare them. Additionally, it could be argued that the expertise and facilities needed to preserve plant isolates markedly exceeds those demanded for compendial strains. For instance, the optimal culturing conditions required for the compendial strains are well known and documented within the industry, advice is on hand. Whereas, when preserving and culturing a plant isolate, it is unknown whether the environmental strain will be as robust or have the same culturing requirements as a known culture collection strain of the particular plant isolate species, so it can quite often be a case of "trial and error" and therefore time-consuming and expensive.

### Practicalities in Implementation

The contention that exists about use of plant isolate derives from a general lack of knowledge of how these wild strains differ from culture collection strains that have been serially subcultured to such an extent that they are "adapted" to rich culture media. The nature of the differences is poorly understood, as are the mechanisms involved. Certainly, serial subculture drives a process of *in vitro* evolution where there is natural selection for clones that grow most luxuriantly on rich media, but the stability of what could be defined as "wild" attributes, and consequent phenotypic and physiological changes, and how quickly these emerge in serially-subcultured strains, is generally not understood.

In this context, the safest approach is to minimize the serial subculture of plant isolates. Compendial references suggest that culture collection strains should be five or fewer subcultures (passages) from the culture originally sourced from a reference culture collection. This "five passages" rule has been extrapolated to plant isolates, but again in the interests of conservatism, we suggest that minimizing serial subculture is the only way likely to minimize the risk of significant strain evolution that would compromise a strain's merit as a stringent challenge to media fertility or RMM performance. So, it could be argued that the ideal candidates will be minimally subcultured plant isolates, with phenotypic characteristics stabilized through sophisticated preservation techniques, and standardized to deliver a reliable inoculum for consistent growth promotion testing and ➤

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for repeatable and reproducible validation studies. That is an ambitious objective! Few laboratories have the competencies and resources outlined above to accomplish this, and it is a fact that some very useful techniques are the subject of patents or proprietary know-how. There are three main techniques to reliably store microbial cultures, namely ultra low freezing at below -70°C, cryopreservation in liquid nitrogen, or freeze drying (lyophilization). Each technique has advantages and disadvantages. However, selection of a technique is more often based on the availability of equipment and expertise than on the suitability of the technique to the particular strain to be preserved. Some strains survive well in a frozen matrix, whereas others can only be frozen in liquid nitrogen for long term survival. Freeze drying is the technique of choice for long term microbial preservation (8), for cells that can tolerate freezing and drying, but this technique can be too harsh for more fragile microbes (e.g., mycoplasma). It must be kept in mind, no matter which technique is used, there is still a degree of selection happening during storage, and viability cannot be sustained indefinitely, and therefore the longer the storage, the greater the possibility of genetic or phenotypic drift. It is for this reason that extensive profiling of strains prior to storage should occur, so that any change in the strain can be detected by comparison with the original profile. The value of experience in the cataloguing and storage of strains in a culture collection can be easily under-estimated, hence the reason why most companies that hold commercially important microbial strains invest in back-up storage of their strains at off-site facilities with relevant expertise and capabilities.

Accordingly, specialist service providers with the appropriate focus, experience and facilities now offer to acquire from labs their minimally subcultured strains and return standardized inocula to cover a year (or more) of testing with minimized risk of compromising the strains' "wild" traits. Leaders in this field use the most sophisticated techniques available for strain preservation, standardization and delivery and seek to provide premium service to match the regulatory and operational context that is peculiar to microbiological quality in the pharma industry. When assessing the capabilities of such service providers, we recommend a thorough review of their track-record with a wide range of compendial strains, the potential for their technologies to minimize the *in vitro* evolution or "adaptation" of plant isolates, and their ability to provide plant isolates in formats that are consistent with and as convenient as the compendial strains they supply.

**We find few convincing arguments against the use of plant isolates to more effectively challenge the media and methods used in pharmaceutical quality**

### Conclusion and Future Trends

We've outlined here our perception that there is now a very strong trend to increased use of plant isolates to challenge pharmaceutical microbiology media, methods and systems, both in routine QC testing and validation. We've observed the regulatory pressures for greater compliance in this area, but acknowledge the practical and economic challenges that accompany a commitment to the routine use of plant isolates. Nevertheless, given the ethical, legal and economic imperatives that compel rigorous quality management in the pharmaceutical industry, we find few convincing arguments against the use of plant isolates to more effectively challenge the media and methods used in pharmaceutical quality. It is not costless to do so and must therefore deliver real value. We suggest that real value derives from significantly greater confidence in media, methods and systems that are validated and tested using strains that are more typical of target organisms than those referenced in compendial methods, that is, strains acquired from culture collections where they've been serially passaged under atypical conditions for many years. Certainly, the very isolation of wild-type strains and their minimal subculture for preservation are selective pressures that threaten the traits we'd hope to retain in the strains we use to challenge our microbiology tests, but we don't see practical alternatives beyond use of the most sophisticated techniques to preserve strains as close to their primary isolation as possible. Accordingly, we argue that there is real value, albeit difficult to quantify, in maximizing confidence that media and methods we use in pharmaceutical microbiology are effective and reliable to the greatest extent that we're practically able to demonstrate, and therefore contribute more assurance of the quality of our pharmaceuticals, medical devices and personal care products.

It seems inevitable that there will be sustained or increased attention paid to critical environment monitoring, detection of objectionable organisms and other microbiological practices intended to minimize contamination and adverse outcomes from the use of therapeutic and nutritional products. There is little indication from regulators or any other authorities in the pharma industry that vigilance will decline or expectations will be relaxed. Increasingly litigious developed markets, growing healthcare standards and expectations in emerging markets all have the effect of encouraging greater regulation, despite economic pressures. We would also expect to see greater use of methods not based on microbial growth, where these RMMs need to be shown, through extensive validation, to be equivalent to traditional compendial methods, at least according to current requirements.**(9)** For instance, is a slow growing plant isolate (that takes >5 days to grow in traditional culture) detectable by a RMM? This is why, if such plant isolates are found, they may be relevant for method validations. Indeed, such questions only serve to fuel discussions about the merits of using plant isolates to ➤

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complement culture collection strains in important pharmaceutical microbiology testing. But, it seems the tide of opinion now shows that many have accepted the value of additional strains selected for their relevance in individual sites and products. The challenge remains to execute this practice well, so its value is realized, either through investment in the competencies and skills required to reap the value of plant isolate strains preserved as close to their original state as possible, or by partnering with service providers whose focus, expertise and experience in the specialized area of microbiological strain preservation can provide stable and quantitative plant isolate strains that are minimally passaged since isolation.

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## About the Authors

**David Myatt** has more than 20 years experience in diagnostic and industrial microbiology, having held senior roles in quality management, marketing and commercial leadership in global microbiology companies. His pharma microbiology experience began with a QA management role implementing a quality system, cGMP and compliance with international regulatory standards. His subsequent commercial roles in the pharma and bioprocessing markets included focus on microbiological culture media, pharmaceutical quality control, critical environmental monitoring, and biopharma production. He holds a PhD in Microbiology and an MBA in International Business and Marketing. He leads strategic marketing at BTF, a bioMérieux company in Australia. To contact email david.myatt@btf.biomerieux.com

**Charlotte Morgan** has more than 10 years experience in research related to precise detection and dispensing of microbial cells and maintaining viability through techniques such as freeze drying. Her role as a principle researcher in the development of the commercial microbial reference material "BioBall" has developed into managing a team of dedicated scientists to expand the BioBall range and the techniques to improve long term precise preservation of microbial cells. She holds a Masters in Water Microbiology and a PhD in Microbiology. She is currently a R&D Manager at BTF, a bioMerieux company in Australia. To contact, email charlotte.morgan@btf.biomerieux.com.

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The *July/August PDA Journal of Pharmaceutical Science and Technology* will include an article by **Tim Sandle** called, "A Review of Cleanroom Microflora: Types, Trends and Patterns"

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# Delamination Propensity of Pharmaceutical Glass Containers by Accelerated Testing with Different Extraction Media

**Emanuel Guadagnino (ret.) and Daniele Zuccato, PhD, Stevanto Group**

How can injectable drug manufacturers prevent glass delamination? The issue of delamination is a serious one as it can cause glass particles to appear in vials, a problem that has forced a number of drug product recalls in recent years. To combat this, pharmaceutical and biopharmaceutical manufacturers need to understand the underlying reasons for glass delamination.

The delamination of glass when it is exposed to certain environments is a very well-known phenomenon. For instance, the occurrence of flakes in soda-lime glass bottles intended to get into contact with food and beverages has been documented since the early forties. In that case, storage of the empty bottles under uncontrolled conditions of humidity and temperature showed to be a key factor. Along the production line, the packing stage is located at the exit of the annealing lehr, where bottles have a temperature of about 60°C. Then, bottles are placed on a pallet and covered with a polyethylene foil shrink wrap that can trap humid air within. The consequence is an early interaction with the inner glass surface, which is still sufficiently hot to react vigorously, giving rise to extensive weathering. This results in the formation of an altered alkali-depleted and silica-rich layer that has an expansion coefficient which is fairly different from the glass substrate underneath. When bottles are filled with any kind of liquid, even water, the substrate and the altered layer are subject to strong re-hydration, to an extent which depends on their chemical durability and relative thickness. When the thickness and flexibility of the altered layer becomes critical as compared to the substrate, the layer begins to crack and simple shaking is sufficient to start its complete demolition. **[Author's Note:** Type III glass containers also are made of soda-lime glass and safe storage conditions are needed before filling.**]**

The most recent cases of product recall due to the presence of particles in the filling liquid have involved Type I glass containers* carrying drugs made of active components with known ability to corrode glass and to dissolve the silica matrix. Sometimes these ingredients are dissolved in an alkaline medium which dramatically increases the glass corrosion and potentially causes the issue. As this action is strongly affected by time and temperature, flaking may become visible only after a long incubation during storage and requires a systematic monitoring to be detected at its early stage. If the nature of the filling liquid is the driving force of the phenomenon, other factors are of primary importance. The surface morphology created during vial forming is a key issue, being a function of the forming temperature being is higher in the cutting step and in forming the bottom. Delamination occurs generally on the vials' bottom and shoulder, where extensive flaming can favor a strong evaporation of alkali and borate species and the formation of heavily enriched silica layers. As in the case of soda-lime containers, the formation of these layers represents the first stage of an incipient delamination that develops according to the same mechanism described above.

***Definition of Container Glass Types according to European Pharmacopoeia***

***Type I:*** *A borosilicate glass with a high hydrolytic resistance due to the chemical resistance of the glass itself*

***Type II:*** *Usually of soda-lime-silica glass with a high hydrolytic resistance due to the chemical resistance resulting from suitable treatment of the surface*

***Type III:*** *Usually of soda-lime-silica glass with only moderate chemical resistance*

Reducing the risk of delamination is therefore a serious problem, as one has to consider and keep under control all the production stages, including the optimization of the conversion process, the choice of the most appropriate glass type as a function of the chemistry between glass and parenteral solution, the filling operations and the shelf life of the product.

Many open questions require a precise answer. For instance:

How can delamination be predicted? What parameters can be used to investigate delamination propensity? Are European Pharmacopoeia (EP) titration values a reliable indicator of delamination resistance? Which glass type is more suitable to which preparation?

The authors have conducted a study in the Stevanato Group laboratories in collaboration with external institutional laboratories to answer some of these questions. The aim was to highlight the interaction between several glass types in contact with different extractants, including slightly alkaline preparations, and to investigate whether there is a correlation between EP titration values and evidence of delamination.

Several types of borosilicate glasses, both sulfur treated and untreated, were tested by contact with different extraction media for repeated autoclave cycles of 1h at 121°C. The propensity for delamination was observed measuring by Inductively Coupled Plasma-Optical Emission Spectrometry (ICP-OES) the increase of $SiO_2$ concentration in the extraction solutions, while the presence of particles was monitored by optically assisted visual inspection. Results obtained with neutral aqueous solutions ($H_2O$ and 0.9% KCl, pH=6) indicate that $SiO_2$ concentration correlates with hydrolytic resistance, increasing according to the same order. The unexpected high silica concentration found in the extracts coming from expansion 33 glass vials was explained by the surface damage induced by the conversion process, as it is confirmed by the relatively high EP titration value. Under these conditions the sulfur treated glass showed the best performance in terms of dissolved silica, no flakes were observed in the examined glass types. When slightly alkaline solutions were used as extractants (0.9% KCl solution, adjusted to pH=8), $SiO_2$ concentrations in the extracts increased very steeply, irrespective of their EP values. In this case, the glass ranking found with neutral solutions is reversed; in sulfur treated glass vials flakes occur very soon even if the $SiO_2$ concentration is low. It was concluded that under alkaline attack EP values do not respond as performance indicators and that $SiO_2$ concentration is not sufficient to reveal flaking by itself, being visual inspection an essential support to detect it. Extractions with 0.9% KCl solutions indicate that expansion 51 borosilicate glasses are the best performing glasses, sulfur treated and expansion 33 showed early flaking.

**The conclusions developed by this study can help arm pharmaceutical manufacturers with information needed to help prevent glass delamination in their processes**

The same ranking was observed with extractions carried out with organic acids like glutaric and citric, but at far much higher $SiO_2$ concentration levels. Heavy flaking was also observed. The extraction ability of citric acid is as high as three times the ability of glutaric acid, $SiO_2$ concentration in expansion 33 extracts is around 200 mg/L after 2 autoclave cycles, indicating that the inner surface is subject to a very pronounced dissolution process. Citric acid extractions carried out under milder conditions (80 °C for up to 48 hours) showed early flaking in sulfur treated and expansion 33 glass vials, confirming the results and the ranking already observed.

Scanning Electron Microscope-Energy Dispersive Spectrometry (SEM-EDS) analyses carried out on samples treated with a 0.9% KCl neutral solution, confirmed that particles contained the same constituents of the origin glass, micrographs obtained from the bottom areas and 5 mm from the bottom of expansion 33 glass vials showed enlarged spots with heavy signs of corrosion and scales detachment.

It was concluded that EP titration values can be used as indicators of the chemical durability of the glass against neutral aqueous solutions only. When vials are in contact with alkaline solutions and similarly aggressive media, the glass performance is better represented by the concentration of the extracted silica. An increase in silica concentrations indicates glass corrosion and an increasing risk for further delamination. Under such conditions expansion 33 glass is extensively corroded and shows early flaking. An exception is the sulfur treated glass, where delamination can occur even at low $SiO_2$ concentration.

Extractions with 0.9% KCl solution can be used as an accelerated test to highlight the propensity of a glass to delaminate, but in no case can be taken as a guarantee that the glass shall not delaminate when it is exposed to the pharmaceutical drug, whose extraction ability requires to be studied case by case.

The conclusions developed by this study can help arm pharmaceutical manufacturers with information needed to help prevent glass delamination in their processes. It is the authors intent to submit the full dataset to a peer reviewed journal, like the *PDA Journal of Pharmaceutical Science and Technology.* You can contact us if you want more information on the results.

**[Editor's Message:** This article is based on a paper presented by Emanuel at the *Rx-360 Symposium on Glass Delamination* which followed the *PDA/FDA Glass Conference* in Arlington, Va. on May 25.**]** ➤

# 2011 PDA UPCOMING EVENTS

## JULY 2011

**11-12**

### Biotechnology: Overview of Principles, Tools, Processes and Products

Bethesda, Maryland
www.pdatraining.org/biotechnologyoverview

**25-26**

### PDA TRI Risk Management Week

Bethesda, Maryland

- A Risk Based Approach to Technology Transfer (July 25)
- Practical Applications of Risk Management (July 26)

www.pdatraining.org/riskmanagement

## AUGUST 2011

**1-5**

### Basic Microbiology for Aseptic Processes

Bethesda, Maryland
www.pdatraining.org/basicmicro

**22-26**

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

**(Week 2: September 12-16)**
Bethesda, Maryland SOLD OUT
www.pdatraining.org/aseptic

Seats are still available in session 5!
(October 10-14, 2011 and November 14-18, 2011)

## SEPTEM

**1**

### Process Validation for Pharmaceuticals - Current and Future Trends

Bethesda, Maryland
www.pdatraining.org/processvalidation

**19-23**

### 2011 PDA/FDA Joint Regulatory Conference & TRI Courses

Washington, D.C.
www.pda.org/pdafda2011

**21-22**

### PDA 2011 Combination Products Workshop

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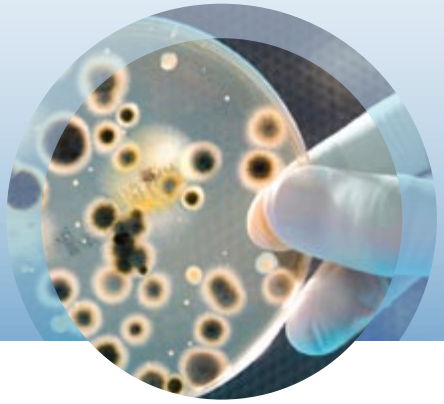
www.pda.org/2011comboproducts



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For an updated PDA calendar of events please visit www.pda.org/calendar.

# Save these dates!

## BER 2011

### 27-28
**Developing and Validating a Cleaning and Disinfection Program for Controlled Environments**
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www.pdatraining.org/DVCD

### 27-28
**Pharmaceutical Cold Chain Management & Good Distribution Practice**
Berlin, Germany
https://europe.pda.org/ColdChain2011

### 29-30
**Good Temperature-Controlled Management Practices**
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https://europe.pda.org/TCColdChain2011

## OCTOBER 2011

### 3-6
**2011 PDA Visual Inspection Forum & TRI Course**
Bethesda, Maryland
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### 4-6
**Pharmaceutical Quality System (ICH Q10) Conference**
Arlington, Virginia
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### 10-14
**Aseptic Processing Training Program – Session 5 Week 1**
**(Week 2: November 14-18)**
Bethesda, Maryland
www.pdatraining.org/aseptic

### 17-21
**PDA's 6th Annual Global Conference on Pharmaceutical Microbiology & TRI Courses**
Bethesda, Maryland
www.pda.org/2011microbiology

### 24-28
**PDA TRI Filtration Week**
Bethesda, Maryland
- Filters and Filtration in the Biopharmaceutical Industry - *Basics Course* (October 24-25)
- Filters and Filtration in the Biopharmaceutical Industry - *Advanced Course* (October 26-28)

www.pdatraining.org/filtrationweek

### 25-28
**Freeze Drying Technology - Modern Trends in Production**
Barcelona, Spain
https://europe.pda.org/FreezeDrying2011

### 27
**Risk Management for Freeze Drying Processes**
Barcelona, Spain
https://europe.pda.org/WSFreezeDrying2011

### 27-28
**Development of a Freeze Drying Process - From Formulation to a Robust Process**
Barcelona, Spain
https://europe.pda.org/TCFreezeDrying2011

## About the Authors

**Emanuel Guadagnino** (retired) is active as a contract professor at the Cà' Foscari University in Venice and as scientific advisor for the Stevanato Group. His career began following graduation in Pure Chemistry from Padova University in 1972. He joined the Stazione Sperimentale del Vetro, Murano-Venezia (SSV) in 1977 and developed his main activity in the field of the chemical characterization of glass and raw materials, development of new analytical methods and normative research, study of the chemical durability of glass (lead crystal glass, foodware and paharmaceutical glass, bioglass, dishwashing of glassware). As head of the chemical analytical department (from 1991 to 2001) and later as Coordinator of SSV research activities, he coordinated a number of European collaborative projects for the preparation and certification of glass reference materials for the determination of trace elements in glass. He served in technical committees and international commissions (UNI, ISO, CEN, ASTM) for the standardization of glass as a material and its intended use. He has been an appointed Italian delegate at the European Pharmacopoeia ad-hoc Working Party "Glass Containers" since 1998. He has served as the Honorary Secretary of TC2 "Chemical durability and analysis" of the International Commission on Glass since 1992. He received the Turner Award in 2007 from the International Commission on Glass. He has published 95 papers, many of them were presented at international meetings and conferences.

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**Daniele Zuccato** achieved his Master Degree in Industrial Chemistry at Venice Cà' Foscari University in 2009. His master thesis was focused on the development of analytical methods using ICP-MS techniques in the environmental field. In 2007 he collaborated with the Italian National Research Institute on the speciation of heavy metals in foodstuffs with HPLC-ICP-MS hyphenated techniques. He worked for one year as the head of an environmental laboratory for the development of analytical methods using GC-FID and GC-MS. In 2009, he joined the R&D glass division of the Stevanato Group as a project leader for an investigation focused on the migration of trace elements from the glass surface. Today Dr. Zuccato is following all the forensic activities required within the Stevanato Group for the development of the pharmaceutical primary packaging.

To contact Daniele Zuccato you can email him at daniele.zoccato@stevanatogroup.com.

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# Root Cause an Elusive End for Micro Investigations

## Lessons Learned Regarding Microbiological Investigations

**Randy Hutt, PhD, San-Mar Laboratories**

This article will cover my experiences and lessons learned within my roles in the QA, QC and Production departments for over 30 years in the pharmaceutical and biological industries handling microbiological investigations due to non-conforming results in sterility testing, environmental/personnel monitoring and media fills. While there are some guidance documents available (e.g., the United States Pharmacopeia and the Aseptic Guidelines for products marketed in the United States and the Orange Guide for the UK), it is truly through years of experience that one knows how to properly handle investigations into non-conforming microbiological results. This article will focus on sterility testing failures, environmental monitoring non-conformance results and media fill failures.

An investigation should be performed to find the true root cause, correct and prevent it from reoccurring. I have seen many investigations over the years that have not found the true problem or were conducted poorly. It is important for any company to have a system in place for when something goes wrong, therefore, when it does go wrong (and it will), you won't waste time worrying about what to do—you can immediately get to work.

Let us review first what things can go wrong regarding microbial investigations. First of all, some companies do not have any prescribed methods on how to handle them. These types of investigations differ substantially from OOS chemical/physical results. It is important to conduct good investigations or the U.S. FDA will slap companies with 483 observations, warning letters or consent decrees.

### Sterility Test Investigation Issues

Below are examples of FDA Warning Letter or 483 comments related to sterility test investigations:

- "Procedures designed to prevent microbial contamination of drug products purporting to be sterile do not include adequate validation of the sterilization process." **(1)**
- "APR# ____ dated 8/24/2006 was issued for sterility failure of _____ bulk lot _____. The investigation failed to assess a recent change in the SIP cycle for tank ____. The validation of this SIP Change was subsequently implicated during investigation of the failure of a media challenge, which ultimately led to the recall of _____ and _____. **(2)**
- "Supervisor discarded first Sterility Test data, because it was invalid." **(2)**

Through my many years in various QC and QA departments, I have learned the following lessons:

a. Doing repeat testing or stage 2 without invalidating stage 1 is unacceptable (See section below on invalidation of stage 1). In the past I worked for a company where the first Sterility Test for a batch of product was positive with mold. The second Sterility Test (Resample) was also positive with a different mold. My report was written to reject the batch, because the first stage was not invalidated and we did not have environmental data to show that the origin of the mold was from the lab. We were waiting for some data to close the report and err on the side of safety, but when I left on vacation for a few days, Management changed the conclusion and released the batch. I was horrified and lost all respect for my direct boss, that he did that.

b. Inadequate environmental monitoring or poor selection of sampling locations in production or the sterility suite reduces the likelihood of being able to identify a root cause.

c. Use of an aseptic room and laminar flow hood for sterility testing instead of an isolator leads to more false positives in sterility testing.

d. Not seeing the big picture can lead to erroneous conclusions from the collected data e.g., contaminated swabs used in Freeze-dryer after sterilization, prior to product, but product passed sterility testing, could lead someone to think the batches are releasable. The sterility test only tests a small volume of product out of a large batch.

e. To invalidate the first sterility test:

i. Data from monitoring Sterility test Suite shows the same as the organism recovered as that from the test.

ii. The lab technician made an error during the test procedure.

iii. Microbial growth is found in the negative or manipulative controls.

iv. The growth of the organism from the test can be determined to be caused by problems with materials or the technique used to perform the test.

**Note:** If the original test is declared invalid, it may be repeated with the same number of units (e.g., retain samples).

### EM Investigation Issues

It would be remiss of me to leave out environmental monitoring as it plays a big part within microbial investigations. However, many companies drop the ball

while doing environmental monitoring investigations. The FDA has cited many firms for laboratory imperfections:

- "The inspection reported numerous deficiencies regarding the lack of approved procedures, and inadequate laboratory controls for documentation, storage and handling of samples pertaining to stability and environmental monitoring programs." **(3)**
- "Non-viable particulate monitoring was not performed in the class 100 area immediately adjacent to the ____ where partially stoppered vials are exposed." **(3)**
- "Production personnel perform monitoring (fingers on agar plate) on each other. An operator was observed spraying 70% ethanol on gloved hands just before sampling and on two separate occasions, operators were observed sampling with wet gloves." **(3)**

I, personally, have seen in one company:

- Batches rejected due to microbial contamination as gram-negative organisms were found on the floor
- Spore formers found in the aseptic area

Working with the line operators, who are typically the most knowledgeable people regarding what is actually occurring, and with engineers to look at pipe sloping, air gaps, etc., I was able to find the sources of water causing the presence of the Gram-negative organisms and correct the problems. Use of dedicated shoes, which were put on just prior to gowning, eliminated the spore-forming organisms coming in from the surrounding rural areas where the operators lived. These observations required me to act like Sherlock Holmes in aseptic garb, with RODAC plates and swabs, watching how things were being handled in the aseptic area.

## Media Fill Investigation Issues

Media Fills, a parameter for assuring that a manufacturing process is capable of producing sterile pharmaceuticals using an aseptic process, have also been the target of the FDA. Plants have also been written up by the Agency based on how it has carried out manual interventions and discarded media fill units:

"Failure to demonstrate that planned manual interventions during media filling operations do not contaminate (negatively impact) the media filled containers. Following these manual interventions an unspecified number of units containing media near the intervention areas are discarded and not incubated, which could result in a bias of the media fill results." **(3)**

Discarding of unspecified numbers of media filled units indicates that the media fill qualification would not be able to substantiate that the contamination rate was not exceeded in order to obtain the confidence level described in the validation protocol. (3)

Interventions need to be adequately covered in media fills including both inherent interventions such as loading the stopper hopper, taking breaks, checking fill weight, and corrective interventions. These include maintenance coming in, changing filling needles, removing fallen vials, etc. When these are properly included, a failed media fill can lead you to the root cause, especially if one keeps track of interventions and the portion of the batch that positives are found in. It is also critical to identify any organisms which have grown in the media fill and to have adequate environmental monitoring during its execution.

Investigations should be finalized once the root cause is found. If the root cause is from the laboratory itself, then the investigation is done at that point, but if not, then QC must notify QA so that Production must be contacted. While running a carefully planned microbial control strategy can reduce the number of incidents, which is always preferable to conducting investigations after an incident has occurred, if the lab tests have shown to be true positives, and not laboratory error, it is critical for QA to request that an investigation be performed by a Production Representative.

## Production Investigations

There are many different methods which can be used to perform these investigations, such as: the Kepner-Tragoe method of Analytical Trouble-shooting; the Fishbone (Ishikawa) method; The Five Whys; or any recognized investigational methodology. It is even possible to use a combination of these methods. These can be helpful for a company to adopt so that its "lead investigators" are trained in these methodologies and can use them specifically to conduct microbial investigations.

Even if you have a method in place to handle microbial investigations, problems can still occur. Including:

1. Inadequate resources are available to allow the conduct of a thorough investigation.

As mentioned, there are many different methods which can be used to perform investigations. Descriptions of some of my favorites include:

**Kepner-Tragoe's Analytical Trouble-shooting (ATS):**

The Kepner Tregoe Analytical Trouble-Shooting is a systematic step-by-step approach to solving problems that can be used to detect, analyze and avoid problems. ATS helps the QA team find root causes and take action. Part of the ATS process is to examine other areas that could be similarly affected, plan the implementation of any actions, and prepare for the unexpected.

**The Fishbone (Ishikawa) method:**

This is a causal diagram that shows the causes of a certain event. Common uses include product design and quality defect prevention, identifying potential factors causing an overall effect. Each cause or reason for imperfection is a source of variation. Causes are usually grouped into major categories to identify these sources of variation.

**The Five Whys:**

This a questions-asking method used to explore the cause/effect relationships underlying a particular problem. Ultimately, the goal of applying the 5 Whys method is used to determine a root cause of a defect or problem.

Please note that there are many other recognized investigational methodologies.

2. Symptoms are treated, i.e., contributing symptoms are the ones being fixed, rather than root cause. By changing too many variables at once, the true root cause is missed.
3. Lack of root cause determination, but identifying one anyways; some companies will find an assignable cause, without a thorough investigation.
4. Inadequate training--failure to provide a structured program for investigators to train personnel on how to conduct and document investigations.
5. Lack of template for investigation report.
6. Lack of timeliness (i.e., within 30 days) or not documenting rationale for extensions over 30 days.
7. Determination of impact on other batches or other products which may be involved directly or indirectly in the incident.

To combat the above list, and if you want to ensure that your investigation uncovers your problems, it is necessary to:

1. Train people well.
2. Establish roles of lead person and investigation team members. Note that bigger companies tend to use QA as the team leader and others as members, who will perform the critical work of the investigation.
3. Perform a thorough investigation and get to root cause, or most probable cause.
4. Test solutions against where the problem is vs. where it is not.
5. Document root cause and Corrective and Preventive Actions (CAPA).
6. Determine impact on batch immediately involved and consider if other batches and / or other products might be impacted. Document all of the above.
7. Document what the rationale is for the investigation extension, if it needs to extend past 30 days.

A simple Manufacturing Investigation Report Step I can be written by production supervision when the problem is obvious, such as a major maintenance problem that occurred during filling. Note that this investigation must be reviewed and approved by QA. If production cannot determine the true root cause of the problem, then Step II can "kick in." This is where QA can assume the leadership role of a complex investigation. This involves recruiting a team to explore the problem including personnel from Production, Maintenance, Research & Development, where necessary, etc.

The team would then use either the Analytical Trouble-Shooting or the Fishbone method or a combination thereof, to ask sufficient questions to determine what must have caused the problem. Once the problem has been diagnosed, a risk assessment needs to be initiated to determine if the organism(s) in question could have indeed contaminated the batch. Once the root cause has been determined, then corrective actions can be implemented* and appropriate preventive actions can be identified and established.

*If the organism has not contaminated the batch, it might be possible to save the batch. If the organism has contaminated the batch or there is a likelihood that it could have, then the batch needs to be rejected.*

In many cases, the CAPA will need future follow-up to ensure effectiveness. It is important to have a database tracking system to ensure that this follow-up is performed and appropriately documented.

In conclusion, when there is a microbial non-conformance, a laboratory investigation must be performed first to determine if there is a known laboratory error (which invalidates the original test) or if it is a true con-conformance. If it is the latter, then QA must be notified immediately. Production must then perform their investigation. If a root cause is discerned right away, it could be documented as a Simple or Step I investigation. If the root cause is unknown, then Production should proceed to the Step II or Complex investigation with QA guidance. If necessary, some possible root causes may need testing to be performed.

When conducting a root cause investigation, it should be possible to identify most probable cause or causes. If staff is adequately trained on trouble-shooting techniques, the company provides ➤

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adequate resources to handle this task, and the people are really motivated to solve the problems, perform corrective actions and prevent recurrences (CAPA). But, if CAPA follow-up effectiveness needs to be determined, it is helpful to have a system to track it. If the root cause(s) and CAPA were correct, then companies can presume not to see the same problem again.

### References


1. Voluntary Product Recall and FDA 483, TriadGroup, U.S. FDA, tinyurl.com/44ff4hm
2. "Investigations in Aseptic Processing: Focus on Sterility Testing." Randy Hutt Presentation for PDA November 2010 Aseptic Processing Conference
3. Warning Letter, Lanstrafiken Mälardalen, U.S. FDA, tinyurl.com/44khu33


### About the Author


**Randy Hutt,** PhD, is the Director of Quality Assurance for San-Mar Laboratories since May 2011. Previously, she was a Senior Associate at the Lachman Consultants group for three years and also consulted with Libra Laboratories, Inc. for over a year. She has performed microbiological troubleshooting, GMP audits and systems creation. She has over 30 years of experience in the pharmaceutical/biological industry in Quality Assurance, Aseptic Production and Quality Control. She has worked at Wyeth Biotech, Burroughs Wellcome Co and Schering Plough in leadership roles.

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# Preview

## RAQAB Activities Schedule

**Washington, D.C. • September 18-22 • www.pda.org/pdafda2011**

PDA members and volunteers will dedicate some of their time at the *2011 PDA/FDA Joint Regulatory Conference* conducting the business of the Association.

The following is the schedule for the Regulatory Affairs and Quality Advisory Board meeting (closed to board members only) and the RAQAB Interest Groups (open) and Task Force (closed) meetings.

**Sunday, September 18**

Regulatory Affairs and Quality Advisory Board 11:00 a.m.–4:00 p.m.

**Monday, September 19**

Quality Systems Interest Group Session: 4:30 p.m.–6:00 p.m.

**Tuesday, September 20**

GMP Considerations for Clinical Trials/Investigational Medicinal Products Task Force 3:00 p.m.–4:00 p.m.

Concurrent Interest Group Sessions: 4:45 p.m.–6:15 p.m.

- Regulatory Affairs
- Clinical Trial Materials
- Risk Management

**Wednesday, September 21**

Quality Requirements for the Extemporaneous Preparation of Clinical Trial Materials Task Force 12:30 p.m.–3:30 p.m.

# In *Print*

## EU GMP Annex 1 on Sterilization Processes

**Roland Marie Frédéric Guinet, Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS)**

*The following article was excerpted from the chapter, "European Expectations for Thermal Validation," by the author, published in the PDA/DHI book,* Thermal Validation in Moist Heat Sterilization, *edited by Jeanne Moldnhauer and available in July at the PDA Bookstore: www.pda.org/bookstore.*

Sterilization is of course an important part of Annex 1—from points 83 to 97 for general principles and sterilization by heat. Hereunder are the most important points of this part of Annex 1 not already mentioned in the previous paragraphs.

### General Principles for all Sterilization Processes

The interval between the sterilization of components, containers and equipment and use should be minimized and subject to a timelimit appropriate to the storage conditions (Annex 1 § 78).

There are two main possibilities for the aseptic processing for the manufacture of parenterals which cannot be terminally sterilized—traditional processes in Grade A with Grade B surrounding, and process using isolator technology with different variations like RABS. It should be noted that manufacturers are using more and more RTU components, like sterilized and siliconized syringes and stoppers, having shelf-lives after sterilization varying from three to five years, which cannot be considered as time-limit minimized! Moreover, only some of these components, like stoppers, are wrapped in bags sealed under vacuum, allowing a control of integrity at the point of use, but this is not the case for most RTU syringes.

The monitoring of bioburden before sterilization is one of the four modifications of Annex 1 in place since March 1st 2009 (Annex 1 § 80). In principle, for terminally sterilized products, the bioburden should be monitored for each batch, but for overkill sterilization approach it is acceptable to monitor it at scheduled intervals. When parametric release is used, the bioburden should be known for each batch, and this is considered as an in-process test. Endotoxin levels should also be monitored where appropriate, and this is the case for parenterals. Furthermore, a sterilizing filtration on 0.22 µm filter of all solutions is recommended, including large volume infusion fluids, if possible immediately before filling.

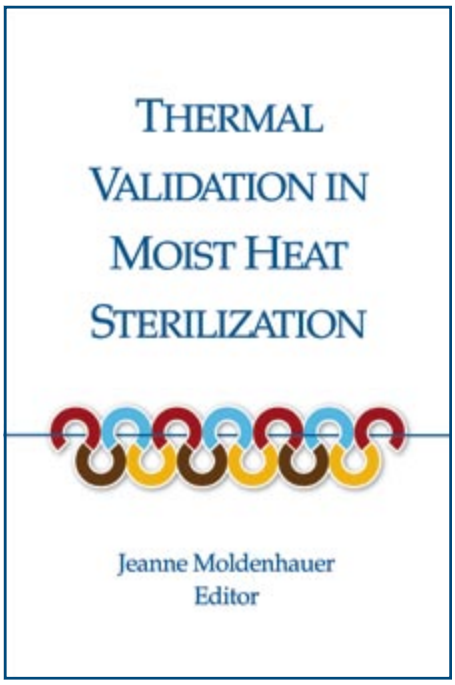
Where possible, heat sterilization is the method of choice. Particular attention should be given for methods not described in the European Pharmacopoeia, or for products difficult to sterilize. In any case, the sterilization process must be in accordance with the marketing and manufacturing authorizations (Annex 1 § 83).

The suitability of process development for the product and its efficacy in achieving the desired sterilizing conditions in each part of each type of load to be processed should be demonstrated by physical measurements and biological indicators where appropriate (Annex 1 § 84). For effective sterilization, the process should be designed in order to ensure that the whole of the materials is subjected to the required treatment (Annex 1.85). Biological indicators should be considered as an additional method for monitoring the sterilization (Annex 1 § 87).

Each basket, tray or other carrier of products or components should be clearly labelled with material name, batch number and a clear means of differentiating whether or not it has been sterilized (Annex 1 § 88). Sterilization records should be available for every sterilization run and approved as part of the batch release procedure (Annex 1 § 89).

### General Principles for Heat Sterilization Processes

- Record of a time/temperature chart for each cycle, with an appropriate scale.
- Positioning of probes used for controlling and/or recording according to the results of validation.
- A second independent temperature probe at the same position is recommended (Annex 1 § 90).
- Use of chemical or biological indicators is possible only in addition to physical measurements (Annex1 § 91).
- Time for the whole of each type of load to reach the required temperature should be determined and allowed before starting measurement of the sterilizing time period Annex 1 § 92).

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*continued at bottom of page 62*

# Atypical Actives Breakout Sessions Formulate Call for Action

## Full Transcript of Breakout Summary Remarks From PDA/FDA Atypical Actives Workshop

*The following is a transcript of the breakout session summaries, presented in the final session of the* PDA/FDA Atypical Actives Workshop, *March 9-10, 2010, in Bethesda, Md.* ***David Schoneker,*** *Colorcon, and* ***Janeen Skutnik-Wilkinson,*** *Pfizer, provided the summary of the "Regulatory breakout group. International Pharmaceutical Quality produced this transcript in cooperation with the two speakers, and has permitted PDA to republish it. David Schoneker is the Global Regulatory Affairs Director at Colorcon, Janeen Skutnik-Wilkinson is the Quality Strategy Director at Pfizer and is a member of the PDA Board of Directors and* PDA Letter *Editorial Committee.*

### David Schoneker: Technical Considerations Breakout

"We are going to talk about:

- Issues discussed
- Shared understandings and agreements (and I say shared understandings, not always on the agreement side, but certainly shared understandings in some cases)
- Some remaining challenges that we identified from the discussion that we think are going to be hurdles that we are going to have to overcome to move forward
- Some recommendations that we took out of the discussion as maybe a place to start putting some attention to and figuring out how, along with what Janeen is going to present, we can make some sense out of this, and then have further discussion with the regulators and throughout industry

#### Issues Discussed

We had several topics that we threw out there on the technical considerations piece—not so much saying these were issues that had to be addressed as being different between atypical actives and excipients, but saying here are some areas where we know there is controversy and discussion that comes up:

- composition and variability
- Specifications
- Stability
- Change control, and
- Risk management

#### Shared Practices and Improvements

It seemed that most everybody is saying excipient GMPs are appropriate for atypical actives.

We felt that there is a real need to discuss design criteria before going into specification setting and into further determinations. Those design criteria are something that really can get at a lot of the technical issues we are talking about. It is not necessarily that they have to be different between excipients and atypical actives. But the fact that you are talking about the design criteria that the drug product manufacturer needs vs. what the excipient supplier can do—that alone is a major step forward. The specs and everything else can come out of that as to whether there actually are any additional technical requirements or not for a specific application….

[We need to] make a path so that discussion can occur in a more proactive way between maker and user, and ultimately lead to an agreed-upon design criteria… It was brought up that [getting agreement and signatures] may be difficult when you have long distribution chains. We have got to find a way to solve that problem, because without an agreed-upon design criteria to talk about, a lot of this stuff gets really hairy and difficult.

It seemed for a lot of the discussion—although I do not know that everybody agreed—that really no additional technical requirements should be necessary across the board that is any different for atypical actives than it is for excipients, unless there is a very specific application need that has been identified in negotiating between the maker and user. ➤

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In general, since most of these excipients have been made under excipient GMPs and have always met excipient standards and have not necessarily met any special requirements for years and years, why is there really any reason to think that they need any special requirements just because we are calling them APIs today? That may not be popular in the way some regulators might look at this, but I can tell you that certainly came out strongly… Just because you call it an API does not change the fact that there are not really any technical needs that are different. There may be some exceptions to the rule, but we should not stress that there needs to be something more across the board.

There is certainly a lot of feeling that the use of IPEC guides that exist today for GMP, stability, validation, composition, and significant change, should be acceptable for use with atypical actives as well. There really does not seem to be a need to have additional stability data for the excipient, and not necessarily more information on composition, unless you have a specialized need for your particular application—but not necessarily across the board for atypical actives. When we talked about a significant change, we [thought] the same level of change notification is needed between user and maker whether it is an excipient or an API.

### Remaining Challenges

The challenge that has come across loud and clear throughout is that communication between the maker and the user must be improved. We have to find a way to force that discussion to take place if we stand any chance of resolving some of these issues. And if we want to get regulators to have any flexibility in terms of how atypical actives need to be handled, that communication is going to be a key part of justifying why flexibility exists.

We feel there is a significant challenge in regulator understanding of the issue. As much as the realities exist out there today, there are many barriers to that in terms of guidances that exist that people tend to use as checklists—people who come from a certain environment and say, 'this is what we always expect.' Is that necessary? There are going to be some educational aspects in working together to make sure that everyone is on the same path with this.

There needs to be flexibility in interpretation. If something is not a law, it is not a requirement. If it is a guidance, it is guidance. It means it can be interpreted and good science should rule the day. If you have a good science argument, that should rule the day, regardless of what you do in another circumstance. That flexibility in interpretation is going to have to both be justified by industry and accepted by regulators if there is a good scientific argument. That is not going to be easy—it is going to be a challenge. We are talking about a paradigm change as soon as you put the term 'active' on there.


The next challenge we talked about was to develop an appropriate rationale to apply to controls that we feel are justified, when in fact those controls might be less than what might be interpreted as Q7 expectations. We cannot ignore the fact that Q7 is out there, but we are going to have to have a rationale to justify if we have controls at lower levels—why and how does that play out scientifically. That rationale should be documented.

### Recommendations

From a recommendations standpoint, [Iain Moore, Product/QA Manager from Croda Europe] brought a really interesting idea, both in his talk and in the [breakout session], and we really think this makes a lot of sense to think about in our path forward: we really need to have some sort of decision tree process to define an atypical active in a specific circumstance.

That is a difficult thing—how we define it. There is not going to be a list out there. In each of your situations you are going to have to define when it is an atypical active vs. an excipient vs. a typical or standard API. Iain mapped out a few ideas on how a decision tree process could be put together, and what information might be then available to determine appropriate control depending on different circumstances… This would tie in nicely with some of the thinking that is happening in Europe already. We could put it into a process that we could all start to think about in the right way. A lot of what we are trying to do is to

***The challenge that has come across loud and clear throughout is that communication between the maker and the user must be improved***

make sure that everybody is asking the right questions at the right time so we can come up with a good scientific conclusion and not run into a lot of regulatory hurdles that are not based on science….

Trying to develop a decision tree might not be easy. But trying to develop something that seems to make sense, that can be very easy for industry to understand how they came to this conclusion and for a regulator to look at and say, 'ok, that makes sense, you went through this process, you thought about this and that, you looked at the data and came to this conclusion'—it starts to standardize the approach, which is what this is all about.

Another recommendation was that we have to maximize how we utilize confidentiality and quality agreements to improve the sharing of technical and use information, and recognize that this is a two way street. A confidentiality agreement is not just about the user signing a confidentiality agreement so the maker will tell them everything about the process. It needs to be a confidentiality agreement that also has the user telling the maker what they are doing with it, and why. That is critical to this whole understanding and how all these things play out.

So we may have to take a look at how we handle confidentiality and quality agreements—add some information into the templates. We talked yesterday a little bit about the quality agreement—maybe having a section where you could tick off what kind of application you are using this material in, at least as an indicator to get the discussion going. Good idea. Maybe there are some other things that we can do.

Finally, to sum it all up…a big part of what we need to accomplish here is to find a way to develop an appropriate risk mitigation plan template, which walks you through the process—and this might tie in nicely with the decision tree concept—that addresses the key differences that we think exist between excipient GMP and Q7. That would include some discussion of the various design criteria where, in fact, controversy sometimes exists.

The areas that we came up with that need to be incorporated in the risk mitigation plan in terms of what are the key areas a rationale needs to be built for: If you are going to say you are not Q7 or whatever, how are you addressing this?

- If we do not feel there is any need for additional **composition and variability** information, justify why we do not think there is any need for that—why, in fact, what we know about the excipient is what we need to know about the API.
- **Process capability vs. validation:** we have got to have a better discussion that is documented about why we are using process capability data and how—rather than getting into this idea of validation studies all the time, which does not compute to many of the chemical manufacturers.
- **Stability:** why we believe the stability information—I say information as opposed to data—that we have on an excipient is good enough for the use that we have. If it is not, then let's recognize it and say we need more. But if it is, and it has been a stable excipient and a stable atypical active for a hundred years, and nobody has ever had a problem with the level of stability information you have, do you really need to have to have ICH condition proactive studies? If not, explain why not as part of your risk mitigation plan.
- For **specifications,** the same thing. Do we really need tighter specs? Probably not. You never had them before. You have been using this as an atypical active all along, you are probably meeting the specs that you have always met. Just because now it is defined as an API does not mean that it changes things. There might be some circumstances where it does. Discuss that and justify why you are doing what you do….
- For **change control,** the same thing…. There is really no difference between a need for change control for excipients and atypical actives. That may need some explanation in your risk mitigation plan, and maybe not in some circumstances, but it needs to be addressed….
- **Cleaning validation** tends to be discussed a lot when people talk about Q7. That does not really come into play many times with a lot of these dedicated manufacturing facilities where…you would not want to clean out the lines—that would cause all kinds of problems that you do not want to cause. But because it is a little different than what people are used to in a Q7 environment, there may be a need to explain how cleaning is handled in

the risk mitigation plan, and why maybe a true cleaning validation is not a good idea all the time.

Those are the areas that we think need to be added into the risk mitigation plan. I am sure there are others, but these were the ones that came out of the discussion points that we had up for this particular session. ”

## Janeen Skutnik-Wilkinson: Regulatory Considerations

### Barriers

“ First we started with the barriers. What are some of the barriers that we heard from everybody? I think across the board we heard a real strong barrier which, interestingly enough we also heard from [Schoneker's group] is a real misperception, misunderstanding, and misuse of Q7 from both regulators and industry. A lot of it is being applied verbatim as law, when perhaps that is not necessarily the case, and in some cases not necessarily even needed. I think there really needs to be a refresher on the use of guidance across the board. [There is] a real lack of understanding of the actual issue that we are trying to resolve. I do not think that is surprising, because one of the key things that we thought would be an outcome from this workshop is really raising awareness of what the issue is, and that there is an issue…. Certainly from the perspective of this meeting we are beginning to raise awareness.

Perhaps an audit guide from FDA would be useful. [The lack of] clear understanding on expectations of FDA could be a barrier going forward and whether there is consistency in terms of atypical actives on inspections.

The training of excipient manufacturers on how to deal with FDA, what to expect, and what the whole situation is [is important]. If you think about, on the pharma side, how much training do you have within your company on how to handle an FDA inspection, how to work with FDA? We do an awful lot. But obviously if you are an excipient supplier and you do not even know FDA could ever show up at your door, you are not going to have programs in place. Even if you were to try to, if you have never had experience with it, it could be very difficult to accomplish that—so really trying to help everybody help each other.

There has been a lot of discussion about legacy products, and actually that we need to define what a legacy product is and what does that encompass. Are we talking about solely everything that is already on the market? Or are we talking about the formulations that are on the market, in terms of if another company comes to put on the market a similar formulation, is that a legacy product? There needs to be some further clarification. That could be a barrier for us moving forward….

We have a lot of distributors, and it is very difficult to know all the key players. Also, at the moment, we do not have distributors engaged. We have one distributor here today, which I am happy about, but [for the most part] they are not engaged in this discussion at this time. That could be a barrier, because if we as makers, users and regulators were to go off and try and solve this challenge without bringing the distributors into the discussion on how to move forward, we are not going to be successful. I think it is a really strong barrier that we need to consider. We have to engage with distributors on whatever solutions we come up with going forward….

The education of quality units came up as a barrier. There is a lot of discussion… about this box-checking mentality that we need to continue to move away from. We have certainly moved away from it a bit over the last couple of years, but it is something that we need to continue to work on.

There was a lot of discussion about the Colorcon situation [with] CalCarb. We do not want to end up in situation where we have products discontinued—and not just atypical actives, but [also] excipients. We need to be very careful in the approach that we take or we could be creating a significant barrier in terms of the availability of materials and medicines.

### Addressing the Barriers

[There were] some really good ideas for helping to address some of the barriers for education and training, [for example] using webinars to get the issues out to regulators and industry…. There was a lot of good discussion about using technology, using webinars as ways to get out this information to industry and regulators.

We need a clear rationale for why atypical actives of legacy products do not need Q7 scrutiny, which I think is quite similar to what we heard from session A, and clear criteria checklists based on risk assessment to decide how to deal with them…. ➤


There was a lot of concern raised about foreign sourcing overseas, not focused so much on just the quality, but in terms of how we engage them in this discussion, how we make sure they are aware of the use of materials as atypical actives, what are the expectations, and so forth.

The need to educate regulators on how excipients are made, and that it is different from an API—there still seems to be a misunderstanding of how the chemical industry functions and how excipients are made. If we want to be truly successful—not just here with atypical actives, but also in terms of this evolution that we have going on with supply chain and with Q8, Q9 and Q10—we really need to make sure that all the players and all the actors understand each others' business better.

Help the excipient manufacturers to understand the new excipient regulations or anything that may come out from an atypical actives perspective. Make sure that they are aware of expectations coming out from regulators.

[We need a] mechanism to inform drug manufacturers, regulators and excipient manufacturers on the use of excipients as atypical actives. We really need a mechanism to help educate people on any differences that we see. So if we are involved with a decision tree, if we are going to come up with criteria, we need a mechanism to make sure all the parties are educated.

### Regulatory Hurdles

The next topic that we addressed was the regulatory hurdles….

This is not an issue solely within the US and Europe. We need to engage foreign regulators. We need to not only educate them on what the issues are, but also make sure that they are part of the solution going forward.

There are some issues from the pharmacopeial perspective that were raised. We also heard some discussions during the plenary sessions about whether both USP and NF monographs are needed for all of these materials. If you have a USP and NF monograph and a PharmEur monograph, then how do you know if the PharmEur monograph is meant to be for an API or an excipient? There are still some challenges and concerns there that we need to look at.

There is a real strong request for FDA to acknowledge that atypical actives exist. [Jeff Medwid, CDER ONDQA Review Chemist] did volunteer to take this back and follow up with FDA. And I think just the fact that FDA agreed to partner on this workshop means that they want to address this issue…. I think it was just never really raised, so there really was not an awareness of what this issue is. I do thank FDA for partnering with PDA on this….

Another hurdle is that we have emerging markets. Their regulators are starting to ask a lot of questions, and the questions may not necessarily be appropriate or work with these materials. We need to address the hurdles in those markets as well and recognize that their knowledge and understanding of the state of play in Europe and the US may not be what we think it is.

We have seen this when we work with regulators. They may have been led to believe that there is a current situation in certain markets, and that may not be accurate. Not only do you have to work with them, but you also have to figure out what they understand about the current situation. Unless you understand where they are coming from, you cannot possibly work with them. That is a key thing that we have noticed in the work we have done in emerging markets.

[Also a hurdle is] the availability of excipient manufacturers' processes and the information on GMP, providing that information to drug manufacturers, and what type of information is available. A lot of times companies ask their suppliers for certain information that just does not exist, so we need to understand how we communicate that and how we understand what information is critical.

# U.S. FDA's Office of Compliance Elevated to "Super Office"

U.S. FDA's CDER/Office of Compliance (CDER/OC) will now house subordinate offices within its organizational structure.

In a May 26 "all hands" memo **Janet Woodcock,** MD, Director, CDER, U.S. FDA, announced that the Office of Compliance has been elevated to a "super office," and **Deb Autor** (currently the Director of the Compliance office) will serve as the Acting Director.

"Given CDER/OC's expanding role, size, and importance in achieving the Agency's mission of safeguarding the U.S. drug supply, this structural transition makes a great deal of sense. The reorganization will enable [the office of] Compliance to align its scientific, technical and legal capabilities with closely related program areas, leveraging our resources and maximizing its ability to achieve its public health mission."

CDER/OC will also now have three office-wide functions established in its Immediate Office, with counterparts in all sub-Offices: risk science, intelligence, and prioritization; policy and communication; and organizational strategy (strategic planning, organizational development, and QMS).

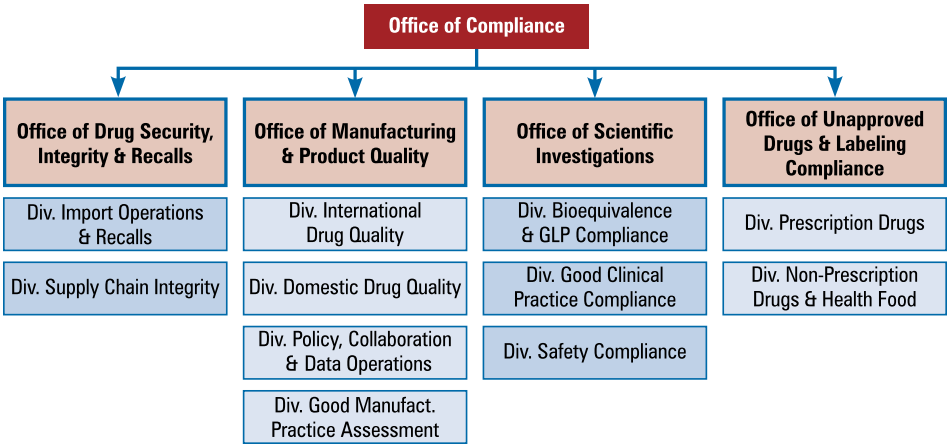
Woodcock said that there will be four new offices within the super office:

- Office of Manufacturing & Product Quality
- Office of Scientific Investigations
- Office of Unapproved Drugs & Labeling Compliance
- Office of Drug Security, Integrity & Recalls (ODSIR)

Three of these new offices are similar to currently existing divisions, while the fourth, ODSIR, is entirely new. ODSIR will be dedicated to addressing the challenges of globalization and an increasingly complex drug supply chain. ODSIR staff will take the lead in dealing with issues such as supply chain security, counterfeit and diverted drugs, economically motivated adulteration, import operations and drug recalls.

The Office of Compliance joins five other "super offices" that currently exist in CDER.

### CDER Office of Compliance: Super Office Structure




# PIC/S Celebrates 40th Anniversary

The Pharmaceutical Inspection Co-operation Scheme (PIC/S), which is a technical arrangement between 39 Competent Authorities in the field of GMP inspections of pharmaceutical manufacturing sites, celebrated its 40th anniversary at a landmark symposium in Geneva on May 31.

The symposium was opened by PIC/S Chairman, **Tor Gråberg** (Sweden/MPA) who underlined the need for PIC/S to further promote co-operation based on communication, mutual trust and harmonization.

Over 160 participants from all continents participated in the event, including Competent Authorities from Argentina, Australia, Brazil, China, Chinese Taipei, Croatia, most EU/EEA Member States, Georgia, Hong Kong SAR, Indonesia, Iran, Israel, Japan, Malaysia, New Zealand, Nigeria, Russia, Singapore, Saudi Arabia, South Africa, South Korea, Switzerland, Thailand, Turkey, Uganda, Ukraine and the United States. The long list demonstrates that the organization, created by 10 European Authorities back in 1971, has now become truly global. PIC/S co-operates with the European Commission and has partnership agreements with the European Medicines Agency, EDQM, UNICEF and WHO; it also co-operates with non-profit organizations like ISPE and PDA and industry associations such as APIC,


U.S. FDA Commissioner, Dr. Margaret Hamburg stands with PIC/S Chairman, Tor Gråberg at PIC/S' 40th Anniversary. At the meeting, Hamburg called for closer and more global co-operation on GMP

*continued at bottom of page 71*

# 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.**

## International Harmonization

### ICH Q11 Available for Comment

For more details, see story on page 6. For comment due dates see Key Regulatory Dates at right.

## North America

### Help the U.S. FDA Advance Global Access to Safe and Effective Vaccines

The U.S. FDA wants companies to advance global access to safe and effective vaccines and other biologicals that meet international standard by establishing strong regulatory systems that will support regulatory science through a funding opportunity announcement (FOA).

There are three research objectives to the project:

- Contribute to the knowledge base of the current state of regulatory oversight of influenza and other vaccines and biologicals by supporting analysis, synthesis, and application of assessments of associated regulatory frameworks and processes in select countries/regions.
- Enable the timely and effective sharing of scientific findings and data, e.g., on safety and effectiveness of adjuvanted influenza and other vaccines and other emerging technologies in support of developing WHO guidance where appropriate, the utility of new technologies for assessment of product safety, among other areas.
- Support the sharing and application of knowledge, data, and information through active participation in regional and global networks, such as the African Vaccine Regulatory Forum (AVAREF) and the Developing Countries' Vaccine Regulators Network (DCVRN).

FDA/CBER anticipates providing up to $800,000 (total costs including indirect costs for one award subject to availability of funds) in support of this project in fiscal year 2011. With the possibility of four additional years of support up to $2,000,000 of funding contingent upon successful performance and the availability of funding.

The application due date is July 8 and the anticipated start date is August 15.

To obtain detailed requirements of the project, please refer to the full FOA located at www.grants.gov.

### Draft Guidance on FDA's Current Thinking about Nanotechnology Released

The U.S. FDA has released a draft guidance about FDA's current thinking on whether FDA-regulated products contain nanomaterials or otherwise involve the application of nanotechnology.

As a first step towards developing FDA's framework for considering whether its regulated products include nanomaterials or nanotechnology, the Agency has developed some points to consider in the draft guidance to be broadly applicable to all FDA-regulated products, with the understanding that additional guidance may be articulated for specific product areas, as appropriate, in the future.

Comments are due on the draft guidance entitled, *Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology* by August 15.

### U.S. FDA Collects Information on Formal Dispute Resolution Process Guidance

The U.S. FDA is requesting public comment on the collection of information relating to the process outlined in their *Guidance for Industry on Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical Good Manufacturing Practice.*

The guidance was initiated in response to industry's request for a formal dispute resolution process to resolve differences related to scientific and technical issues that arise between investigators and pharmaceutical manufacturers during FDA inspections of foreign and domestic manufacturers.

Under this guidance, firms seeking formal dispute resolution are required to submit documentation supporting a Tier One request for resolution. If a firm is not satisfied with the outcome of the Tier One review, they may enter into a Tier Two review process.

Comments are due by August 19.

### U.S. FDA Proposes Changes to Sterility Test Requirements For Biologics

The U.S. FDA has proposed changes to the current sterility test requirements for biological products.

According to the Agency, the proposed changes will provide manufacturers of

**Key Regulatory Dates**

**Comments Due**

**July 8- Advance FDA's Global Access to Safe and Effective Vaccines**

**August 15 — ICH Q11 MHLW Japan; Draft Guidance on FDA's Current Thinking about Nanotechnology**

**August 19 — U.S. FDA Collects Information on Formal Dispute Resolution Process Guidance**

**August 31 — EMA offers Guideline on Biotechnology-Derived Proteins as Active Substances**

**September 1 — ICH Q11 EMA Europe; U.S. FDA**

**September 19 — U.S. FDA Proposes Changes to Sterility Test Requirements For Biologics**

**September 28 — U.S. FDA Grants Period of Enforcement Discretion Related to Drug Safety Reporting Requirements**

biological products greater flexibility and encourage use of the most appropriate and state-of-the-art test methods for assuring the safety of biological products.

Comment by September 19.

### U.S. FDA Grants Period of Enforcement Discretion Related to Drug Safety Reporting Requirements

The U.S. FDA has issued a guidance that grants a 6-month period of enforcement discretion relating to the new drug safety reporting requirements that became effective on March 28 until September 28.

Called, *Enforcement of Safety Reporting Requirements for INDs and BA/BE Studies,* the guidance extends the deadline set forth in the *Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies.*

FDA expects all sponsors and investigators to be in compliance with the new regulations no later than September 28.

### U.S. FDA's Shares Information on Its Transparency Initiative

The U.S. FDA has announced, as part of their transparency initiative, that information will be made available to the public on enforcement activities, including inspections and court actions.

Under this initiative, a web portal has been created providing access to summary data of inspectional observations, as well as a searchable inspections database which includes the names and addresses of inspected facilities, inspection dates, types of products manufactured and final inspection classification.

By the end of 2011, the Agency will begin to disclose additional information about FDA evaluations of filers, expand disclosure of Untitled Letters, and in appropriate situations, support industry efforts during a food recall to inform consumers of products that are not subject to the recall.

Access to this information about FDA's enforcement and compliance activities will provide the following to the public and regulated industry:

- More information about company practices that may jeopardize public health, as well as about companies that have had satisfactory FDA inspections
- Information about recall and enforcement activities that will help consumers make decisions about products
- Information about inspection results, which can be expected to create a greater incentive to bring practices into compliance with the law
- Information about food products that are not subject to a particular recall, which can help reduce consumer confusion.

### EMA and U.S. FDA Collaborate Together on Biosimilar Medicines

The European Medicines Agency and the U.S. FDA have identified biosimilar medicines as an area of common interest and will be working together to increase their degree of interaction and will begin with a kick-off meeting to discuss the group's activities.

This biosimilar "cluster" is the latest step in the two agencies' ongoing collaboration on regulatory issues under their confidentiality arrangements, which they first signed in 2003. The degree of interaction between the EMA and the FDA has increased significantly since then, to the current stable level of around 55 interactions per month, according to a report issued by the two agencies.

## Asia-Pacific

### Australia's Therapeutic Goods Administration to Amend Current Guidelines for OTC Medicines

Australia's Therapeutic Goods Administration (TGA) has begun a project which will review and amend the current Australian Regulatory Guidelines for over-the-counter (OTC) medicines.

The ARGOM Review Project will bring the 2003 guidelines that are currently used up-to-date to reflect the current TGA regulatory environment and business practices for over-the-counter medicines.

The ARGOM 2003 is being updated to:

- Ensure that the guidelines reflect current legislative regulatory requirements

- Streamline processes where possible
- Improve the usability and consistency of the information available to stakeholders in relation to the Australian regulatory requirements for OTC medicines
- Provide increased transparency about decision making processes
- Clarify post-market monitoring of OTC medicines

It is anticipated during the ARGOM update process the TGA will initiate additional longer-term projects to consider particular aspects of the current regulatory requirements and business processes related to OTC medicine regulation.

## Europe

### Annex 14 from the EU GMP Guide Revised Due to Directive 2002/98/EC

The European Commission has posted a revised version of Annex 14 from the EU GMP guide that will go into effect on November 30 to its website.

Relating to the manufacture of medicinal products derived from human blood or plasma, Annex 14 has been modified due to Directive 2002/98/EC in order to set standards of quality and safety for the collection and testing of human blood and blood components for all uses, including the manufacture of medicinal products.

### EDQM Revises General Chapter 5.2.8

The European Directorate for the Quality of Medicines & Healthcare (EDQM) has revised general chapter 5.2.8 on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products.

This third technical revision takes into account the advancement of science in the area of transmissible spongiform encephalopathies, as well as the evolving situation regarding Bovine Spongiform Encephalopathy across the world. For the classification of countries or regions according to their BSE risk, the revised chapter makes reference to the rules laid down by the World Organization for Animal Health, replacing the previous United Kingdom of Great Britain and Northern Ireland classification.

New criteria for the sourcing and processing of gelatin and bovine blood derivatives used in the manufacture of medicinal products for human or veterinary use have been introduced, as well as a new subsection on Peptones.

The revised chapter was adopted by the European Pharmacopoeia Commission on May 3. Implementation will go into effect on July 1.

### EMA offers Guideline on Biotechnology-Derived Proteins as Active Substances

A concept paper has been published by the Biologics Working Party (BWP) of the EMA about the need for a guideline on process validation of medicinal products containing biotechnology derived proteins as active substance.

The working party stated that even though guidelines related to the quality of biotechnological/biological products have been developed at the EU level, and several documents have been harmonized through the ICH process, those documents do not satisfactorily address the specific aspects of validation and evaluation for biotechnology derived products.

Specifically, the BWP recommends developing a guideline on the guideline should focus on data requirement for process validation/evaluation for submission of a marketing authorization application or variation. It is anticipated that the draft guideline will be released for consultation in the first quarter of 2012, followed by a six month external consultation period prior to finalization of the document.

Comments are due on the proposal by August 31 to BWPSecretariat@ema.europa.eu.

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- Precautions against contamination of sterilized load with cooling fluid or gas during cooling should be adopted (Annex 1.93).

### Moist Heat Specific Points

*Annex 1 § 94*

- Temperature and pressure should be used to monitor the process.
- Control instrumentation should be independent of monitoring instrumentation and recording charts have to be kept and assessed.
- System and cycle faults should be registered by the system and observed by the operator.
- Temperature of the independent indicator should be routinely checked against the chart recorder during the sterilization period.
- Temperature of the drain (if any) at the bottom of the chamber should be recorded throughout the sterilization period.
- Frequent leak tests for cycles with a vacuum phase should be carried out.

*Annex 1 § 95*

The items to be sterilized if not in sealed containers should be wrapped in a material allowing air removal, penetration of steam, and prevention of recontamination after sterilization. Consequently, the sealing machine used to seal the bags in which the materials are wrapped should be qualified and the integrity of the sealed bags should be verified periodically.

*Annex 1 § 96*

Suitable quality of the steam used should be achieved without additives.

### Dry Heat Specific Points

- Air circulation within the chamber should be ensured.
- A positive pressure should be maintained in order to prevent entry of non-sterile air.
- No air should be admitted to pass through the HEPA filter.
- For depyrogenation, challenge tests using endotoxins should be carried out as part of the validation (Annex 1 § 97).
- Depyrogenation tunnels entering to the Grade A filling zone should be classified and monitored as a Grade A area, at least for the cooling zone of the tunnels (Annex 1 §§ 4–20).

# ProPharma Group


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# We Heard You! Quality, Compliance Focus of 20th PDA/FDA Conference

**Washington, D.C. • September 19-23 • www.pda.org/pdafda2011**

**John Finkbohner, PhD, MedImmune**

After listening to feedback from participants of the *2010 PDA/FDA Joint Regulatory Conference,* the programming committee decided on *Quality and Compliance in Today's Regulatory Enforcement Environment* as the theme of the 2011 conference.

As in previous years, a mixture of both plenary presentations and parallel presentation tracks are planned to provide a venue for exploration of topics of interest to the wide range of PDA members and their interests. The Foundations track presentations from last year were intended to provide content of value to newer PDA members and was so well received by the audience that the track returns this year with new content to expand on that provided last year. Two additional parallel tracks make an appearance this year, Innovation/Regulatory Science and Quality and Compliance. All participants can be assured that there will be a topic that they will find both relevant and interesting throughout each day of the conference.

The opening of the second day of the conference provides a rare opportunity for industry and regulatory health authority experts to explore factors that impact the ability to efficiently and successfully implement a recall action. The opportunity for discussion of these challenges provides pharmaceutical industry professionals and regulatory policy makers with an invaluable venue for direct information exchange and thus foster enhanced understanding. The heightened visibility of pharmaceutical recalls over the past few years has highlighted the need for having a robust process for handling recall actions. Recalls demand not only significant pre-planning to ensure efficient operation of the quality unit but also well-defined processes for material handling and effective communication with stakeholders.

The plenary session starting day two of the upcoming conference will expand upon this topic to explore the challenges of implementing recall actions and draws upon the expertise of presenters from academia, industry, and the FDA. Our first presenter, **Dirk Gibson,** PhD, Associate Professor, Mass Communication, University of New Mexico, was part of the team that prepared a USDA report on the dynamics of recalls in the food arena. In addition, he conducts research in the area of communications with the broader range of stakeholders in recall situations. Stakeholders in a pharmaceutical recall include not only consumers and government agencies, but also consumer protection groups, retailers, distributors, pharmacists and other members of the healthcare provider community. Managing the communications related to the recall action is further impacted by the need to effectively interact with the media. The media serve as part of the strategy for ensuring that all impacted stakeholders are made aware of the recall action while ensuring that confusion is avoided. These communication dynamics will be our first focus area in this session.

We then transition to the industry perspective. A fully defined set of processes and procedures for implementing a recall are required under the cGMP regulations, but the scope of effort required to *implement* a recall can test any firm undertaking the effort. The number of tasks to be performed in a timely manner provides logistical and tactical challenges that demand efficient management and oversight of the recall operation. While the array of specific stakeholders and the nature of the product undergoing recall make each situation unique, some general lessons can be learned from past experiences in recall implementation. **Ray Godlewski,** Vice President, Quality and Compliance, Medimmune, will draw upon years of experience in pharmaceutical quality assurance to share some observations relevant to the topic.

***The opening of the second day of the conference provides a rare opportunity for industry and regulatory health authority experts to explore factors that impact the ability to efficiently and successfully implement a recall action***

The FDA perspective will wrap up the formal presentations, and the audience will have an opportunity to pose questions to the panel of speakers. We know that this portion of the conference will be yet another session with highly valued content for this landmark conference.

We look forward to seeing you in September in Washington, D.C. For more information or to register for the conference, visit www.pda.org/pdafda2011.

Read more on page 76 about the TRI courses offered at the conference.

# Pharmaceutical Quality Systems (ICH Q10) Conference

## *Co-sponsored by FDA and Supported by EMA*

*A Practical Approach to Effective Lifecycle Implementation of Systems and Processes for Pharmaceutical Manufacturing*

**October 4-6, 2011** | Crystal Gateway Marriott | Arlington, Virginia
**November 14-16, 2011** | Sheraton | Brussels, Belgium

**Register Before August 12, 2011** - the first registration savings deadline!

**ADVANCED NOTIFICATION:** Sign up to receive an email when more information about this conference is available!

PDA, ISPE, the U.S. FDA and EMA have created a special joint conference dedicated to teaching the principles of ICH Q10. This will be a unique opportunity to learn from companies that have implemented a Pharmaceutical Quality System across the product lifecycle according to the ICH Q10 model.

While this conference is intended to explain the principles of ICH Q10, it is not a conference that only tells you *what* ICH Q10 says, it is an event where you can learn the practicalities of *how* to implement Q10 based on real-life case studies. The conference will take place in Washington, D.C. and in Brussels drawing on the best industry and regulator contributors on this topic from both the United States and Europe. Moreover, key regulators from these areas will also share their views on the necessity of a Pharmaceutical Quality System.

You need to join us for this conference if you have the responsibility to enhance the quality and availability of medicines around the world in the interest of public health.

**www.pda.org/Q10**

Connecting a World of Pharmaceutical Knowledge

Register By August 9th and Save Up To $200!

*The Parenteral Drug Association presents...*

The Post Conference Workshop Following the
*2011 PDA/FDA Joint Regulatory Conference & TRI Courses*

# PDA 2011
# Combination Products Workshop
## *Life-Cycle Design Validation for Combination Products*

**September 21-22, 2011** | Renaissance Hotel | Washington, D.C.

This year's workshop focuses on the device design validation requirements of FDA's Quality System Regulation and the international harmonized quality standard ISO 13485:2003 which may be applied during the life-cycle of a combination product. The workshop will provide a discussion, review and interpretation of regulations and guidance applicable in the United States and in Europe to the clinical evaluation of human factors, utilization of post-market data and risk management, functional stability and manufacturing as they relate to combination product design. It will include case studies and presentations by companies currently developing and managing the life cycles of combination products.

Sessions at this year's meeting include:

- Introduction to Combination Product cGMPs
- Design Input
- Design Verification and Validation
- Clinical Trial Considerations
- Human Factors for Combination Products
- Post Market Considerations
- Panel Discussion

Join us at this workshop to gain key information, requirements and solutions that address many of the challenges faced by the medical products industry!

Remember this workshop follows the conclusion of the *2011 PDA/FDA Joint Regulatory Conference & TRI Courses*. If you join us for both events you can receive a discounted price to attend this workshop.

For details and to register, visit:

**www.pda.org/2011comboproducts**

# Lifecycle Design Validation for Combination Products

**Washington, D.C. • September 21-221 • www.pda.org/2011comboproducts**

**Doug Mead, Johnson and Johnson**

The program chairs invite anyone with an interest in the development and regulation of combination products to join us in Washington, D.C. on September 21 and 22, immediately following the close of the PDA/FDA Joint Regulatory Conference, for PDA's second workshop on combination products.

This workshop goes beyond the first PDA Combination Product Workshop, held in 2009, by exploring the details of the effective application of design controls to parenteral and inhalation delivery devices and other combination products. It also focuses on human factors assessments, users studies, and clinical trial requirements, which are part of the validation of the design of these products.

While the development of safe and effective drugs is paramount, it is also true that what the patient sees and uses is often the medical device constituent part of the combination product. Therefore, delivery devices must not only ensure safe and effective administration of the drug product, but be designed for ease-of-use. This meeting should be of interest to individuals at all levels who are engaged in development, manufacture and postmarketing activities involving combination products.

The opening session will provide an overview of combination product cGMPs and device design controls as outlined in FDA's proposed rule for Good Manufacturing Practices for Combination Products. Building a quality system applicable to drugs and devices based on this approach will be covered as well as the broader FDA requirements for combination products. This session will serve as a foundation for the more detailed topics in later sessions.

Another session will review the principles in establishing the initial user requirements and technical design requirements for these combination products when patient self–administration is the objective. How to assure that these design inputs are met through design verification and validation will also be discussed in individual sessions during the workshop.

As part of design validation, dedicated sessions have been prepared on the topics of human factors testing and the incorporation of the to-be-marketed presentation into pivotal clinical trials. Health authorities increasingly expect that objective evidence of usability and reliable administration is included in initial BLA, NDA and MAA applications. However, the design of these studies is a specialty unto itself. Experts in these fields will present their views on best practices for clinical trial designs and human factors studies as well as what regulators are looking for.

*During the conference, there will be adequate time for discussions and networking*

The postmarket experience is always the truest test that design expectations have been met, both in terms of usability and reliability. Complaints and their root cause investigation will typically lead to insight into how to improve on the designs or provide greater clarity in instructions for use. Design changes are an important part of the lifecycle management of combination products and are highly likely to be needed. Session experts will present their views on these activities and regulatory strategies need for their implementation.

The workshop is intended to go beyond the fundamentals and to address the practical challenges industry faces in the development, approval and lifecycle management of these combination products in terms of design controls and especially design validation. Health authorities reviewing combination product applications have become increasing knowledgeable on design controls, human factors testing and, in some cases, have specific requirements for how combinations products are assessed in clinical trials. The program committee has sought out the leading experts on these topics as well as key FDA staff who focus on these combination product issues. The workshop culminates in a panel discussion with these key leaders giving the audience the opportunity to ask both industry experts and regulatory authorities about their perspectives on the challenges with combination products, including design controls, human factors testing, clinical trial designs and quality systems.

During the conference, there will be adequate time for discussions and networking; a networking luncheon is planned that will allow participants to sit with others and collaborate on common interests and problems. It will provide a venue for industry and regulatory health authority experts to discuss how to manage difficult combination product regulatory issues in an evolving regulatory environment and provided an opportunity for face-to-face dialogue with their colleagues and policy makers.

We hope you will be able to join us at the *2011 Combination Products Conference* and take advantage of this unique opportunity to interact on important combination product issues and hot topics with your colleagues and regulatory health authorities. For more information on the conference, visit www.pda.org/2011comboproducts.

We hope to see you there!

# Using a Magic Eight Ball to Make Your Micro Decisions?

**Bethesda, Md. • October 17-21 • www.pda.org/2011microbiology**

**Marla Stevens-Riley, PhD, U.S. FDA**

Are you unable to find answers for many of your pharmaceutical microbiology questions? The Parenteral Drug Association can help.

The theme of this year's *PDA's 6th Annual Global Conference on Pharmaceutical Microbiology & TRI Courses,* October 17-21 in Bethesda, Md. is Challenges Facing Pharmaceutical Microbiology in the 21st Century. This conference offers one of the few opportunities to hear and interact with industry microbiologists, global regulatory affairs representatives, regulators, key product vendors and other global leaders in pharmaceutical microbiology.

This year's two keynote speakers from Kansas State University and the U.S. FDA will give presentations on global developments of rapid methods and automation in microbiology and a thirty year review and predictions into the future and challenges facing pharmaceutical microbiologists to define and control objectionable microbes.

In addition sessions will focus on:

- New technologies
- Risk assessment and environmental monitoring
- Challenges in radiation sterilization of pharmaceuticals and devices
- Contamination control
- Objectionable organisms

Some sessions will also discuss current provocative topics such as reconstitution, administration, and products and container closure integrity testing favoring physical test methods over the microbial immersion method.

The program also features two unique breakfast sessions: "USP Update" and "Microbiologist of the Future-Future Leadership Panel Discussion." Recent revisions to the USP as well as current and future USP activities will be discussed and future microbiology leaders in industry will discuss their strategies for increasing collaboration between the QC microbiology laboratory and the manufacturing floor.

In response to previous attendees' requests, issues related to non-sterile products will also be presented in two sessions this year: "Challenges for Non-sterile Multi-dose Products" and "Developing a Meaningful Environmental Monitoring Program for Sterile and Non-Sterile Operations/ Trending." Finally, the ever popular "Urban Myths" and the "Ask the Regulators" sessions will be held again. These sessions will focus upon scientific reality versus current microbiological practices (good and bad), and representatives from the FDA and WHO will participate in a panel discussion formal answering questions posed by the audience.

In times of limited funding for travel and the increasing demands on our time to do more with less, this conference offers a unique opportunity ("one stop shopping") for enhanced learning, professional development and scientific rejuvenation, just in two and 1/2 days.

In addition to the conference sessions, there are four training courses from industry experts on a myriad of microbiology topics.

Courses include:

"Environmental Control and Monitoring for Regulatory Compliance" and "Auditing for Microbiological Aspects of Pharmaceutical and Biopharmaceutical Manufacturing" taught by **Frank Kohn,** PhD, President, FSK Associates.

In "Environmental Control and Monitoring for Regulatory Compliance," Frank will teach students about facility design and validation, including personnel flow, equipment flow, baseline monitoring, media fills and quality control. The tracking and trending of the data will be reviewed, and a focus on the "best industry practices" to employ when performing environmental monitoring. Also, U.S. FDA and international standards related to microbiological issues will be covered with an emphasis on how to avoid quality problems. In "Auditing for Microbiological Aspects of Pharmaceutical and Biopharmaceutical Manufacturing," Frank will focus on the various techniques, tools and methods for auditing manufacturing operations from a microbiological viewpoint. Current FDA and international boards of health GMP regulations will be reviewed.

"Microbiological Issues in Non-Sterile Manufacturing," will be taught by **Barry Friedman,** Consultant, and will discuss various issues in non-sterile manufacturing including setting of specifications, process development, holding times, preservation, cleaning, sanitization and approaches to evaluating recovered organisms.

"Rapid Microbiological Methods: Overview of Technologies, Validation Strategies, Regulatory Opportunity and Return on Investment," taught by **Michael J. Miller,** PhD, President, Microbiology Consultants, will provide a comprehensive review of currently available RMM technologies, validation strategies, applications, regulatory expectations, financial justification models and implementation plans. Taught by one of the industry's leaders in rapid methods, attendees will be immersed in discussions that will provide a meaningful and understandable roadmap for how to evaluate RMMs and employ them in laboratory and manufacturing environments.

The conference and courses are always interactive and exciting and provide a great atmosphere for exchanging information, meeting new people, and catching up with Microbiology industry experts. We look forward to seeing you at the *PDA's 6th Annual Global Conference on Pharmaceutical Microbiology & TRI Courses!*

For information about the conference, courses and how to register, visit www.pda.org/2011microbiology.

*The Parenteral Drug Association presents...*

# PDA's 6th Annual Global Conference on Pharmaceutical Microbiology & TRI Courses

## *Challenges Facing Pharmaceutical Microbiology in the 21st Century*

**October 17-19, 2011**

**EXHIBITION:** October 17-18 | **COURSES:** October 20-21
Bethesda North Marriott Hotel | Bethesda, Maryland

"This conference has provided me with valuable knowledge that I can bring back to my company that helps us to enhance our processes, ensure compliance, and educate my staff."

K. Van Antwerpen,
*OSO BioPharmaceuticals Manufacturing, LLC*

*PDA's 6th Annual Global Conference on Pharmaceutical Microbiology & TRI Courses* will bring together all levels of industry professionals to network and benefit from a program that demystifies the underlying science of microbiology and seeks to solve the problems that our industry faces on a daily basis.

Here is a look at the plenary session topics at this year's meeting:

- **Keynote Address: Global Developments of Rapid Methods and Automation in Microbiology: A Thirty Year Review and Predictions into the Future**
- **Keynote Address: Challenges Facing Pharmaceutical Microbiologists to Define and Control Objectionable Microbes**
- **Microbiological Issues Associated with Reconstitution, Administration and Holding of Products**
- **Urban Myths**
- **Impact of Objectionable Microorganisms on the Industry and on Patient Safety**
- **Ask the Regulators Panel Discussion**

Don't miss out on the foremost conference on pharmaceutical microbiology!

Immediately following the conference, the PDA Training and Research Institute (PDA TRI) will be hosting four stand-alone courses in conjunction with the conference on October 20-21.

For details and to register, visit
**www.pda.org/2011microbiology**

# Adventitious Workshop Focuses on New Detection Methodologies

**Rockville, Md. • November 2-4 • www.pda.org/adventitious2011**

**Co-Chairs Arifa Khan, PhD, U.S. FDA, Kathryn King, PhD, U.S. FDA and Anthony Lubiniecki, Sc.D., Centocor**

The *PDA/FDA Adventitious Agents and Novel Cell Substrates: Emerging Technologies and New Challenges Workshop* will be held on November 2-4 in Rockville, Md. and is being organized to provide a forum for discussion of new technologies for adventitious agent detection and to expand upon emerging issues related to novel cell substrates.

Recent technological advances have resulted in novel virus detection methodologies and the ability to produce biological products for human use more efficiently and in a wider variety of cell substrates. Alongside the benefits derived from these advances, come new challenges in ensuring biopharmaceutical product safety. This workshop will focus on new methods for adventitious agent detection, microbial agents associated with novel cell substrates and sources/mitigation of adventitious agents in raw materials.

The first day of the workshop will center on the application of emerging molecular methods for adventitious agent detection, such as high throughput sequencing, virus microarrays and PLEX-ID. Data driven talks will provide a basis upon which a discussion panel will be convened to focus on the technical and regulatory challenges of these new methods including issues such as bioinformatics analysis, assay standards and GMP validation. Discussion will identify gaps in the current knowledge base; address what must be done; and when it may be appropriate to integrate these assays into routine use.

On the second day, the focus will turn to novel cell substrates and related potential safety and quality issues. In particular, this session will highlight plant cell substrates and plant derived materials that are used in other biologics production processes, as well as specific issues related to novel insect, avian and mammalian cell substrates. Discussions will include the risks associated with plant viruses as well as appropriate models viruses for clearance studies, sources of virus contamination, and facilities issues related to a potential contamination event.

A session on sources and mitigation of adventitious agents in raw materials will take place on the third day of the meeting. This session will include talks on raw material supply chain with focus on raw materials treatment strategies for reducing risk and will be followed by a discussion on the challenges associated with adventitious agent screening and mitigation and what steps, including enhanced communication with vendors, might aid in the mitigation of safety risks associated with raw materials.

This workshop will be followed up with an expert panel discussion to determine in which areas consensus may be reached and identify issues that remain unresolved for further discussion. We look forward to seeing you in Bethesda in November for this workshop!

The 2010 PDA Adventitious Virus Workshop successfully generated thoughtful audience discussions. Proceedings of the event are being prepared and will appear in an upcoming edition of the *PDA Journal of Pharmaceutical Science and Technology.*

# Latest Developments in Visual Inspection Covered

**Bethesda, Md. • October 3-6 • www.pda.org/visual2011**

**Program Co-chairs John Shabushnig, PhD, Pfizer, and Markus Lankers, PhD, rap. ID**

Visual inspection continues to be an important element of the manufacturing process and the quality assurance of injectable products. Product inspection provides necessary information for lot release and coupled with defect identification, contributes to a strategy of continuous process improvement. Since 2000, PDA has organized the Visual Inspection Forum to discuss new technical and regulatory developments in this field. It has grown into the leading event for those working in the field of visual inspection and is scheduled to be held this year in Bethesda, Md. from October 3-6.

The *2011 PDA Visual Inspection Forum & TRI Course* will provide an opportunity to present and discuss new develop-

ments in the field of visual inspection, including contributions to a basic understanding of the sampling and inspection process, practical aspects of manual and automated methods. A highlight of the forum will be the regulatory and compendial requirements session covering three important driving forces influencing the inspection process: Our understanding of the medical risks associated with particulate matter, FDA concerns in this area, and an update on the work of the USP Visual Inspection Expert Panel.

A further goal of this conference is to build a network of experts and interested professionals working in this important and specialized field. For this purpose, we have scheduled time for both formal and informal panel discussions. Sessions cover topics such as particle standards and identification, case studies, special requirements for biopharmaceuticals, packaging materials, emerging technologies and more. Poster presentations are scheduled for both Monday and Tuesday.

As in past years, the meeting will feature an exhibition where attendees can see the latest in commercial inspection hardware and discuss production needs with key suppliers of inspection systems and services.

We are also pleased to add an optional two-day training course offered through PDA's Training and Research Institute. "An Introduction to Visual Inspection" covers the basics of visual inspection, establishing and managing a visual inspection program and qualification and validation of inspection processes as applied to injectable products. The skills developed through this course may be applied to both manual human inspection and automated machine inspection. This course will be held on October 5-6.

We look forward to seeing you at this exciting and informative meeting. Visit www.pda.org/visual2011 for more information and to register.

*PIC/S Celebrates 40th Anniversary continued from page 59*

EFPIA, IFPMA in the field of training.

The 40th Anniversary symposium coincided with the first-time attendance of the Ukrainian State Inspectorate for Quality Control of Medicines (SIQCM) and the U.S. Food and Drug Administration as full members of the Organization. U.S. FDA Commissioner Dr. **Margaret Hamburg** delivered a keynote address to the symposium and called upon all regulatory authorities to cooperate more closely and share information on GMP inspections, in particular in third countries. PIC/S' main advantage over a Mutual Recognition Agreement is that it is not legally binding, thus allowing participating authorities to co-operate and share information informally (subject to confidentiality) while keeping complete control over imported medicinal products.

For more information on PIC/S' 40th Anniversary, see www.picscheme.org.

# EMA Regulator to Give Update on Quality Guidance

**Washington, D.C. • September 19-21 • www.pda.org/pdafda2011**

If you think the *2011 Joint Regulatory PDA/FDA Conference & TRI Courses* is all about US regulations, think again. European regulatory concerns will be addressed throughout the conference by the following speakers:

**Katrin Nodop,** Head of Sector Support, Sector Compliance and Inspector Support, European Medicines Agency, will give an update during the Quality and Compliance track about the GMP and Quality Guidance on Monday, September 19.

On Tuesday, September 20, **Stephan Rönninger,** PhD, Head of External Relations Europe/Japan, F. Hoffmann-La Roche, will speak at a breakfast session on ICH Q8, Q9 and Q10 working group outcomes and implications for the future. Later in the day, he will speak about PIC/S and the U.S. FDA and the impact and opportunity this relationship has on both parties.

As part of the Foundations Track, **Sabine Kopp,** PhD, Quality Assurance and Safety: Medicines, Medicines Policy and Standards, World Health Organization, will give a presentation on Tuesday that will update audience members about the WHO Office of Quality Assurance & Safety: Medicines.

**Claire Barber,** Head of Global Product Security, AstraZeneca, will apprise those interested in the Supply Chain Track on Tuesday of the conference about EFPIA's European Vision on how to fight counterfeiting with serialization.

On Wednesday, September 21, a breakfast session about Qualified Persons will be given by **Claudio Puglisi,** a practicing QP, and Technical Director, Magis Farmaceutici, about the QP program in Europe.

# Workshop Addresses Slow Development of ATMPS

**Co-Chairs Stephen Brown, Vivalis and Paula Salmikangas, Finnish Medicines Agency**

The PDA Europe Workshop on ATMPs was held in collaboration with the Finnish Medicines Agency (FIMEA) in Helsinki, Finland on June 7-8 and was opened by the Director General of FIMEA, Dr. **Sinikka Rajaniemi.**

In her introductory talk, Rajaniemi highlighted the advances in molecular and cell biology and biomaterial technology that have created the foundation for a new era in medicine such as the correction, replacement or even the rebuilding of tissues and organs responsible for essential functions using Advanced Therapy Medicinal Products (ATMPs, gene/cell therapy, tissue engineering). She further reminded the audience that ATMPs also carry risks such as immunotoxicity, cell transformation and transmission of infections, which was the reason for creating a regulatory pathway that ensured adequate quality and a positive benefit/risk ratio for products entering the market. According to Rajaniemi, the regulators equally realize that it is difficult to apply standard regulatory requirements to the development and assessment of ATMPs. "The regulatory requirements have to be tailored for ATMPs in the same manner as they were previously tailored for blood products and vaccines and subsequently for biotechnology-derived therapeutic proteins," she said.

She also mentioned that while expectations have been high, the development of ATMPs has proceeded painfully slowly. Despite hundreds of clinical trials, only one product had obtained marketing authorization in the European Union as of June 2011. The very modest progress in product development is partly due to outstanding scientific problems and difficulties in complying with regulatory requirements. Furthermore, decisions on a national level concerning the reimbursement of innovative products and the implementation of hospital exemption may impact future commercialization of ATMPs. Therefore, regulatory authorities need to balance their requirements between safe and efficacious products and patients access to ATMPs. "We must realize that successful development will require that the key parties, academia, industry and regulatory authorities engage in ongoing dialogue in order to solve the outstanding problems," she concluded.

The conference brought together 148 ATMP experts from academia, industry and regulatory bodies from 20 countries around the world. All aspects of ATMP development were discussed including CMC issues, non-clinical and clinical development, as well as the recent scientific results, novel technologies and regulatory advances. The high-quality agenda was

*continued at bottom of page 74*

## Audio Recordings for ATMPS Workshop Available for Purchase

Subsequent to this year's conference, we are now offering presentations with voice-over commentary. Session recordings will provide those who could not personally attend the workshop a chance to take part in the lectures and allows the people who did come the chance to hear sessions that they missed.

If you are interested or would like more information, please visit europe.pda.org.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

PDA
Parenteral Drug Association

## PDA/EMA 2011 Conference

# Plenary sessions now available on video

Dear Colleagues,

As you may well know, the forth PDA/EMA Joint Conference convened at the Hotel Sofitel in London early this May. This year's agenda was broadened to include a full range of GMP, Quality and CMC issues relating to the pharmaceutical, production and quality management.
For those of you who were not able to attend but wish to benefit from the plenary sessions, we are now offering video recordings of them online, unfortunately with the exception of only one presentation (Ms' Anne Juttonen's contribution from Fimea). These videos cost € 495 for members, € 595 for nonmembers and € 195 for our guests having participated, with all recordings lasting approx. 8.5 hrs. Upon having purchased them, simply log in and share our experience. We hope you enjoy these video productions and look forward to bringing you more videos in the future!



**https://europe.pda.org/PDAEMA2011**

# Maik Jornitz, Sartorius Stedim Biotech

**Course that you teach for PDA:**

Basic and advanced course for "Filters and Filtration in the Biopharmaceutical Industry."

**How long have you been an instructor for PDA?**

Since 2005.

**What are the challenges/problems that this course identifies and offers solutions to?**

Sterilizing filtration has been a key processing step in the pharmaceutical and biopharmaceutical industry, which determines the quality and safety of a drug product. The process validation of filters is very well-defined and most often diligently accomplished. However, when the filter-user is not properly trained, the costly and time-consuming validation is meaningless, as mistakes will happen. Often the mistakes are minor oversights with major repercussions, for example, integrity test failures due to insufficient wetting of the filter-membrane or filter-damage due to inappropriate steam sterilization.

The courses focus on practical experiences and advise how to avoid such mistakes, to recognize what happened if failure occurred and how to handle such. On the other hand, the initial filter choice becomes more and more significant due to the variety of filter applications and parameters. Questions will be answered in regard to filter designs, membrane material choices, pre- and final filter combinations, etc. In addition, regulatory guidances will be reviewed and applied to filtration processes. This is only a snapshot of the courses topics.

**What makes this course different than others which may be out there?**

There is no independent course out there which is more thorough and especially practical, as the advanced course is mainly a hands-on training. The TRI facility creates a unique capability of classroom segments and practical laboratory work. Both are combined with discussions and interactions. Not to forget; we always had and have fun within these courses learning from each other.

**Why should people attend this course over others?**

The interesting part with sterilizing grade filtration is the fact that this essential process step is not been taught at universities or colleges. The main teaching happens as a training-on-the-job, as tricky as it is. Other training courses on filtration are mainly given by the filter vendors about their own products. This course encompasses all filters and filtration, as well as filter testing in a comprehensive format. It also creates a solid foundation for people who are new to this technology.

Maik is the SR VP of Marketing & Product Management and current Chair of PDA

**What would you say to people considering taking a PDA course?**

If anybody wants to participate in a practical, comprehensive and fun-learning experience, this is the course to be in. PDA TRI creates the optimal environment to learn from each other, as every question asked by participants helps the faculty learn as well!

Other instructors for the class include **Ted Meltzer,** Capitola Consulting and **Wayne Garafola,** Sartorius Stedim Biotech

*Workshop Addresses Slow Development of ATMPS continued from page 72*

(l-r) Stephen Brown, Vivalis; Sinikka Rajaniemi, FIMEA; Paula Salmikangas, FIMEA; Georg Roessling, PDA

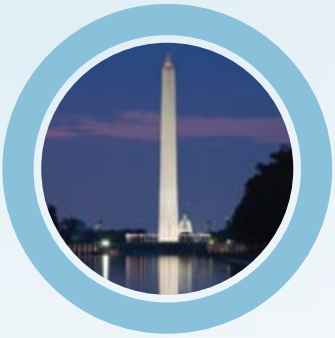
appreciated by the participants and the workshop met all the expectations of both the organizers and the attendees.

The host venue, the Hilton Hotel Kalastajatorppa, provided an outstanding environment and atmosphere for the participants. The conference attendees also enjoyed some unusual sunny and warm weather and the very light summer nights of Finland during their stay in Helsinki.

The next PDA Europe Workshop on ATMPs will be built on the successful experience of the Helsinki meeting and will be held in Lisbon, Portugal on June 5-6, 2012.

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

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



### August 2011

**Basic Microbiology for Aseptic Processes**
August 1-5, 2011 | Bethesda, Maryland | www.pdatraining.org/basicmicro

### September 2011

**Process Validation for Pharmaceuticals - Current and Future Trends**
September 1, 2011 | Bethesda, Maryland | www.pdatraining.org/processvalidation

**2011 PDA/FDA Joint Regulatory Conference & TRI Courses**
September 22-23, 2011 | Washington, DC | www.pdatraining.org/pdafdacourses

Course Series:

- Effective Investigations and Corrective Actions (September 22)
- Quality by Design for Biopharmaceuticals: Concepts and Implementation (September 22)
- Active Pharmaceutical Ingredients - Manufacture & Validation (September 22-23)
- Documenting and Conducting OOS Investigations (September 22-23)
- Preparing for Regulatory Inspections for the FDA and EMA (September 22-23)
- Role of the Quality Professional in the 21st Century (September 22-23)
- GMPs for Manufacturers of Sterile and/or Biotechnology Products (September 23)

**Developing and Validating a Cleaning and Disinfection Program for Controlled Environments**
September 27-28, 2011 | Bethesda, Maryland | www.pdatraining.org/DVCD

### October 2011

Hosted in conjunction with the *2011 PDA Visual Inspection Forum & TRI Course*

**An Introduction to Visual Inspection**
October 5-6, 2011 | Bethesda, Maryland | www.pda.org/visualinspection2011

**PDA's 6th Annual Global Conference on Pharmaceutical Microbiology & TRI Courses**
October 20-21, 2011 | Bethesda, Maryland | www.pda.org/2011microbiology

Course Series:

- Environmental Control and Monitoring for Regulatory Compliance - *New Course* (October 20)
- Rapid Microbiological Methods: Overview of Technologies, Validation Strategies, Regulatory Opportunities and Return on Investment (October 20)
- Auditing for Microbiological Aspects of Pharmaceutical and Biopharmaceutical Manufacturing (October 21)
- Microbiological Issues in Non-Sterile Manufacturing (October 21)

**PDA TRI Filtration Week**
October 24-28, 2011 | Bethesda, Maryland | www.pdatraining.org/filtrationweek

- Filters and Filtration in the Biopharmaceutical Industry - Basics Course (October 24-25)
- Filters and Filtration in the Biopharmaceutical Industry - Advanced Course (October 26-28)

Save 10% when you register for both 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.

All 2011 Aseptic Processing Training Program Sessions are sold out. The 2012 schedule will be available soon.

For more information on these and other upcoming PDA TRI courses please visit **www.pdatraining.org**


# Meet our Instructors During PDA/FDA

**Washington, D.C. • September 22-23 • www.pda.org/pdafda2011**

**Stephanie Ko, PDA**

The PDA Training and Research Institute (TRI) will be hosting seven training courses in conjunction with the upcoming PDA/FDA Joint Regulatory Conference that is taking place this September. These courses will be held immediately following the conference from September 22–23 at the Renaissance Hotel in Washington, D.C.

As much as we pride ourselves in the selection of courses that we offer specifically for this event, we are also proud of the instructors who teach these courses.

Here is a brief look at the training courses that are available and the instructors that you'll have the opportunity to meet:

Expert **Michael Anisfeld,** President, Globepharm Consulting, will present two courses, "Effective Investigations and Corrective Actions (CAPA)" and "GMPs for Manufacturers of Sterile and/or Biotechnology Products." Mike's extensive experience includes performing about 30 full scale mock-FDA and mock-EU inspections annually for clients around the world. He also performs regulatory inspections on behalf of international agencies such as the World Health Organization, the Union of Industrial and Employers' Confederations of Europe (UNICE) and the United Nations Industrial Development Organization (UNIDO). He regularly trains worldwide government inspection agencies on how to perform inspections and is a monthly columnist for five international GMP journals in Europe, Japan, and the United States.

In "Effective Investigations and Corrective Actions," Mike will discuss the expectations of FDA and EU authorities on risk management, OOS and deviation investigations, and trend analysis. Participants also will know how to rapidly and cost-effectively implement programs and practices that will satisfy the authorities and provide speedy and efficient methods that can be used by their companies.

In "GMPs for Manufacturers of Sterile and/or Biotechnology Products," Mike will cover the practical implementation of GMPs in facility and equipment design, process design and operations. Participants will be able to discuss terminal sterilization technologies and identify the challenges of aseptic processing in the manufacture of sterile and/or biotechnology products.

Co-taught by two instructors, including a member of the U.S. FDA staff, the course, "Quality by Design for Biopharmaceuticals: Concepts and Implementation" is essential for anyone seeking clarification of the key concepts that interplay in defining and implementing QbD towards the manufacturing of biotech products.

A team of two highly qualified professionals, **Anurag Rathore,** PhD, Consultant and Faculty Member, Department of Chemical Engineering, IIT Delhi, and **Ruth Cordoba-Rodriguez,** PhD, Product Quality Team Leader, Division of Monoclonal Antibodies, OBP-OPS-CDER, U.S. FDA, are well-versed in Quality by Design.

Anurag is co-author of the book, *Quality by Design for Biopharmaceuticals: Perspectives and Case Studies,* and co-author of one of the top-cited papers on QbD, "Quality by Design for Pharmaceuticals: Regulatory Perspective and Approach."

Ruth joined the FDA in 2002 and is responsible for the assessment of chemistry and manufacturing controls of therapeutic and diagnostic antibodies submitted to the FDA. She also coordinates various training programs in the Office of Biotechnology Products.

Their course will introduce participants to QbD concepts, such as:

- Critical Quality Attributes
- Design Space
- Risk Assessment
- Control Strategy
- Process Analytical Technology
- Process Validation
- Process Monitoring
- QbD Filling

**Nathan Conover,** Senior Partner, Pathwise, has spent nearly a decade working within the Pharmaceutical and Life Science Industries with a main focus on managing worldwide integrations of risk and corrective/preventive action systems, investigation procedures, processes, and skills. Nathan has completed global rollouts with many of the Fortune 500 companies in the Life Science Industry. Over the past five years, much of Nathan's time has been spent in the European Life Science Community, working with both companies and regulatory investigators. He regularly presents and consults with large- to-medium-sized organizations around the world on how to improve quality and how to stay in compliance with FDA and ISO standards and regulations.

In "Documenting and Conducting OOS Investigations," Nathan uses a blended approach of classroom and real-life work application to provide the knowledge, tools and skills necessary to facilitate a successful OOS investigation and improve product quality and regulatory compliance.

In his course, he will thoroughly cover:

- An overview of the industry guidance for OOS
- FDA expectations
- Responsibilities of analysts and supervisors
- How to determine when a full investigation should be initiated
- Various testing types to determine the validity of an OOS,
- Investigation phases
- Frequency for retesting and resampling

- Common problems and solutions for OOS Investigations
- Corrective and Preventive Action (CAPA)

Instructor **Dave Chesney,** VP, Strategic Compliance Services, Parexel Consulting, has helped organizations solve problems related to organizational structure, quality system development, quality agreements and vendor auditing, among other issues. He brings 23 years of FDA experience and 16 years worldwide consulting experience to his course, "Preparing for Regulatory Inspections for the FDA and EMA." Dave will help attendees better understand the regulatory requirements and distinguish those from what is "expected" and what is and to apply that knowledge to their specific circumstances. This course offers solutions to startup companies and others who work primarily through outsourced partners who often struggle to understand what the FDA requires and expects of them. Participants will be prepared to host an inspection, primarily focusing on EMA GMP or U.S. FDA pre-approval site inspections. The presentation will cover current FDA inspection initiatives, the EMA inspectorate, and inspection techniques and methodologies that are used.

**Robert Kieffer,** President, RGK Consulting has over 35 years of experience working with hundreds of different operations in over 50 countries in the pharmaceutical, medical device and chemical industries. In his years studying best practices, he came to the belief that compliance is necessary but insufficient to meet today's need for quality and cost control. Teaching the popular "Role of the Quality Professional in the 21st Century," he will present a new and much more proactive and exciting role for the quality professional than in the past. This course will not only describe this new role, its importance and relationship to other groups in the company but will also provide opportunities to learn and practice new skills which include process/systems design, evaluation and management, risk analysis, promotion of quality, change management, quality planning, quality costs and metrics, and useful quality tools.

Finally, **Daniel H. Gold,** PhD, President, D. H. Gold Associates, Inc, a member of FDA's Pharmaceutical Sciences Advisory Manufacturing Subcommittee; a past Chairman of the Pharmaceutical Research and Manufacturers of America (PhRMA) Production, Engineering and Materials Management Committee; and a past Chairman of PhRMA's Bulk Pharmaceutical Chemicals Committee, will teach "Active Pharmaceutical Ingredients: Manufacture and Validation." The course will give participants a thorough foundation in manufacturing operations related to the production of active pharmaceutical ingredients and how to operate an API plant. All aspects of plant operations are covered, including how to manage the relationship with the regulatory authorities.

With such a selection of topics, how can you go wrong?! For more information about any of the courses, visit www.pdatraining.org.

# Editor's Message

## Tell Us What You Think, Online!

A few months ago, we launched an E-Letter tool for the *PDA Journal of Pharmaceutical Science and Technology* that allows readers to comment on any article. Now, readers of the *PDA Letter* can comment online on any article we post outside of the full-issue PDF. Each month, the editors select three or four articles and make them available to all members and non-members outside of the full-issue PDF (www.pda.org/pdaletter). With the new PDA website (which looks fabulous), any reader can post a comment to these articles. Of course, we are always open to comments on any article in the Letter, and we welcome and encourage readers to send us emails to let us know how we are doing.

Summertime is here, and PDA has just concluded what seems a marathon season of great conferences, workshops, lectures, lab courses, website enhancements and overhauls, and other projects to keep our members engaged and informed. In other words, business as usual.

The first half of the year has been good for the *PDA Letter*, as well, with numerous member and expert contributions helping us provide engaging and useful articles on a variety of topics important to our community. I want to thank the hard work of the Letter's Editorial Committee for helping shepherd these articles to press each issue.

Now that we are in the not-so-lazy days of summer, it is time to gear up for PDA's biggest event of the year—the *PDA/FDA Joint Regulatory Conference*. Now in its 20th year, the Joint Conference has become an enduring symbol of how PDA's volunteer members—both in industry and in the regulatory agencies—work tirelessly to Connect People, Science and Regulation™. Because the success of this meeting, PDA is honored to work with the FDA on other conferences and workshops of high-importance, like the recent *PDA/FDA Glass Quality Conference* and the *PDA/FDA Pharmaceutical Supply Chain Conference* (see Faces & Places for Photos of each event). Because the *PDA/FDA Joint Regulatory Conference* is such an important event in PDA's history, we chose to celebrate its platinum anniversary by putting the special anniversary badge on this issue's cover.

Our traditional theme of the July/August issue is PDA's bread and butter topic: sterile products and aseptic processing. Our three feature articles focus on three areas of great importance: microbial testing, glass delamination and micro investigations. Our authors are all experts on their respective subjects, and we are sure our readers will find useful information in each article.

Admittedly, this is a big issue—our biggest ever, in fact. So it might take you some time to get through all the content, but we won't publish another one until September. As mentioned, these are the lazy-days of summer, so hopefully all of you will have some time to enjoy this issue.

**PDA Letter**

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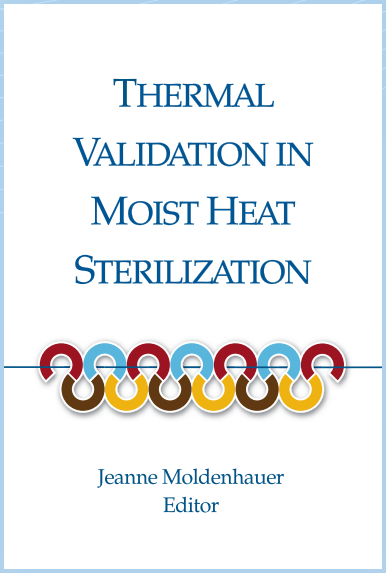
# New Release at the PDA Bookstore




## Thermal Validation in Moist Heat Sterilization

*Edited by* Jeanne Moldenhauer

Since the advent of PDA's Technical Report on Moist Heat Sterilizer Systems, it has been recognized that both the physical and the biological characteristics of a cycle must be included in the validation.

*Thermal Validation in Moist Heat Sterilization* features leading validation experts discussing the physical parameters of moist heat sterilization with a focus on the thermal validation. This comprehensive guide provides readers with a step-by-step approach to understanding, implementing, navigating the regulatory expectations and analyzing thermal validation.

Chapters and Authors:

1. Thermal Validation and Why it is Important, **Jeanne Moldenhauer**
2. Steam Sterilization Process Validation, **James Agalloco**
3. Regulatory Expectations for Thermal Validation - USA, **Jeanne Moldenhauer**
4. European Expectations For Thermal Validation, **Roland Marie Frédéric Guinet**
5. The EMEA's Decision Tree for Selection of Sterilisation Methods, **Jeanne Moldenhauer**
6. Importance of Accurate Measurements in Thermal Validation Studies, **Göran Bringert**
7. Performance of Thermal Validation Studies, **Kevin Trupp**
8. Practical Aspects of Thermal Validation for Moist Heat Sterilization, **Angela S. Coon** and **Michael J. Sadowski**
9. Analysis of Heating and Cooling Data, **Dr. Irving Pflug**

**www.pda.org/ThermalValidation**

## The PDA Bookstore's June Top 5 Best Sellers

**1 Quality By Design: Putting Theory Into Practice**
*Edited by* Siegfried Schmitt
Item No. 17296
PDA Member $210
Nonmember $259

**2 Validation by Design®: The Statistical Handbook for Pharmaceutical Process Validation**
*By* Lynn D. Torbeck
Item No. 17266
PDA Member $265
Nonmember $329

**3 Recent Warning Letters Review for Preparation of an Aseptic Processing Inspection**
*By* Jeanne Moldenhauer
Item No. 17292
PDA Member $280
Nonmember $349

**4 Laboratory Design: Establishing the Facility and Management Structure**
*Edited by* Scott V. W. Sutton
Item No. 17294
PDA Member $280
Nonmember $349

**5 The Bacterial Endotoxin Test: A Practical Guide**
*Edited by* Karen Zink McCullough
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