

People

Science

Regulation

# PDA Letter

Volume XLIX • Issue 6

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

June 2013

## SHOULD SCIENTIFIC DATA DETERMINE CYTOTOXIC LIMITS?

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10 Chapter Explores  
Process Validation

28 An Interview with  
Mark Sebree

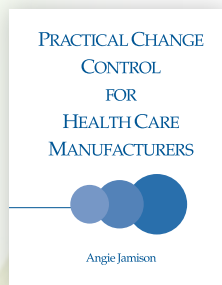
42 In-House Aseptic Training  
Offers Many Advantages

# PDA's 2013 Summer Sale



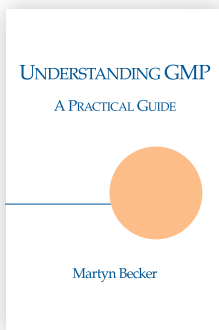
June 15 – August 31

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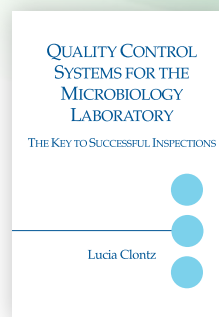
**Practical Change Control for Healthcare Manufacturers**  
By Angie Jamison

Item No. 17173



**Understanding GMP: A Practical Guide**  
By Martyn Becker

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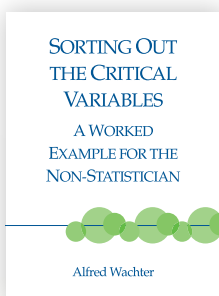
**Quality Control Systems for the Microbiology Laboratory: The Key to Successful Inspections**  
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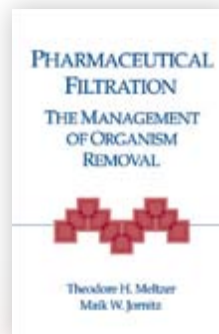
**Microbiology in Pharmaceutical Manufacturing**  
Edited by Richard Prince

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**Sorting Out The Critical Variables: A Worked Example for the Non-Statistician**  
By Alfred Wachter

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**Pharmaceutical Filtration: The Management of Organism Removal**  
By Theodore Meltzer and Maik Jorntz

Item No. 17235

Visit [www.pda.org/bookstoresummer2013](http://www.pda.org/bookstoresummer2013) for more information

## Booklets for sale include

**Designing a Contamination Control Program**  
By Sandra Lowery

Item No. 17229

**Environmental Impact on Media Fills**  
By John Lindsay

Item No. 17271

**Identification of Environmental Isolates**  
By Klaus Haberer

Item No. 17173

**Microbiological Validation Master Plan**  
By Trevor Deeks

Item No. 17230

**Packaging Considerations for Steam Sterilization**  
By Edward Smith

Item No. 17274

**Validation of Sterilization Processes**  
By James Agalloco

Item No. 17231

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

### AUGUST 2013

#### 2013 Pharmaceutical Products Supply Chain Integrity: A Five Day Training Series

August 12-16 | Bethesda, Maryland  
[www.pda.org/pharmaintegrity](http://www.pda.org/pharmaintegrity)

- Global Regulations and Standards: Influences on Cold Chain Distribution, Packaging Testing and Transport Systems (August 12-13)
- From Cold Chain to Temperature Controlled Good Distribution Practices (August 14-15)
- Pharmaceutical Products Supply Chain Security (August 16)

#### Validation of Dry Heat Processes Used for Depyrogenation and Sterilization – *New Course*

August 13-15 | Bethesda, Maryland  
[www.pda.org/valdryheat](http://www.pda.org/valdryheat)

#### 2013 Single-Use Systems for Manufacturing of Parenteral Products

August 20-21 | Bethesda, Maryland  
[www.pda.org/singleusemanf2013](http://www.pda.org/singleusemanf2013)

#### Aseptic Processing Training Program

Bethesda, Maryland  
[www.pda.org/2013aseptic](http://www.pda.org/2013aseptic)

- Session 4: August 26-30 and September 23-27, 2013
- Session 5: October 14-18 and November 4-8, 2013

**SOLD OUT**

### SEPTEMBER 2013

#### Preparation of Virus Spikes Used for Virus Clearance Studies and Virus Filtration – *New Course*

September 9-11 | Bethesda, Maryland  
[www.pda.org/viruspikes](http://www.pda.org/viruspikes)

#### 2013 PDA/FDA Joint Regulatory Course Series

September 19-20 | Washington, D.C.  
[www.pda.org/pdafdacourses2013](http://www.pda.org/pdafdacourses2013)

- Implementation of Quality Risk Management for Commercial Pharmaceutical and Biotechnology Manufacturing Operations (September 19)
- GMPs for Manufacturers of Sterile and/or Biotechnology Products (September 19)
- CMC Regulatory Requirements in Drug Applications – *New Course* (September 19)
- Implementing Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations: *Case Studies in the Manufacturing of Biotechnological Bulk Drug Substances* – *New Course* (September 20)
- Implementing Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations: *Case Studies in the Packaging and Labeling of Drug Products* – *New Course* (September 20)
- Implementing Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations: *Case Studies in the Manufacturing of Pharmaceutical Drug Products* – *New Course* (September 20)

#### 2013 Lyophilization Week

September 30-October 3 | Bethesda, Maryland  
[www.pda.org/lyophilization](http://www.pda.org/lyophilization)

- Fundamentals of Lyophilization (September 30 – October 1)
- Validation of Lyophilization (October 2 – October 3)



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.





## Cover



Cover Art Illustrated by Katja Yount

## 22 Should Scientific Data Determine Cytotoxic Limits?

Over the past few years, regulatory bodies have explored the issue of exposure limits during the manufacture of cytotoxic drugs in multipurpose facilities. A recent draft EMA guideline and the proposed revisions to chapters 3 and 5 of the EU GMPs appear to propose the use of toxicological data along with some rather stringent and apparently not scientifically based criteria to determine exposure limits when working with potent/highly potent drugs.

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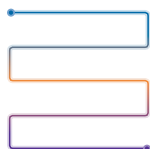
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## Features



### 28 BD Moves into Sterile Injectables Market

This March, BD Rx, a wholly owned subsidiary of BD (Becton, Dickinson and Company), received approval for the first product in the company's line of BD Simplist™ prefilled injectables. BD Rx plans to roll out 20 to 30 more generic sterile injectable drug products over the next few years, including some products that have been in the news as being in shortage. This development has occurred at a time when significant numbers of generic injectables are in shortage, a situation the *PDA Letter* analyzed in the March 2013 cover story. Becton Dickinson opened a facility in 2010 in Wilson, N.C. specifically dedicated to manufacturing these products—the first U.S. facility dedicated to sterile manufacturing built in many years.



### 32 Sterile Product Manufacturing: A History

This issue's infographic highlights key moments in the history of the manufacture of sterile products within the industry.

#### 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®

#### EXECUTIVE STAFF

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#### PDA BOARD OF DIRECTORS

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## What Does PDA Offer You? New Benefits Guide Available

Are you taking advantage of *all* the benefits you get as a PDA member? Do you know about *all* the volunteer opportunities PDA offers that allow you to network with your peers in the industry and regulatory authorities?

Well, look no further than the newly updated PDA Membership guide.

The PDA Membership guide will help you determine how PDA can best serve you and how you “fit” within the Association.

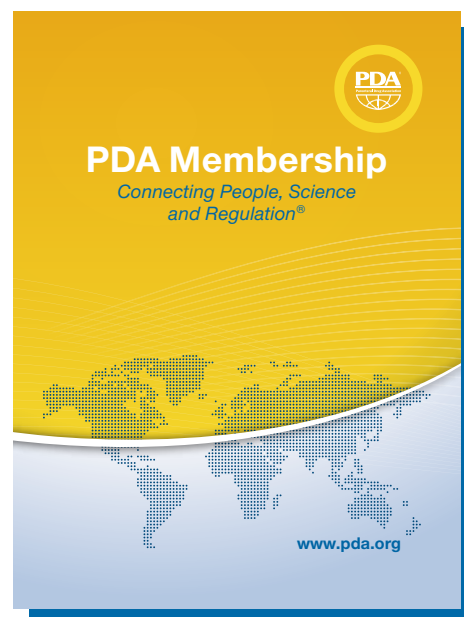
You will find:

- Spotlights on volunteers **Marsha Hardiman, Norbert Hentschel, Lisa Skeens, PhD, Lara Soltis and Anil Sawant, PhD**

- A snapshot of the technical resources available to members
- A showcase of the various volunteer opportunities open to members—both on a general basis and at the leadership level
- A heartfelt message from **Hassana Howe**, PDA’s Director of Membership and Chapters

PDA hopes this new Membership guide helps all members, new and veteran, learn about the unparalleled resources available, as well as the many volunteer opportunities within PDA.

To download the brochure or to request a hardcopy, please visit [www.pda.org/Membership.aspx](http://www.pda.org/Membership.aspx). 🌐



## Over 30 Regulators Appearing at PDA’s Sept. Events

PDA is always pleased to welcome high-level, global regulators to our global conferences and workshops. We recognize that these experts’ regulatory insights are valuable for members, both in industry and in government.

At the *2013 PDA/FDA Joint Regulatory Conference*, Sept. 16–18, in Washington, D.C., **Janet Woodcock**, MD, Director, CDER, U.S. FDA, will serve as a keynote speaker. Her talk will open PDA’s annual conference that brings regulators and industry members to one central location to discuss the current regulatory environment and its impact on pharmaceutical manufacturing. Woodcock joins 31 regulatory officials from FDA and other health authorities who will be speaking at the conference. [See story on p. 38 for more information about the conference.]

Prior to the *2013 PDA/FDA Joint Regulatory Conference*, the following regulators will speak at the *6th Workshop on Monoclonal Antibodies*, Sept. 11–12 in Basel, Switzerland:

- **Martijn van der Plas**, PhD, Senior Assessor for Biological Products, Medicines Evaluation Board (Netherlands)
- **Hartmut Krafft**, Head of Clinical Trials, Paul-Ehrlich-Institut (Germany)
- **Steffen Gross**, PhD, Head of Section, Monoclonal and Polyclonal Antibodies, Paul-Ehrlich-Institut
- **Günter Waxenecker**, Head of Preclinical Assessment, Austrian Federal Office for Safety in Health Care
- **Robin Thorpe**, Head of the Biotherapeutics Group, National Institute for Biological Standards and Control (United Kingdom)
- **Jörg Engelbergs**, PhD, Scientific Expert, Paul-Ehrlich-Institut

The *6th Workshop on Monoclonal Antibodies* focuses on the quality attributes of developing products based on monoclonal antibodies (mAbs). The main topic for the two-day workshop will be CMC issues as they relate to immunogenicity assessments. For more information, about the workshop, see story on p. 40. 🌐

# PDA Honors Contributors at Annual Meeting Banquet

**Each year,** PDA recognizes members whose contributions have helped the Association fulfill its Mission. These special members are chosen by a committee composed of current and former volunteer PDA Directors. Honored members are recognized at the PDA Awards Dinner, held during the Annual Meeting. This year's honorees were recognized at a fun-filled dinner at the Peabody Hotel on April 14.

PDA congratulates each winner and thanks them for their service to the Association.



## Honorary Membership

This is PDA's most prestigious award, conferring lifetime membership benefits to the recipient. The award is usually given in recognition of very long service, of a significant nature, to PDA. This year's recipient is:

**Jim Lyda**

## Gordon Personeus Award

This award is intended to honor a PDA member, other than a member of the PDA Board of Directors, for long-term acts or contributions that are of noteworthy or special importance to PDA. This year's recipient is:

**Kurt Brorson, PhD, U.S. FDA** (not in photo)

## Frederick J. Carleton Award

This award is designated for a past or present member of the PDA Board of Directors whose services on the Board are determined by his/her peers as worthy of such recognition. This year's recipient is:

**Amy Scott-Billman, GlaxoSmithKline**

## Distinguished Service Award

Given for special acts, contributions or service that has contributed to the success and strength of PDA. This year's recipients are:

**Barbara Allen, PhD, Eli Lilly**

**Emmabelle Ramnarine,**  
Genentech

**Kenneth Nolan, U.S. FDA** (not  
in photo)

**Izumi Saitoh, PhD, Takada Seiyaku**

**Elizabeth Leininger, PhD,**  
Consultant

**Wendy Zwolenski Lambert,**  
Novartis

## Martin VanTrieste Pharmaceutical Science Award

New Award! Presented as a tribute to former Board Member and long-time PDA contributor **Martin VanTrieste** for outstanding contributions to the advancement of pharmaceutical science.

**John Shabushnig, PhD, Insight Pharma Consulting**

## Frederick D. Simon Award

The Frederick D. Simon Award is presented annually for the best paper published in the *PDA Journal of Pharmaceutical Science and Technology*. This year's recipients are:

**Daniel Berdovich, Micro**  
Measurement Lab. Inc.

**James A. Melchore, Consultant**

## Service Appreciation Award

The Service Appreciation Award is presented annually for special acts, contributions or services that have contributed to the success and strength of PDA. This year's recipients are:

**Brendan Cahill, Pfizer**

**Associates Inc.**

**Jose Cotto, PhD, Amgen**

**Elizabeth Leininger, PhD,**  
Consultant

**Robert L. Dana, PDA**

**Russell Morrison,**  
Commissioning Agents

**Mordechai Izhar, PhD, Ludan**  
Engineering Co. LTD.

**Thomas Pamukcoglu,**  
MedImmune

**Robert Johnson, PSC Biotech**

**Zena Kaufman, Hospira**

**Shelley Preslar, ProPharma Group**

**Frank S. Kohn, PhD, FSK**

**Martin VanTrieste, Amgen**

## PDA Europe Service Appreciation Award

Chosen by the PDA Europe Senior Staff. This award is given in recognition of special acts, contributions, or service that has contributed to the success and strength of PDA Europe. This year's recipient is:

**Stephan Rönninger, PhD, Amgen GmbH**

## James P. Agalloco Award

The James P. Agalloco Award is presented annually to the PDA faculty member who exemplifies outstanding performance in education. This year's recipients are:

**James Cooper, PharmD,**  
Endotoxin Consulting Services

**Dale A. Seiberling**

## Michael S. Korczynski Award

This award funds travel expenses for an international guest to deliver the "Korczynski Paper" at a PDA Meeting. This year's recipient is:

**Maik W. Jornitz, G-Con**

## President's Award

This award recognizes a PDA staff member, other than Senior Staff, whose exemplary performance has contributed to PDA's success during the previous year. This year's recipient is:

**Wanda Neal, PDA**



# PDA Volunteer Spotlight

## Daikichiro Murakami

- Technical Advisor
- *Taikisha*
- Member Since | March 1995
- Current City | Ryugasaki, Japan
- Originally From | Sapporo City, Japan

*The PDA Japan Chapter has allowed its members to contribute to the pharmaceutical industry*

**If you were telling a new member why they should get involved with their local PDA chapter, what would you tell them?**

Your local PDA chapter allows you to obtain the latest global information on pharmaceutical technology in addition to building up your network.

**How do PDA members benefit from chapters that are located outside of North America?**

PDA members benefit from chapters outside North America through extensive real-time networking opportunities. The PDA Japan Chapter has allowed its members to contribute to the pharmaceutical industry through scientific discussions as well.

**Has being a part of an English-speaking organization, like PDA, helped you in any unexpected ways?**

Yes, being part of an English-speaking organization has allowed us easier access to the full spectrum of available websites.

**I see that the Japan Chapter's website is written in Japanese; do you also hold your meetings and events in Japanese? How does this help with your membership?**

Yes, holding our meetings and events in Japanese allows us to communicate fully with chapter members.

**If you had any other job, what would it be?**

Engineering Management Counselor

**What are your three favorite books?**

*The World is Flat* by Thomas L. Friedman

*The Black Swan* by Nassim Nicholas Taleb

*Bushido: the Soul of Japan* by Inazo Nitobe, PhD

**Why did you choose to get involved with PDA?**

I joined PDA to gain a better understanding of pharmaceutical quality systems from an engineering standpoint.



# Environmental Monitoring



Particle Counting



Microbial Sampling



Real-Time Microbial



Validation and Compliance



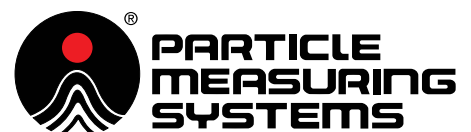
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# Missouri Valley Chapter Explores Process Validation Topic

Eldon Henson, Mallinckrodt

The Spring Meeting of PDA's Missouri Valley Chapter was held April 15 in Overland Park, Kan. Close to 70 attendees gathered to hear presentations from U.S. FDA and industry representatives associated with the implementation of the FDA's process validation guidance.

Following a social hour and dinner, **Tara Breckenridge**, Investigator, Pharmaceutical Inspectorate, FDA, presented her Agency's perspective on process validation. She began by providing an overview of FDA's intent around the development of the 2011 guidance. Primarily, the Agency desired to more closely connect current scientific approaches to the practice of process validation by driving the entire product lifecycle approach.

Breckenridge also illustrated how the process validation guidance aligns with

existing FDA regulations and other regulatory bodies' perspectives on the topic, including ICH documents (Q8-Q10). She provided insight into current FDA thinking on acceptable process validation approaches by using FDA-483 observation examples. Her presentation showed the Agency expects firms to use scientific data and extensive product knowledge to demonstrate the acceptability of any process used for production of commercial pharmaceutical products.

Following Breckenridge's talk, **Alfredo Canhoto**, PhD, Associate Director, Technical Solutions, ProPharma Group, provided an industry perspective titled, "Process Validation Guide: Regulatory Expectations and Best Practices." He also emphasized the importance of the lifecycle approach to process validation.

He described the direct linkage of successful process qualification to the adequacy of process design.

As an example of a lifecycle approach, Canhoto discussed validating legacy products. As many firms have expressed concern over how to address the staged approach to process validation for legacy products, he provided a rational approach to demonstrate control over variation through the examination of data from previously manufactured product. As process variation is detected, the need to reassess process design should lead to enhanced confidence at the process qualification and ongoing monitoring stages. He emphasized that current best practices involve the *ongoing* monitoring and analysis of production data, not merely an annual requalification based on historical data reviews.

Register by July 26 and save up to \$400



The Parenteral Drug Association presents the...

## 2013 PDA Analytical Methods Development & Validation Workshop

*Navigating the Biotechnology Product Life Cycle*

**October 7-8, 2013** | Renaissance Baltimore Harborplace Hotel | Baltimore, Maryland

The 2013 PDA Analytical Methods Development & Validation Workshop will focus on the entire lifecycle of analytical methods from development to post-validation maintenance. The workshop will provide participants with a review of laboratory and documentation standards expected during the development, qualification, validation, and transfer of analytical methods.

A variety of regulatory and industry speakers will present, including:

- **Rajesh Gupta**, PhD, Deputy Director, Office of Compliance and Biologics Quality, FDA
- **Dwayne Neal**, Principal Scientist, Novartis Vaccines and Diagnostics
- **Horacio Pappa**, PhD, Principal Scientist, U.S. Pharmacopeia
- **Melissa Smith**, Senior Consultant, Quality and Analytical Consulting, MJ Quality Solutions



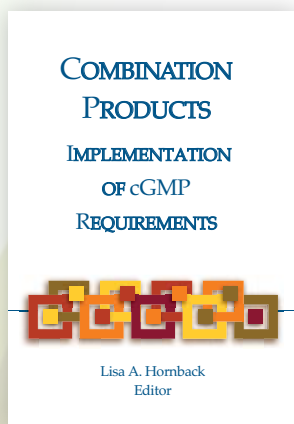
Attendees at this workshop will gain information on regulatory expectations and current industry best practices for the development and validation of analytical methods for biopharmaceutical products.

[www.pda.org/amd2013](http://www.pda.org/amd2013)  
Exhibition: October 7-8

# New Release at the PDA Bookstore



Receive a 20% discount through July 31 by pre-ordering.  
Enter CPIR during checkout.



Item no. 17313

## Combination Products: Implementation of cGMP Requirements

*Edited by* **Lisa A. Hornback**

The goal of this book is to provide the reader with a well-rounded exposure to the unique aspects and considerations for implementation of cGMP in a combination product environment and also includes information from leaders in the industry regarding the unique requirements for several common combination products situations. PDA hopes that this book can answer many of the reader's questions on the evolving world of combination products.

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

[www.pda.org/bookstore](http://www.pda.org/bookstore) | Tel: +1 (301) 656-5900 | Fax: +1 (301) 986-1361

Next, **Jeff Wiegers**, Sr. Director, Quality Operations, Mallinckrodt Pharmaceuticals, provided an overview of process validation of API manufacturing. Wiegers shared that the new guidance has challenged his organization to more thoroughly characterize product critical process parameters (CPP). Failure Mode and Effect Analysis (FMEA) has been an important tool to better understand and verify critical to quality attributes (CQA) and CPP data. His firm has also increased utilization of leading indicators and real-time process data available to operators. Wiegers also emphasized the use of statistical tools to improve the robustness of manufacturing data and detection of variability. By properly managing processes, operators can focus on the "critical few" rather than the "trivial many." Ultimately, the manu-

facturing vision in Mallinckrodt API manufacturing is the combined use of Quality by Design, CPP review, statistical process control and Process Analytical Technology to provide online verification of data and, possibly, parametric or real-time product release.

Closing industry comments were provided by **Alan Southards**, Validation Section Manager, Hospira. In essence, he stated that Hospira is striving to better understand their processes to reduce variability and improve production reliability/product performance.

The speakers then convened to take questions from the attendees. Breckenridge made a key comment that FDA is unlikely to be overly concerned with legacy processes that are consistently demonstrating robustness, little variability,

minimal deviations and no compliance concerns. When any of these issues appear, however, work is needed to better understand the process design.

We thank our sponsors for the evening's events:

- cGMP Validation (annual and social hour sponsor)
- Commissioning Agents, Inc. (dinner and booth sponsor)
- Particle Measuring Systems (booth sponsor)
- ProPharma Group (booth sponsor)

Our next event will likely occur in September 2013 in the St. Louis, Mo. area.

**[Editor's Note:** Slides from this presentation are available on the Missouri Valley Chapter page of the PDA website.]





#### Opening Remarks

PDA President Richard Johnson opens the meeting on April 15.



(l-r) Conference Co-Chairs Hal Baseman, ValSource and Maik Joritz, G-Con



#### Plenary Session 1

(l-r) Hal Baseman, ValSource; David Cutler, PhD, Harvard University, Joyce Bloomfield, Merck; Maik Joritz, G-Con



#### Plenary Session 2

(l-r) Hal Baseman, ValSource; Martin VanTrieste, Amgen; Marty Nealey, Hospira enjoy a smashing good plenary.



#### Plenary Session 3

(l-r) Carl June, MD, University of Pennsylvania Abramson Cancer Center, Ursula Busse, PhD, Novartis; John Yu, MD, Cedars-Sinai Medical Center



#### Plant-Made Pharmaceuticals

(l-r) Barry Holtz, PhD, Caliber Therapeutics; Ursula Busse, PhD, Novartis; Karen Ginsbury, PCI Pharmaceutical Consulting



#### Modular Systems–Facility Consideration

Hank Rahe, Enguard Systems



#### Trends in Process Validation

Julia O'Neill, Merck



#### Expression Systems for Biopharmaceutical Products

(l-r) Peter Steiner, PhD, ESBATech; Rickey Lu, MedImmune; Fred Porter, PhD, Novartis



#### Innovative Approaches to Sterile Product Packaging

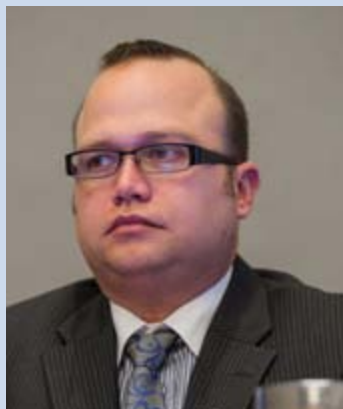
Rob Swift, Amgen; Andreas Toba, PhD, Medical Instill Technologies



#### A.Vax: A QbD Case Study and Study Guide

Cristiana Campa, PhD, Novartis





Complementing Your Quality Systems with Technology While Meeting New Regulatory Requirements in a Global Market

(l-r) Cyndi Poetker, Abbott; Miguel Nogueras, PhD, Abbott; Peter Noverini, BioVigilant

Fundamentals – Sterile Product Manufacturing

John Shabushnig, PhD, Consultant



Contemporary Practice in the Manufacture of Sterile Products

(l-r) James Akers, PhD, Akers Kennedy & Associates; Mike Sadowski, Baxter; Patrick McCormick, PhD, Bausch & Lomb



Outsourcing Related

(l-r) Edwin Rivera-Martinez, Sanofi; Miguel Montalvo, Expert Validation Consulting; Ian Elvins, Lonza



Fundamentals—Quality Systems

(l-r) Scott Bozzone, PhD, Pfizer; Greg Flexman, Grifols



April 15–17 | Orlando, FL

Passport Drawing



bioMérieux

Louis Zackkiewicz, Genzyme, walked away with a \$100 Apple iTunes gift card



Aptar Stelmi

Edwin Rivera-Martinez, Sanofi-Pasteur, won a \$100 dollar gift card



Coldstream Laboratories

Mike Avram, Bayer, took home a bottle of Blanton's Original Single Barrel Bourbon



Lancaster Labs

Ge Bai, MedImmune LLC, won a Kindle Fire



BioLumix

Thomas Ingallinera, PhD, PII, received a Kindle Fire



PDA

Tamara Mandell, University of Florida, won wine made by PDA Chair Anders Vinther, PhD





2013 PDA Annual Meeting

PDA Annual Walk/Run



7<sup>th</sup> Annual PDA Walk/Run

Sartorius Stedim Biotech sponsored this year's run/walk to benefit the BASE Camp Children's Cancer Foundation.





April 15–17 | Orlando, FL.

PDA Golf Tournament



7<sup>th</sup> Annual PDA Golf Tournament

Attendees showed off their swings at Grande Pines Golf Club.



To view more photos from the 2013 PDA Annual Meeting go to [PDA.org](http://PDA.org)



# PDA Surveys Enhance Industry Knowledge, Support TRs

Jahanvi (Janie) Miller and Josh Eaton, PDA

To support the development of technical reports, PDA has integrated the use of surveys to garner knowledge and information on best practices from the collective expertise of PDA's membership. The surveys alone are valuable resources that members can apply to daily work/professional settings and to increase awareness of PDA technical reports, and they are invaluable tools in the development of scientifically balanced consensus documents developed by subject-matter experts from the pharmaceutical and biotechnological industry.

Currently, PDA is working on the following surveys to be rolled out in 2013:

The **Bioburden and Biofilm Management Practices in the Manufacture of API or Drug Substance** Task Force conducted a survey in the first quarter of 2013. The focus of this survey was to enhance industry knowledge and understanding of best practices and challenges in bioburden testing and management and support the drafting of the accompanying technical report.

The **Parenteral Glass Handling** Task Force is currently drafting a series of **four surveys** to determine origination points and causes of damage to glass containers during pharmaceutical manufacturing operations. The surveys will separately investigate the handling of cartridges, ampules, syringes and vials from receipt of the glass through fill and finish operations and shipping, and cover incidents from simple scratches and scrapes to broken items.

The **Objectionable Microorganism** Task Force is working on a survey to poll industry leaders on how they evaluate objectionable microorganisms and which nonspecified microorganisms are considered to be objectionable. The scope ranges from the microbial analysis of nonsterile finished product formulations to the factors being used to conduct a risk analysis of the recovered nonspecified microbial isolate as an objectionable microorganism. The information collected will drive the development of the technical report and help address pressing issues within the biopharmaceutical industry (please see "Objectionable Microorganisms TF to Release Survey" in the March 2013 edition of the *PDA Letter*).

Surveys are simple, but effective tools for supporting technical reports, and the results alone add value to industry. Keep an eye out for opportunities to participate in one! 🍷



## Journal Preview

### May–June Issue Explores Drug Delivery, Other Topics

The May/June includes two research contributions exploring the topic of drug delivery systems. **Sunny R. Shah, Rajesh H. Parikh, Jayant R. Chavda** and **Navin R. Sheth** write about a self-nanoemulsifying drug delivery system while **Swati C. Jagdale, Monali S. Sali, Ajay L. Barhate, Bhanudas S. Kuchekar** and **Aniruddha R. Chabukswar** investigate a floating pulsatile delivery system.

#### Editorial

Govind Rao, "Threat or Opportunity?"

#### Research

Sunny R. Shah, et al., "Self-Nanoemulsifying Drug Delivery System of Glimepiride: Design, Development, and Optimization"

Swati C. Jagdale, et al., "Formulation, Development, and Evaluation of Floating Pulsatile Drug Delivery System of Atenolol"

Nader Shafiei, et al., "Transformation in the Pharmaceutical Industry: Transformation-Induced Quality Risks—A Survey"

#### Technology/Application

Daniel L. Norwood, et al., "James O. Mullis, Mark Davis, Scott Pennino, Thomas Egert, and Nina C. Gonnella"

#### Review

Stephen E. Langille, "Particulate Matter in Injectable Drug Products"

John-Bruce D. Green, et al., "Interactions between Parenteral Lipid Emulsions and Container Surfaces"

Kedar S. Gokhale, Sriramakamal Jonnalagadda, "Preparation and Evaluation of Sustained Release Infliximab Microspheres"

Silvino A. Olivera, et al., "Effect of Resolution of Measurements in the Behavior of Exponentially Weighted Moving Average Control Charts" 🍷

## Tech Trends

### Single-Use Technology Can Reduce Oxidation

Hiroo Nakano, PhD, Hosokawa Yoko

As single-use technology using plastic bag containers expands across the pharmaceutical industry, there is growing concern about oxidation of methionine (Met) as a major degradation pathway, particularly for interleukin-2, human growth hormones and monoclonal antibodies (Mab). Recombinant humanized Mab, Met256 and Met432, which are located in the CH2-CH3 interface of Fc region, have been shown to be especially susceptible to oxidation (**1**). Measures to minimize oxidation include use of a gas barrier pouch, removal of head space oxygen, consideration of container closure, and control of pH, temperature, light exposure, etc.

At the *2013 PDA Annual Meeting*, representatives from packaging material manufacturer Hosokawa Yoko presented a poster titled, "Novel Plastic Bag Container for Monoclonal Antibody Final Bulk Storage to Prevent Oxidation." This presentation showed that, when storing the solution (using the example of water) in the POLYELITE AOB-L1, it gives undetectable oxygen concentration level (~0.0ppm) for up to 400 days under the storage condition of 40°C, or 75% relative humidity (RH).

*Continued on page 21*

## Journal POV

### Microbial Risk in Pharmaceutical Manufacturing and ICH Q9

Dennis E. Guilfoyle, et al.

Pharmaceutical manufacturing generally comprises a complex, multi-step processing system in which significant risks from microbial contamination are presented by diverse sources including raw materials, personnel, equipment, the facility, the environment, and container-closures. A comprehensive and rigorous approach to process design, operational control, and maintenance minimizes contamination risk to the product. A robust program should be in place to identify potential sources of microbiological contamination and to mitigate such risks. The risk management program should incorporate new information as knowledge and understanding regarding potential sources of risk expands. Indeed, as has often been found, subtle changes or anomalies that develop throughout the process lifecycle may introduce significant new microbial hazards that should be identified, evaluated, and appropriately addressed.

ICH Q9 describes important principles of sound quality risk management (QRM) that should be implemented by manufacturers to mitigate microbial hazards. The tools described

*Continued at top of page 45*

## Interest Group Corner

### Sterile Processing IG Explores Investigations Issues

Rebecca Stauffer, PDA

In a joint session with the Inspection Trends Interest Group at the *2013 PDA Annual Meeting*, **Ken Muhvich**, PhD, Principal Consultant, Micro-Reliance, and the Co-leader of the Sterile Processing Interest Group, discussed recent sterility testing and inspections issues. He told the audience of a West Coast facility with a slow-growing filamentous mold. The presence of this slow-growing microorganism could not be mitigated at that facility. Therefore, the U.S. FDA agreed with the firm's approach to perform sterility tests and media fills that were incubated for 21 days, and to perform 100% visual inspection of the products release.

Ultimately for the facility, there was "Nonsufficient evidence to invalidate the sterility test but retesting of additional samples was allowed [at that time] and the product lot was released for distribution to the marketplace," according to Muhvich.

He added, "It's really pretty simple [to decide if a retest can be performed or not] if you have a sterility test failure these days. Back in the day there used to be all kinds of reasons, in USP Chapter <71> that one could invalidate and then repeat a sterility test...most all of those reasons have gone away now. Typically, you've got to show some issue [a fault] nowadays with the testing procedure itself or the area where the testing is performed."

Next, Muhvich touched on environmental monitoring.

"I think we've all beat this to death too," he said. "Environmental monitoring samples...their limits are *not* specifications. You are not automatically rejecting a batch when an alert or action limit is exceeded for an environmental sample [active air, passive air, surface or personnel]."

He then discussed the importance of proper root cause analyses.

"As far as any sterility assurance failure investigation is concerned, the things I see people do wrong the most are two-fold: they put a CAPA in place that has no real root cause supported by data behind it, and then on the backend they don't have an effectiveness check to ensure that the CAPA's performed mitigated the problem(s)—that's the biggest problem, because failure to follow up with effectiveness checks can lead to multiple contamination events when one contamination could have been effectively resolved," Muhvich said.

In the end, the price of sterility assurance lapses can be high. Muhvich cited his experience working with the owner of a compounding pharmacy to improve his employees' aseptic technique. Despite considerable investment in training, however, the owner was forced to recall product due to obvious breaches in aseptic procedure.

*Continued at bottom of page 21*

# Important Considerations for Aseptic Processing Validation

Anne Connors, EMD Millipore

The key to successful validation of the sterility of aseptic processing lies in the analysis of a number of core considerations. For the uninitiated, aseptic processing validation is the complete set of key validations, such as component sterilization, cleaning, disinfection, HVAC systems, water systems, operator training, environmental controls, and others which together contribute to the aseptic process. An essential element is the process simulation (media fill tests) which is a required tool to demonstrate the effectiveness of contamination control. While manufacturers of aseptically processed materials can label their product to be sterile, the very nature of aseptic processing is not a guarantee of sterility, only achievement of meeting validated criteria of the aseptic process. Knowing this, terminal sterilization can be attributed to a sterility assurance level, while aseptic processing incorporates further controls to reduce risk to the end user.

In order to implement and maintain a successful aseptic process, many factors must be determined and analyzed through a formal risk assessment. As a result of the criticality of the process, validation must take a representative approach and weigh all risks to the final release of manufactured product, meaning that we must represent normal operating conditions during validation trials. Risks include everything from the manufacturing environment to the products used in an aseptic process itself. Vendors must be qualified to ensure quality and suitability, and operators must be trained thoroughly in aseptic technique. The overall goal of validating an aseptic process is to have a robust process as possible even under challenging operating conditions.

Regulations and guidance stress the importance of control, repeatability and definition of critical quality attributes. Industry and regulators are in agreement that generally aseptic technique is the

most critical factor for the prevention of contamination.

Cleanroom training is another crucial element of aseptic processing validation, along with qualification programs and SOPs. So, what exactly does this training program consist of? A thorough and robust training program should include a qualification process where cleanroom personnel demonstrate impeccable aseptic technique through gowning qualifications, as well as other aseptic manipulations they are required to perform. The understanding of air flow dynamics is another powerful tool in operator training. Such a training program should also include an understanding of basic microbiology to evaluate how a product is contaminated along with resulting consequences.

With proper cleanroom personnel training, one can overcome some of the obstacles encountered as part of continuous process verification. Well-trained cleanroom personnel are readily able to identify elements that could potentially lead to contamination of the process and environment.

Although operator training and aseptic technique is a leading factor for handling contamination control aspects, there are other considerations. Without an aseptic environment to process in, there is no aseptic process. One of the most scrutinized factors in an aseptic process is the environmental controls.

The design of a manufacturing environment plays a key role in the outcome of a final drug product. Routes of entry and egress must be established, as well as incoming material and waste transfer (unidirectional flow). This requires an imperative demonstrated knowledge of air flow dynamics and the capabilities of the facility air handling systems.

Environmental monitoring data is the primary source of information to determine the control of a manufacturing environ-

ment. Through trending history, we can define whether our sampling locations are representative to the process, justify the selection of alert and action limits, as well as identify when the environment may be moving out of control. Overall, EM demonstrates the control, independent of the drug being manufactured.

Other important design components to an aseptic process simulation include definition of line speed, number of units to be filled and the selection of a medium to use in the media fill test. All of these factors must be weighed for the most representative outcome. A line speed that is slow might be a "worst-case" representation when filling wide mouth containers, due to environmental exposure, while a fast line speed may test operator capabilities. The number of units filled should also be considered with the principal goal of representing the production operation as closely as possible. The goal is to stress the process without compromising the process. The number of units filled and their containers should be representative of the final container. After the risk assessment is built, designs implemented, SOPs put in place and an aseptic environment ensured one more determining factor is the addition to a growth promoting media into our process. This media addition, generally Tryptic Soy Broth, is an indicator of the success of the run it was introduced to. While the results of a media fill run cannot be representative of the entire validated process, it is an indicator of where certain risks may lie that could lead to contamination events.

As we know through Process Analytical Technology initiatives, we are constantly evaluating our controls and processes for continuous improvement. In the end, while aseptic processing validation can ensure production of a drug product is of the highest standard of quality, the manufacturer still must continuously verify the process.



[**Note:** The author gives special consideration to OSO Biopharmaceuticals of Albuquerque, NM for contributions.]

### About the Author

**Anne Connors** has been a Regional Marketing Manager with EMD Millipore since 2011. Previous to her marketing role, she worked in as a senior scientist in a pharmaceutical QC microbiology laboratory. 🌊



### Tech Trends continued from page 19

On the other hand, solution stored in the conventional gas barrier pouch showed approximately 7ppm (the saturated oxygen concentration under 40°C, or 75% RH) during the whole evaluation period.

The presentation indicates that, in addition to increased oxygen scavenging performance, POLYELITE AOB-L1 showed very low extractables and superior impact strength under the low temperature of -80°C. Even though the effectiveness of POLYELITE AOB-L1 for the storage of actual biopharmaceutical solution is still unknown, the difference between POLYELITE AOB-L1 and conventional gas barrier pouch is considerably huge.

While oxidation remains a potential threat, this presentation indicated that there are single-use technologies available that can reduce the threat. As a result, the company expects enhanced plastic bag containers to become more widespread across industry.

### Reference

1. G. Gaza-Bulsecu, S. Faldu, K. Hurkmans, C. Chumsae, H. Liu, *J. Chromatogr. B*, **870** (2008) 55-62

### About the Author

**Hiroo Nakano**, PhD, is a R&D scientist for Hosokawa Yoko. He has more than 15 years of experience in R&D of materials used for the manufacture of biopharmaceuticals. 🌊



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### Interest Group Corner continued from page 19

Anyone who is interested in joining the Sterile Processing Interest Group is encouraged to contact PDA's Volunteer Coordinator, Megan Kuhman at [kuhman@pda.org](mailto:kuhman@pda.org).

### About the Expert

**Ken Muhvich**, PhD, is the Principal Consultant for Micro-Reliance LLC, which specializes in microbiology and regulatory compliance consulting. He has conducted numerous mock prior approval audits of sterile manufacturing facilities, including their microbiology laboratories. 🌊



# SHOULD SCIENTIFIC DATA DETERMINE CYTOTOXIC LIMITS?

Hank Rahe, EnGuard Systems



## The next question is, why a factor of ten reduction to the proposed limit?

**OVER** the past few years, regulatory bodies have explored the issue of exposure limits during the manufacture of cytotoxic drugs in multipurpose facilities. A recent draft EMA guideline and the proposed revisions to chapters 3 and 5 of the EU GMPs appear to propose the use of toxicological data along with some rather stringent and apparently not scientifically based criteria to determine exposure limits when working with potent/highly potent drugs.

In the *Guideline on the Limits of Genotoxic Impurities* from 2006, the EMA Safety Working Party issued recommendations that drug substances with genotoxic potential be assigned a threshold limit of 1.5 micrograms per person per day as part of a general framework on dealing with genotoxic impurities within new active substances. Then, last December, EMA released the Safety Working Party's draft, *Guideline on Setting Health Based Exposure Limits for Use in Risk Identification in the Manufacture of Different Medicinal Products in Shared Facilities*, for public consultation. The new guideline is needed, according to EMA, along with revisions to Chapters 3 and 5 of the EU GMPs in order to achieve a more scientific approach to the issue of handling different products in shared facilities.

Previous requirements for cytotoxic and other certain highly potent drugs to be manufactured in dedicated facilities were neither very clear, nor scientific, and failed to take into consideration specific toxicological/pharmacological data—something many manufacturing companies routinely do in setting internal exposure limits, both for personnel safety and for the use of shared facilities and/or equipment.

The Safety Working Party noted that for genotoxic active substances without a

discernible threshold, any level of exposure is considered risky. For substances with no discernible threshold, EMA uses a predefined level of acceptable risk in the threshold limit of 1.5 micrograms per person per day. Yet, the permitted daily exposure (PDE) approach can be used for genotoxic substances with evidence of a threshold.

One can make the case that this is contrary to a pharmaceutical company's usual method of establishing exposure limits for workers manufacturing these products. Exposure limits are commonly set by the manufacturing company using data generated during the testing of the drug. Such limits are at least an order of magnitude higher than the 1.5 microgram level cited, and are different based on route of entry into a person.

The use of personnel exposure limits is questionable as a standard, however, if the exposure limit is intended for establishing an acceptable level for cross contamination or cleaning validation. There is a magnitude of difference between exposure to an active substance in large quantities e.g. when weighing or mixing powder, and cross contamination due to residual amounts left on a cleaned vessel whereby one or two dosage units with residuals may potentially be delivered to different individuals. Given the significant variances in values from toxicologists, the number selected by EMA seems, on the surface, to have no consideration of the risk-based approach. Nor is it based on scientific data from manufacturers.

The Safety Working Group's 2012 draft guideline refers manufacturers to the Threshold of Toxicological Concern concept as discussed in the *Guideline on the Limits of Genotoxic Impurities*. A threshold of 1.5 µg/person/day is established for genotoxic impurities. In contrast to impurities intrinsic to production,

residual active substances principally are avoidable, and therefore, EMA sets a stricter limit dose of 0.15 µg/person/day. This leads to the question: how does this threshold relate to cleaning limits and potential cross contamination? Is the acceptability of multiuse facilities being tied to personnel exposure limits rather than the ability to clean and detect residues as in cleaning limits? Cleaning limits are supposed to be developed on a risk-based approach based on the potential impact of product cross contamination.

The next question is, why a factor of ten reduction to the proposed limit? Residual active substances principally are avoidable, thus the EMA's stricter limit dose of 0.15 µg/person/day. While the PDE approach is consistent, it is not necessarily based on scientific data. If the stricter exposure limit of a 0.15 microgram/person/day criteria were to be used instead of current exposure limits, the argument can be made that many facilities currently manufacturing medically essential drugs would no longer be allowed to operate, resulting in severe drug shortages in an environment where this is already a serious issue.

Although not suggested in the document, should there be a single limit for all cytotoxic drugs? Product form and physical characteristics play an important role in personnel exposure. Liquids are much less likely to become airborne ➤

### Article at a Glance

- EMA draft guideline sets a risk level of 1.5 micrograms for substances lacking a threshold
- Questions remain about impact of threshold on cleaning limits
- Cleaning guidelines should be based on toxicological data



# 2013 PDA

## UPCOMING EVENTS

### JUNE EVENTS

**3**  
**Pre-Conference Workshop:  
Virus Spike Characterization  
and Virus Removal by  
Filtration – New Trends and  
Developments**  
Berlin, Germany  
<https://europe.pda.org/WSVirusTSE2013>

**3-5**  
**PDA/FDA Pharmaceutical  
Supply Chain Workshop**  
Bethesda, Maryland  
[www.pda.org/supplychain2013](http://www.pda.org/supplychain2013)

**3-7**  
**Aseptic Processing Training  
Program – Session 3  
(Week 2: June 24-28)** **SOLD OUT**  
Bethesda, Maryland  
[www.pda.org/2013aseptic3](http://www.pda.org/2013aseptic3)

**4-6**  
**4th Virus & TSE Safety Forum**  
Berlin, Germany  
<https://europe.pda.org/VirusTSE2013>

**6**  
**PDA/FDA Pharmaceutical  
Supply Chain Workshop  
Course Series**  
Bethesda, Maryland  
[www.pda.org/supplychaincourses2013](http://www.pda.org/supplychaincourses2013)

**10-14**  
**Training Course: Fundamentals  
of Aseptic Processing Training  
Course, Session 1**  
Bethesda, Maryland  
[www.pda.org/apfundamentals](http://www.pda.org/apfundamentals)

**18-19**  
**PDA Aseptic Processing-  
Sterilization Conference  
Course Series**  
Chicago, Illinois  
[www.pda.org/asepticsterilizationcourses](http://www.pda.org/asepticsterilizationcourses)

**20-21**  
**PDA Aseptic Processing-  
Sterilization Conference**  
Chicago, Illinois  
[www.pda.org/aseptic2013](http://www.pda.org/aseptic2013)

**25-26**  
**Advanced Therapy  
Medicinal Products**  
Florence, Italy  
<https://europe.pda.org/ATMP2013>

### JULY

**9-10**  
**Emerging EU Regulations and  
Inspection Trends Conference**  
Dublin, Ireland  
<https://europe.pda.org/EU2013>

**11**  
**Training Course: GDP –  
The new EU Good Distribution  
Guideline**  
Dublin, Ireland  
<https://europe.pda.org/GDP2013>

**11-12**  
**Training Course: An  
Introduction to Visual  
Inspection**  
Dublin, Ireland  
<https://europe.pda.org/TCVisInsp2013>

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*Save these dates!*

## EVENTS

## AUGUST EVENTS

**11-12**

**Training Course: Process  
Validation and Verification:  
A Lifecycle Approach**

Dublin, Ireland

<http://europe.pda.org/Process2013>

**23-24**

**Training Course: Fundamentals  
of an Environmental  
Monitoring Program**

Bethesda, Maryland

[www.pda.org/environmental2013](http://www.pda.org/environmental2013)

**29-2 August**

**Training Course: 2013 Filtration  
Week**

Bethesda, Maryland

[www.pda.org/filtrationweek2013](http://www.pda.org/filtrationweek2013)

**12-16**

**Pharmaceutical Products  
Supply Chain Integrity: A Five  
Day Training Series**

Bethesda, Maryland

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

**20-21**

**Training Course: Single Use  
Systems for the Manufacturing  
of Parenteral Products**

Bethesda, Maryland

[www.pda.org/singleusemanf2013](http://www.pda.org/singleusemanf2013)

**26-30**

**2013 Aseptic Processing  
Training Program – Session 4  
(Week 2, September 23-27)**

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[www.pda.org/2013aseptic](http://www.pda.org/2013aseptic)



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than powders with a low bulk density. Studies conducted at Purdue University showed the main factors associated with the ability of a powder to become airborne were the bulk density and particle size of the powder. Large dense particles are less likely to result in exposure than lighter less dense powders. Based on product form and characteristics, the answer is no.

If the goal is to measure amounts of drug substance on surfaces, the factor of ten increases proposed by the agency makes little scientific sense. Surface drug substance would most likely be transferred to personnel via touch contact with the surface. It has been a long standing rule that dermal transfers are a ten to one factor compared to inhalation via absorption. The proposed guidance does not take into account this fact.


The ability to measure at the low concentration also represents additional challenges. Typically, the validation of equipment and handling of hazardous drug substances is with a placebo marker. The unit operation is simulated using the placebo and sampling is conducted to determine the ability to clean using analytical instruments to measure amounts of placebo in the cleaning rinse fluid. There are few choices of placebo to use if we are required to demonstrate a level below the 0.15 microgram concentration.

While not addressed in the EMA documents, personnel monitoring is another important aspect of operating a cytotoxic facility. The monitoring of personnel draws the following questions:

- What is the goal?
- Are we monitoring exposure for route of entry into the person; e.g., inhalation, oral or dermal?
- Does one size fit all?
- Do all cytotoxic compounds have the same exposure limit?

It is appreciated that EMA's guideline is an effort to implement regulation based on sound science and allowing for a risk based approach. That is to be commended. In order to be of value to industry and regulator alike, it is recommended that EMA reach out to companies that have already developed toxicological data to assess what is out there. Orders of magnitude of differences can be obtained by different toxicologists using different data sets and methodologies and if some standardization is to be agreed on, data must be first be analyzed. This would ensure that guidance is meaningful, practical and scientifically defensible.

## About the Author

**Hank Rahe** has over forty years of experience in the pharmaceutical industry, four years in academia and twenty years plus in contamination control in pharmacy applications. At Eli Lilly, he headed up the technology group for advanced sterile processing and containment of hazardous drugs. 







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# BD Moves into Sterile Injectables Market

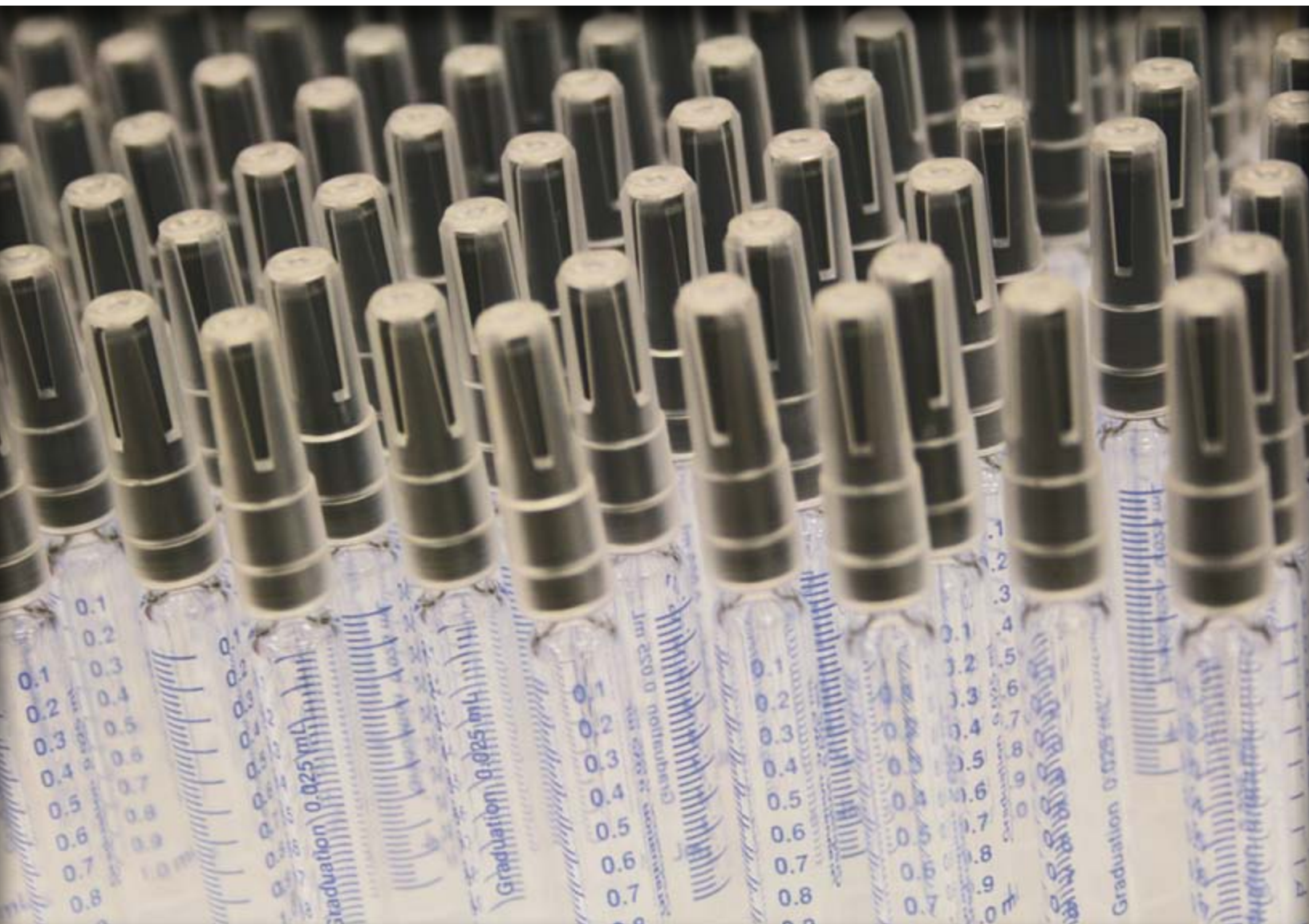
Rebecca Stauffer, PDA

*This March, BD Rx, a wholly owned subsidiary of BD (Becton, Dickinson and Company), received approval for the first product in the company's line of BD Simplist™ prefilled injectables. BD Rx plans to roll out 20 to 30 more generic sterile injectable drug products over the next few years, including some products that have been in the news as being in shortage. This development has occurred at a time when significant numbers of generic injectables are in shortage, a situation the PDA Letter analyzed in the March 2013 cover story. Becton Dickinson opened a facility in 2010 in Wilson, N.C. specifically dedicated to manufacturing these products—the first U.S. facility dedicated to sterile manufacturing built in many years.*

*To learn more about BD Rx's plans to manufacture sterile products in prefilled syringes, the PDA Letter spoke with **Mark Sebree**, President, BD Rx. The entire interview was recorded and is available at [www.pda.org/pdaletter](http://www.pda.org/pdaletter). Below are selected questions and answers from the interview.*

**PDA Letter:** Mark, it's a pleasure to speak with you today. We're interested in how BD Rx is focusing on manufacturing sterile generic injectables in prefilled syringes, and I want to start by just asking a couple of questions about the approval process with the U.S. FDA. And we're curious how BD Rx is working with FDA.

**Sebree:** Well, these drugs were approved as ANDAs, so they're somewhat traditional in the approval process, because this is also, obviously, a drug device combination product. We needed to work with other parts of the Agency other than the Office of Generic Drugs to demonstrate the appropriateness of our syringe for these drugs. But they are actually approved as ANDAs.





**PDA Letter:** My next question is about the first drug that BD Rx received approval for, the generic antihistamine. Is there any particular reason that drug was selected?

**Sebree:** Actually, the first drug was diphenhydramine, which is generic Benadryl. And that drug was selected as really the first of 20 to 30 drugs that we will launch over the upcoming years. So, it was important for us to start with drugs that allowed us to basically develop several manufacturing processes. We will manufacture drugs that require both terminal sterilization and aseptic filling. And the first drugs that you'll see were selected because they allow the largest clinical change. In other words, we've selected drugs that are the most commonly used drugs in the marketplace, and our goal is to really change the paradigm by which these drugs are administered. So, the selection really boils down to...we're trying to create the greatest possible impact in the shortest possible time.

**PDA Letter:** I also did a little background research on the generic Benadryl, and from what I understand this particular drug product was also manufactured by Hospira, and at one point last year was listed on the FDA website as being in shortage.

**Sebree:** That is correct.

**PDA Letter:** So, of the 20 or 30 other prefilled injectables that BD Rx will be manufacturing, will any of these be injectable products that are currently shortage, or have been in shortage in the past?

**Sebree:** Absolutely. I mean, we didn't start out to work on drugs that we thought would be in short supply, however, because of the fact that we've chosen drugs that are used so widely, a number of the drugs that we will launch are currently on the FDA shortage list. Again, our goal was to basically reduce medication errors. The fact that some of the drugs are on the shortage list makes us feel a little bit better about what we're doing but that wasn't our primary thrust.

For instance, one thing just to round that out, you mention that you just saw that we just got approval for metoclopramide, which is our second drug. And that drug *is* still on the shortage list.

**PDA Letter:** So, sort of related to the last question, how does BD Rx plan to avoid the quality issues that have plagued other manufacturers of these products? Is the new Wilson, N.C. facility key to this?

**Sebree:** Absolutely! You just hit the nail on the head. If you look at the infrastructure that supports generic drug supply in the United States today, those manufacturing facilities are quite old. There was a recent paper, in fact, in *Nature* [see the story, "Global Regulators Address Role of Quality in Shortages, Seek Solutions" on p. 18 of the March *PDA Letter* for an analysis of that paper] that basically specified that these facilities were, for the most part, built well over 40 years ago. What we've done in Wilson is to basically bring all of the state-of-the-art manufacturing that we could muster to one central location, and frankly, automate that as much as possible.



So, our belief is that through that automation, and through that state-of-the-art facility, we'll be far better able to maintain the reliability of supply.

**PDA Letter:** And according to what I've read, the facility has been open since 2010. Are there any plans to build other facilities to support the BD Rx line of products?

**Sebree:** What we're planning is to grow that facility commensurate with need. The facility has all the necessary land and infrastructure to expand it on a modular basis, so we do expect that we will expand it in the future, and again, that will be based on market uptake.

**PDA Letter:** And I also saw that there are plans to add 25 new job positions at this facility, so is there a timeline for filling these positions?

**Sebree:** I'm not exactly sure where you got the 25 number but that's actually a relatively short-term projection. So, I believe that we're already implementing the hiring of those additional staff. Over the longer range...the number will go up not insignificantly from that point.

**PDA Letter:** We're also currently wrapping up our career issue of our newsletter (the May 2013 *PDA Letter*), and our members are always interested in career-related topics. So, are there any particular skill sets that BD Rx is looking at for any of these positions?

**Sebree:** I think it's pretty much what you would expect in a sterile manufacturing facility. Obviously, we will continue to need pharmaceutical engineering, quality—both compliance and quality assurance people—and people who are well-versed in procurement of active pharmaceutical ingredients and pharmaceutical equipment.

**PDA Letter:** And can you tell us more about the cleanroom at the Wilson facility? How is it classified?

**Sebree:** Actually, that's proprietary information, in terms of the various classifications. I can tell you that the facility itself is designed in such a way that it maintains the highest sterility possible. So, we've done everything we can to make sure that there's no supply interruptions due to a sterility challenge.

**PDA Letter:** Going back to quality, are prefilled syringes advantageous from a quality perspective, either in manufacturing or in use?



**Sebree:** Again, I'm not sure I know exactly what you mean by "quality perspective." In other words, we think they bring advances and benefits to the clinician. So, if you're using the term "quality" more globally, there's clearly benefits to the clinician being able to reduce the number of steps needed for the administration of these drugs, which is the real reason we're doing this. We think there's going to be a reduction in medication errors, specifically around preparation and administration, because a prefilled syringe inherently requires less steps for administration than a vial or an ampoule. So, there's certainly a quality aspect to what we think will be a potential reduction in medication errors.

From a pure quality standpoint in terms of manufacturing, the same high quality standards have to be used to manufacture a prefilled syringe that are used to manufacture a vial or an ampoule.

So, I hope that answered your question.

**PDA Letter:** I think it does. And I guess the other question that I have is by using prefilled syringes BD Rx will be marketing combination products. So, do the new combination product rules that FDA has released help your company with its filings?


**Sebree:** Well, I think some of the new requirements that the FDA have released are probably a direct outgrowth of the work that we've done to kind of champion the need for these drugs being available in prefilled syringes. So, it's hard to say what effect they've had on the filings we've had in the past. But clearly they'll help provide a roadmap for the filings in the future.

**PDA Letter:** Anyway, that's all the questions I have. Is there anything you would like to add?

**Sebree:** Well, I think we're very excited about the approval of these drugs

and our entrance into the marketplace. We're convinced that having these drugs in prefilled syringes is going to enable clinicians to practice the administration of medicines far more safely than they're able to today. And we're looking forward to additional FDA approvals so that we can basically provide greater and greater possibilities for clinicians to do that.

### About the Expert

**Mark Sebree** is the President of BD Rx, a wholly-owned subsidiary of BD. In this role he oversees all of the development, manufacturing and commercialization of the newly-launched BD Simplist<sup>TM</sup> ready-to-administer, prefilled injectables. Prior to joining BD Rx in 2005, Sebree held various leadership positions at U.S. generic injectable companies. 



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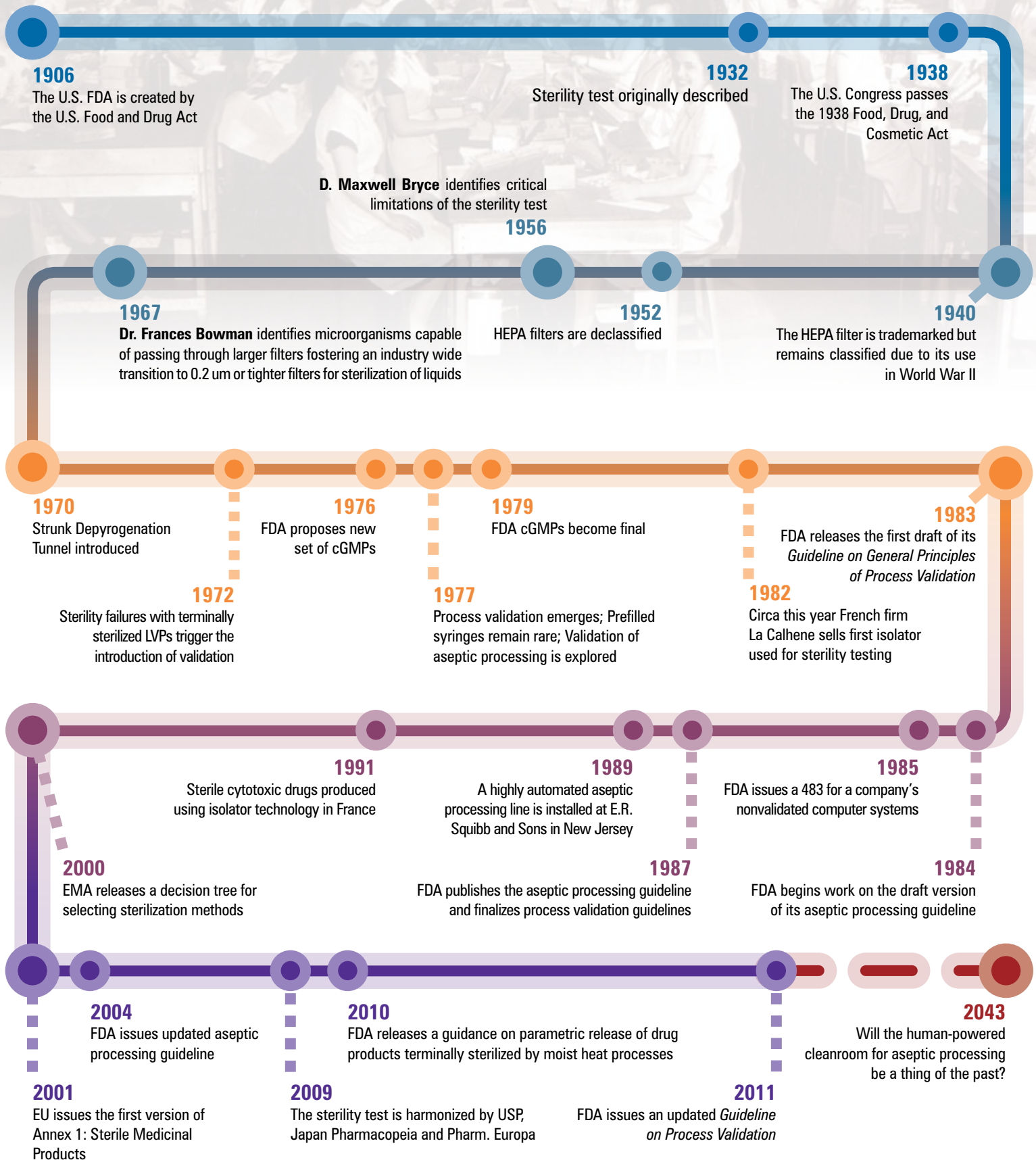


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# PDA Comments on European GDP Guidelines

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

30 April 2013

European Commission  
Health and Consumers Directorate –General, Brussels  
[sanco-pharmaceuticals-d6@ec.europa.eu](mailto:sanco-pharmaceuticals-d6@ec.europa.eu)

Ref: Guidelines on the Principles of Good Distribution Practices for Active Substances for Medicinal Products for Human Use



To the Health and Consumers Directorate-General:

PDA is pleased to provide comments on the template submitted for public consultation. PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our review was completed by an international group of expert volunteers with experience in investigational medicinal products, regulatory affairs and GMP on behalf of our Regulatory Affairs and Quality Advisory Board.

PDA believes this guideline should reference existing regulations and legislation and only add additional clarification, where warranted.

We do not see the need for repeating large parts of the text already published in EudraLex Vol 4 Part II, and Chapters 7, 10 and 17. In evidence we have included a comparison table between the draft guideline and the ICH Q7 document with our comments. If you have any questions, please contact me.

With very best regards,

Georg Roessling, PhD  
Senior Vice President,  
PDA Europe gGmbH

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**Alan Burns**, Sartorius  
**Robert Counce**, Hospira  
**Claudio Correa**, Roche  
**John Finkbohner**, PhD, MedImmune

**Karen Ginsbury**, PCI Pharmaceutical  
Consulting  
**Jeffrey Hartman**, Merck  
**Steven Mendivil**, Amgen  
**Elizabeth Meyers**, Amgen  
**Shin-ichiro Mohri**, Kyowa Hakko Karin  
Pharma  
**Edwin Rivera-Martinez**, Sanofi

**Stephan Roenninger**, Amgen  
**Siefried Schmitt**, PhD, PARAXEL  
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# Regulatory Briefs

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

## North America

### Regulatory Commissioner Leaves U.S. FDA

**Deborah Autor**, Deputy Commissioner for Global Regulatory Operations and Policy, will officially leave her position at the U.S. FDA June 1. She will then join Mylan as SVP, Strategic Global Quality and Regulatory Policy. Before serving as Deputy Commissioner, Autor spent several years within CDER's Office of Compliance, including a five-year stint as OC's director.

On May 18, **John M. Taylor, III**, Counselor to the Commissioner, began serving as Acting Deputy Commissioner while the Agency looks for a replacement.

### New Pilot Program for INDs

The CBER division of the U.S. FDA is inviting IND sponsors to participate in the Center's eSubmitter Program, which is an automated, electronic program, as part of a pilot of the system. eSubmitter includes a template geared specifically for IND applications pertaining to antivenom drugs. This pilot is supposed to provide industry and regulatory staff an opportunity to review the new system.

Companies interested in participating must submit a request by July 8.

### Guidance on Beta-Lactam Drugs Now Available

On April 17, the U.S. FDA released a guidance concerning implementation of controls for prevention of cross contamination of pharmaceuticals and APIs with nonpenicillin beta-lactams. At this time, cGMPs only require separation measures for penicillin products. Due to potential cross contamination health

risks, FDA would like to expand the framework to include separation measures for all classes of beta-lactam drugs.

Comments can be submitted at any time for this proposed guidance.

### El Salvador Passes New Medicines Law

In early April, El Salvador's General Medicine Law came into effect. This law creates an independent entity, the General Directorate of Medications, responsible for supervising supply chain activities, including distribution, imports and prescriptions. In addition, the law reduces the prices of over 6,000 medications to better reflect medication prices in other Central American countries.

## Europe

### EMA Upgrades EudraGMP to Include GDPs

EMA announced on April 18 that the Agency had updated the EudraGMP database to include GDP information in addition to GMP information. The new database will now be called EudraG-MDP and will be gradually updated by various EU regulatory bodies to include information on wholesale distribution authorizations, GMP certificates, statements of GMP noncompliance, and registrations of active substance manufacturers, importers and distributors.

### ECA Conducts Process Validation Survey

The European Compliance Academy recently released results of a survey of industry respondents on EMA's planned Annex 15 revision. Over 90% indicated they would like to follow the process validation lifecycle. More than 75%, how-

## Key Regulatory Dates Comments Due

### July 8 — New Pilot Program for INDs

ever, would prefer to retain the DQ-PQ concept. Only 50% want to use 3-batch validation for cleaning.

ECA plans to send results of the survey to EMA. The survey will also be discussed at ECA's June GMP conference.

### European Commission Publishes Active Substances Q&A

In April, the European Commission published Version 4.1 of its Q&A document concerning importation of active substances into the European Union. Version 4.1 includes two new questions—2A and 10A. Question 2A deals with applicability of the rules to blood plasma while Question 10A deals with applicability of the rules for starting materials undergoing additional purification or chemical synthesis.

## Asia-Pacific

### India Publishes API Export Revised Guidances

The Central Drugs Standard Control Organization in India has published revised draft guidelines on "written confirmation" for exporting APIs into the European Union. This guidance lays out procedures that must be followed in addition to identifying which documents are required for applications. It is supposed to centralize all activities pertaining to API exports into EU countries. 🇮🇳



## Are You Current?

Carol Rehkopf, CBER, U.S. FDA and Program Committee Member

Whether you're a seasoned veteran of the industry or just getting your feet wet, you won't want to miss the *2013 PDA/FDA Joint Regulatory Conference* this September. Our theme, *Driving Quality and Compliance throughout the Product Life Cycle in a Global Regulatory Environment*, is what it's all about. If you are in the business of bringing great products to market, you will find meaningful information, regardless of your position!

As in the previous 20 years, the U.S. FDA is supporting the conference through active participation of the program plan-

ning committee, and by offering quality presenters on significant topics. The PDA/FDA partnership is strong, which is evident in the quality of the program. Industry and FDA representatives alike work hard to bring you current regulatory, quality, compliance, development and manufacturing information that applies throughout the product lifecycle.

Besides the conference topics, the *2013 PDA/FDA Joint Regulatory Conference* is also your opportunity to interact shoulder to shoulder with peers and representatives from FDA in both formal

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and informal settings. The continental breakfasts, refreshment breaks, networking reception and gala reception all provide wonderful opportunities for you to get to know others better and become plugged into the larger medical product community. 🍷

As an added benefit, there will be six PDA Training and Research Institute courses offered immediately after the conference from September 19–20. To learn more about these courses, visit [www.pda.org/pdafdacourses2013](http://www.pda.org/pdafdacourses2013).

### Relevant topics include the following:

- The Food and Drug Administration Safety and Innovation Act (FDASIA)
- Quality agreements
- New facility design options
- Understanding GMPs
- GMP's for API's/drug products, excipients and components
- Outsourcing
- The EU's GDPs
- Novel dosage forms
- Inspections and inspection collaboration
- Managing supply crises
- And much more!!

### If this isn't enough, breakfast sessions and interest group sessions will be offered, too. Here's a sneak peek at some of those topics:

- Inspection trends
- Filtration
- Process validation
- Visual inspection
- Understanding metrics
- Microbiology and chemistry lab FDA inspectional findings



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# Workshop Addresses Monoclonal Antibody Complexities

Conference Co-chairs Juan Giménez, PhD, GSK Biopharmaceuticals, and Ilona Reischl, PhD, BASG/AGES

On behalf of the Program Planning Committee and PDA, we are pleased to invite you to the *6th Workshop on Monoclonal Antibodies* which will be held in Basel, Switzerland this September.

Monoclonal antibodies (mAbs) and related products continue to be the main focus of biotechnology and biopharmaceutical companies, as increasing numbers of these therapeutic molecules are currently being evaluated in clinical trials and continue to be licensed worldwide. While the industry invests in new and improved mAbs for various disease targets, there is an increasing need to consider product quality attributes that impact patient safety and efficacy of these glycoproteins, such as unwanted immune responses.

Because of its molecular complexity, a therapeutic mAb can induce immunogenic responses that may lower the effective dose or reduce its half life via neutralization or, in some cases, lead to severe reactions, jeopardizing the safety of patients. Therefore, issues around product immunogenicity are of great importance when assessing a product's clinical profile.

This workshop focuses on the topic of immunogenicity with an emphasis on aspects important to chemistry, manufacturing and control (CMC). Through a combination of lectures and case studies presented by industry and regulatory professionals, participants will learn how these CMC issues relate to quality attributes that have the potential to influence

**6<sup>th</sup> Workshop on Monoclonal Antibodies • Basel, Switzerland • Sept. 11–12 •**  
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immune responses. Emerging regulatory guidelines will be reviewed and panel discussions with experts from both the biopharmaceutical industry and health authorities will address questions from the audience. The practical knowledge gained from this workshop will provide a valuable opportunity to benchmark best practices and clarify regulatory expectations.

We look forward to providing an informative and enjoyable workshop. 🌐

Register by July 8 and Receive the Largest Registration



The Parenteral Drug Association presents the...

## 2013 PDA/FDA Improving Investigations Workshop

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The 2013 PDA/FDA *Improving Investigations Workshop* is an opportunity to learn about the technical aspects of an investigation as well as how to conduct investigations.

The workshop will include such speakers as:

- Thomas J. Arista, National Expert Investigator, ORA, FDA
- Veronica Cruz, Vice President, Quality and Compliance, McNeil Consumer Healthcare
- Swroop K. Sahota, PhD, Vice President, Quality Operations, Catalent Pharma Solutions
- Sharon Timmis, Vice President, Operational Excellence, Pfizer
- Juan Torres, Senior Vice President, Quality, Biogen Idec
- Martin VanTrieste, Senior Vice President, Quality, Amgen, Inc.



Visit [www.pda.org/investigations2013](http://www.pda.org/investigations2013) for more information and to register.

**Exhibition: September 18-19**

# Protect Your Biologics From Viral Contamination

**Program Planning Committee Co-chairs**  
**Arifa Khan, PhD, CBER, U.S. FDA and**  
**Dominick Vacante, PhD, Janssen Pharma-**  
**ceutical R&D**

The *PDA/FDA Advanced Technologies for Virus Detection in the Evaluation of Biologics Conference: Applications and Challenges* will be held this November. Recent discoveries of virus contamination of biological materials used to manufacture biomedicinal products, and the challenges of addressing virus safety concerns in novel cell substrates, emphasize the need for sensitive, broad spectrum assays to detect adventitious viruses and other microbial agents in biological products. This conference will provide a forum for discussing new molecular virus detection technologies, including: massively parallel or deep sequencing, broad range PCR with mass spectrometry and virus microarrays.

On Nov. 12, prior to the conference, PDA's Training and Research Institute will hold two courses. The "Virus Contamination in Biomanufacturing: Risk Mitigation, Preparedness and Response" course will provide the necessary information and tools to enable companies and participants to understand and implement best practices to reduce the risk of viral contamination during the manufacture of biologics. The second course, "An Introduction to the Advanced Molecular Methods for Virus Detection," will provide a thorough description of the advanced molecular methods for virus detection including: massively parallel sequencing, virus microarrays and PLEX-ID.

**PDA/FDA Advanced Technologies  
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Following two days of presentations covering regulatory and industry perspectives on virus detection methods and bioinformatics as an analysis tool for massively parallel sequencing, the conference will end with an expert panel comprised of representatives from industry and regulatory agencies. The panel will discuss the benefits and limitations of these new technologies and their applications for characterization and evaluation of biologics. Discussions will aim for consensus and identify issues that remain unresolved, requiring further discussion.

We look forward to seeing you at this conference! 🍷



# In-House Aseptic Training Offers Many Advantages

Over the past few years, the demand for aseptic processing training has grown, and the training has now extended beyond the traditional courses we have offered at our facility since 1999. Recently, PDA developed a specialized one-week, hands-on training program on aseptic processing meant to be delivered at a customer's facility.

The main reason for the success of this program has been the team of instructors that have delivered the training. This month, we thought we'd give you a little insight into these instructors and how an in-house course is a little different than our traditional offerings in Bethesda, Md. and those associated with our conferences.

The core team of instructors for this in-house consists of:

- **Joseph Lasich**, *Consultant*
- **Brent Watkins**, *Veltek Associates, Inc.*
- **Rainer Newman**, *Consultant*
- **Cheryl Custard**, *Consultant*
- **Carol Lampe**, *Consultant*

## How long have you been associated with PDA?

**Newman:** 30 Years

**Watkins:** Member since 2000, Exhibits Committee member since 2007, TRI faculty since 2010

**Lampe:** Over 30 years. I joined within the first couple of years of working in the industry for Baxter Healthcare.

**Custard:** I've been a PDA member since 2000 and on the PDA faculty since 2001.

**Lasich:** I have been associated with PDA for at least 15 years of my industry experience.

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

**Newman:** Aseptic processing consists of many interrelated, often complex requirements and technologies. These must be understood and appropriately applied in order to successfully produce sterile product while best meeting regulatory, quality and business needs. The course defines these requirements and technologies using highly experienced instructors who provide insights.

**Watkins:** The most important thing this course identifies is how the multiple aspects of an operation (strands of the rope) affect and rely on each other. With all aspects of the operation working in harmony, the chance for product contamination is extremely low. Many times, individual employees who may not necessarily have exposure to multiple departments within a facility have the unique opportunity to experience the different "strands of the rope" function together.

**Lampe:** I think that this course provides the industry with demonstrated best practices. It also points out where pitfalls have occurred in the past, knowledge gained either through personal experience or those written up in U.S. FDA warning letters.

**Custard:** This course addresses how individuals from the same company interpret internal operating procedures and allows these same individuals to see what, if any, differences, each has in interpretation. It creates a safe, open environment for employees to discuss not only the inconsistencies they may have in their internal procedures, but perhaps offer areas for improvement for items/areas they work on in their day-to-day activities.

**Lasich:** Helping students at the client firm learn that there are many integrated factors that comprise aseptic processing. These factors comprise both functions and the people who perform the functions. This is the primary challenge in aseptic processing.

## How is this course different than others you have been asked to teach for PDA TRI?

**Watkins:** It is very similar to the aseptic processing course taught at TRI. The format is different in that we only have a week with the students. Also, the demographics of the students are different with on-site training. Generally, at TRI we have salaried supervisors and managers, whereas our on-site training focuses more on hourly workers and operator-level staff.

**Lampe:** Generally, when you are teaching for PDA it occurs in conjunction with PDA meetings. The individuals who attend are generally comprised of meeting attendees. These individuals



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# 2013 PDA Europe Pharmaceutical Cold Chain Integrity

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- Challenges for wholesalers to commit to new EU GDP guidance
- Vision and best practices to secure the supply chain during storage and transportation
- New technology developments towards active and passive shipping
- Air, road and ocean solutions to secure and to temperature control shipments
- Network opportunities with members of regulatory agencies, PDA PCCIG, IATA, TAPA, GIRP, pharma industry, logistic service providers, partners in Good Supply Chain Practices and vendors

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are looking to build on limited experience or have operations that need more direction.

**Custard:** The two main differences, in my personal career with PDA, are 1) the classroom is filled with employees who all report to the same company, and 2) the training will be conducted over several weeks, with different company employees each week, with different levels of experience. This allows for better understanding of each other's role at the company and may help the company identify areas needing improvement more quickly.

**What would you say to people considering contracting TRI for in-house training?**

**Newman:** That they might get the best of two worlds by this approach. The first class training that PDA is known for, and the benefits of on-site training discussed above.

**Watkins:** I would say that it is beneficial, with one stipulation: management has to do their part in supporting PDA's efforts on site. From director to first line supervisor, individuals who are being trained must begin with the proper attitude, and with a desire to learn and improve.

**Lampe:** I think that before the client contacts PDA, very specific goals for the training program (product, process, testing, areas which need improvement or regulatory concerns) need to be defined and agreed upon. If you can define what you want from a training program, it can be a pertinent and an effective training tool.

**Custard:** We offer a wide range of training provided by industry experts who can tailor the course to individual company needs. And it is provided by PDA, a recognized leader in aseptic processing training.

**Lasich:** The benefits to a firm considering an in-house course are that it provides an opportunity to customize the sessions and provide an understanding of the firm's products and processes.

**[Editor's Note:** To learn more about how TRI can conduct aseptic training at your facility, please visit the PDA website.]

## About the Experts

**Cheryl Custard** is an aseptic processing and training consultant with 15 years of pharmaceutical and training experience.



**Carol Lampe** is a senior consultant with JMHA.




**Joseph Lasich** owns JLL Global Pharma Services. He retired from Alcon as Director, Corporate QA



after 33 years with the company.

**Rainer Newman** has nearly 40 years of experience in sterile product supply chain operations.



**Brent Watkins** works as a Technical Manager with Veltek Associates. 





Mike Sadowski, Baxter Healthcare

## PDA Technical Reports: Built on a Foundation of Science

I've had a passion for science for as long as I can remember. On my first day at a new school back in the second grade, my teacher, Sister Christina Marie, ordered the class to get into line to go to the "laboratory." My excitement turned to disappointment when we stopped at the restroom and apparently ran out of time to go to the laboratory. The exact same thing happened the next day. On the third day, I raised my hand and asked if we could skip the restroom so that we would have enough time to finally go to the laboratory. Much to my dismay, she stated that there was no laboratory and that *lavatory* was another name for the restroom. My kids believe that this is the ultimate indisputable evidence that I am a science nerd—they are probably right!

Over the course of my career, I have been a member of many science-based organizations, however, none of these have come close to offering the comprehensive membership benefits and resulting overall value proposition of PDA. Similar to the majority of PDA members, I believe that one of our greatest member benefits are the technical reports containing science-driven guidance, usually culminating in best practices for industry. The efficient development and timely publication of technical reports continues to be a featured priority of our strategic plan.

To provide further illustration, I will summarize my experience with *PDA Technical Report No. 1 (Revised 2007)* on moist heat sterilization which superseded PDA's flagship *Technical Monograph No. 1 (1987)*.

During the development of the updated TR1, it became evident that the content needed to be expanded to address industry needs across the spectrum of moist heat sterilization topics that had significantly evolved since 1987. It was decided that the "handbook" format of PDA technical reports would be preserved, and that incremental content would be addressed through the development of a series of companion technical reports that would serve to provide complementary content to TR1.

The developmental phase for TR1 consisted of the initial drafting of content followed by a series of "live" interactive feedback sessions presented to industry, pharmacopoeial and regulatory professionals in Ireland, the United Kingdom, Italy and the United States. Based on that feedback, a final draft was completed and then vetted across PDA membership. After all comments were reconciled, the document was issued in 2007.

After completion of TR1, similar efforts began with its companion documents and each of these has now been completed with the issuance of *Technical Report 61: Steam In Place*, which was preceded by *Technical Report 48: Moist Heat Sterilizer Systems* and *Technical Report 30: Parametric Release of Pharmaceuticals and Medical Device Products Terminally Sterilized by Moist Heat* as well as books focused on moist heat sterilization fundamentals that addressed the use of biological indicators, thermal process validation and environmental control and monitoring. It is important to note that all PDA technical reports are now available continuously to members through a dedicated portal on the PDA website.

Many adjacent benefits are also realized from technical reports to strengthen the comprehensive portfolio of scientific offerings for the benefit of our members. PDA Training and Research Institute (TRI) courses have also now been developed and implemented across the globe to further enhance the knowledge of our membership on the topics covered by TR1 and each of the companion documents. The content of these courses is now owned by PDA and the instructors consist of task force members that contributed their expertise in the development of these documents and associated courses. Participation in TRI courses represents a unique opportunity to interact with colleagues and subject matter experts to gain additional technical insight for technical report topics.

PDA technical reports also serve as the subject matter centerpiece for PDA conferences. As I write this article, we are in the final planning stages of a second conference on aseptic processing and terminal sterilization which will be held during the week of June 17 in Chicago featuring dedicated sessions and TRI courses on sterilization-related technical reports. I hope to see you in Chicago this June!

As you can see, PDA technical reports offers each of us a unique and valuable opportunity to enhance our careers and improve operations within industry through collaborative documents built on a foundation of science and best practices. 🌐



*Journal POV continued from page 19*

in ICH Q9 can help manufacturers become aware of emerging microbial risks not only in emphasizing investigations into potential hazards, but in also stressing that risk management is not a “one time” exercise. Rather, “risk management should be an ongoing part of the quality management process” and “the output/results of the risk management process should be reviewed to take into account new knowledge and experience.” Thus, in regard to microbial contamination, manufacturers should monitor microbial profiles of natural raw material sources, and maintain current knowledge of contamination experiences reported by firms at technical conferences or in relevant literature (e.g., new veterinary findings of viral or bacterial risks from source animals). Appropriate measures should then be undertaken to mitigate risk based on such knowledge.

This awareness includes acquiring knowl-

edge of the microorganisms that may enter or grow in the manufacturing process and cause upstream bioburden issues. Examples include viruses in raw materials that amplify in production cell culture, Gram-negative microorganisms that may proliferate at the pre-filtration stage, or downstream bioburden issues including finished product contamination. Recent examples of contamination problems have included bacteria that pass through sterilizing filters (e.g., *Leptospira*) and viruses present in raw materials (e.g., Vesivirus 2117) that are amplified during cell culture steps. We recommend that firms share these experiences in as open a manner as feasible, as these are public health risks that transcend competitive interests. As knowledge of emerging possible routes of contamination is made available, we also encourage manufacturers to share any appropriate risk mitigation measures that were adopted to better

safeguard the product.

A risk-based assessment incorporating the five recommendations above should be conducted by appropriate technical staff, including microbiology personnel with specialized training in the interpretation of microbiological data. Medical expertise may also be necessary to assess potential patient hazard. A final determination of process consistency and product safety that is both objective and collaborative should be supported by management. Ultimately, by incorporating a lifecycle approach to QRM, the quality system will help prevent surprises and assure the consistent supply of safe and effective medicines.

**[Editor's Note:** This editorial was excerpted from the March/April 2013 edition of the *PDA Journal of Pharmaceutical Science and Technology*. To read it in its entirety, please go to [journal.pda.org](http://journal.pda.org).]



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## Awards, Photos, History, Podcast and a Correction!

The June issue came together very nicely for the editorial and design team. Working closely with the PDA Letter Editorial Committee, we were able to produce an informative article on new requirements on exposure limits in the manufacture of highly potent drugs. **Rebecca Stauffer** worked closely with the author, who presented his information at the *2013 PDA Annual Meeting*.

Rebecca also used some of her time at that meeting to meet with **James Akers** to develop the theme of this issue's infographic: a history of sterile product manufacturing. Dr. Akers advised Rebecca to follow up with another expert on the subject, James Agalloco—both are well-known former leaders of PDA. The history touches on many milestones.

The Annual Meeting is also a place for PDA to honor those members whose volunteerism goes above and beyond. Read all about the winners in the News and Notes section of this issue. A six-page "Photostream" documents many of the speakers and other activities at this year's Annual Meeting (you can see them in People). This year, Letter designer **Katja Yount** is working with PDA's web master, **Faramarz Kolivand** to post additional Annual Meeting photos on Flickr. The information on accessing it can be found in the Photostream.

The second PDA Letter Podcast is available. Rebecca Stauffer interviewed **Mark Se-bree** from BD Rx on the company's move into the sterile injectable drug business. The interview focuses on the new facility BD Rx built in North Carolina and touches on some of the career opportunities at the high-tech plant. A portion is excerpted in this issue (Features) and the full podcast is available at the *PDA Letter* website.



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

### Correction

Finally, I want to thank long-time PDA member, contributor and volunteer **Destin LeBlanc** for contacting the *PDA Letter* staff to point out an error in the April infographic "U.S. vs. EU Process Val. Guidances" (April 2013, p. 26).

The editorial team mixed up the concepts of "continuous process verification" and "continued process verification." Destin explained to us the difference between "continuous" and "continued." Indeed, the editorial team made a mistake in the graphic by indicating that the EU and U.S. guidance were not in harmony on this subject. In fact, both guidances suggest that "continuous process verification" is acceptable: FDA does so in a section on PAT; the EU describes it as an alternative approach. Both documents are completely harmonious with respect to "continued process verification."

The editorial team made this error, and the advisors listed in the Infographic were not responsible for the mistake.

We apologize for any confusion this egregious mistake might have caused. 🙏

# PDA Letter

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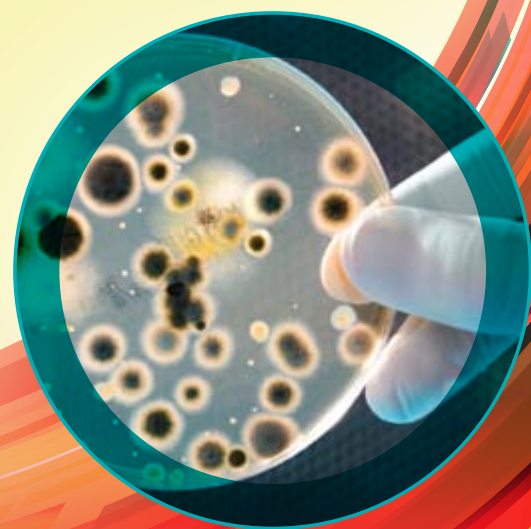


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