

# PDA Letter

Volume L • Issue 4

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

April 2014



## USP LOOKS AT FUTURE OF MICROBIOLOGY WITH NEW STANDARDS

24



**Packaging Show Issue**

Follow the logo to find articles on the 2014 PDA Packaging Conference

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*The Parenteral Drug Association presents the...*

# 2014 PDA/FDA Joint Regulatory Conference

*Connecting Regulatory, Quality, Science & Compliance: Assuring Customer-Focused Outcomes throughout the Product Lifecycle*

**September 8-10, 2014**

**RENAISSANCE WASHINGTON HOTEL | WASHINGTON, DC**



Don't miss out on this unique and unparalleled opportunity to participate with FDA and industry experts in face-to-face dialogues during the *2014 PDA/FDA Joint Regulatory Conference*. Attending this conference offers you an exclusive forum to hear from FDA speakers regarding the current efforts of the agency that may impact the development of global regulatory strategies. In addition, you will also hear from industry professionals representing leading small-and large-molecule pharmaceutical companies as they present case studies demonstrating how their organizations develop and employ global quality and compliance strategies in their daily processes.

**Upon completion of the conference, you will be able to:**

- Understand FDASIA and its new expectations
- Understand the importance of Quality Metrics and how to use them to your organizations advantage
- Be able to articulate how a robust quality system is beneficial in controlling the cost of quality
- Be able to understand the complicated issues facing CMOs and multiple product facilities
- Understand the issues related to aging facilities and how they can be modernized

**Want to learn more?** Following the *2014 PDA/FDA Joint Regulatory Conference*, PDA TRI will host six courses to complement your learning on September 11-12.

- |  |   |
|--|---|
| • GMPs for Manufacturers of Sterile and/or Biotechnology Products (September 11) | • Preparing for Regulatory Inspections for the FDA and EMA (September 11-12)                      |
| • Role of the Quality Professional in the 21st Century (September 11-12)         | • Quality by Design for Biologics: A Practical Approach – <i>New Course</i> (September 12)        |
| • Application of a Quality Systems Approach (September 11-12)                    | • Managing the QC and R+D Laboratory in a GMP Compliant Manner – <i>New Course</i> (September 12) |

Visit [www.pda.org/pdafda2014](http://www.pda.org/pdafda2014) for more information.

EXHIBITION: SEPTEMBER 8-10 | POST CONFERENCE WORKSHOP: SEPTEMBER 10-11 | COURSES: SEPTEMBER 11-12

# Volunteer Opportunities at PDA

## Leadership

- ◉ PDA Executive Officers

- ◉ Director

- ◉ Scientific Advisory Board
- ◉ Biotechnology Advisory Board

- ◉ Regulatory Affairs and Quality Advisory Board

- ◉ PDA Committee Chair/Co-Chair
- ◉ Task Force Co-Chair

- ◉ Author/Contributor to the *PDA Letter*
- ◉ Author/Contributor to the *PDA Journal*
- ◉ Poster Presenter
- ◉ Attend Chapter Committee/Planning Meetings
- ◉ Technical Report Peer Reviewer

- ◉ Speaker
- ◉ Chapter Leader
- ◉ Task Force Member
- ◉ TRI Instructor
- ◉ Interest Group Leader

### PDA Committees:

- ◉ Program Planning Committee
- ◉ PDA Letter Committee
- ◉ Membership Committee
- ◉ Education Committee
- ◉ Audit Committee

- ◉ PDA Membership
- ◉ Attend Global PDA Meetings

- ◉ Attend Chapter Events
- ◉ Survey Reviewer

- ◉ Interest Group Member
- ◉ Attend TRI Courses

## Getting Involved

1,000

Over 1,000 volunteers worldwide actively carry out PDA's Mission

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

## Cover



Cover Art Illustrated by Katja Yount

### 24 USP Looks at Future of Microbiology With New Standards

From a microbiological perspective, pharmaceutical products fall into two categories, nonsterile and sterile. For either category, manufacturers must eliminate or minimize potential health risks to patients related to microorganisms and the toxins they produce, while also maintaining product quality. Many contributing factors may affect the quality of a medicine or its ingredients, but microbial bioburden control and proper sterilization methods are critical considerations for the manufacturer throughout the product's lifecycle.

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## Features



### 30 Industry, Regulators Meet to Drive QbD Implementation

Since the first QbD workshop held in 2009, industry and regulators have continued working together to advance implementation of QbD principles. In January, PDA Europe organized a workshop to address continued progress in this area at the EMA's London headquarters. This workshop was co-chaired by **Jean-Louis Robert**, National Health Laboratory EP (Luxembourg) and Chair of the EMA Quality Working Party, and **Georges France**, Novartis, for the European Federation of Pharmaceutical Industry and Associations (EFPIA).



### 33 Pharmacopoeias: The European System

This infographic spotlights the European Pharmacopoeia and its governance structure.

#### PDA's MISSION

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

#### PDA's VISION

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



Connecting People, Science and Regulation®

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# THE PDA LETTER PODCAST SERIES



The PDA Letter hears from experts on topics important to you. Now you can hear them too.

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



## PDA IN THE NEWS

Below is a listing of various news articles/websites that have mentioned PDA within the past four months.

### ***"The Gold Sheet"***

January 30, 2014

"Breakthroughs for Patients, CMC Regulatory Flexibility"

—**Bowman Cox**

"USP and FDA Look to Improve Drug Packaging Standards"

—**Joanne Eglovitch**

February 27, 2014

"Risk and Reward: Pharmacy Compounding of Clinical Materials"

—**Bowman Cox**

### ***IPQ Monthly Update***

January 2014

"CDER Compliance Office Quality Regulatory Priorities for 2014 Include Implementing DQSA, FDASIA and Reorganization Plans"

"Biotherapeutics Developers Are Wrestling with Challenges of Connecting Quality Attributes to Immunogenicity"

### ***Pharmaceutical Technology***

January 2, 2014

"Metrics Sought to Ensure Drug Quality"

—**Jill Wechsler**

[tinyurl.com/mlg93nu](http://tinyurl.com/mlg93nu)

February 2, 2014

"Large Industry Cross-Section Contributes to PDA Quality Metrics Recommendations"

—**Walter Morris**

[tinyurl.com/khrcsg4](http://tinyurl.com/khrcsg4)

March 2, 2014

"Trends and Best Practices in Visual Inspection"

—**Hallie Forcinio**

[tinyurl.com/n3qq653](http://tinyurl.com/n3qq653)

### ***PharmTech Talk***

January 28, 2014

"PDA Panel Proposes Limited Set of Metrics to Measure Quality Trends"

—**Jill Wechsler**

[tinyurl.com/kgzrg4n](http://tinyurl.com/kgzrg4n)

### ***ProPharma Group Newsletter***

February 2014

"The FDA's Renewed Focus on Quality Metrics"

—**Jeff Hargroves**

# A World of Regulatory Experts Awaits You in Europe

PDA Europe has assembled a strong lineup of speakers representing several European regulatory agencies for the following four meetings. With the strong participation of U.S. FDA officials in PDA's U.S. activities, it is safe to say that PDA leads the way in connecting people, science and regulation.

## Vaccines & Beyond

(April 29–30, Brussels, Belgium, <https://europe.pda.org/vaccines2014>)

- **Mats Welin**, Medical Products Agency (Sweden)
- **Andrew David Meek**, World Health Organization

## Advanced Therapy Medicinal Products

(June 3–4, Madrid, Spain, <https://europe.pda.org/atmp2014>)

- **Margarida Menezes**, Infarmed (Portugal)

## Parenteral Manufacturing


(June 24–25, Istanbul, Turkey, <https://europe.pda.org/parman2014>)

- **Keith Pugh**, MHRA (United Kingdom)

## 7<sup>th</sup> Workshop on Monoclonal Antibodies

(Sept. 24–25, Basel, Switzerland, <https://europe.pda.org/monoclonal2014>)

- **Martijn van der Plas**, Medicines Evaluation Board (Netherlands)
- **Pascal Venneugues**, EMA
- **Margarida Menezes**, Infarmed (Portugal)

Please note that this list remains subject to change. For more information about upcoming PDA Europe conferences, please visit [europe.pda.org](http://europe.pda.org). 

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[www.biomerieux-industry.com/bioballpda12](http://www.biomerieux-industry.com/bioballpda12)



# PDA Volunteer Spotlight

## Chuck Reed

- Director, Sales and Marketing
- Weiler Engineering
- Member Since | 1997
- Current City | St. Charles, Illinois
- Originally From | Rochester, New York

*I find great comfort in the work that my colleagues are doing everyday*



*Chuck is a beekeeper in his spare time. In 2013, he harvested 50 pounds of raw wildflower honey!*



### How did you start volunteering for PDA?

I attended an interest group meeting and asked too many questions. Everyone else took two steps back and I was drafted. Seriously, I found a topic I was interested in and volunteered to help. My first experience was helping put together a session at an Annual Meeting. That led to writing a chapter for the PDA book, *Practical Aseptic Processing Fill and Finish: Volume II* ([www.pda.org/bookstore](http://www.pda.org/bookstore)), and now I chair the Blow/Fill/Seal Interest Group.

### How can volunteers gain leadership roles at PDA?

Demonstrate interest and ability. Begin with a small role such as offering your services as a speaker, then volunteer to help put together a technical session. Exposure and enthusiasm will provide you with the opportunities that may fit you best. If you provide valuable support, you will no doubt be asked to fill more challenging roles.

### What is your favorite technical report and why?

I don't have a "favorite" but I use the reports as reference support on a regular basis. Our task force is currently using several as support material in production of the blow/fill/seal best practices technical report.

### How has your field changed since you started your career?

An interesting question, since my "field" has a variety of definitions, due to the fact that I've held several different positions in several different industries. The most defining changes I've seen have occurred within the pharmaceutical industry in the last dozen years or so. From the sales perspective, the evolution of project management from a simple combination of a project engineer and purchasing agent, to the present expanded team approach, which may include additional personnel from process engineering, validation, quality, automation engineering and regulatory functional groups.

### If you could meet someone living or dead, who would it be and why?

Frank Lloyd Wright. I have studied the persona, the career and the life work of this eccentric architect, who has become more appreciated after death than when alive. I've always been attracted to his architectural style and dramatic flair and I think it would be an interesting (albeit challenging) meeting.



# PDA'S TECHNICAL REPORT PORTAL

VIEW THE COMPLETE LIBRARY OF CURRENT  
PDA TECHNICAL REPORTS ANYWHERE, ANYTIME

Archives

Only active TRs are available in this archive

- ▶ TR 1 2007
- ▶ TR 3 Rev-2013
- ▶ TR 4 1993
- ▶ TR 7 1985
- ▶ TR 12 1988
- ▶ TR 14 2008
- ▶ TR 15 2009
- ▶ TR 21 1990
- ▶ TR 22 2011
- ▶ TR 25 1997
- ▶ TR 26 2008
- ▶ TR 27 1998
- ▶ TR 28 2006
- ▶ TR 29 2012
- ▶ TR 30 2012
- ▶ TR 31 1999
- ▶ TR 33 Rev-2013
- ▶ TR 34 2001
- ▶ TR 38 2006
- ▶ TR 39 2007
- ▶ TR 40 2005
- ▶ TR 41 2008
- ▶ TR 42 2005

PDA
2-3/08

This technical report is organized in a logical progression from the essential elements of SIP system design through SIP cycle development, qualification, and ongoing operation.

In the interest of clarity, the report provides a glossary of technical terms, and begins with a discussion of the SIP Life Cycle as depicted in Figure 1.1-1.

Figure 1.1-1 SIP Life Cycle

The Performance Qualification action focuses on the application of physical and biological test products used to demonstrate the efficacy of particular SIP processes as they relate to intended use.

Finally the Ongoing Process Control action focuses tests to establish and maintain a continuous state of control after the SIP process is implemented. This action includes recommendations for product control, records management, change control, requalification, and maintenance practices.

### 2.0 Glossary of Terms

Terms usage may differ from company to company, and some terms may be subject to change in the future. However, the terms used in a qualification program must be clearly defined and well understood within the company. Regulatory guidelines may offer other definitions that should be considered. This technical report uses the following terms, listed here with their definitions and examples where applicable.

**Bioburden**  
The microorganisms or in a pharmaceutical product or in the manufacturing environment.

**Biological Indicator (BI) Challenge System**  
A test system containing viable microorganisms of a given specified strain providing a defined response to a specified sterilization process (4).  
**(Examples:** *Staphylococcus aureus*, *Bacillus pumilus*, *Microbiological Challenge System*.)

**Biological Qualification**  
A component of performance qualification that demonstrates, by use of biological indicators, that the specified bioburden ( $D_0$ ) or spores log reduction (SRL) is achieved consistently throughout the intended or selected portions of the SIP process.

**Bracketing Approach**  
A scientific approach for defining characteristics (e.g., Tank sizes, system configurations, filter sizes and types) that are tested in a qualification study or validation study to upper and/or lower limits.

**Calibration**  
The determination that an instrument or device produces results within specified limits when compared to those produced by a reference standard or a standard that is suitable as measured or measurement available, over an appropriate range of measurements.

**Cold Spot**  
The location within an SIP system that achieves the lowest process lethality ( $F_0$ ) during a SIP process. **Note:** Where lethality values are not available or not applicable (e.g., a continuous process operating at less than 100 °C) the cold spot is the location with the lowest temperature profile during the SIP cycle.

**Cooldown Phase**  
The phase of an SIP cycle that occurs after completion of the exposure phase. The duration (e.g., time, temperature, pressure) of a cooldown phase are typically defined in order to meet applicable user requirements for system cooling and drying.

**Critical Control Point**  
A step at which control can be applied and is essential to prevent or eliminate a pharmaceutical quality hazard or reduce it to an acceptable level (5).

**Cycle Development**  
A series of actions performed for the purpose of defining or confirming the cycle parameters (e.g., time, temperature, pressure) necessary to ensure sterilization or verification.

**Designs**  
An area of development in the final engineering type that could lead to contamination of the product due to insufficient exposure to moist heat (6).

**D<sub>0</sub> Value**  
The time or minutes required for a one log reduction, or 90% reduction, of the population of microorganisms used as a biological indicator under specified lethal conditions. The more reduction, the D<sub>0</sub> value should always be specified with a reference temperature,  $D_0$ . For example, a BI system with a  $D_0$  of 2.0 minutes requires 1.2 minutes at 121 °C to reduce the population by one log-unit. **(Example:** D<sub>0</sub> value.)

**Exposure Phase**  
The phase of the SIP cycle in which the appropriate parameters (e.g., time, temperature, pressure) are maintained within defined ranges for the time exposure time or dwell period determined to be necessary to achieve the desired lethality.

**F<sub>0</sub> Value (Lethality Factor)**  
A measurement of sterilization effectiveness, the F<sub>0</sub> value is the calculated equivalent lethality using a specified z value, in terms of exposure at a reference temperature (121 °C), followed by a sterilization cycle.

trarchive.pda.org/t/26426

Licensing options available; contact Janny Chua at chua@pda.org

## PDA Japan Chapter Holds 20th Annual Meeting in Tokyo

Japan Chapter Board Member **Osamu Kawamata, PhD, SRL**

The PDA Japan Chapter held its 20th Annual Meeting Dec. 3–4, 2013 at the Tower Hall Funabori in Tokyo. The main theme was “Ensuring the Product Quality and Innovations.” Close collaboration between PDA and Japanese regulators led to this successful meeting that over 400 attended. Talks at the meeting provided participants with updates on major topics in the global quality space.

### PDA Who's Who

**Tor Gråberg**, Head of Inspection, Medical Products Agency Sweden

**Stefan Henke**, PhD, Managing Director, IIS Innovative Injections-System GmbH

**Atsushi Ban**, CBM

**Richard Johnson**, President, PDA

**Shingou Sakurai**, PhD, QCU

Manager, PMDA

**Tomoaki Sakamoto**, PhD, Division of Drugs, Third Sector, National Institute of Health Sciences

**Rumiko Shimazawa**, PhD, Research Associate Professor, Kyushu University

**Stephan Rönninger**, PhD, Head of External Collaboration, Amgen

**Shingou Sakurai**, PhD, PMDA, gave the first lecture, “Steps Taken in the Past to Become a Part of the PIC/S and Future Strategies for Globalization of GMP.” Per his talk, Japan should not only participate actively in the PIC/S activities but also exercise its leadership in the Asian region to further reinforce the relationship among regulatory authorities. To achieve this globalization of GMPs, Japan must expand collaboration between government, industry, and academia within the country.

**Tomoaki Sakamoto**, PhD, National Institute of Health Sciences (NIHS) presented on the Institute’s attempt to obtain authorization as an Official Medicines Control Laboratory (OMCL) by PMDA inspection with PIC/S onsite inspection visits.

The final lecturer of the first day, **Rumiko Shimazawa**, PhD, Kyushu University, spoke of her experiences with approval review. She served as a PMDA officer and a committee member and was involved in new drug approval review.

Three overseas presenters spoke on the last day. **Tor Gråberg**, Medical Products Agency Sweden and ex-PIC/S Chairman, presented “How Can PIC/S Facilitate Global Harmonization?”



The Parenteral Drug Association presents the...

## 2014 PDA Aseptic Processing-Sterilization Conference

June 17-18, 2014 | HYATT CHICAGO MAGNIFICENT MILE | CHICAGO, ILLINOIS

Join some of the most highly qualified experts as they share their experiences in the development, validation and ongoing control of aseptic processing, and terminal sterilization programs during the 2014 PDA Aseptic Processing-Sterilization Conference. Don't miss out on this unique opportunity to engage with experts in discussions regarding the current trends and issues facing aseptic processing and terminal sterilization programs.

This two day conference will focus on topics such as Unique Combination Product Considerations, New Sterilization Methods/Control Techniques and Regulatory Perspectives. The popular “Ask the Experts” session will be included once again this year, ensuring that all of your questions related to aseptic processing and terminal sterilization have been fully addressed.

Don't miss the opportunity to hear from:

- **Roger Asselta**, Vice President – Technical Affairs, *Genesis Packaging Technologies*
- **Jessica Cole**, PhD, Product Quality Microbiology Reviewer, CDER, *FDA*
- **James Polarine, Jr.**, Technical Services Manager, *Steris Corporation*
- **Jeffrey Weber**, Senior Scientist, PAT Projects, *Pfizer, Inc.*
- **Rob Wilson**, CEO, *Food Chain Safety – Microwave Assisted Thermal Sterilization*
- Additional presenters to be announced

Visit [www.pda.org/aseptic2014](http://www.pda.org/aseptic2014)  
for more information.

EXHIBITION: JUNE 17-18 | COURSES: JUNE 19-20

PHOTO COURTESY OF SARTORIUS STEDIM BIOTECH

The Parenteral Drug Association presents the...

## 2014 PDA/FDA Virus and TSE Safety Conference

June 9-11, 2014 | HYATT REGENCY HOTEL | BETHESDA, MARYLAND

Virus and TSE (transmissible spongiform encephalopathy) safety of protein-based medicinal products is a major topic and a public health imperative; we learn year by year that there is a risk of contamination with virus and TSE agents. As you know, the use of current methodologies for virus detection might not be sufficient to avoid viral contamination cases.

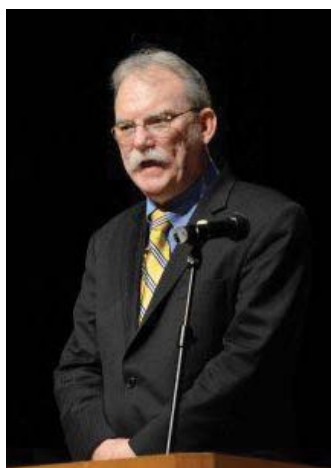
Therefore, one focus of the 2014 PDA/FDA Virus & TSE Safety Conference is the topic of improving detection and mitigation of contamination risks. Hear from experts such as:

- **Olivier Andreoletti**, Ecole Nationale Veterinaire, French National Institute for Agricultural Research
- **Paul Barone**, PhD, Associate Director, Biomanufacturing Research Program, MIT
- **Johannes Bluemel**, PhD, Head of Virus Safety Section, Paul-Ehrlich-Institut
- **Kurt Brorson**, PhD, Staff Scientist, Monoclonal Antibodies, CDER, FDA
- **Eric Delwart**, PhD, Senior Investigator, Blood Systems Research Institute
- **Luisa Gregori**, PhD, Biologist, CBER, FDA
- **Oscar Jun Adan Kubo**, PhD, Research and Development, Japan Blood Products Organization
- **Scott Lute**, Biologist, FDA



Visit [www.pda.org/virus2014](http://www.pda.org/virus2014) for more information.

EXHIBITION: JUNE 9-10 | COURSES: JUNE 12-13



PDA President Richard Johnson spoke about the Association's global objectives

According to him, PIC/S is successfully creating new ways of sharing information and facilitating trading for the pharmaceutical industry with limited resources. PIC/S can act as a bridge for global pharma by leading the international development, implementation and maintenance of harmonised GMP standards

PDA President **Richard Johnson** provided an update on PDA's global activities and discussed highlights from the 2013 PDA/FDA Joint Regulatory Conference. He also presented an

overview of the progress on executing PDA's Strategic Plan.

Finally, **Stephan Rönninger**, PhD, Amgen, and PDA board member, gave the presentation, "Elements of a Modernised Quality System." This presentation provided considerations on how a modernised quality system needs to address innovations. Rönninger used examples of some of these elements with a focus on implementing the lifecycle approach.

Also on Dec. 4, **Stefan Henke**, PhD, IIS Innovative Injections-System GmbH, and **Atsushi Ban**, CBM, both spoke in the "EU New Technology Session." Henke presented "Development of Innovative Injection Systems (IIS) for Parenteral Drug Delivery." This focused on patients' risks and benefits in the technology of needle-free injection Systems. Ban then presented "Aseptic Technologies: Filling Solutions Safer & Easier." The technology he spoke of is based on closed vials which come directly clean, closed and sterile to users, offering an easier aseptic filling process.

In addition, each interest committee of the PDA Japan Chapter held a separate session for both days. All in all, attendees found the event to be a great learning experience and eagerly anticipate the 2014 Annual Meeting of the Japan Chapter. 🇯🇵





**Personnel, Facilities, Equipment, Cleaning**

Betsy Fritschel, J&J, discusses how ICH Q7 addresses aspects of the manufacturing environment.



Stephan Rönninger, PhD, Amgen, takes questions for instructor Betsy Fritschel.



**Closing Plenary/Panel: Future of Implementation**

(l-r) Alicia Mozzachio, CDER, U.S. FDA; Monica Caphart, ORA, U.S. FDA; Jose Melendez, ORA, U.S. FDA; Karen D'Orazio, ORA, U.S. FDA; Carmelo Rosa, CDER, U.S. FDA

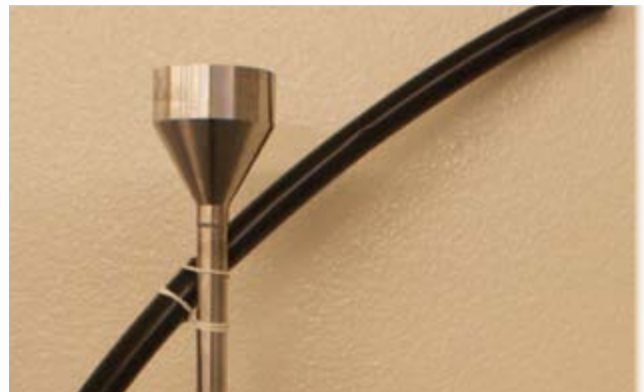


Edwin Rivera-Martinez, Sanofi, takes questions from the audience during the closing plenary.



Attendees were happy to attend the training and learn as much as possible about all 19 aspects of ICH Q7 from inspectors and industry experts.

TRI | PDA Headquarters



PDA's Training and Research Institute recently installed Particle Measuring Systems' FacilityPro facility monitoring system (see Tech Trends story on p. 19).

## UPCOMING LABORATORY AND CLASSROOM TRAINING FOR PHARMACEUTICAL AND BIOPHARMACEUTICAL PROFESSIONALS

### JUNE 2014



#### 2014 Aseptic Processing Training Program

**Space is limited, register now!**

Bethesda, Maryland | [www.pda.org/2014aseptic](http://www.pda.org/2014aseptic)

- Session 3: June 2-6 and June 23-27, 2014
- Session 4: August 18-22 and September 22-26, 2014
- Session 5: October 13-17 and November 3-7, 2014

#### 2014 PDA Pharmaceutical Supply Chain Course Series

June 5-6 | Washington, DC

[www.pda.org/supplychaincourses2014](http://www.pda.org/supplychaincourses2014)

- Developing a Robust Supplier Management Process (June 5)
- Good Distribution and Storage Practices (GDP/GSP) – Securing the Supply Chain – *New Course* (June 6)

#### 2014 PDA Virus & TSE Safety Course Series

June 12-13 | Bethesda, Maryland

[www.pda.org/viruscourses2014](http://www.pda.org/viruscourses2014)

- Virus Contamination in Biomanufacturing: Risk Mitigation, Preparedness and Response (June 12)
- Introduction to Emerging Methods for Virus Detection (June 13)

#### 2014 PDA Aseptic Processing-Sterilization Course Series

June 19-20 | Chicago, Illinois

[www.pda.org/sterilizationcourses2014](http://www.pda.org/sterilizationcourses2014)

- Recommended Practices for Manual Aseptic Processes (June 19)
- Clean Room Design, Contamination Control and Environmental Monitoring for Controlled Environments (June 19)
- Process Simulation Testing for Aseptically Filled Products (June 20)
- Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Validation and Ongoing Control (June 20)

### JULY 2014

#### 2014 DoE Week for Process Design and Process Optimization

July 14-18 | Bethesda, Maryland

[www.pda.org/DoEweek2014](http://www.pda.org/DoEweek2014)

- Pharmaceutical Statistics: DoE Basics for Validation by Design (July 14-15)
- Assay Validation by Design (July 16)
- Pharmaceutical Statistics: Process Optimization by Design (July 17-18)



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



Laboratory Courses

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





Workshop speakers and members of the planning committee pose for a group photo.

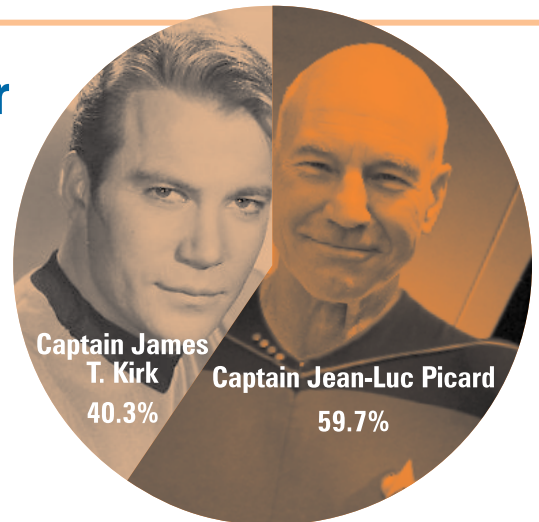


(l-r) Yoshihiro Matsuda, PhD, Japan PMDA; Christine Moore, U.S. FDA; Jean-Louis Robert, National Health Laboratory EP (Luxembourg); Georges France, Novartis



## Going Where No PDA Member Has Gone Before

PDA members made it so! When asked to choose between **Jean-Luc Picard** and **James T. Kirk** as their favorite *Star Trek* captain, close to 60% selected Picard. 🚀





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## Making Yourself Understood: How to Improve Accent Issues Linked to Stress

**Sonja Rauchenberger, The Voice Coach**

**THIS ARTICLE** explains how accent issues and stress are connected. It shows how reducing stress in the preparation phase of a presentation can have a positive effect on speaking clearly and being better understood.

### Doing Business in English

English is the number one business language within international companies and organizations. Most of the highly qualified personnel within high-tech industries (e.g. pharmaceuticals, IT, etc.) who are not native English speakers, usually have a very good level of technical English. They can explain complex concepts without a problem, and even speaking with an accent, they are able to communicate effectively in daily conversations. This has a good effect on their professional performance: when others understand them, they feel more confident and people perceive them as capable and intelligent. A problem arises when—despite their great level of English—they can't make themselves understood. When what they are saying is met with puzzled faces. When no matter how great the content of their presenta-

tion is and no matter how grammatically correct their English is, it is completely lost on their audience.

### Mistakes Linked To Stress and Insecurity

People want to present themselves as competent and convincing, yet public speaking is one of the biggest fears. Being stressed about presenting can have an effect on pronunciation, pace and speech melody. This can turn into a frustrating vicious cycle.

First they are stressed about their presentation, so they forget to breathe and start to talk fast; because they talk so fast they mispronounce important words. As a result their audience does not understand them, which makes the speaker even more stressed out; and even though the person might be completely confident about their subject in other situations, all of a sudden they become self-conscious. The reaction of their audience looking at them questioningly makes them think it has something to do with the content of their presentation or themselves as an expert. This vicious cycle can be frustrating for speaker and listener.

Another situation in which speaking clearly is of great importance is when we

are not able to see our speaking partners. In situations like conference calls or webinars, our listeners pay more attention to the way we speak as they cannot read our faces. As our audience doesn't always respond to our presentations verbally—and we don't see someone nodding their head—not being able to perceive a response to what we are saying can cause a lot of insecurity and stress.

### Incomprehensibility Linked To Interference

We talk about *interference* when the sound of our native language interferes with the sound of the foreign language. Every language has a different speech melody and when we use the speech melody of our native language for talking in English, it becomes difficult to understand us. The intonation of our words is based on how we pronounce our vowels. We cannot add melody to consonants like k, t, p as they do not have a sound. The sound of our vowels is linked to the way we shape our mouths to form them. So, if for example the vowel «a» in our mother tongue is shaped with a slightly more closed mouth and we then use the same vowel when we speak in English,



it will be more difficult to understand us. The vowels in English are in general more open than in Spanish, French or German for example. This is why to native speakers of those languages it might seem exaggerated to open their mouths more in order to pronounce certain words. When we talk fast we don't open our mouths enough to form the vowels correctly, we "swallow" parts of our words. This makes it difficult for others to understand us.

#### What we can do to improve intelligibility

We have now seen that accent issues are not only linked to an inability to replicate certain sounds. Factors that influence the way we speak are:

- being stressed and nervous about public speaking
- being stressed about not seeing our speaking partners or audience
- our native language interfering with the way we pronounce certain words
- not having organized the content of our presentation in a clear and concise manner
- not having rehearsed the delivery of our content

These factors have an influence on the way we speak; being conscious of them can help us find ways to improve our accents and the delivery of our presentations. Here are some actions you can start taking today in order to feel more confident and communicate more clearly:

- **Organize the content of your presentation** in a way that is clear and concise. Use strategies to eliminate unnecessary information and keep the content you are putting on power point slides or posters to an absolute minimum.
- **Break the silence in teleconferences and phone conversations** by asking for verbal confirmation or making breaks to give your speaking partners the chance to react verbally. Make it a habit to ask whether there are any comments or questions

at any point during a presentation where you don't see your audience or speaking partners.

- **Rehearse exactly what you are going to say.** Don't just write the content of your speech on cards, practice delivering it in front of a mirror. You can also practice in front of your spouse or a friend. Ask them whether what you said was understandable.
- **Rehearse exactly what you are going to do.** If you are using more than just one medium, practice turning media on and off during the flow of your speech. If you are just using a power point presentation, practice going through the slides along with what you are saying.
- **Record yourself delivering your presentation or speech.** You can use an audio or video recording device to have an accurate and realistic account of what you look and sound like when you are speaking in front of others. This can be daunting and push you out of your comfort zone, but it is crucial to feeling more confident in front of an audience. If you know exactly what you sound and look like, when you are presenting, you won't be surprised (and potentially stressed) by your own voice coming through the speakers.
- **Listen to or watch your recordings.** Take notes of what you are saying that is difficult to understand, and work on pronouncing it correctly. Listen to the way the words are pronounced on an online dictionary. A good source for this is the website: [www.howjsay.com](http://www.howjsay.com), but most online dictionaries have a little speaker icon next to the word where you can hear the right pronunciation of a word.
- **Make it a habit to work on your pronunciation** on a regular basis. Improving your accent is not something you do once and then it's done. In order to pronounce words differently you need to coordinate your muscles

differently. It's a process that requires regular training. You can do it in the car on your way to work, walking the dog or in the shower. You don't need to make extra time in your busy schedule—you can combine it with other activities.

Ultimately, being more organized about practice, preparation and delivery reduces stress and gives us more time to breathe. We will speak at a slower pace which will have a great effect on the comprehension of our presentation by our audience.

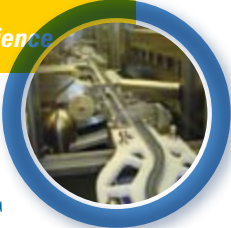
We need to feel confident when having to present our content and we have to know what we can do to prevent situations in which we are not being understood. Companies and organizations should invest in voice training and coaching programs for their employees to make communication easier. This ultimately benefits the company as not only the communication within the office walls is important, but also how we communicate our company's image to the outside world. Employees who are good at effective communication are also shedding a good light on their company or corporation.

#### About the Author

**Sonja Rauchenberger** coaches professionals to make an impact with their voices. She is a vocal coach, business coach and trainer with an academic background in social and cultural anthropology. She lives in Brussels, Belgium. More information on: [www.thevoicecoach.be](http://www.thevoicecoach.be). 🌐

Interested in a career change? Visit the PDA Career Center website at [careers.pda.org](http://careers.pda.org).





# Planned TRs Focus on Packaging Quality

Jahanvi (Janie) Miller, PDA

Do you know what the industry standards are for identifying nonconformities? Are you involved in managing the quality of packaging systems? What do you know about USP's revision of <1207>?

If you answered “no” or “unsure,” fortunately, PDA offers consensus-based technical reports outlining the latest best practices for those involved in managing elements of parenteral packaging.

In 2013, PDA published a revision to once such report, *Technical Report No. 43: Identification and Classification of Nonconformities in Molded and Tubular Glass Containers for Pharmaceutical Manufacturing*, originally published in 2007. This technical report provides guidelines for the identification and classification of nonconformities. This year, we are focusing on elastomeric closures and aluminum seals in an annex to TR-43. The Technical Report Team working on this initiative represents a broad cross section of elastomeric closure and aluminum seal suppliers along with pharmaceutical manufacturing professionals, all of whom are working together to create a well-balanced document.

This technical report will provide the building blocks for developing overall specification for elastomeric closures and aluminum seals by offering consistent and standardized quality criteria that can be used by pharmaceutical companies for the visual inspection of incoming elastomeric closures and aluminum seals and outgoing inspection at the elastomeric closure and aluminum seal supplier.

In other technical report news, PDA is working to provide a global perspective on the challenges faced by industry when utilizing complex packaging systems in an upcoming technical report on container closure integrity. We also are aware of the many revisions to the U.S. Pharmacopeial (USP) General Chapters in this space. Our technical report describes emerging technologies in the field of package integrity testing. The purpose of gathering this information is to supply those involved in pharmaceutical packaging with an advanced technical resource for package integrity testing with particular focus on sterile products. This technical report is meant to compliment the USP <1207> revision and will be available later this year. PDA technical reports are not intended to establish mandatory standards; they are intended to complement existing regulatory requirements.

**[Editor's Note:** Both upcoming technical reports will be spotlighted at the *2014 PDA Packaging Conference*. See [www.pda.org/packaging2014](http://www.pda.org/packaging2014).]



## Journal Preview

### March–April Issue Offers Risk-Based Auditing Commentary

This issue includes commentary from **Susan Vargo**, **Bob Dana**, **Vijaya Rangavajhula** and **Stephan Rönninger** on risk-based auditing for manufacturers. In addition, **Cliff Campbell** looks at the technology applications of the U.S. FDA's 2011 process validation guidance.

#### Editorial

Govind Rao, “There’s Gold in Them Thar Hills”

#### Guest Editorial

Craig Baker, “Understanding the Psychology of Learning in Order To Overcome Noncompliance”

#### Commentary

Susan Vargo, et al., “A Risk-Based Auditing Process for Pharmaceutical Manufacturers”

#### Review

Emily Craven, et al., “Gamma Sterilization of Pharmaceuticals—A Review of the Irradiation of Excipients, Active Pharmaceutical Ingredients, and Final Drug Product Formulations”

#### Research

Ruchi Tiwari, Ankita Gupta, Meenakshi Joshi, and Gaurav Tiwari, “Bilayer Tablet Formulation of Metformin HCl and Acarbose: A Novel Approach To Control Diabetes”

Yuh-Fun Maa, et al., “Filling of High-Concentration Monoclonal Antibody Formulations into Pre-Filled Syringes: Filling Parameter Investigation and Optimization”

#### Technology/Application

Yordan Kostov, et al., “Fluorescence-Based Method and a Device for Rapid Detection of Microbial Contamination”

T. Eaton, C. Wardle, W. Whyte, “Use of a Real-Time Microbial Air Sampler for Operational Cleanroom Monitoring”

Cliff Campbell, “FDA 2011 Process Validation Guidance: Lifecycle Compliance Model”

## Tech Trends

### PDA TRI Installs Facility Monitoring System

James Wamsley, PDA

On Feb. 21, PDA's Training and Research Institute (PDA TRI), in cooperation with Particle Measuring Systems (PMS), completed the installation of a new, state-of-the-art facility monitoring system. PMS generously agreed to provide us with an indefinite loan of its FacilityPro facility monitoring system for use during courses and other activities, such as research.

The equipment consists of a modular rack which houses all the hardware required for an entire facility monitoring system: vacuum pump control, vacuum manifolds and the data cabinet. In addition to the rack, eight fixed particle counters, three active viable air samplers and two rapid microbial sample locations were installed. TRI may now have one of the most highly monitored aseptic processing suites, with five continuous particle counting areas, five active viable air locations and two rapid microbial sample points in its Grade A zone surrounding its filling machine. There are also three more particle counting samplers and fixed active viable samplers in the B areas surrounding the A area.

Facility monitoring systems have been in use for a while, and all-in-one systems like this one are becoming more popular.

This new facility monitoring system will benefit PDA TRI in a number of ways. The new system allows us easier and more precise control over how and when we sample because the entire system, including each sample location, is computer controlled. We have more data available to create reports and analyze the environment at different times. We are also eager to utilize the system during research performed in our cleanroom. Having more sample locations, better control over each and software capable of generating better and more usable data than before will provide us with a better picture of how our environment reacts to changes and activity.

PDA's students will benefit in a number of ways as well. They will have better understanding of how cleanrooms behave while at rest and during operation. Because of the new rapid microbial monitors that will be installed, they will also be able to see a direct and real-time correlation among their actions, particle spikes, and potential viable contamination.

Through the generosity of PMS and other companies over the past 15 years, TRI has been able to provide a high level of training. PDA is working to modernize our facility with more upgrades in the near future. If you would like information on how you can support us, please contact **James Wamsley** at [wamsley@pda.org](mailto:wamsley@pda.org) or 301-656-5900, ext. 137.

**[Editor's Note:** See p. 13 for photos of TRI's new facility monitoring equipment. Several articles on these systems have been published in the *PDA Journal of Pharmaceutical Science and Technology* ([journal.pda.org](http://journal.pda.org)) over the last decade.]

## Task Force Corner

### TR-63 Offers a "Stepping Stone" for Industry

Jahanvi (Janie) Miller, PDA

Extemporaneous preparations require specific quality systems and oversight, but why?

Extemporaneous preparation (EP), as defined in *PDA Technical Report No. 63: Quality Requirements for the Extemporaneous Preparation of Clinical Trial Materials*, is "a type of compounding whereby a drug or combination of drugs and/or excipients is prepared under the supervision of a pharmacist to create a customized medication dosage form in accordance with a clinical protocol." These processes are utilized to prepare a variety of formulations for a variety of dosage forms in nonconventional preparation sites and nonmanufacturing environments. The U.S. Pharmacopeial Convention (USP) also realized the need for additional guidance on compounding and issued updates to General Chapters <795> *Pharmaceutical Compounding—Nonsterile Preparations* and <797> *Pharmaceutical Compounding—Sterile Preparations*.

TR-63 describes the development of quality systems to support EP without compromise to the clinical trial materials, thus ensuring product quality. The subject matter experts that developed this technical report provided valuable recommendations to maintain quality requirements while preparing small-scale clinical trial materials (CTMs) using EP for in-clinic dosing. PDA also developed *Technical Report No. 62: Recommended Practices for Manual Aseptic Processes*, which highlights techniques for nontraditional preparation of drug products. Our membership also understands the urgency of developing best practices for compounding sites, and as a response to this need, **Mark Leney**, PhD, MassBiologics, a TR-63 author, presented an overview of the report at a PDA New England Chapter meeting in March.

As members of the U.S. Congress work together with health authorities and industry, TR-63 can be used to promote best practices along with the new chapters being developed by the USP. One of the new USP chapters will cover unconventional preparation sites/nonmanufacturing environments, as TR-63 did (<800> *Hazardous Drugs—Handling in Healthcare Settings*). The second provides considerations for investigational studies (informational chapter <1168> *Compounding for Investigational Studies*). Given the recent fungal meningitis outbreak, these technical reports are a critical stepping stone as updates are made to existing guidance and new guidance is being developed.



## Protection of Protein-Based Drug Products is Vital

Program Planning Committee Co-Chairs Kurt Brorson, PhD, U.S. FDA, and Hannelore Willkommen, PhD, RBS Consulting

Virus and transmissible spongiform encephalopathy (TSE)

safety of protein-based medicinal products is a major area of concern that has serious public health implications. We learn each year about the risks of contamination from these agents. It is also apparent that the use of current methodologies for virus detection might not always be sufficient to avoid viral contamination cases. This is concerning as animal-derived materials are used for production of some medicinal products for human use. Relating to Creutzfeldt–Jakob disease (CJD) agents, it has recently been discovered that not only variant CJD agents but also sporadic CJD agents might be infectious in animal models.

Currently no screening methods are available for testing blood donations for vCJD agents. For this reason, the development of reference materials is crucial.

Keeping these risks in mind, one focus of the *2014 PDA/FDA Virus & TSE Safety Conference* concerns improving detection and reducing contamination risks. This broad area is the focus of four sessions of the virus safety portion of the conference: emerging viruses and test methods; observed contamination case studies and conclusions drawn from them; the risk associated with new cell substrates, especially human cells; and finally, risks associated with animal-derived reagents used during expression cell coning.

The conference will also cover virus clearance data demonstrating the effectiveness of purification unit operations implemented into manufacturing and surprising results of small-scale virus clearance studies as well as examples illustrating the mechanism of action of virus removal/inactivation and how to avoid technological gaps will be provided.

The last half day of the conference will focus on TSEs and the risk of contaminating medicinal products. An update of bovine spongiform encephalopathy (BSE) prevalence worldwide will be presented, considering not only classical BSE but also atypical BSE cases or TSEs in other species. 🍷

Immediately following the *2014 PDA/FDA Virus & TSE Safety Conference*, the PDA Training and Research Institute will be hosting two courses to complement your learning. On June 12, TRI will offer “Virus Contamination in Biomanufacturing: Risk Mitigation, Preparedness and Response,” and on June 13, TRI will offer “Introduction to Emerging Methods for Virus Detection.” Please visit [www.pda.org/viruscourses](http://www.pda.org/viruscourses) for more information.



29-30 April 2014  
Brussels | Belgium

The Parenteral Drug Association presents...

2014 PDA Europe Workshop

# Vaccines & Beyond

*Applying QbD Principles to complex biologics based on the A-Vax Model*

### Learning Objectives:

At the completion of this program, participants will be able to:

- Participate in discussion of how QbD approaches can / should be applied to enhance the development of robust vaccine manufacturing processes
  - Critical process parameters
- Examine how the rationale for vaccine development may be made more transparent in regulatory submissions
  - Critical product parameters including biological assays
- Explore tools and frameworks to enable ICH Q8, Q9, Q11 implementation strategies
- Gain understanding in how the benefits of better process and product understanding may enhance efficiency of the vaccine development process
- Current regulatory discussions in Europe
  - Data & documents in the submission dossier



WORKSHOP 29-30 April | EXHIBITION 29-30 April

[europe.pda.org/Vaccines2014](http://europe.pda.org/Vaccines2014)



# Keeping an Eye on Pharmaceutical Packaging's Future

Program Planning Committee Co-chair Diane Paskiet, West

**2014 PDA Packaging Conference •  
Washington, D.C. • May 20–23 •  
[www.pda.org/packaging2014](http://www.pda.org/packaging2014)**

Container closure systems are a significant part of delivering safe medicines to patients. There is a broad range of concerns associated with protecting the finished pharmaceutical product until it reaches the patient. The drug or biologic must be compatible with the packaging components and not interact with the materials of construction, affecting safety and/or efficacy of the final product. The safety of packaging components needs to be linked to the material chemistry and potential for leachables. Product lifecycle

On May 22, PDA'S Training and Research Institute will offer the course, "Implementing Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations: Case Studies in the Packaging and Labeling of Drug Products," and on May 23 will offer "Container Closure Integrity—Regulations, Theory, Test methods, Application." Please visit [www.pda.org/packagingcourses2014](http://www.pda.org/packagingcourses2014) for more information.

testing should include comprehensive assessments for leak detection to prove packaging systems will protect final product relative to intended use.

All in all, the state of pharmaceutical packaging is evolving as quality expectations, complex dosage forms and patient outcomes have become powerful driving forces of change. Recent legislation has given the U.S. FDA greater authority over drug manufacturing supply chain. Do you need better insight on how to protect finished pharmaceutical products? Demonstrating that packaging systems are suitable throughout storage and distribution requires evidence of appropriate data and justifications for control. Does your strategy include comprehensive risk assessments to ensure packaging systems will be safe and protect the final drug product throughout the entire lifecycle?

We have taken a holistic look at current and future expectations for packaging pharmaceutical products. The two-day *2014 PDA Packaging Conference* will provide a forum to discuss these challenges with featured presentations from FDA, academics, and pharmaceutical and packaging professionals. 🌐

Last Chance to Save on Registration is April 23, 2014



The Parenteral Drug Association presents the...

## 2014 PDA/FDA Pharmaceutical Supply Chain Conference

with Educational Support from Rx-360 

*Expanding Your Quality System (Q10) for a Robust, Reliable and Secure Supply Chain*

**June 3-5, 2014 | JW MARRIOTT WASHINGTON DC | WASHINGTON, DC**

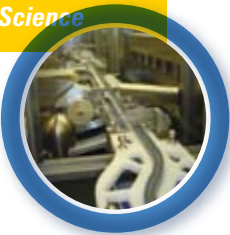
Recent experiences in the market indicate there is a need for improvement in supply chain practices, prompting a surge in activity toward enhanced globally harmonized supply chain controls. At the *2014 PDA/FDA Pharmaceutical Supply Chain Conference* regulators and industry representatives from firms that are thought leaders in prevention of illicit acts (such as counterfeiting, diversion, and economic adulteration) will share their perspectives and solutions to promote supply chain security and integrity. We invite you to engage with regulators, as they speak about their expectations and emerging regulations, and with industry leaders, as they share solutions that are being developed and implemented to work hand in hand with new regulations to secure the supply chain. Through a series of plenary sessions and breakout sessions, the program will provide participants the opportunity to hear from notable presenters, such as:

- **Christian Hughes**, Assistant Director, Pharmaceuticals, Health & Chemicals CEE, *US Customs and Border Protection*
- **Kevin Nepveux**, Vice President, Global Technology Services, *Pfizer, Inc.*
- **Martin VanTrieste**, Senior Vice President, Quality, *Amgen, Inc.*
- **Steven Wolfgang**, PhD, Acting Associate Director, Risk Science, Intelligence and Prioritization, CDER, *FDA*

As an added bonus, all full conference attendees will be granted full access to the Rx-360 5th Year Anniversary Conference scheduled for June 5.

For more information and to view the latest agenda, visit [www.pda.org/supplychain2014](http://www.pda.org/supplychain2014).

EXHIBITION: JUNE 3-4 | COURSES: JUNE 5-6



# Parenteral Packaging Concerns for Biologics

Graham Reynolds and Mike Schaefers, PhD, West

Bringing a new biological drug to market requires a huge financial commitment and entails risks in every stage of the development process. The risks associated with selecting the appropriate component for packaging the drug may not be at the forefront of early stage thinking, but are real nonetheless and can have a profound impact on the drug product. Packaging components must meet functional requirements to ensure safety at the point of administration and protect the purity of the packaged drug product for its shelf-life, usually a minimum of two years.

Growth in biologics has driven the need for novel primary containment materials and unique delivery systems, and the increase in biosimilars has served to heighten the requirement for packaging and delivery innovation. A drug is effective, however, only if it can be delivered to the patient in a way that helps ensure compliance with the prescribed regimen. By focusing on the science, engineering and regulation of primary packaging for injectable biotech drugs early in the drug development process, pharmaceutical companies can not only bring an effective and safe drug product to market, but also differentiate that product with unique packaging and delivery that may help aid patient compliance.

## Start with the End in Mind

The process for selecting primary containment materials compatible with a pharmaceutical product and its intended use is an important aspect of safe and effective delivery. In today's regulatory environment, assessing and managing risk early in the development process is critical to successful development and commercialization of drug products. The physical and chemical nature of the materials used for primary containment, however, can exhibit behavior that has the potential to compromise the drug product, which may result in harm to the patient. Many biologic drug prod-

ucts have known sensitivities, including negative reactions to metal ions such as zinc. There may be additional issues that cannot be predicted based on the protein or the molecule.

Even though glass has a long history of use with a variety of pharmaceutical products, many drug products have been recalled in the past few years due to glass-related issues such as delamination or breakage. It can be difficult to determine the ultimate cause of delamination, but early testing and informed selection of materials may help mitigate risk. Additional considerations such as permeation, leaching, sorption, chemical interactions, dimensional consistency, alteration of the physical properties and ensuring functional characteristics of both drug and packaging during processing, storage and distribution is critical to success.

## Component Selection: Quality Questions

Several considerations can be made during the development process that will help ensure a quick route to market. First, biopharmaceutical manufacturers should consider the needs of the drug product itself. Is the product sensitive to glass? Many products may have characteristics that would require a polymer containment system. Additionally, dose size may affect the packaging decision. Larger or more viscous doses should be administered over a longer period of time to aid in patient comfort and adherence. For a large volume dose, typical delivery systems may not be capable of providing a single dose option. Instead, a multidose primary container that can be used within a pen or other delivery system may be required. Finally, how will the product be stored and shipped? Will glass delamination or breakage—particularly for drugs stored at low temperatures—be a risk?

Understanding these criteria at the beginning of the development cycle requires an integrated approach that takes

not only the needs of the drug product, but also the needs of the patient or caregiver and the final delivery system, into account. High-quality components manufactured based on the identification and control of critical process parameters, rather than a rigid, static operation that is more susceptible to multiple manufacturing changes, will create a more consistent product.

Filling issues should also be considered. Guidance and experience from a filling perspective can be invaluable when it comes to proper handling of components, particularly if the delivery method includes a prefilled syringe, where vacuum placement can be an issue. Modern plunger placement techniques can help avoid issues such as wrinkling and deformation of the plungers.

The right packaging may help engender patient loyalty, particularly in the biosimilar markets where method of delivery may impact a patient's choice of product. By asking the right questions and making the best selections early in the development process, packaging and pharmaceutical manufacturing can mitigate risk and deliver a high-quality product to patients.

## About the Authors

**Graham Reynolds** leads initiatives to market novel delivery systems and develop strategies for future growth, including the acquisition and development of new technologies.



**Mike Schaefers, PhD**, heads the Scientific & Technical Customer Service Group for West's European and Asian-Pacific market.



**[Editor's Note:** West Pharmaceuticals will be exhibiting at Tabletop #11 at the 2014 PDA Packaging Conference.]

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# USP Looks at Future of Microbiology With New Standards

Radhakrishna Tirumalai, PhD, USP

From a microbiological perspective, pharmaceutical products fall into two categories, nonsterile and sterile. For either category, manufacturers must eliminate or minimize potential health risks to patients related to microorganisms and the toxins they produce, while also maintaining product quality. Many contributing factors may affect the quality of a medicine or its ingredients, but microbial bioburden control and proper sterilization methods are critical considerations for the manufacturer throughout the product's lifecycle.

The U.S. Pharmacopeial Convention (USP) is a global health organization that develops standards for the identity, strength, quality and purity of medicines, foods and dietary supplements and their ingredients, which are published in the *United States Pharmacopeia* and *National Formulary (USP–NF)*. USP has no role in enforcement of these, or other provisions that recognize *USP–NF* standards, which is the responsibility of the U.S. FDA and other government authorities in the United States and elsewhere. Standards for drugs or drug ingredients are expressed in *USP–NF* monographs, general chapters and *General Notices*. Monographs are developed for single articles (e.g., drug substance, drug product, excipient, etc.) and general chapters can be applied across multiple articles. General chapters numbered above <1000> in *USP–NF* typically are informational and contain no mandatory requirements, unless specifically referenced in a monograph, *General Notices* or a general chapter numbered below <1000>. General chapters designated as below <1000> contain tests and procedures that are intended to apply to items recognized in *USP* or *NF* when called out in a monograph, *General Notices* or other applicable general chapters. The FDA may also require manufacturers to conform to USP standards that may not otherwise apply by the terms of *USP–NF*, if determined by the Agency to be within the scope of cGMPs. *USP–NF* is available for use globally. Besides this role, USP's standards are also recognized and used around the world.

Through its Microbiology Expert Committee (Microbiology EC), USP develops and revises general chapters for the advancement of pharmaceutical microbiology. The Microbiology EC has an established work plan for its five-year operating cycle. The work plan is intended to help meet USP's standards-setting goals. Major initiatives in the current USP 2010–2015 cycle regarding microbiological contamination include sterilization processes and sterility assurance. These key activities are discussed below.

## Sterility Assurance and Sterilization

While all products purported to be sterile have to meet the requirements of General Chapter <71> *Sterility Tests*, sterility assurance can only be achieved by the use of robust sterilization processes. USP's current General Chapter <1211> *Sterilization and Sterility Assurance of Compendial Articles* addresses principles of sterility assurance and provides information on various sterilization processes. In response to stakeholder feed-

### Article at a Glance

- New <1229> series addresses individual sterilization processes
- Depyrogenation now part of the <1228> series of chapters
- USP seeks new microbial test methods due to current limitations



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back that greater detail is needed to address specific sterilization methods, USP initiated a two-stage revision approach in 2009. Phase 1 focused on updating content with current information. The general chapter became official in *USP 33–NF 28* (2010). Phase 2 involves a significant rewrite of the general chapter. The initial focus of this second phase is on sterilization, to be followed by sterility assurance. In determining how to update the sterilization material in the general chapter (which originated in the late 1980s), the Microbiology EC decided to split the content of the general chapter into two major parts—sterility assurance and sterilization processes. Information related to sterilization processes was removed from the existing General Chapter <1211> and developed separately as the <1229.x> series. In a future revision, General Chapter <1211> will be renamed *Sterility Assurance of Compendial Articles*. The focus of the revised General Chapter <1211> will be limited to sterility assurance and will include aseptic processing, environmental monitoring, as well as a brief review of sterility testing and parametric release.

The new series of general chapters (the “<1229.x> series”) is dedicated to individual sterilization processes, with an overarching general chapter (<1229>), covering the overall concept of sterilization. In the development and organization of these general chapters, the Expert Committee has decided to develop a parallel series of chapters on depyrogenation separate from sterilization, in alignment with current industry practices. Depyrogenation processes will be addressed in a manner similar to those for sterilization processes. Moist heat sterilization will be divided into hard goods (direct contact approach) and aqueous liquids. Gas and vapor sterilization will be addressed in separate general chapters.

To date, the Microbiology EC has planned twelve general chapters, which will provide valuable information and guidance on distinct methods of sterilization (listed below). Currently, nine of these (shown in bold in the list below) have already been approved for inclusion in *USP–NF*.

## <1229> ***Sterilization of Compendial Articles***

### <1229.1> ***Steam Sterilization by Direct Contact***

### <1229.2> ***Moist Heat Sterilization of Aqueous Liquids***

### <1229.3> ***Monitoring of Bioburden***

### <1229.4> ***Sterilizing Filtration of Liquids***

### <1229.5> ***Biological Indicators for Sterilization***

### <1229.6> ***Liquid Phase Sterilization***

### <1229.7> ***Gaseous Sterilization***

### <1229.8> ***Dry Heat Sterilization***

### <1229.9> ***Physicochemical Integrators and Indicators for Sterilization***

### <1229.10> ***Radiation Sterilization***

### <1229.11> ***Vapor Phase Sterilization***

The other general chapters will be proposed for public comment in 2014 in *Pharmacopeial Forum* ([tinyurl.com/mskd-na8](http://tinyurl.com/mskd-na8))—USP’s free access, online tool for public comment on USP’s quality standards and monographs.

Some of the new official and proposed general chapters are detailed below.

#### Steam Sterilization

Although many steam sterilization approaches related to hard goods are relevant to aqueous liquids, <1229.1> *Steam Sterilization by Direct Contact* and <1229.2> *Moist Heat Sterilization of Aqueous Liquids* have been written separately for greater clarity and for distinction between the two. For example, when using the direct contact approach, overkill is the method of choice because overprocessing of parts or hard goods usually is not a concern. On the other hand, when developing sterilization pro-

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# 2014 PDA

# UPCOMING EVENTS



## APRIL EVENTS

**21-25**  
**2014 PDA Biotechnology Week**  
Bethesda, Maryland  
[www.pda.org/biotechweek2014](http://www.pda.org/biotechweek2014)

**28-30**  
**Management of Aseptic Processing**  
Bethesda, Maryland  
[www.pda.org/apmanagement](http://www.pda.org/apmanagement)

**29-30**  
**Vaccines & Beyond Workshop**  
Brussels, Belgium  
<https://europe.pda.org/Vaccines2014>



## MAY EVENTS

**19-20**  
**2014 PDA Knowledge Management Workshop – Enabler for ICH Q8-Q11, WRM and Continued Process Verification**  
Bethesda, Maryland  
[www.pda.org/km2014](http://www.pda.org/km2014)

**20-21**  
**2014 PDA Packaging Conference**  
Washington, DC  
[www.pda.org/packaging2014](http://www.pda.org/packaging2014)

**21-22**  
**2014 PDA Knowledge Management Workshop – Enabler for ICH Q8-Q11, WRM and Continued Process Verification Course Series**  
Bethesda, Maryland  
[www.pda.org/KMcourses2014](http://www.pda.org/KMcourses2014)

**22-23**  
**2014 PDA Packaging Course Series**  
Washington, DC  
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# Save these dates!

## JUNE EVENTS

**2-27**

**2014 Aseptic Processing Training Program – Session 3**

Bethesda, Maryland  
[www.pda.org/2014aseptic3](http://www.pda.org/2014aseptic3)

**3-5**

**2014 PDA/FDA Pharmaceutical Supply Chain Conference**

Washington, DC  
[www.pda.org/supplychain2014](http://www.pda.org/supplychain2014)

**5-6**

**2014 PDA/FDA Pharmaceutical Supply Chain Course Series**

Washington, DC  
[www.pda.org/supplychaincourses2014](http://www.pda.org/supplychaincourses2014)

**9-11**

**2014 PDA/FDA Virus & TSE Safety Conference**

Bethesda, Maryland  
[www.pda.org/virus2014](http://www.pda.org/virus2014)

**12-13**

**2014 PDA/FDA Virus & TSE Safety Course Series**

Bethesda, Maryland  
[www.pda.org/viruscourses2014](http://www.pda.org/viruscourses2014)

**17-18**

**2014 PDA Aseptic Processing-Sterilization Conference**

Chicago, Illinois  
[www.pda.org/aseptic2014](http://www.pda.org/aseptic2014)

**19-20**

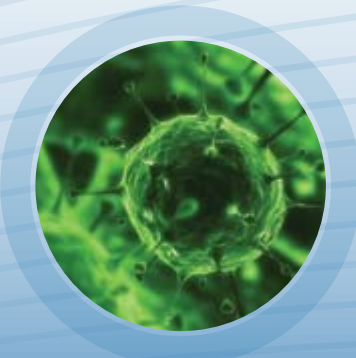
**2014 PDA Aseptic Processing-Sterilization Course Series**

Chicago, Illinois  
[www.pda.org/sterilizationcourses2014](http://www.pda.org/sterilizationcourses2014)

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## Vapor phase processes require careful process control to achieve reproducible efficacy

cesses for liquid-filled containers, consideration of the overkill method will depend on the impact of the cycle on the fluids and container attributes. If the impact is too high, then alternatives to overkill cycles may be developed.

### Sterilizing Filtration of Liquids

General Chapter <1229.4> *Sterilizing Filtration of Liquids* describes how filtration is a retentive, nondestructive process relative to the microbial cell. Due to the methodology's nondestructive nature, critical factors that can impact retention of microorganisms include the conditions of filtration, characteristics of the filter, and bioburden. A good understanding of these parameters will enhance the potential for successful retention.

### Radiation Sterilization

General Chapter <1229.10> *Radiation Sterilization* is not meant to repeat what is already described in the ANSI/AAMI/ISO 11137 standards. Due to the importance of determining radiation dose, however, the general chapter will briefly discuss dose setting per ANSI/AAMI/ISO standards. This is the only commonly accepted sterilization method that does not require biological indicators for validation due to the accuracy of dose measurement and its extensive correlation to microbial destruction. It is important to understand the bioload or bioburden of material being irradiated.

### Vapor Phase Sterilization

General Chapter <1229.11> *Vapor Phase Sterilization* focuses on the use of vaporized chemical agents for sterilization and decontamination, which is common practice, especially in isolators used in manufacturing. Currently, the technology of vapor sterilization mandates that two phases can potentially occur simultaneously—a gas phase and a liquid phase. Kill rates for each phase appear to be quite different. Vapor phase processes require careful process control to achieve reproducible efficacy.

### Monitoring of Bioburden

General Chapter <1229.3> *Bioburden Monitoring* discusses bioburden control and monitoring as they relate to sterilization in particular. Since an understanding of bioburden is crucial to appropriate sterilization design, this chapter will enhance the understanding of key elements in detection and identification of microorganisms with regard to survival, population and related patient health risks.

### Depyrogenation

Parenteral products not only need to be sterile, but also free from harmful levels of pyrogens, or fever causing agents. For the purposes of this chapter series, “depyrogenation” refers to the destruction or removal of bacterial endotoxin, the most prevalent pyrogen. Depyrogenation may be accomplished by a variety of methods and processes which may be combined to assure endotoxin reduction to a safe level. The intent and processes for depyrogenation are very different from those of sterilization. Thus, for greater clarity of understanding the methods intended for depyrogenation have been separated into the <1228.x> series of general chapters. Commonly used depyrogenation pro-

cesses and associated control measures will be the subject of this chapter series:

<1228> *Depyrogenation*

<1228.1> *Depyrogenation by Dry Heat*

<1228.2> *Depyrogenation by Chemical Inactivation*

<1228.3> *Depyrogenation by Filtration*

<1228.4> *Depyrogenation by Physical Means*

<1228.5> *Endotoxin Indicators for Use in Depyrogenation*

<1228.6> *Endotoxin Control and Monitoring*

<1228.7> *Other Endotoxin Reduction Methods*

### **Monitoring of Aseptic Environments**

Another major consideration for manufacturers with regard to microbial presence is contamination control. Keeping pace with changes in regulations and technologies, General Chapter <1116> *Microbiological Control and Monitoring of Aseptic Processing Environments* has recently undergone a major revision and became official in 2012. By changing the focus from evaluation of cleanrooms to key guidelines that support aseptic pharmaceutical processing environments, revised General Chapter <1116> stresses prevention of contamination rather than merely attempting to measure contamination using methods unlikely to correlate with process outcome.

Recommendations in the general chapter as well as monitoring parameters given for microbiological evaluation should be applied only to cleanrooms, restricted-access barrier systems (RABS) and isolators used for aseptic processing. Changes to <1116> include clarification of limitations of counting methods used in microbiological evaluation, including sampling, recovery, data tracking and trend analysis. The use of microbial recovery frequency provides a more practical and useful concept for indicating that an environment is in a state of “control.”

The general chapter provides a key description of microbiological incubation conditions relative to intended recovery.

### **Bioburden Control of Nonsterile Drugs**

There is very little information available regarding bioburden control for nonsterile pharmaceutical products, in the pharmacopoeias or regulatory guidance documents. Clearly, the quality of raw materials, the microbiological cleanliness of processing equipment, and proper facility design are just some of the factors that can contribute to the bioburden of a product. General Chapter <1115> *Bioburden Control of Nonsterile Drug Substances and Products* outlines a risk-based approach to control potential contamination in nonsterile product manufacturing. It is important to understand that the manufacture and management of microbiological content of nonsterile products are distinctly different from what is required for sterile products. Therefore,

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Validation of Neutralization Methods	•	•	•	•	
Antimicrobial Effectiveness Test					•

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the contamination recovery rates defined in <1116> *Microbiological Control and Monitoring of Aseptic Processing Environments* are not intended for nonsterile environments. By looking at specific factors that may affect product quality and patient safety and considering the best approaches to dealing with them, manufacturers can identify the risks associated with a product and apply appropriate methods for bioburden control.

### Replacing Conventional Microbial Tests

Conventional microbiology tests currently found in pharmacopoeias, such as sterility tests, rely on the demonstration of microbial growth. Limitations of these tests include their low sensitivity as well as their time- and labor-intensive nature. Certain cytotераpy or regenerative medicine products and radiopharmaceuticals are administered to patients prior to results from sterility testing. A more rapid result test would be very beneficial in those cases. USP is seeking to identify new referee tests or proce-

dures (used by FDA or third parties to assess regulatory compliance) based on modern methods that can detect and enumerate microorganisms in a more rapid and sensitive manner. Objectives for such test method development include broad application, multisourced and nonpatented instrumentation and supplies and the method applicability in any laboratory setting.

Protocols are being developed to conduct proof-of-concept studies to demonstrate the reliability and suitability of the proposed methods. Based on these studies, General Chapter <71.1> *Rapid Sterility Tests* will be developed and published in *Pharmacopoeial Forum* for public comments.

USP also is currently in the process of revising General Chapter <1223> *Validation of Alternative Microbiological Methods*, which provides guidelines for validating alternative microbiological methods, including those based on modern technologies.

On Sept. 8–9, USP will host a workshop titled, *Alternative Microbiological Methods—A Workshop on Current Status and Future Directions of Compendial Standards*, which will take place at USP's headquarters in Rockville, Md. ([tinyurl.com/mtuoedo](http://tinyurl.com/mtuoedo)).

### Conclusion

USP is committed to continuous revision and improvement of its standards and values the input of users in the field. Indeed, this input is critical to the success, not only of USP, but of the industry as a whole. Stakeholder feedback helps to ensure that USP's standards are sufficiently comprehensive in application or scope and reflect current and emerging practices in industry.

### About the Author

**Radhakrishna Tirumalai**, PhD, is currently a Principal Scientific Liaison in the Global Science and Standards Division. 🇮🇳



# Industry, Regulators Meet to Drive QbD Implementation

Ursula Busse, PhD, Novartis; Stephan Rönninger, PhD, Amgen; Georg Rössling, PhD, PDA Europe

Since the first QbD workshop held in 2009, industry and regulators have continued working together to advance implementation of QbD principles. In January, PDA Europe organized a workshop to address continued progress in this area at the EMA's London headquarters. This workshop was co-chaired by **Jean-Louis Robert**, National Health Laboratory EP (Luxembourg) and Chair of the EMA Quality Working Party, and **Georges France**, Novartis, for the European Federation of Pharmaceutical Industries and Associations (EFPIA).

## Enacting QbD Remains a Challenge

In his opening remarks, Professor **Guido Rasi**, MD, Head of EMA, expressed the Agency's support for the implementation of ICH Q8–Q11. Adopting QbD and risk management principles should lead to fewer manufacturing and quality problems, benefit regulators by simplifying their work, and ensure reliable supply of high-quality medicines to patients.

Meeting co-chairs then introduced workshop goals, starting with a short historical overview on how ICH Q8–Q11 concepts emerged. These guidelines were prompted by the need to move away from traditional approaches towards harmonized pharmaceutical development and integrated science and risk management practices throughout the lifecycle of a pharmaceutical product (1). The initial intent of QbD

was to spark innovation in the pharmaceutical industry, facilitate continual improvement and develop a better product and process understanding.

These efforts have since led to an increase in science-based market applications, more emphasis on control strategy and more robust manufacturing processes. ICH Q8–Q11 concepts have opened the door to opportunities such as real-time release and increased manufacturing flexibility. Although some benefits have been achieved through the application of QbD and risk management principles, however, challenges related to submissions and global alignment still need to be resolved. There is a need to clarify a number of topics, including content of submissions and regulatory commitments.

## Challenges Highlighted in Six Case Studies

To further discussion on implementation challenges and address open questions, the workshop featured six case studies of recent QbD submissions, jointly prepared and presented by the applicant companies (AstraZeneca, GSK, Novartis, Novo Nordisk and Pfizer) and assessors/inspectors involved in the evaluation. Case studies focused on key learnings in different areas: risk assessment, design space, criticality assessment, design of experiment (DoE), real-time release testing, QbD in manufacturing, lifecycle management, control strategy, model verification and

scalability. Participants also heard from invited U.S. and Japanese regulators about how they handle QbD submissions, and the challenges they face. Ample time for discussion allowed participants to share their views and propose solutions to open questions. Several questions have already been addressed by Q&A (2) and Points to Consider (3) documents, and by the ICH Q-IWG Training Materials (4) to which the reader is referred.

## Risk Assessment

Risk assessment as part of a risk management approach to quality generates huge amounts of data, which are difficult to summarize and prone to misinterpretation. In addition, companies experience difficulties in communicating in the dossier how quality risk management drove the development work. To ease dossier review, applicants shall explain risk assessment tools, use tables to summarize results, reference to the respective parts in the dossier for details and add ample explanations and justifications (5). The use of ICH terminology is strongly recommended. ICH classifies risks into two categories, "critical" and "noncritical." Companies can use a 3-tier classification system in development, to better adapt to the "continuum of criticality," but should not translate this system into the dossier since the current regulatory framework does not allow for it. ➤



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## Model Verification and Scalability

Time was devoted to discuss open questions related to the development, qualification, description and use of models. High impact models, which are sole indicators for release, need to be described in detail in the dossier. Information on model development, qualification and testing needs to be provided.

Several case studies featured models using near-infrared spectrometry (NIR), which involve a high degree of automation. For these models, it is important to qualify interfaces between probes and data storage systems, and to train operators. Model validity over time should be verified periodically. Model changes resulting in a better or unchanged fit do not require health authority notification.

## Design Space and Lifecycle Management

Case studies addressed the development of a design space, its verification, presentation in submissions, and the link to operational flexibility during lifecycle management. It was recommended that companies request a design space only when there is a specific intent, for example, to increase operational flexibility or gain additional knowledge. In submissions, companies should clearly state whether they claim a design space or not. Assessors need a comprehensive development “story” to understand the rationale for design space.

The impact of scale on the design space was also discussed. The predictability of small-scale models needs to be demonstrated. Regulators expect small-scale studies to address worst case conditions but it is acceptable to operate at normal ranges at commercial scale. Management of postapproval changes needs to be described in a design space verification protocol submitted as part of the application. This protocol describes the steps that will be taken to complete design space verification at commercial scale, specifically for scale dependent parameters whose impact on the CQAs has not been verified at time of submission (6).

Part of the discussions addressed the current EU regulatory framework for postapproval changes and operational flexibility. Current EU legal requirements require cer-

tain changes within the design space (for example, equipment or scale) to be filed as variations. Postapproval change management protocols should be used to ease the regulatory burden. The EU Variations Regulations do not require filing of changes to noncritical process parameters. If these parameters have been registered as part of a design space, however, changes have to be filed. It was advised to use “Qualified Person (QP) regulatory discretion” when isolated minor deviations occur for parameters in the design space. Some details from a 2009 reflection paper by EMA (7) on how to deal with minor deviations will be incorporated into the update of EU GMP Annex 16 “Certification by a Qualified Person and Batch Release.”

Changes within the design space should be supported by procedures in an adequate quality management system (QMS) that does not need to be mentioned in the dossier. How the QMS will support changes might be explained in postapproval change management protocols. Regulators need confidence that changes are evaluated and implemented adequately, and will check the related QMS during inspections.

## Communication is Key

Throughout the workshop, the importance of clear and frequent communication between companies and competent authorities was mentioned. When preparing for a QbD submission, companies are advised to consult early and nurture dialogue with relevant agencies.

In the dossier, information needs to be presented in a clear, logical way. The use of summary tables, some of which were shown in presented case studies, is recommended. Assessors would like to see a high-level summary, which could be part of the Quality Overall Summary (Module 2), in addition to detailed information displayed in the different relevant parts of the dossier. Non-binding information should be provided in the “development” sections of the dossier. The level of detail needs to be commensurate with the level of complexity and risk.

## Conclusion

The joint two-day workshop illustrated that, although not yet fully integrated into daily routine, QbD as a concept has

made progress since its inception, or, as the U.S. FDA’s **Christine Moore** put it: “Ten years ago, people asked **if** they should do QbD. Now, they ask **how** they should do QbD and how to register.” **Yoshihiro Matsuda**, PhD, PMDA, stated that postapproval change management is possible in Japan and that the understanding of QbD is not different.

Intense exchanges during the workshop testified to both the industry’s and the regulatory agencies’ commitment to advance the adoption of QbD to its full potential. Discussions around QbD, focused on PAT applications in the 2009 workshop, now touch on all elements linked to the enhanced approach.

The outcome of the workshop will be shared with ICH’s quality informal brainstorming group and fed into a Q&A document that will be prepared by EMA. Learnings will also be incorporated into the currently ongoing update of Annex 16. A joint EMA/EFPIA steering team will follow up on these items.

[The authors would like to thank co-chairs Jean-Louis Robert and Georges France, as well as the workshop planning committee, for this successful and very informative workshop.]

## References

1. ICH Quality Guidelines, International Conference on Harmonisation [tinyurl.com/65e2yjf](http://tinyurl.com/65e2yjf)
2. Quality Implementation Working Group on Q8, Q9 and Q10 Questions & Answers (R4), International Conference on Harmonisation: November 2010 [tinyurl.com/p6rxhls](http://tinyurl.com/p6rxhls)
3. ICH QUALITY IMPLEMENTATION WORKING GROUP POINTS TO CONSIDER (R2), International Conference on Harmonisation: December 2011 [tinyurl.com/d6hqrd2](http://tinyurl.com/d6hqrd2)
4. ICH Q8–Q10 Training Materials, International Conference on Harmonisation: October 2010 [tinyurl.com/q2epdko](http://tinyurl.com/q2epdko)
5. EMA-FDA pilot program for parallel assessment of Quality-by-Design applications: lessons learnt and Q&A resulting from the first parallel assessment, European Medicines Agency: August 20, 2013 [tinyurl.com/nk239yu](http://tinyurl.com/nk239yu)

*Continued at bottom of page 44*



# Pharmacopoeias: The European System

## EUROPEAN PHARMACOPOEIA



- EP governs in all signatory states and is enforced by national competent authorities
- EP is *not* governed by the EU
- Signatory states can have “national interest only” standards
- All signatories inform EP of national interest only monographs
- If two or more signatories are interested in drafting a monograph, it is added to the work program of the EP
- No obligation to file public standard for new chemical entities, but companies can voluntarily participate in P4 Procedure for substances still under patent



### Country-Specific Pharmacopoeias

Any country that is signatory to the EP must follow its monographs, though some countries maintain their own pharmacopoeias.

#### United Kingdom

British Pharmacopoeia

- Republishes EP & includes unique British standards

#### France

Pharmacopée française

- Only publishes monographs unique to the country
- EP effective for all other standards

#### Germany

Deutsches Arzneibuch

- Only publishes monographs unique to the country
- EP effective for all other standards
- In addition, together with Austria and Switzerland, translates the EP into German

#### Spain

Royal Spanish Pharmacopoeia

- Republishes EP & includes unique Spanish standards

The following countries also have their own pharmacopoeias:

Austria, Croatia, Czech Republic, Greece, Hungary, Italy, Poland, Portugal, Romania, Slovakia, Switzerland, Turkey and Ukraine

The PDA Letter wishes to thank **Susanne Keitel**, PhD, Director, EDQM, for assisting us with the development of this infographic. You can access the EDQM website for more information here: [tinyurl.com/occe74j](http://tinyurl.com/occe74j).

## OBSERVERS



- 7 countries in Europe, 17 non-European nations, the Taiwan FDA and WHO
- Nonvoting representatives participate in EP meetings
- EP accepted in these nations, however, acceptance of the EP is not an obligation for an observer

## RAQAB Update

### RAQAB Quarterly Report Q1 2014

#### RAQAB Expanding Global Regulatory Commenting to BRIC Countries and Korea

Participating in the regulatory public commenting process is a traditional activity of PDA and its members. PDA has actively commented on draft guidances, guidelines, and regulations from the U.S. FDA, EMA and local EU authorities, WHO and USP. As the diagram below attests, PDA's Regulatory Affairs and Quality Advisory Board (RAQAB) is comprised of numerous individuals who have a wide range of backgrounds and experience, which helps provide meaningful submissions to the commenting process. These submissions have been received positively as thoughtful, scientifically based responses and have frequently opened up further dialogue between PDA members and health authorities.

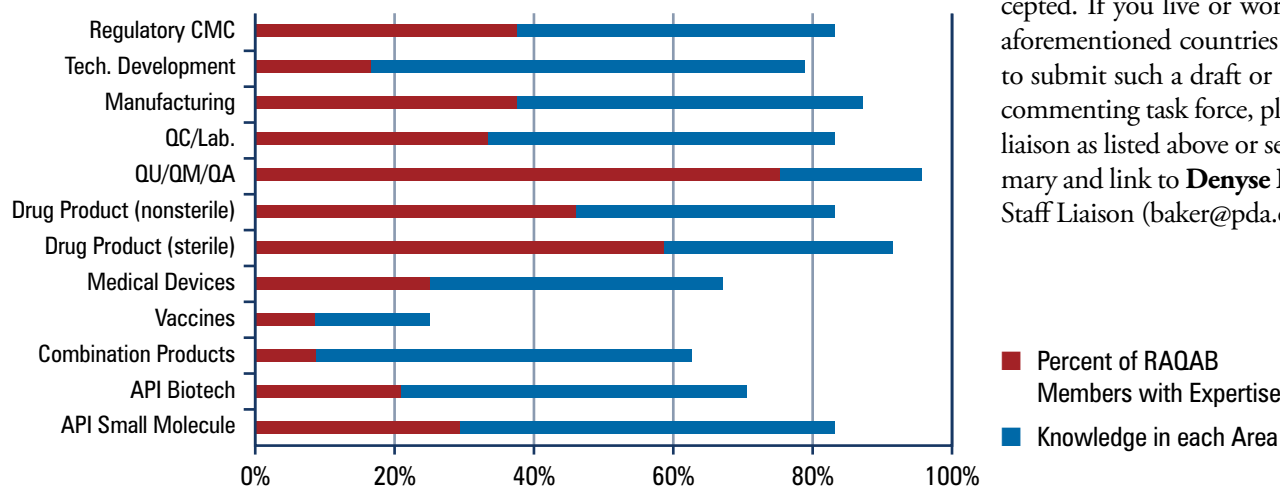
Recently, PDA commenting task force members have participated in an EU Interested Parties meeting on drug shortages and an EU Expert Working Group meeting on the use of shared facilities. In the United States, PDA's comments to the FDA Drug Shortages Task Force's request for quality metrics in February 2013 resulted in PDA being invited to meet with **Janet Woodcock** on the subject, and then to the *PDA Pharmaceutical Quality Metrics Conference*. The discussions at the conference resulted in a Points to Consider document ([tinyurl.com/kosju9q](http://tinyurl.com/kosju9q)), which PDA published in 2013.

Through the contributions of **Cláudio Cappai Corrêa**, the existing commenting process has been adapted and expanded to also include health authority publications from Brazil, Russia, India, China and Korea, all of whom must often publish in local languages rather than English. The key to making the new process work is vigilance and participation from RAQAB Regional Liaisons for those countries (Corrêa in Brazil, **Elizabeth Meyers** in Russia, **Anil Sawant** for India, **Hongyang Li** in China, and **Hailey Park** in Korea). Each is tasked with identifying draft documents from local health authorities that are within the PDA commenting scope and preparing a brief English summary for RAQAB.

Once RAQAB initiates a commenting task force, these liaisons contribute to the comments and assist with translation of the final comments and cover letter back to the local language. They are also the first contact for their local health authorities in case of questions or further dialogue regarding the PDA comments. All comments are approved by the RAQAB and PDA Board of Directors through formal ballots before translation and submission. **[Editor's Note: see page 34 of the March 2014 PDA Letter for an extensive overview of the commenting process.]**

Members are welcome to suggest regulatory documents for RAQAB consideration on whether to comment. Any draft guidance, guideline or regulation that impacts PDA's core competencies and mission, (e.g., parenteral products and quality-related regulations and guidance) and that allows at least a 60–90 day commenting period is likely to be accepted. If you live or work in one of the aforementioned countries and would like to submit such a draft or participate on a commenting task force, please contact the liaison as listed above or send a brief summary and link to **Denyse Baker**, RAQAB Staff Liaison ([baker@pda.org](mailto:baker@pda.org)).

#### RAQAB Members bring a broad range of experience to their deliberations



#### PDA Who's Who

**Janet Woodcock, MD**, Director, CDER, U.S. FDA

**Cláudio Cappai Corrêa**, Global Supply Chain Quality Manager, Roche

**Elizabeth Meyers**, Senior Manager, Amgen

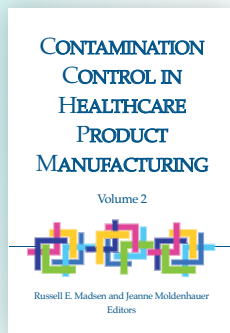
**Anil Sawant**, PhD, VP, Enterprise Regulatory Compliance, J&J

**Hongyang Li**, VP, Quality, Novo Nordisk

**Hailey Park**, Associate Deputy Director, South Korean Ministry of Food and Drug Safety

**Denyse Baker**, Senior Advisor, Scientific and Regulatory Affairs, PDA

# New Release at the PDA Bookstore



## Contamination Control in Healthcare Product Manufacturing, Volume 2

Edited by Russell E. Madsen and Jeanne Moldenhauer

Volume 2 addresses some microbial control issues as well as other types of contamination.

### Topics covered in this volume include:

Item No. 17317

- **Guenther Gapp** reveals a new tool for risk assessment in sterile manufacturing processes that has been used successfully at Novartis and Sandoz
- **Jim Aker** discusses the changing technology in both sterile and non-sterile environments
- **Hilary Chan** explains The Microbiologist's Contamination Control Kit
- **Stephen Langille** discusses particulates present in injectable products
- **Kevin Lorcheim** covers the use of chlorine dioxide as a contamination control methodology
- **Miguel Nogueras** discusses the application of human factors in aseptic processing
- **Art Vellutato** covers cleaning validation
- **Jeanne Moldenhauer** describes various contamination control sterilization processes
- **Mark Hunter, Michelle Luebke and Mark Pasmore** explain contamination risks and the impact to patients
- **Jane Wyatt** offers a strategy for implementing contamination control in the Biotech industry
- **David Fletcher** considers contamination control in drug substance manufacturing

These valuable chapters will provide a great deal of information for contamination control.

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# Preventing and Managing Drug Shortages

Emma Ramnarine, Genentech; Stephan Rönninger, PhD, Amgen; and Anders Vinther, PhD, Genentech

*“I have to rely on this life-changing product for treating my disease/ medical condition; nothing else works...if only I could rely on its availability every time I need it.” — a patient’s perspective.*

Medical and pharmaceutical science has made incredible advances in providing therapies to patients that are transforming quality of life and survival. As a pharmaceutical company, delivering safe, efficacious quality products to patients has always been, and continues to be paramount and what we must strive for. Unfortunately, “drug shortages” have increased in frequency and severity since the early 2000s for many reasons. Though the drivers in Europe and the United States are somewhat different, data suggests that approximately 40–50% of shortages are due to manufacturing quality issues.

A patient’s reality due to a drug shortage underscores the fact that while improving patient care is important, being able to sustain reliable, uninterrupted and timely supply is even more fundamental to patient care. PDA is working with EMA and the U.S. FDA as well as coordinating with other industry associations on ways to reduce drug shortages caused by man-

ufacturing quality issues. PDA is doing this by developing a risk-based approach, having a workshop in September 2014, an upcoming technical report, and several other activities on this topic.

ICH Q9 Quality Risk Management defines harm as “damage to health, including damage that can occur from *loss of product quality or availability*”. It is simply not enough to focus primarily on manufacturing safe, efficacious products.

As the complexity of supply chains increases, global regulatory expectations continue to evolve, and economic and business motivators introduce more competition, ensuring availability and uninterrupted supply of products, especially medically necessary products that do not have an effective alternative, is a challenge that is drawing higher focus from regulators, legislators, health care providers, manufacturers, and patients.

Until recently, investigation and management of drug shortages was not routine for many health authorities and their primary responsibilities did not extend to the management of supply, or resolving supply shortages. Hence in many ways, leg-

## A Triage: Categorization, patient impact, and end-to-end controls

### 1 Define Risk

		Access to Therapies		
		No Alternative	Alternative Exists: Similar Therapy	Alternative Exists: Same Therapy
Product Indication	Life Saving	Risk Level A	Risk Level A	Risk Level B
	Acute short term	Risk Level A	Risk Level B	Risk Level C
	Minor indications, et	Risk Level B	Risk Level C	Risk Level C

2 At each risk level consider the probability of a drug shortage and ways to avoid this

### 3 Define priority

		Probability of Shortages		
		High	Moderate	Low
Risk Level	Risk Level A	Risk Priority Level 1	Risk Priority Level 1	Risk Priority Level 2
	Risk Level B	Risk Priority Level 1	Risk Priority Level 2	Risk Priority Level 3
	Risk Level C	Risk Priority Level 2	Risk Priority Level 3	Risk Priority Level 3

### 4 Triage output: Preventive Actions

Risk Priority	Suggested Controls
Level 1	<ul style="list-style-type: none"> <li>Appropriate inventory and safety stock management</li> <li>Multi-sourcing with higher manufacturing capacity reserves</li> <li>Supplier management controls (see sec. 5.4 of T54)</li> <li>Supply chain/transportation line security, business continuity and communication plan</li> <li>Extended Value Stream Mapping (VSM)</li> </ul>
Level 2	<ul style="list-style-type: none"> <li>Consider multi-sourcing</li> <li>Value Stream Mapping (VSM)</li> <li>Proactive Inventory management</li> <li>Process capability and robustness exercises (Quality Metrics)</li> </ul>
Level 3	<ul style="list-style-type: none"> <li>Generally accepted risk level</li> </ul>

## Proactive Management of Drug Shortage



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isolation and regulatory processes for shortage-related work are under-developed.

Currently there is no harmonized definition for “drug shortage” and alignment is needed on this. Health authorities primarily focus on drug shortages that have patient impact. While not all shortages impact patients, health authorities have an interest in understanding the causes of such issues, “near misses,” and their preventive actions to avoid a similar recurrence. Therefore FDA, EMA and several other Health Authorities are taking the “crisis” situation around drug shortages seriously, and have published various documents on this topic. PDA supports the European Federation of Pharmaceutical Industries and Association’s (EFPIA) description of “a potential drug shortage as the occurrence of internal or external situations (single or in a combination of both) which could result in an interruption of supplies of a medicinal product, if not properly addressed and controlled.”

In the United States, FDA has established a task force on drug shortages and in October 2013, published a Strategic Plan to prevent and mitigate drug shortages. One element of the FDA’s Strategic Plan addresses mitigation improvements. This includes early notification of potential drug shortages so that steps can be taken in collaboration with the FDA to plan, coordinate actions, and reduce supply disruption through measures such as:

- ramping up/activating supply of alternate therapies where available
- expediting inspections and submission reviews for new manufacturing sites, suppliers, and specification changes
- exercising regulatory discretion on controlled importation of similar products approved in other countries
- working closely with manufacturers on quality issues that might lead to supply disruption.

The second element of FDA’s Strategic Plan is focused on preventive strategies such as positive incentives for manufacturing and quality improvements, and use of proactive risk-based approaches for early identification and prevention of manufacturing and quality problems.

In the European Union, EMA has similarly initiated multiple actions such as establishing an internal catalogue of Centrally Authorised Products (CAPs) and nonCAPs, developing a decision tree to assist National Competent Authorities (NCAs) in determining when a coordination of assessment and response is required at the EU level, clarifying reporting requirements for supply restrictions, and establishing a procedure for handling reports of shortages. EMA has also written a couple of draft documents on the topic and reached out to industry associations including PDA to work on proactively avoiding drug shortages. Due to challenges such as parallel trade, different pricing, economic and business environment in different EU countries, decentralized registration procedure, the issue is more complex than in the United States.

Given its importance and criticality, PDA has been actively working on this topic and engaging in dialog with FDA and EMA to find ways to collaborate in driving solutions to the problem of drug shortages. The efforts are aligned with FDA's Strategic Plan and EMA's direction on managing drug shortages; they are mainly focused on a science and risk-based approach including how improvements in manufacturing operations and post approval regulatory changes might be implemented in an expedited way.

In 2012, PDA initiated a task force as part of the Paradigm Change in Manufacturing (PCMO<sup>SM</sup>) project to focus on developing a risk-based approach for prevention and management of drug shortages. This is a continuation of PDA's Technical Report No. 54 series of documents where a new technical report will be added on "A Risk Based Approach for Preventing and Managing Drug Shortages." It is important that a Quality Risk Management (QRM) application addresses both proactive prevention of manufacturing quality issues that can potentially lead to drug shortages, and also risk-based actions in the event a shortage were to occur. The TR54 series provides a QRM framework and application case studies to proactively identify, assess and control product quality risks that in combination with supply chain factors might result in a drug shortage. Additionally, *Technical Report No. 59: Utilization of Statistical Methods for Production Monitoring* supports these risk-based activities using statistical methodologies for quality control and manufacturing shop floor to better understand and monitor a manufacturing process.

PDA's risk-based approach for prevention of drug shortages emphasizes the importance of looking at end-to-end controls at a product and manufacturing site level, in order to identify potential risks at various stages of the supply chain. Drug supply needs to be managed appropriately based on the medical necessity and criticality of the product in order to prevent shortages (i.e., stock levels, scale and impact of the problem, alternative sources of supply etc.).

The risk-based approach is a 3-step triage model that:

1. Categorizes the criticality of a shortage in terms of patient impact based on product indication and access to alternative therapies
2. Assesses the probability of a shortage occurring based on identification of i) sources for manufacturing quality risks, ii) weak links in the demand to supply process, iii) inventory considerations, and finally
3. Results in decisions on controls to mitigate and manage the risk to both patient safety and product availability

Another element of PDA's efforts for prevention of drug shortages is related to quality metrics. This work focuses on continuous improvement, early detection of control drifts, and ensuring stable product supply. It includes metrics that assess overall product quality and facility state of control, and metrics to minimize drug shortages.



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## 2014 PDA Europe Advanced Therapy Medicinal Products

This year's program will specifically focus on CMC development topics both in early and late development as well as illustrate new technical developments in the field. The Program Committee also intends to select a number of submitted posters for short oral presentation and discussion.

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In October 2013, at EMA's request, a joint team was established with membership from PDA, ISPE, EFPIA and the European Generic Medicines Association (EGA). The team will collaborate with EMA and NCAs to establish an integrated action plan for managing shortages caused by manufacturing quality issues including baseline measures to show effectiveness in managing drug shortages. This effort will also include communication strategies with Health Authorities in the event of a drug shortage. Each association has ongoing complementary activities on this topic. The joint team will build on and coordinate the unique perspectives and competencies of each organization to address the topic of drug shortages.

PDA is organizing the two-day *2014 Drug Shortage Workshop* in September with active engagement from members of FDA's Drug Shortage Task Force. The workshop will explore application of risk and knowledge management for addressing and preventing drug shortages, incentives for manufacturers to build in proactive controls (such as redundant capacity, new technology, transparency and linkages to supply planning, manufacturing site metrics and quality status for potential manufacturing partners, etc.). The workshop will also discuss technological improvements that can have a positive impact on preventing drug shortages, economic and regulatory barriers to implementation, and potential incentives or regulatory changes that could improve the business case for quality improvements.

The common unifying objective of preventing drug shortages to ensure uninterrupted supply of safe, efficacious products to patients, is bringing regulators, legislators, health care providers and industry together in developing and driving solutions that will serve the best interests of patients and bring patient care to a reliable, sustainable and improved state. It is not an easy challenge to overcome, but a patient's reality makes this a nonnegotiable. PDA and our volunteer members have a significant role and opportunity in this respect. Join

us in this work by commenting on our plans and ideas.

#### Reference

1. Ramnarine, E., Long, M. & O'Donnell, K. (2013, September). Risk Based Approach to Prevent and Manage Drug Shortages; Presented at 2013 Annual PDA/ FDA Joint Conference, Washington D.C.

#### About the Authors

**Emma Ramnarine** is Head of Biologics QC Network at Roche Pharma and is accountable for the biologics QC network strategy.



**Stephan Rönninger, PhD**, is the Head of External Affairs Europe, International Quality at Amgen (Europe) GmbH.



**Anders Vinther** is Quality responsible for the Biologics Technical Operations at Roche and Genentech. This includes operational quality leadership for ten biologics sites and for Roche and Genentech's biologics products. 🇩🇰



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# Illicit Acts Threaten the Global Supply Chain

Program Planning Committee Co-chair Martin VanTrieste, Amgen

A robust and reliable supply of high quality, safe and effective medicines depends upon having adequate control over the sourcing of pharmaceutical ingredients, manufacturing operations and the distribution of medicines to patients. To assure complete control over drug quality and safety, manufacturers should aim to have as much knowledge as possible about the manufacturing and distribution practices in their supply chains.

Globalization is impacting most industries and the pharmaceutical industry is no exception. On the positive side, it has enabled our industry to enter markets all over the world and provide life-giving medicines to millions of patients. With the benefits of globalization, however, come significant challenges and responsibilities. One of those challenges is ensuring the authenticity and quality of mate-

rials moving through the supply chain.

Globalization of pharmaceutical manufacturing and distribution is bringing manufacturers and suppliers to public forums to discuss how to manage emerging concerns including illegal acts such as counterfeiting, diversion and intentional adulteration. Globalization is also prompting legislators and regulators to seek enhancement to existing standards and practices for improved supplier quality management, manufacturing and distribution. Regulators are also developing cooperative approaches to share information and the burden of oversight.

Recent experiences in the market indicate there is a need for improvement in supply chain practices, prompting a surge in activity toward enhanced globally harmonized supply chain controls. Regulators

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and members of industry are acting jointly to identify and implement improved practices that will ultimately secure the drug supply chain and assure patients receive safe, high quality medicines.

On behalf of the Program Planning Committee, we would like to invite you to attend the *2014 PDA/FDA Pharmaceutical Supply Chain Conference with Educational Support from Rx-360*. In this conference, regulators and representatives from firms that are thought leaders in prevention of illicit acts (such as counterfeiting, diversion and economic adulteration) will share their perspectives and solutions to promote supply chain security and integrity. New laws, regulations and guidances continue to

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evolve and help stimulate innovation toward enhancing good manufacturing, distribution, and importation practices. We invite you to engage with regulators as they speak about their expectations and emerging regulations and with industry leaders as they share solutions that are being developed and implemented to work hand in hand with new regulations to secure the supply chain.

Through a series of plenary sessions and breakout sessions, the program will provide participants the opportunity to:

- Hear from senior U.S. FDA personnel and other global regulators on the current regulatory environment/situation
- Identify any barriers and associated actions to enable implementation of feasible solutions
- Share improvements in programs and technology
- Benchmark with leading pharmaceutical companies

As a bonus, all full conference attendees will be granted full access to the *Rx-360*

*5 Year Anniversary Celebration & Conference* after the PDA conference and further their knowledge of the supply chain security threats against our industry and how it continues to evolve and put our patients at risk as well as the work being done to prevent, detect, and respond to these threats.

Patient safety and the quality of the pharmaceutical supply will remain at risk unless the industry takes action to prevent and detect these threats. We encourage you to take a stand, attend this conference and network with industry and regulatory professionals devoted to supporting the development of initiatives to ensure the integrity of the global pharmaceutical supply chain and save the lives of patients everywhere. 

The PDA Training and Research Institute will be hosting two courses to complement your learning. On June 5, TRI will offer “Developing a Robust Supplier Management Process,” and on June 6 will offer “Good Distribution and Storage Practices (GDP/GSP)—Securing the Supply Chain.” For more in-depth information, visit [www.pda.org/supplychaincourses2014](http://www.pda.org/supplychaincourses2014).

# Regulators, Industry, Embrace Changes in Oversight, Quality

David Cummings, Rick Friedman, Alicia Mozzachio, Mahesh Ramanadham, U.S. FDA, and Program Committee Members

In recent years, industry and the U.S. FDA have worked to strengthen their quality systems to better position the industry to meet future needs. At FDA, there have been significant advancements in quality systems implementation over the last decade, including adding dedicated quality management staff, drafting internal policies/procedures and staff manual guides and hiring process improvement staff trained in process mapping and continuous improvement.

Other activities underway by FDA include proposed changes in our oversight of drug products to better monitor and assure lifecycle quality and availability. For example, CDER has initiated efforts to establish an integrated drug review program that positions staff to better accommodate increasing product complexity and enhance public health protection. In addition to integrated review, we have implemented other collaborative programs such as knowledge transfer memos that strengthen preapproval communications between CDER and Office of Regulatory Affairs field staff.

The pharmaceutical industry has been undergoing its own notable advances in quality management. The industry has implemented critical enhancements in quality management such as knowledge management, supplier qualification, technology transfer, crossfunctional training and integration of staff, and assuring those with proper skillsets are hired, developed, and deployed.

Some major industry changes are also underway in the area of quality risk man-

agement. While a number of mock risk assessments have been developed and are publicly available, however, there remains a need to mature QRM programs in order to better address system biases and establish more effective approaches to reducing quality risks throughout the lifecycle. Many organizations have made major strides in risk management in accord with ICH Q9 in one or more facets of their operation, resulting in improvements in drug quality decision making. Yet these systems are still not broadly ingrained throughout pharma.

The process performance and product quality monitoring system (PPPQMS) is also an area that is evolving. Key to this effort is management support that enables companies to take a contemporary approach to monitoring processes to promptly detect variation, and using statistical process control to identify out-of-trend events so that a drift in process control can be corrected before product quality failures occur. Process performance and product quality monitoring must be supported by effective quality indicator inputs, root cause analysis processes, strong statistical analysis competencies, timely quality management oversight and capable technologies. Ultimately, much of the information that is monitored by the PPPQMS is also at the core of meeting an organization's knowledge management objectives.

It is important that organizations continue to improve and adequately resource change management systems. Key considerations for organizations

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include management accountability for supporting needed changes, and linking change management to the quality risk management system to ensure that the change is carefully managed and change effectiveness is verified.

The critical underpinning of all of these quality system efforts is a strong quality culture. Again, engagement and commitment by senior management are essential to support a quality-focused organizational culture. Visible support for quality from the top of the organization provides the essential foundation that drives quality behaviors and decisions that assure that pharmaceuticals are consistently safe, effective and available.

With this in mind, the FDA and PDA are again collaborating to plan the 2014 PDA/FDA Joint Regulatory Conference. The objectives for this are to promote the adoption of more robust design practices, quality systems, and use of modern manufacturing technology. Together, these two organizations, along with a number of other stakeholders, are working to move manufacturers toward a future state that has been described as:

“A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight.”

—Janet Woodcock, 2005

This year the PDA/FDA Joint Regulatory Conference will address a number of topics that cover the progress made toward reaching the objective set forth by Woodcock. 

Following the 2014 PDA/FDA Joint Regulatory Conference, PDA Training and Research Institute will offer six courses to complement what attendees learned at the conference on Sept. 11–12. To find out what these courses will cover, please visit [www.pda.org/pdacourses2014](http://www.pda.org/pdacourses2014).

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Martin VanTrieste, Amgen

## PDA Supports Quality in Manufacturing Operations

Today, when I ask the question, “who owns quality?” I typically get the common reply that “everyone owns quality.” This concept is not new; for example, **Juran’s** (1951) and **Feigenbaum’s** (1961) quality handbooks were based on this concept. And let’s not forget that **Dr. Deming** routinely stated that “quality is everyone’s responsibility.”

If we accept this basic tenant, then why are many of our manufacturing colleagues absent from events where exceptional knowledge about quality and best practices are shared, taught, benchmarked and discovered, like PDA educational courses, advisory boards, interest groups, working teams and conferences?

The PDA Board of Directors has recently asked our self this question in order to better serve our manufacturing colleagues, and have developed many theories about why our manufacturing colleagues are absent. For example:

- They defer to their regulatory and quality professions to disseminate the knowledge
- They do not have the resources or the time to participate in PDA events
- They really don’t believe that they own product quality
- They don’t see how PDA can make their lives easier

• Etc., etc., etc...

Still, we really want to know from manufacturing professionals and leaders what would make them more involved in the pursuit of quality, and we want to know how PDA can help. As a manufacturing professional or leader, please feel free to email me at martin@pda.org with your thoughts on what PDA can do to provide value for you and your colleagues.

Supporting PDA membership on manufacturing issues has been a long tradition in PDA. In 2008, the PDA Board established the Paradigm Change in Manufacturing Operations (PCMO<sup>SM</sup>) project. This project was initiated with the mission to facilitate sharing and promotion of best practices for the manufacturing of pharmaceuticals and biopharmaceuticals. The vision is about moving pharmaceutical manufacturing into a new paradigm with robust business and production processes, improving quality and facilitating state-of-the-art technologies. The goal is to utilize PDA’s volunteers to drive the establishment of “best practice” documents and training events to aid pharmaceutical manufacturers and the understanding of regulators in current practices. This is based on the paradigm on risk- and science-based operations facilitated by the harmonized ICH guidance published in the ICH Q8/11, Q9 and Q10 guidance.

In this regard PCMO<sup>SM</sup> covers the product lifecycle concept for manufacturing operations by

- Putting science into manufacturing practice
- Enabling increase of process robustness and knowledge
- Enabling an innovative environment for continual improvement of products and systems
- Fostering communication among industry and regulatory authorities

Under PCMO<sup>SM</sup>, 20 task forces with more than 250 active volunteers are developing and delivering best practice documents such as technical reports and training on topics in the area of lifecycle approach, quality systems, process management and quality risk management. This was, and is, a successful endeavour to share knowledge about reality in manufacturing operations among industry and with regulators. Most of these teams have finalized and published their work.

We are in the process of onboarding new projects reflecting today’s interests in manufacturing shop floor topics for the benefit of our membership. If you are interesting in volunteering, please send us an email at volunteer@pda.org. ☞

*Industry, Regulators Meet to Drive QbD Implementation continued from page 32*

6. Questions and Answers on Design Space Verification, EMA: October 24, 2013 tinyurl.com/krvwhx5
7. Reflection paper on a proposed solution for dealing with minor deviations from the detail described in the Marketing Authorisation for human and veterinary Medicinal Products (Rev1), EMA: January 6, 2009 tinyurl.com/q2mon3o

### About the Authors

**Ursula Busse, PhD, MBA,** currently holds a global position as Head of GxP Regulations Coordination at Novartis.



**Stephan Rönninger, PhD,** is the Head of External Affairs Europe, International Quality at Amgen (Europe) GmbH.

**Georg Rössling, PhD,** is the SVP of PDA Europe. ☞



# Where do leading experts turn to communicate with the PDA community?

*The PDA Letter and PDA Journal of  
Pharmaceutical Science and Technology*

JANET WOODCOCK  
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Authors wanted

## How Should PDA Cover the Pharmacopoeias?

Many PDA members are involved with pharmacopoeias around the world. For example, the USP Microbiology Expert Committee consists of past PDA leaders and volunteers. USP's **Radhakrishna Tirumalai**, one of the committee's documentary standards staff, regularly participates in the annual PDA conference on pharmaceutical microbiology. Many active members in Europe participate in the EP process, as well, including **Susanne Keitel**. The Letter is fortunate to have both of them contributing to this issue: Dr. Tirumalai with the cover story and Dr. Keitel with assistance on the issue's InfoGraphic.

The Letter used to run a regular, short updates from USP, but in recent years, we've provided larger, more in-depth coverage on a less frequent basis. Both approaches have merit. The editors want to know if we should resume a regular feature on the various standards setting bodies or if less frequent coverage is enough. Go to [www.surveymonkey.com/s/pharmacopoeial](http://www.surveymonkey.com/s/pharmacopoeial) to let us know what you think.

This issue also contains several article on important regulatory topics, including Quality by Design, drug shortages and supply chain security. These issues are a top concern of PDA members, and the expert authors who contributed this month have a lot of experience with them. The Regulatory Snapshot ties together PDA's role in connecting such experts to the regulatory process with an explanation of how PDA participates in the public commenting process for new regulations/guidance (primarily in the United States and Europe). PDA's scientific offerings are well known, but some members might not be aware of the number of comments on a variety of regulatory topics PDA volunteer task forces produce each year. The update on PDA regulatory activities also explains how these activities are ramping up in the BRIC nations and Korea.

The PDA Photostream spotlights events from the first quarter of 2013 and shows off the latest upgrade to the PDA Training and Research Institute's cleanroom. **James Wamsley** proudly discusses the new air sampling system in the Science Snapshot Tech Trend.

The April *PDA Letter* Podcast is of an interview conducted by GSK's **Robert Darius** of Vetter's **Joachim del Boca**, Vetter's VP of Regulatory Affairs/Quality Compliance. The interview touches on Del Boca's experience with inspections over his 25 year career, the evolution of aseptic processing and tips for working with a CMO. The interview will be featured in the upcoming July/August *PDA Letter*, but for those who don't want to wait, check out the podcast. 🎧

### Authors Wanted on the Following *PDA Letter* Topics

CMOs/Quality Agreements (due June 6)

Pharmaceutical Microbiology (due July 25)



The *PDA Letter* podcast is available at [www.pda.org/pdaletter](http://www.pda.org/pdaletter).

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### PDA LETTER STAFF

Walter Morris  
PDA Letter Editor,  
Director of Publishing  
+1 (301) 656-5900, ext. 148  
[morris@pda.org](mailto:morris@pda.org)

Rebecca Stauffer  
Assistant Editor  
[stauffer@pda.org](mailto:stauffer@pda.org)

Katja Yount  
Publication Design Specialist  
[yount@pda.org](mailto:yount@pda.org)

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