People • Science • Regulation

PDA Letter

Volume LIII • Issue 8 www.pda.org/pdaletter September 2017

Company Sees Success With Automated Endotoxin Testing 26

RUN YOUR FACILITY. DON'T LET IT RUN YOU.

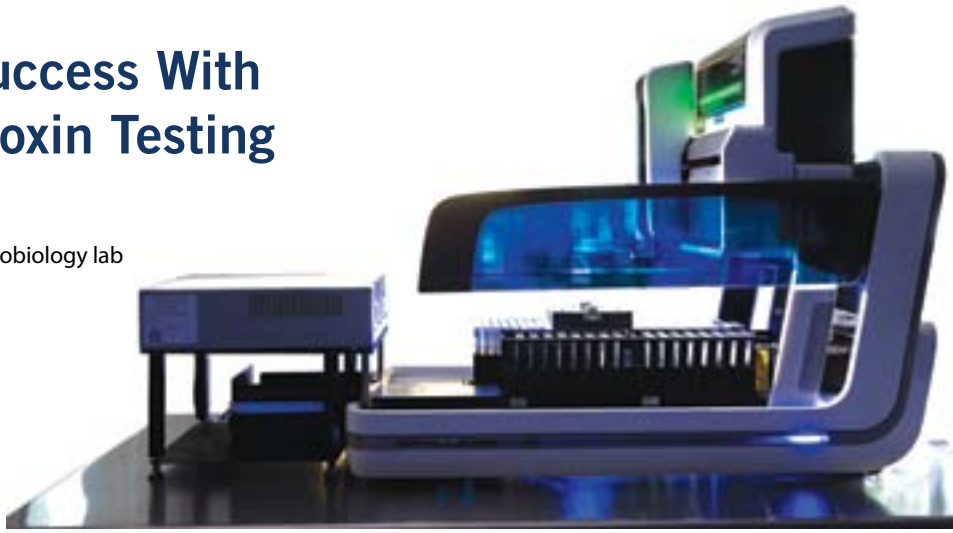
Concerned about maintaining your data integrity compliance status? Managing your equipment fleet? Upcoming regulatory inspections? You're supposed to run your facility, not the other way around. As an all-encompassing endotoxin test management platform, Charles River Cortex™ empowers you to make informed, confident decisions while maintaining a centralized state of control throughout your manufacturing facility. Discover how to take charge of your data, equipment, and reporting at **www.criver.com/cortex**.

September 2017 PDA Letter

12th Annual PDA Global Conference on Pharmaceutical Microbiology

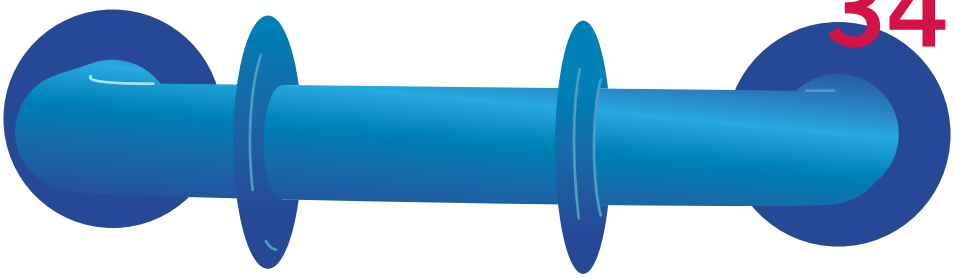
Show Issue

How can today's microbiologists solve the latest pressing challenges in microbial control? By achieving a culture of collaboration. In this spirit, look for articles previewing sessions of this year's microbiology conference with this banner at the top of the page.



Cover Photo Courtesy of Charles River Laboratories

InfoGraphic



PDA Letter

Volume LIII • Issue 8 www.pda.org/pdaletter

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Subscriptions are not available.

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Departments

Digital Exclusives

> A Stepwise Approach to Effective Data Management and Analysis
PDA Education Instructor **Gilberto Dalmaso** discusses how to develop a data management plan for environmental monitoring. This is a preview of his course that follows the *12th Annual PDA Global Conference on Pharmaceutical Microbiology.*

> The Future of Cell and Gene Therapies is Here
Both industry and regulators are working together to resolve the challenges of manufacturing new therapies.

> **On the Issue | Continuous Microbial Monitoring: Four Points to Consider**
Pfizer's **Jeffrey Weber** discusses how biofluorescent particle counting can benefit a manufacturer's operations.

pda.org/letter

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Calling All Active PDA Members – Vote Now!

Online voting is now open for the 2018 PDA Board of Directors and Officers Election

PDA members, online voting has opened for the **2018 PDA Board of Directors and Officers Election**. Take a moment and vote for your candidates of choice at **pda.org/vote**.

All PDA members in good standing as of **midnight on August 24, 2017 are eligible to vote**. Voting closes at **11:59 p.m. EST on November 15, 2017**. Any votes cast after this date and time will not be accepted.

If you need assistance, please contact PDA at +1 (301) 656-5900 or vote@pda.org.

Thank you for being a valued PDA member and for voting.

Instructions for Voting:

- Go to **pda.org/vote**
- Log into the system using your PDA Member number and last name
- Please read the instructions for each question carefully
- Review the choices for each position then select a candidate for that position
- When you complete your ballot, review your selection and then check the participant consent box and click on the "SUBMIT" button
- You have now completed the voting process
- You can view and print your receipt or just exit the PDA eBallot System

pda.org/vote

The Parenteral Drug Association presents the...

2017 PDA Modern Biopharmaceutical Processing Conference

November 28-29, 2017 | Singapore
Hilton Singapore
Exhibition: November 28-29
#PDASingapore


Image supplied courtesy of Pall Corporation

From Facility Design to Product Distribution

Singapore has become an established global center of biopharmaceutical manufacturing. Join us for this important conference addressing critical considerations when manufacturing modern biopharmaceuticals.

Sessions will include a case study of a new Singapore facility for biopharmaceuticals manufacturing, details on experiences with process, regulatory agencies, and business-related advantages as well as a technology update session that will showcase new trends in technologies for the pharmaceutical industry. There will be plenty of time for dialogue and questions during the panel discussions and networking opportunities with your peers. There will also be an exhibition presenting equipment and services.

Other topics to be addressed include:

- The latest developments in regulations
- Technology transfers and upscaling from research to manufacturing site
- Processing, especially in single-use systems
- Continuous manufacturing approaches
- Challenges of temperature-controlled distribution of biopharmaceuticals in the global supply chain

Speakers will include experts from U.S. FDA and regional health authorities, biopharmaceutical and pharmaceutical experts, and key suppliers and equipment manufacturers from around the world.

Don't miss this unique chance to hear from industry and regulatory authorities about these important pharmaceutical manufacturing challenges!
Register today.

pda.org/2017BiopharmSingapore

The Pulse of Microbial Control

Summer is ending, ushering in autumn, a time of change and transition. But as the cliche goes, "some things never change." And one of those things is the importance of microbial control.

A look at some recent news headlines certainly illustrates this point. In August, the U.S. FDA sent out a warning for consumers and healthcare professionals to avoid products from a Florida-based pharmaceutical company due to contamination with *Burkholderia cepacia* ***(1).*** This followed a May announcement from FDA that *B. cepacia* poses a contamination risk in nonsterile, water-based product ***(2).*** Also in August, FDA sent out another alert; this one in response to concerns about lack of sterility assurance in sterile products distributed by a Florida compounding pharmacy ***(3).***

(I pulled these news items from the PDA *newsuPDAte*, PDA's latest offering that includes up-to-date articles from the news sources most pertinent to our industry. I hope you are finding it as valuable as I am! Go to www.pda.myindustrytracker.com)

Speaking of pharmaceutical compounding, this year marks the fifth anniversary of the New England Compounding Center tragedy, which led to the passing of the 2013 Drug Quality and Security Act and FDA's increasing oversight of pharmacy compounding in light of concerns about microbial control and sterility in compounded products.

Fortunately, PDA offers a way for industry to keep abreast of the latest developments in microbial control—the annual fall microbiology conference in the United States. This year, the meeting returns to Bethesda, Md. (PDA's stomping ground, so to speak), and will feature a number of sessions on the topic, including nonsterile microbial control, bioburden control, mold isolation and an update on FDA initiatives involving pharmacy compounding.

I am very excited about this conference and have found it to be one of the more hands-on PDA conferences. And next year's will be even more exciting as PDA plans to combine both the U.S. meeting and PDA Europe micro conference via simulcast. Just as our microbial control technologies are evolving, so too are our conference formats!

I hope to see you at this year's *12th Annual PDA Global Conference on Pharmaceutical Microbiology!*

Rebecca Stauffer

References

1. "FDA Announces Recalls of Contaminated PharmaTech Drugs." *Pharmaceutical Manufacturing.* (Aug. 13, 2017) http://www.pharmamanufacturing.com/industrynews/2017/fda-announces-recalls-of-contaminated-pharmatech-drugs-supplements/ (accessed Aug. 14, 2017)

2. "FDA advises drug manufacturers that Burkholderia cepacia complex poses a contamination risk in non-sterile, water-based drug products." U.S. FDA (May 22, 2017) https://www.fda.gov/Drugs/DrugSafety/ucm559508.htm (accessed Aug. 14, 2017)

3. "FDA Alerts HCPs, Patients Not To Use Sterile Drug Products from Vital Rx, Dba Atlantic Pharmacy, Compounding." American Pharmaceutical Review. (Aug. 11, 2017) http://www.americanpharmaceuticalreview.com/1315-News/341157-FDA-Alerts-HCPs-Patients-Not-To-Use-Sterile-Drug-Products-from-Vital-Rx-Dba-Atlantic-Pharmacy-Compounding/?catid=6262 (accessed Aug. 16, 2017)

What is the Current State of Compounding?

FDA Representatives to Discuss Impact of DQSA in Special Plenary at PDA Micro Conference

This fall marks the fifth anniversary of the New England Compounding Center meningitis outbreak. In recognition of this tragedy and the importance of ensuring microbial control, three U.S. FDA representatives have been confirmed to speak in a special plenary session at this year's *12th Annual PDA Global Conference on Pharmaceutical Microbiology.* Moderated by CDER's **John W. Metcalfe,** PhD, Plenary 4, "FDA Update on Human Drug Compounding: Regulatory Policy and Drug Quality" (Tuesday, Oct. 17, 4:15 p.m.), will feature the following FDA staff:

- **Julie Dohm,** PhD, Agency Lead on Compounding and Senior Scientific Advisor for Compounding, CDER
- **Sara Rothman,** Senior Policy Advisor, Office of Unapproved Drugs and Labeling Compliance, Office of Compliance, CDER
- **Ian F. Deveau,** PhD, Chief, Global Compliance Branch 1, Division of Drug Quality I, Office of Manufacturing Quality, Office of Compliance, CDER

All three will discuss the 2013 Drug Quality and Security Act (DQSA) and its impact on FDA's oversight of compounding facilities. To learn more, visit www.pda.org/2017micro.

Make Your Voice Heard: Vote for the 2018 BoD

Each year, PDA members have an opportunity to help set the strategic direction of the Association by voting for Board of Directors candidates. This year, there are three open Officer seats (Chair-Elect, Treasurer and Secretary) and four open Director positions. Due to the change in PDA's bylaws, three of these Directors will be directly elected by members with the fourth appointed by the Board.

Elections are open until Nov. 15; members in good standing as of Aug. 24, 2017 can vote online at www.pda.org/vote or at conferences held before Nov. 15 in the United States and Europe.

Vote Online

You will need your member ID and password.

www.pda.org/vote

If there are any questions about the voting process, please email **vote@pda.org** or call (301) 656-5900.

Officer Candidates

Chair-Elect

Jette Christensen

Treasurer

Michael Sadowski

Secretary

Steven Lynn

Director Candidates

Masahiro Akimoto

Aaron R. Goerke, PhD

Kerry Ingalls

Ivy Louis

Mary Oates, PhD

Emma Ramnarine

PDA Volunteer Spotlight

Cylia Chen-Ooi

- External Affairs Quality
- *Amgen*
- Member Since | **2014**
- Current City | **Los Angeles, California**
- Originally From | **Taiwan**

You will be surprised how much you can achieve when you try new things

What has been your best experience as a PDA volunteer?
I have had the honor to lead the Quality Culture Task Force. It has been a pleasure to work with such a talented group of experts in the industry. I think we all have learned a lot from each other. Looking back, I am really proud of what the team has accomplished over the last few years. We are always going above and beyond.

Why did you decide to volunteer for PDA?
I have always heard a lot of good things about PDA, not only about the quality of work but the volunteers involved. So when I had the opportunity to get involved on a topic that I am passionate about, I joined. And I have enjoyed working with PDA ever since!

What significant changes have you seen take place in your area of expertise?
There are increasing complexities in the products we develop in the industry. Not only are there novel modalities, there are also new delivery devices and digital health apps—and all of these advances drive more complexities in regulatory requirements. We are entering a period where innovation is the focus, and we will likely see more advancement in our industry than ever before in the next decade.

What are some topics you would like to see covered at future PDA events?
I would like to see more coverage of regulatory requirements for emerging technologies and digital health/new drug delivery devices.

How would someone describe you in one sentence?
She is persistent and always seeks opportunities to improve.

What is your favorite place to visit?
Taiwan, my hometown. I still have a lot of family members and friends there and it is always good to spend time with them while enjoying the great food.

What did you want to be when you grew up?
I wanted to be a teacher. I was inspired by one of my teachers in elementary school; she was so knowledgeable, patient and passionate about her work. I felt that it must be a rewarding job.

What do not many people know about you?
I grew up living in Latin American countries, such as Honduras, Costa Rica and Panama. That experience changed me and I have made friends all over the world.

The Parenteral Drug Association presents...

2017 PDA Container Closure, Devices and Delivery Systems: Compatibility and Material Safety Workshop

October 2-3, 2017 | Washington, DC

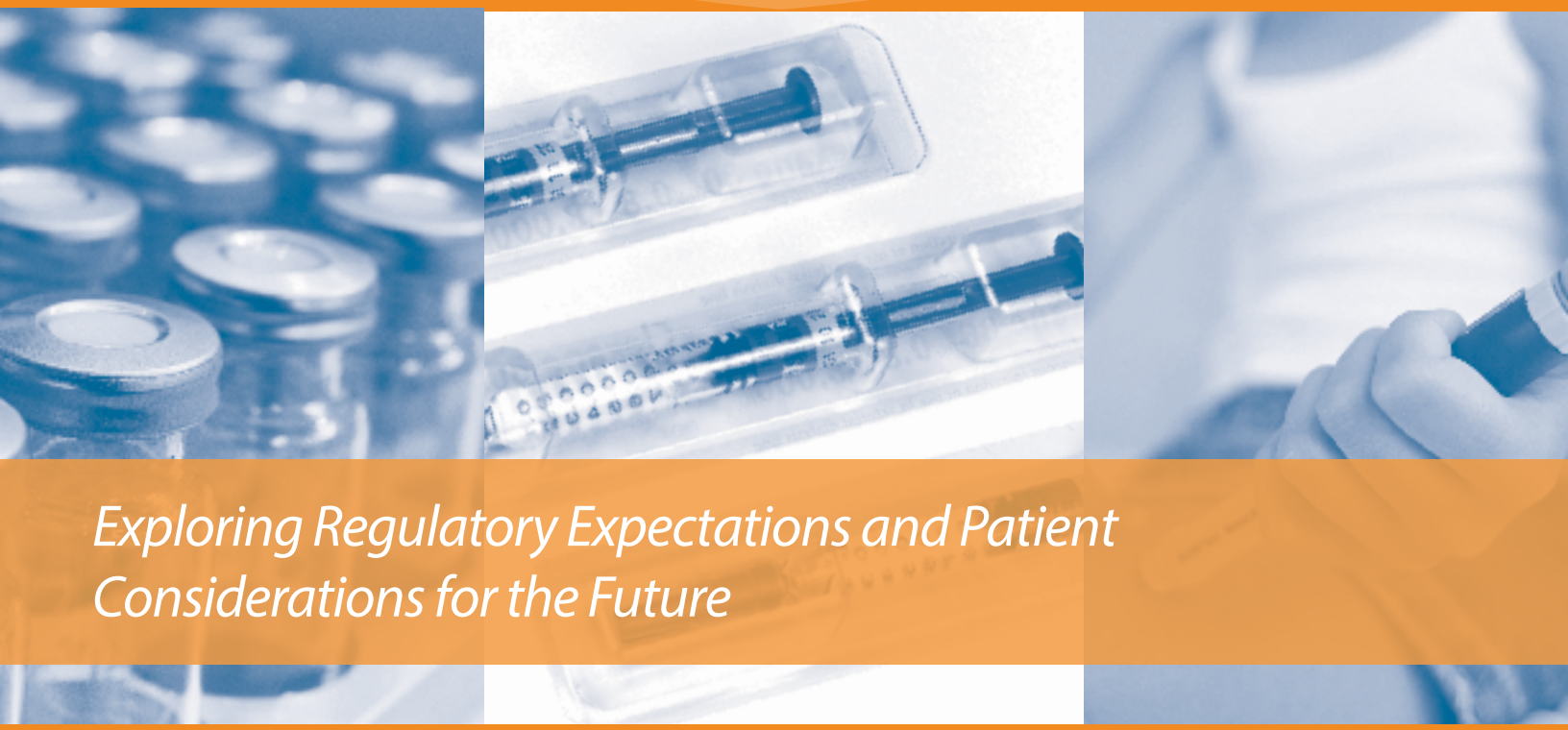
Omni Shoreham Hotel

Exhibition: October 2-3

#2017CC

Co-sponsored by

PQRI Product Quality Research Institute



Exploring Regulatory Expectations and Patient Considerations for the Future

Recent advances in disease treatment have revolutionized how patients receive care. With these changes come revisions in regulatory requirements. Explore industry and regulatory perspectives on this progress at the *2017 PDA Container Closure, Devices and Delivery Systems: Compatibility and Material Safety Workshop*, which will cover topics critical to the development of new devices and delivery systems being considered for use with advanced therapeutic products.

Industry and regulatory speakers will discuss the future of drug delivery, leachables and extractables for combination products comprised of drugs and delivery devices, current activities in the area of parenteral packaging, and the compatibility of delivery systems with biologics.

This Workshop will encourage an open forum for discussion regarding the complexity of assessing compatibility and safety issues for combination products. You will also expand your knowledge on the evolution of combination products as delivery systems and the increased required testing to demonstrate safety and drug product compatibility.

To learn more and register, visit pda.org/2017CC

Women in Biotech Offer Career Advice for All Sexes

Fabio De Martino, PDA West Coast Chapter President-elect, F. Hoffmann La-Roche, and Beth C. Keij, Sangamo Therapeutics

The challenges faced by women in the workplace are not as unique as they once were, so when a panel of women leaders in biotech convened, the advice was universal.

On June 22, 130 industry professionals gathered to hear this panel openly discuss the successes, failures and challenges they have faced as women in biopharma. This was the second "Women in Biotech" panel sponsored by the PDA West Coast Chapter.

Moderated by **Beth C. Keij**, panelists **Carolina Valoyes, Janet Hsu, Kathleen Meyer, Jacquelyn Chester** and **Patricia Lufburrow** shared their personal journeys and offered key advice for both women and men hoping to build careers in biotech. All agreed that mentorship, either formal or informal via "coincidental mentors," has played an important role in their career growth (coincidental mentors are those that provide guidance not via a formal mentoring process). One panelist advised the audience to take mentor selection into their own hands and to look at parts of the business they do not know well as a potential source of a mentor.

The panelists also extolled the benefits of working with managers who instill a sense of personal integrity. For example, a great ➤

manager provides guidance on dealing with problematic situations, such as when it is appropriate to engage a difficult colleague directly as opposed to laying low.

Networking also is essential to career development, according to the panel. Participating in industry conferences, associations and activities organized by local organizations like the West Coast Chapter and PDA's national headquarters have provided the panelists occasions to meet like-minded individuals and build long-lasting professional relationships. Although networking can be a challenge, requiring individuals to move out of their comfort zones, it offers access to new opportunities. The panelists found that networking has given them insight into what they really want to do with their careers and the confidence to seek it.

Does the focus on career-building mean sacrificing personal life? The panelists concurred that attaining a good balance requires dedicating enough quality time to themselves, their families and their careers so they are fully present and effective in each role. There is no secret formula or one-size-fits-all solution, however, and the panelists recommended learning to prioritize, working flexibly and recognizing that sometimes it is acceptable to slow down or say "no." Some notable quotes that came out of this session were: "work to live, don't live to work" and "manage your energy, not your time."

During Q&A, panelists were asked "what is the one thing that you wish someone had told you much earlier in your career?" The panelists provided a variety of responses: "Don't be afraid," "Fail and fail fast," "Get into the game," "Believe, be confident" and "Recognize the value of accountability"

There was also some lively discussion around salary equality. A few of the panelists recounted how they had to deal with managers who rationalized lower salaries as the individual panelists were not "primary breadwinners" for their families. One panelist shared how disappointment about being passed over for a prime position motivated her to hone her negotiation skills and arrive at the table armed with salary information and firm expectations.

Although this was billed as a "Women in Biotech" panel, the West Coast Chapter hopes that both women and men can use the panelists' experiences to grow their own careers in industry.

PDA Who's Who

Jacquelyn Chester, Associate Director, Commercial Quality Assurance, Gilead Sciences

Janet Hsu, Executive Director, Development Sciences Compliance, BioMarin

Beth C. Keij, Senior Director, QA, Sangamo Therapeutics

Patricia Lufburrow, Head, Biologics Product Quality Management, Roche/Genentech

Kathleen Meyer, Vice President, Nonclinical Development, Sangamo Therapeutics

Carolina Valoyes, Director, QA, Boehringer Ingelheim

2nd PDA Europe Annual Meeting

June 13–14 | Berlin

The *2nd PDA Europe Annual Meeting* offered a number of interesting sessions and panel discussions. In addition, attendees had opportunities to network during breaks and even headbang to PDA's very own rock band during the Tuesday night Summer in Berlin celebration!

Pictures courtesy of Jens Liebchen

Martin Lush, NSF Health Sciences

(l-r) Stephan Rönninger, PhD, Amgen; Emma Ramnarine, Genentech/Roche; Yvonne Stewart, GSK; Terence Madigan, MHRA

(l-r) Falk Klar, PhD, PDA Europe General Manager, VP; Stephan Rönninger, PhD, Amgen; Veronique Davoust, PharmD, Pfizer

(l-r) Richard Johnson, PDA President; Lutz Uharek, Charité University Hospital Berlin; Yves Mayeresse, PhD, GSK

PIC/S Chair Paul Hargreaves discusses GMP harmonization in the opening plenary

(l-r) Christopher Procyshyn, Vanrx; Jeffrey Weber, Pfizer Global Supply; Aidan Harrington, PhD, DPS Engineering; Irene Zakrzewski, Vaisala

The Parenteral Drug Association presents...

2017 PDA Annex 1 Workshop

October 2-3, 2017 | Washington, DC
Omni Shoreham Hotel
Exhibition: October 2-3
#2017Annex1


Photo courtesy of Sartorius AG

The Annex 1 Revision: A Unique Opportunity to Better Understand and Influence the Guidance

As industry anticipates the release of the revision to *Annex 1: Manufacture of Sterile Medicinal Products*, how prepared is your company for the changes the guidance will bring? At the *2017 PDA Annex 1 Workshop*, contributors to the document and other industry experts will provide an in-depth understanding of the revisions and related expectations.

Andrew Hopkins, GMP Inspector, *Medicines and Healthcare Products Regulatory Agency*, and Committee Chair of the PIC/S EMA Working Group for the revision of Annex 1, will open the Workshop with a session exploring the needs, background, procedure, and content of the revised guidance.

Take part in a unique point/counter point discussion on debated topics that may impact aseptic processing operations, focusing on areas in which there is not yet consensus and those in need of further explanation. Other topics covered will include the results of PDA's recent Aseptic Processing and PUPSIT surveys, risk-based thinking and clean room design, personnel and environmental monitoring, and more.

Attend the Workshop and voice your opinion – input on the Annex 1 revision generated at the Workshop will be provided to health authorities.

Visit *pda.org/2017Annex1* to learn more and register.

Aseptic Processing

2018 SCHEDULE

OPTION 1
Week 1: January 22-26
Week 2: February 19-23

OPTION 2
Week 1: March 12-16
Week 2: April 9-13

OPTION 3
Week 1: May 7-11
Week 2: June 4-8

OPTION 4
Week 1: July 23-27
Week 2: August 13-17

OPTION 5
Week 1: September 17-21
Week 2: October 15-19

FOR MORE INFORMATION CONTACT:

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Fax: +1 (301) 986-1093

For more than 70 years, PDA has been recognized worldwide as a leader in aseptic processing. With the advent of new biological therapies, the importance of proper aseptic processing has never been greater. Turn to PDA for the most comprehensive aseptic processing education, taught in PDA's unique, onsite cleanroom filling facility.

PDA's two-week Aseptic Processing course, taught by numerous industry leading experts in their fields with more than 300 years of combined experience, will give you the training and information needed to properly evaluate and improve your aseptic processes to ensure sterile products. This course provides the perfect balance of hands-on laboratory and lecture training, equipping you with tools and practical experience you can apply immediately on the job.

YOU'LL LEARN HOW TO:

- Evaluate and improve current aseptic processing procedures at your facility
- Correlate basic microbiology concepts and techniques to multiple aspects of aseptic processing
- Evaluate your environmental monitoring program to collect appropriate data, identify and interpret trends
- Develop robust media fill protocols including appropriate interventions, observations and documentation procedures
- And much more!

SPACE IS LIMITED
Register Today
pda.org/2018Aseptic

*PDA **Education** – Where Excellence Begins*

Receive the same training regulators receive when you attend a PDA course. PDA is accredited by ACPE and offers continuing education for professional engineers.

Novartis' Nicholas Stones explains user-centered design

(l-r) Jez Clements, Cambridge Design Partnership; Serge Dubeau, Worrell; Matt Gottschalk, Worrell; Nicholas Stones, Novartis; Borke Van Belle, Janssen J&J

Maik Jornitz, G-Con, covers the costs and benefits of comparing cleanroom designs and structures

Professional facilitator Anja Ebers moderates an interactive session on the future of the pharma industry

Emma Ramnarine discusses how to manage single- and multi-source supply chain challenges

SNAPShot

Task Force *Corner*

New PDA Task Force Hopes to See Zero Defects for Visible Particles

Jahanvi (Janie) Miller, PDA

Visible particulate matter has long been a popular topic for PDA members. In fact, the PDA Paper, "Industry Perspective on the Medical Risk of Visible Particles in Injectable Drug Products," has been viewed over 9000 times on the *PDA Journal of Pharmaceutical Science and Technology* website ***(1).*** Ideally, both industry and regulators seek a clearly defined, risk-based particle specification (e.g., size, type and quantity). While such specificity is desirable, the lack of relevant clinical trials limits the ability to establish specifications typically done for other "impurities." Therefore, sterile manufacturers have relied on a large body of anecdotal information to guide understanding of clinical risk. While this is useful, it does not offer an exact limit for setting acceptance criteria for injectable products and the primary packaging used in their preparation. This, coupled with the normal variability of human visual inspection, has led to a wide range of practices and limits applied to particles in injectable drug products and their packaging materials. Due to PDA members' involvement in providing consensus-based guidance to the industry, the Pharmaceutical Manufacturing Forum (PMF) has tasked PDA members with diving deeper into developing particle specifications.

A new task force has formed to align on a common, harmonized rationale across the industry and develop a practical guide intended for use along with existing compendial, regulatory and industry standards. The Zero Defects for Visible Particles in Injectables Task Force plans to identify gaps in current risk assessments and methods used to detect and quantify visible particles in order to develop a series of best practice documents. The purpose of these documents would be to potentially reduce defects related to particles. Within this group, subgroups will work on separate workstreams, each working to identify a visible particle size threshold, analytical method gap analysis (for elastomer and glass components) and validation strategies. Volunteers working within these subgroups will consist of representatives from both manufacturers and suppliers to ensure a well-balanced perspective for resulting documents.

PDA intends to expand the resources relating to visible particulates to support continuous improvement and development of new best practices for the industry and its members. In fact, the *2017 PDA Visual Inspection Forum* in October will offer opportunities to learn more about the latest practices in this area and discuss some of the task force's developments (see p. 42).

1. Bukofzer, S. "Industry Perspective on the Medical Risk of Visible Particles in Injectable Drug Products." *PDA Journal of Pharmaceutical Science and Technology* 69 (2015): 123-139

Journal *Preview*

September/October Issue Includes QRM Survey Results

Where does the industry stand when it comes to quality risk management (QRM)? PDA members **Kelly Waldron, Emma Ramnarine** and **Jeffrey Hartman** provide results from the 2015/2016 Quality Risk Management Benchmarking Survey.

Review

Kelly Waldron, Emma Ramnarine, Jeff Hartman, "2015/2016 Quality Risk Management Benchmarking Survey"

Research

Dennis Jenke, "Extractables Screening of Polypropylene Resins used in Pharmaceutical Packaging for Safety Hazards"

Ruojia Li, Weiguo Cai, Marcel Zocher, "A Novel Lack-of-Fit Assessment as a System Suitability Test for Potency Assays"

Technology/Application

Christopher L. Timmons, Chi Yuen Liu, Stefan Merkle, "Particulate Generation Mechanisms during Bulk Filling and Mitigation via New Glass Vial"

Neil McLeod, M. Clifford, J.M. Sutton, "Evaluation of novel process indicators for rapid monitoring of hydrogen peroxide decontamination processes"

Jay Bolden, Kelly Smith, "Application of recombinant Factor C reagent for the detection of bacterial endotoxins in pharmaceutical products"

Commentary

Derek Willison-Parry, et al., "Mold Control and Detection in Biological Drug Substance Manufacturing Facilities: An Industry Perspective"

2017 PDA Annual Meeting

One Simple Way to Manage Aseptic Risk Assessments

Guenther Gapp, Independent Consultant

Aseptic processing presents many risks to sterile product. How can manufacturers address these risks to effectively prevent contamination?

In 2006, I created a sterile risk assessment tool, the Hazard Operability Analysis (HAZOP). This tool proactively identifies microbial contamination risks for aseptically filled sterile products. I have since refined this tool into what I now call the Sterile Product Compliance Risk Assessment (SPCRA).

Like any risk assessment tool, it is only as good as the individual or team behind it. In my years in the industry, I have seen companies use various risk assessment tools to justify all sorts of weak quality practices. When implemented appropriately, however, this simplistic tool offers many potential benefits for manufacturers.

The Risk Analysis Concept

The SPCRA tool, which consists of a comprehensive list of specific questions, is a deep-dive assessment into the manufacturing process and controls for product quality. It spans the microbiological laboratory, quality culture, manufacturing facility and filling technologies, media fills and environmental monitoring. Furthermore, several questions relate to current regulatory requirements, audit findings and best practices.

To reflect the different microbial contamination risks inherent in the various types of aseptic manufacturing, these risks are separated into individual units per process flow ***(1).*** For example, working with sterile API is a complex, five-step process while a sterile finished dosage form (FDF) manufacturing line for liquid or solid product filling, with or without sterile filtration, incorporates either two or four production steps. A four-step FDF site involves raw material introduction, sterile filtration, aseptic filling and packaging of units such that manufacturing lines render liquid product sterile. A two-step site consists only of aseptic filling of sterile liquid or solid API and a final packaging step.

With this in mind, I have created three different SPCRA tools. The one for a sterile API plant consists of 263 questions; the one for a two-step FDF plan consists of 203 questions; and the one for a four-step FDF plant consists of 243 questions. In general, the greater the number of questions, the more detailed the specific production units assessed. And the number of questions can be changed based on new information and regulatory requirements.

Within each analysis, a number of specific questions are asked for each step to address areas of potential risk involved in aseptic manufacturing. Each question can be answered on a scale of 1 (excellent) to 5 (very poor).

In the initial tool, a five-point scale was applied to all answers in the questionnaire. After some years of practical experience, it became apparent that certain questions carried a higher impact on overall sterility assurance than others. To ensure that a negative answer has an impact, a value of 100 is assigned. Questions scored with a 100 are now referred to as "Knock Out Questions" as their answers indicate a high impact on the sterility of the product if the requirement is not met. A rating of 100 increases the sum and renders the whole unit at a higher risk. The latest version incorporates 36 Knock Out questions.

For each step, the sum of the numbers resulting from the question-answer scale is divided by the number of questions to provide the **Unit Average Risk Factor**. The smaller the Unit Average Risk Factor, the lower the evaluated risk with regard to sterile product quality and potential for audit findings.

Each production unit has an inherent risk on the overall sterility of the product; therefore, **Risk Emphasis Factors (REF)** have been ➤

defined with different impact factors: 1 (low), 3 (medium) or 5 (high) **(Figure 1).** For example, the raw material unit, which carries a lower risk of contamination in the final product, is assigned REF 1, whereas sterile API production units that use significant pressure differences are considered especially risky, so are assigned the maximum value of REF 5. To correctly address lower contamination risks of advanced filling isolators, a variable unit REF was introduced for aseptic filling units. This ensures that an isolator receives a significantly lower REF (such as 1) than a conventional open filling line (likely 5), even if the respective individual unit average risk factors are identical. I based these numbers on my previous industry experience.

Each Unit Average Risk Factor is multiplied by its corresponding Unit-REF to achieve the **Unit Risk Factor.**

Unit Risk Factor = Unit Average Risk Factors × Unit REF

The SPCRA analysis is finally concluded by calculating the **Total Risk Factor (TRF),** which is the sum of all Unit Risk Factors (refer to **Figure 2**).

TRF = ∑ Unit Risk Factors

The SPCRA Tool in Action

But how does the tool actually work in action?

An executed risk analysis using the SPCRA tool at a specific FDF site (with sterile filtration) resulted in a considerable improvement of the TRF after one year of implementing recommended CAPAs. The improvements have been made mainly at the aseptic filling unit, resulting in an acceptable low risk range for the site (**Figure 3**). **[Editor's Note:** See the online version of this article for a full graphic of an SPCRA for an FDF with a moderate risk outcome**.]**

Figure 3 One Year Following Risk Assessment

Figure 1 Schematic Overview of Process Units and Related REFs

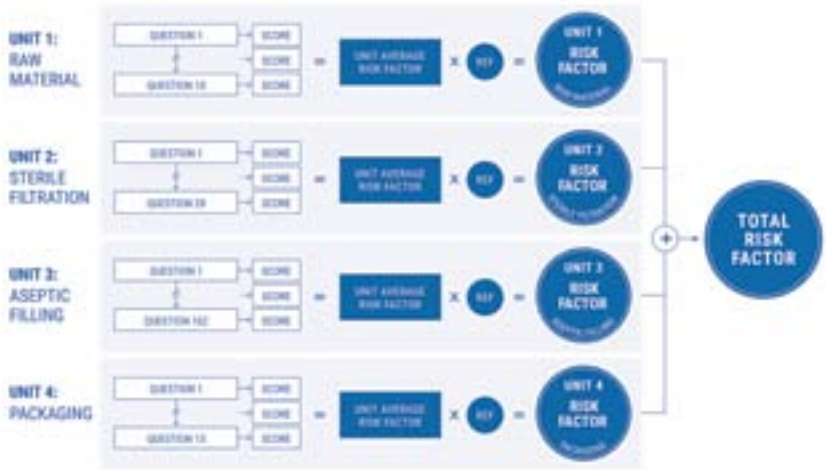

Figure 2 Schematic Overview of the SPCRA

The benefit of the tool is its simplicity, since the TRF provides for valuable information about the overall risk of microbial contamination. It enables companies to estimate compliance status and make potential observations in advance of upcoming regulatory audits. By providing simple numerical and color-coded answers in each unit questionnaire, the SPCRA tool serves to uncover potential weaknesses in the process, enabling CAPAs for further systematic improvement. The target should always be green-colored with a low TRF, and no Knock Out questions answered with 100.

So far, this tool has proven to be a very effective and useful measure for reducing microbiological contamination risks and helping companies comply with regulatory requirements. But while the SPCRA tool provides a simple way to conduct microbial risk assessments, its success depends on the honesty of the reviewers combined with a high level of expertise. For this reason, I recommend the tool be used by an independent third party, or at least moderated by an external expert. This is particularly important if the outcome will be used to compare different manufacturing sites.

[Editor's Note: This article is based on

Continued at middle of page 39

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14-15
2017 PDA Regulatory Course Series
Washington, DC
pda.org/2017RCCS

14-15
Quality Metrics and Quality Culture for Pharmaceutical Manufacturing
Melbourne, Australia
pda.org/2017QMQC-AU

18-19
Quality Metrics and Quality Culture for Pharmaceutical Manufacturing
Suntec City, Singapore
pda.org/2017QMQC-SG

19-21
Validation of Biotechnology-Related Cleaning Processes
Bethesda, MD
pda.org/2017SeptBio

19-20
Pharmaceutical Freeze Drying Technology Conference
Cologne, Germany
pda.org/EU/FreezeDrying2017

21
Application of a Risk-Based Approach to Freeze Drying Processes
Cologne, Germany
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21-22
Development of a Freeze Drying Process
Cologne, Germany
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21-22
Einfache und Prozessorientierte Qualifizierung
COURSE IN GERMAN LANGUAGE
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21-22
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Hyderabad, India
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25
Particle Identification in Parenterals
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25-28
Filtration Processes in the Pharmaceutical and Biopharmaceutical Industry
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28
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28-29
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28-29
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Berlin, Germany
pda.org/EU/E-and-L2017

28-29
Mastering Automated Visual Inspection
Berlin, Germany
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OCTOBER

2-3
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2-3
2017 PDA Container Closure, Devices and Delivery Systems: Compatibility and Material Safety Workshop
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5-6
PDA Italy Chapter – Manufacturing Trends in Parenterals, a Glance to the Future
Bari, Italy
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9-13
PDA #100 Aseptic Processing Option 5 SOLD OUT
Week 2: Nov. 6-10
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10-11
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12
Good Qualification Practice of Pharma Storage and Transportation Equipment
Prague, Czech Republic
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12-13
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19-20
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25-26
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pda.org/2017OctVI

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1
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2
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6
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6
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pda.org/EU/CONNECTED

6
Pre-Conference Workshop: Innovative Drug Delivery Systems/Combination Products
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7-8
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9
Container Closure Development
Vienna, Austria
pda.org/EU/CCD2017

9-10
Best Practices and Points to Consider in Aseptic Processing
Vienna, Austria
pda.org/EU/BP-Aseptic2017

9-10
Container Closure Integrity Testing
Vienna, Austria
pda.org/EU/CCI2017

9-10
Development and Manufacturing of Pre-filled Syringes
Vienna, Austria
pda.org/EU/DEV_SYRINGE

9-10
Drug Delivery Systems: Global, Technical, Regulatory and Quality Challenges
Vienna, Austria
pda.org/EU/DRUGDELIVERY

9-10
Rapid Microbiological Methods
Vienna, Austria
pda.org/EU/RMM2017

14-16
Validation of Moist Heat Sterilization Processes
Bethesda, MD
pda.org/2017NovMH

14-17
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15-16
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pda.org/EU/TRACK-UND-TRACE2017

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pda.org/EU/Outsourcing2017

23-24
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23-24
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28-29
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Singapore
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2017 PDA Cell and Gene Therapy Conference
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7-8
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Bethesda, MD
pda.org/2017Rapid

11-14
PDA Quality Risk Management Training Program
Bethesda, MD
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The Cost of Microbial Control

Edward Tidswell, PhD, Merck, and Walid El Azab, STERIS

Microbial contamination control remains a critical focus for the pharmaceutical industry. Microbial controls can be found throughout the manufacturing process including, but not limited to, raw materials, equipment, cleanroom environments, finished product manufacturing and storage and shipping processes. Bioburden control programs are also essential for both sterile and nonsterile manufacturing. Many similarities exist between bioburden control and contamination control—in fact, the terms are frequently used interchangeably—however, the differences can result in ineffective or excessive control programs for sterile and nonsterile products.

Nonsterile products are allowed to possess certain types and levels of bioburden within the manufacturing process and in the final product. The challenge for a nonsterile manufacturer, therefore, is identifying how to control bioburden and achieve microbial contamination control without implementing sterile manufacturing requirements. In contrast, sterile products must be devoid of microorganisms, yet are produced in manufacturing facilities that possess a microbiome that can never be removed entirely. For a sterile manufacturer, the challenge is identifying effective controls with an appropriate level of redundancy that ultimately assure product sterility.

But why is bioburden and microbial control so critical? Failure to adequately control bioburden or microbial contamination has the potential to significantly impact patients receiving sterile or nonsterile products. Consequently, ensuring that the manufacturing environment and processes are well controlled is essential. The costs of resolving product quality problems and cGMP compliance issues arising from poor microbial control or recurring microbial contamination should eclipse concerns about operational costs.

A 2012 industry study found that the cost to fix complex failures ranges from approximately $100,000 to more than $2 billion for a consent decree ***(1).*** Naturally, a recall due to microbial contamination presents a financial drain for a manufacturer. Of a series of recalls conducted from 2004 to 2011, 80% involved sterile products, and 20% of these were recalled due to "microbial contamination" ***(2).*** Moreover, the most prevalent reason for recalls of over-the-counter drugs and personal care products was contamination of nonsterile product with objectionable microorganisms ***(2).*** Robust processes that ensure product quality, especially in terms of bioburden and contamination control, rather than a heavy reliance on testing (microbial enumeration, sterility, etc.) are key; otherwise, the cost to a manufacturer can run to 20–30% of total sales ***(3).***

Recently, the U.S. FDA advised drug manufacturers that *Burkholderia cepacia* complex poses a contamination risk in nonsterile and water-based drug products. The Agency reminded manufacturers of the importance of developing effective microbial contamination control and root cause investigation strategies to avoid adverse events or quality problems ***(4).*** Over the past few years, numerous repeated recalls of high profile products, including sterile large volume parenterals, small volume parenterals and nonsterile dosage forms, have occurred ***(5).*** In one case, mold contamination of cleanroom HEPA filters in a large volume parenteral manufacturing facility resulted in $18.2 million in criminal and civil penalties for the manufacturer ***(6).*** Recurring microbial contamination generally results from inadequate procedures and/or ineffective root cause investigations. These two elements are among the top ten most-observed deficiencies by the U.S. FDA since 2012 ***(7).*** The situation in Europe is no different based on recent reports from the UK MHRA and European inspectors ***(8–10).***

Bioburden and microbial contamination control is technically challenging with the potential for significant adverse patient impact and financial implications for the manufacturer. With this in mind, how can pharmaceutical microbiologists become more informed in order to ensure their microbial control processes and systems are sufficient? One way to learn the latest in contamination control is by attending the *12th PDA Annual Global Conference on Pharmaceutical Microbiology.* The goal of the conference is to solve microbiological challenges and sustain success through a culture of collaboration. This year's conference has a session dedicated to microbial control. Several case studies on effective root cause investigation and collaboration between departments and suppliers to address recurring microbial contamination will be presented in this session moderated by **Edward Tidswell,** PhD, Executive Director, Microbiology QA.

The pharmaceutical industry is facing pressure to continuously challenge and improve its manufacturing processes to achieve regulatory compliance and produce high quality product. New technologies to improve microbial control, support root cause investigation and provide faster response are expected to become available over the next few years. Thus, the conference will also present innovative, next-generation microbiological methods and regulatory updates to ensure companies are up to date on the best methods to ensure microbial safety for patients.

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Continued at bottom of page 39

Company Sees Success With Automated Endotoxin Testing

Scott Kaszuba, Pfizer

Photo courtesy of Charles River Laboratories

Pharmaceutical manufacturers are embracing automation and robotics, mainstays of other manufacturing fields, but can automation and robotics be brought into the QC lab as well?

Pfizer's biotechnology site in Andover, Mass., has used Charles River Laboratories' Endosafe® Multi-Cartridge System (MCS™) for testing routine water samples in the QC microbiology lab since 2010. Although this system reduces the individual sample testing time from 60 to 15–20 minutes, each unit can only process five samples at a time. In order to process all samples received on a given day, analysts were often required to rely on three MCS™ systems and remain at the bench for up to six hours. This led the site to perform a beta evaluation of Charles River Laboratories' Nexus™ testing system in 2013.

The Nexus™ system relies on robotics and automation to conduct LAL testing. First, an analyst loads a robotic deck of cartridges and then sets up the robotic software. Next, the analyst starts the robotic automation cycle. During this cycle, the system performs dilutions, tests samples, discards cartridges and reports the results. This process removes the analyst from much of the testing compared to traditional methods where the analyst prepares sample dilutions and standard curves, plates all samples, adds lysate to the plate and then sets the plate on a plate reader.

During the original evaluation, a Pfizer analyst attempted to process six independent test sessions. Although the instrument was not successful in completing full assay runs, the data obtained was evaluated in regard to spike recovery, spike coefficient variation (CV) and sample CV. Due to these results, the site agreed to perform a second evaluation of the Nexus™ testing system once the issues uncovered during initial testing were addressed.

After updating the system, Charles River Laboratories delivered and installed a commercially available Nexus™ testing system at the Andover facility. In order to determine if the system issues identified during the original evaluation had

> **This process removes the analyst from much of the testing compared to traditional methods**

been fixed, the site management designed a second evaluation. Whereas the initial evaluation consisted of 180 samples, the second evaluation included a minimum of 600 samples. In addition to evaluating if the original issues had been resolved, spike recoveries and spike CVs generated by the Nexus™ testing system were compared against spike recoveries and spike CVs by an analyst using the stand-alone MCS™ systems. In order to avoid having the results skewed by sample matrix issues, all testing was performed with water samples.

While the Andover site chose to evaluate the Nexus™ system, the company recognizes that there are other automated endotoxin solutions on the market and what works best for another lab may be a different product. Still, the author believes that the implementation and evaluation of Nexus™ at the Andover site offers lessons learned for other labs considering an automated endotoxin solution.

System Trial Shows Promise

The spike recoveries obtained from the secondary evaluation were compared to 600 spike recoveries that had been obtained using the stand-alone MCS™ readers during the same timeframe. Although the stand-alone MCS™ readers had a mean spike recovery closer to 100% (103% vs 95%), the standard deviation for the Nexus™ testing system was smaller (14 versus 22). The data was then analyzed using a two-sample t-test to determine if the difference in results was statistically significant. A ➤

Article at a Glance

- QC lab in Andover needed a less time-consuming LAL testing solution
- 600 samples tested using Endosafe® Nexus™ platform
- Spike recoveries little different from data using old equipment

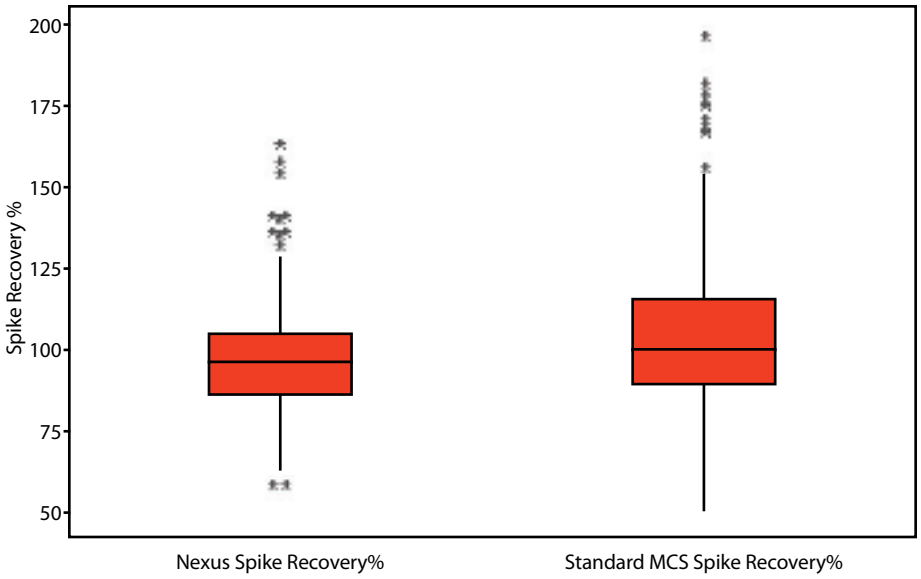

Figure 1 Boxplot of Nexus Spike Recovery % and Stand-alone MCS Spike Recovery%

p value of 0.00 was obtained, indicating that the results obtained were statistically significant **(Figure 1).**

As with the spike recovery evaluation, the spike recovery CVs obtained from the Nexus™ testing system were compared to CVs from the 600 spike recoveries that had been obtained using the stand-alone MCS™ readers. The CVs were similar (3.1% compared to 3.4%) with a standard deviation of 2.5% for the Nexus™ testing system and 3.3% for the stand-alone MCS™ readers.

This data was also then analyzed using a two-sample t-test to determine if the difference in results was statistically significant. A p value of 0.116 was obtained, indicating that there was no statistically significant difference in the results obtained **(Figure 2).**

In addition to focusing on spike recoveries and spike recovery CVs, the secondary evaluation allowed the Andover site to look at efficiencies that could be gained by implementing the Nexus™ testing system into the routine testing lab. Analyst touch time decreased from >3 hours to around one hour per testing session for 50 to 60 samples. The Nexus™ testing system's bar code scanner decreased documentation errors on the front end of the assay by removing the need for the analyst to manually type each sample into the laboratory information management system (LIMS). Another benefit was that the results generated by the Nexus™ testing system were directly transferred into the LIMS, saving on additional opportunities for documentation errors and reducing assay review time. Finally, the rate of invalid assays obtained was compared for the Nexus™ testing system and the stand-alone MCS™ readers. Although the data set for the Nexus™ testing system was very small, there was a large difference, with the Nexus™ testing system having an invalid assay rate of 1% compared to 5% for the stand-alone MCS™ readers (four years of testing or ~75,000 samples evaluated for the invalid rate for the stand-alone MCS™ readers). Invalid assays are those assays where the spike CV or sample CV is >25% or the spike recovery is not between 50 and 200%.

Following this successful evaluation, Pfizer ultimately chose to purchase the Nexus™ testing system in 2014. The instrument is now validated and used for routine water endotoxin testing. This process suggests that endotoxin testing can be automated using robotics in the QC lab, just as product can be manufactured using automated isolators on the floor.

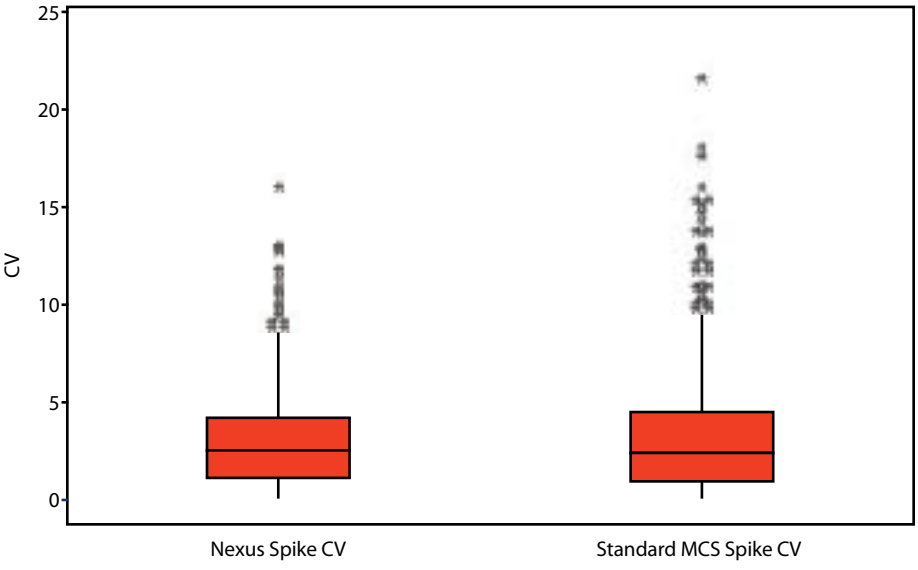

Figure 2 Boxplot of Nexus Spike CV and Stand-alone MCS Spike CV

About the Author

Scott Kaszuba is a manager overseeing the nontesting-related activities performed by the QC Microbiology Group at the Pfizer Andover, Mass. facility.

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Why the Surface is Critical to Disinfection Testing

James Polarine, Jr., and David Shields, STERIS

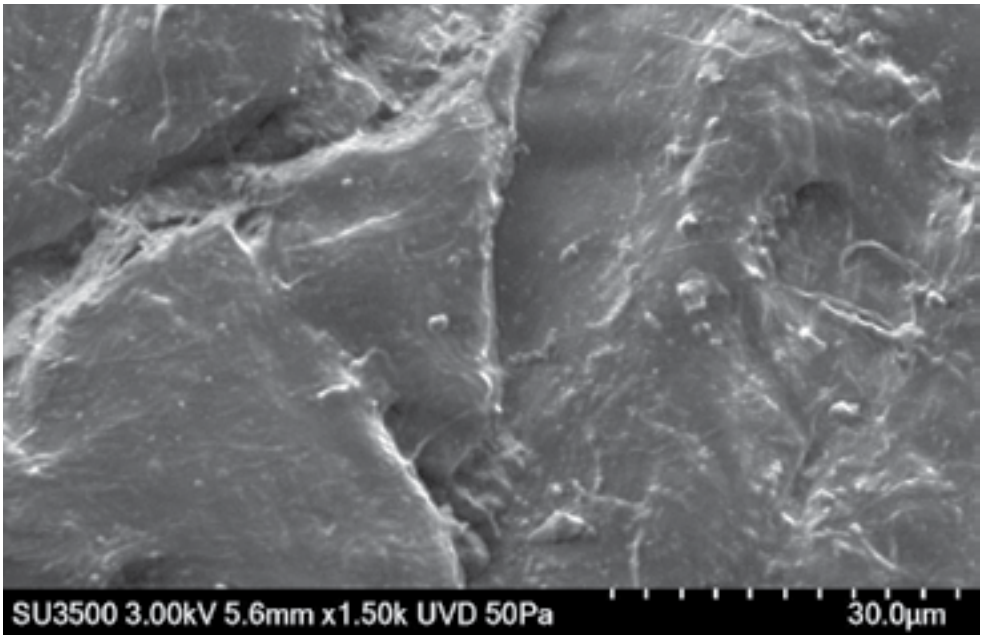
Central to recent debates about disinfectant validation is whether value is added by individual facilities performing studies, or if a large central study could be relied upon to demonstrate the efficacy of biocides. Regulators expect disinfectant validation to be conducted by facilities in the pharmaceutical, biotech, medical device and 503B compounding pharmacy industries. As regulators look more closely at disinfectant validation, the role of the surface in the disinfectant process has been heightened.

A number of U.S. FDA 483 Warning Letters have established regulatory expectations for disinfectant validation testing. One recent 483 stated: "Your firm has not conducted disinfectant efficacy studies to demonstrate that the disinfectants and application methods (e.g., spray, wipe, mop, aerosol, etc.) used to clean the walls, ceilings, work surfaces and other items in the work areas can sufficiently reduce bioburden" ***(1).*** Another FDA Warning Letter related to disinfectant validation noted: "In addition, you have not sufficiently established the efficacy of disinfectants you use in aseptic processing cleanrooms. Your disinfectant study only challenged **(b)(4)** and **(b)(4)** manufacturing surfaces. You did not provide an adequate scientific rationale for not challenging other representative surfaces, such as glass windows, **(b)(4)**, **(b)(4)**, **(b)(4)**, **(b)(4)**, or other interior RABS surfaces" ***(2).***

There has clearly been an increased focus on disinfectant validation studies, including scrutiny of the selection of surface coupons and their associated log reductions. And it is not only U.S. inspectors looking at disinfectant validation, either. Inspectors from the United Kingdom, Ireland, France, Brazil, China and EMA have also been paying close attention to cleaning and disinfection programs, as well as to disinfectant validation studies. For well over a decade, expectations for disinfectant validation have become more clear and consistent between different regulatory agencies. FDA regulators have focused on the specific surfaces used for coupon testing, as stated in one 483: "There is no documentation that disinfectant efficacy study results performed by contractor… were reviewed by responsible quality management. Examination of the reports from the contractor found that the contact time challenge…against *Bacillus subtilis* was effective on stainless steel surfaces. However, the contact time on the…surfaces for the same organism was ineffective. There was no evidence to indicate that the study was repeated. Results from the disinfectant efficacy studies also reported that challenges of contact time on surfaces mimicking flooring and front curtain track surfaces found that agent process…was not effective" ***(3).***

In other words, the surface is crucial to the disinfectant process. Below is an analysis of some potential surface specific effects on disinfectant validation testing.

Figure 1 shows a scanning electron microscopy (SEM) image of gypsum board (a cleanroom wall surface). A specific surface's roughness and contour can have a significant impact on efficacy testing based on our disinfectant testing experience. There are several factors that can affect disinfectant efficacy testing ***(4).***



Courtesy Bruce Ritts, STERIS Corp.

Figure 1 SEM of Gypsum Cleanroom Walls Surface

Table 1 Phenolic A Efficacy Testing on Cleanroom Surfaces

Organism	Surface	Disinfectant	Log_{10} Reduction (≥3.00)
S. epidermidis (Site Isolate)	Stainless Steel	Phenolic A	>5.2
S. epidermidis (Site Isolate)	Vinyl	Phenolic A	**<2.3**
S. aureus ATCC 6538	Stainless Steel	Phenolic A	>5.2
S. aureus ATCC 6538	Vinyl	Phenolic A	3.9

> **A specific surface's roughness and contour can have a significant impact on efficacy testing**

Table 1 shows that some biocide/strain/surface combinations can present a greater challenge to disinfection. The *Staphylococcus epidermidis,* Vinyl, Phenolic A test combination was repeated on multiple test days, and inefficacious disinfection was consistently observed. **Table 2** shows that similar biocides can have different levels of efficacy with the same microorganism and the same surfaces found in cleanroom construction.

The data in **Table 1** and **Table 2** were generated by first inoculating six coupons of each surface type with 50 µL of target organism suspension. After the inocula were fully dried, three surface coupons were exposed to 100 µL of Phenolic A or Phenolic B for the same contact time; disinfectant tests and three surface coupons were exposed to Water for Irrigation as carrier controls. The log reduction was calculated by subtracting the mean of the disinfectant test log values from the mean of the carrier control log values.

Table 1 also compares the efficacy of Phenolic A against a *Staphylococcus epidermidis* site isolate and a *Staphylococcus aureus* reference strain on the same surfaces. This data demonstrates that disinfectants can have differential efficacy against specific site isolates when compared to some commonly used reference strains. These differences are possibly related to the interfacial tension of the disinfectant, bacterial cells and surface. The efficacy against the *S. epidermidis* isolate on the stainless-steel surface demonstrates that the *S. epidermidis* is not inherently resistant to Phenolic A. **Table 2** compares the efficacy of two phenolic biocides against the same *S. epidermidis* isolate. Phenolic B demonstrates ➤

Table 2 Phenolic A and Phenolic B Efficacy Testing on Cleanroom Surfaces

Organism	Surface	Disinfectant	Log_{10} Reduction (≥3.00)
S. epidermidis (Site Isolate)	Stainless Steel	Phenolic A	>5.2
S. epidermidis (Site Isolate)	Vinyl	Phenolic A	**<2.3**
S. epidermidis (Site Isolate)	Stainless Steel	Phenolic B	>5.1
S. epidermidis (Site Isolate)	Vinyl	Phenolic B	>5.4

efficacy against the *S. epidermidis* on vinyl, while Phenolic A does not demonstrate efficacy against the *S. epidermidis* on vinyl, which is indicative of an interaction between the surface, cells, and biocide, rather than a strain inherently resistant to phenolics.

Disinfectant efficacy testing will continue to play a role in development of good contamination control practices. The data shared herein illustrate that surface interactions can play a significant role in efficacy. The results in this study indicate that surface interactions can significantly impact efficacy, however, this conclusion should not be considered definitive. This finding demonstrates the importance of individual facilities performing disinfectant efficacy testing using their site isolate strains with a variety of worst-case substrates. The worst-case evaluation may be based upon the microscopic or submicron features of the substrates, or other factors known to play a role in disinfectant performance.

[Editor's Note: Hear coauthor **James Polarine** speak on fungal spore excursions in session "A1: Microbial Control" at 11:15 a.m. on Oct. 16 at the *12th Annual PDA Global Conference on Pharmaceutical Microbiology*.**]**

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About the Authors

James Polarine is a senior technical service manager at STERIS Corporation. His current technical focus is microbial control in cleanrooms and other critical environments.

David Shields currently holds the position of Senior Scientist, Analytical Services & Development at STERIS/Biotest Laboratories, disinfectant efficacy testing.

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"This service went far beyond what I had expected. The attention to detail, knowledge and importance of my understanding were so evident in the training session. Additionally, they offered assistance in future as well.

The life science business of Merck
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2017-05545

MilliporeSigma

A Case Study in Biofilm Contamination

Biofilm control is critical to any manufacturing operation, as one company learned when it installed an ambient WFI subloop on a continuously recirculating hot WFI loop.

What could go wrong?

The Event

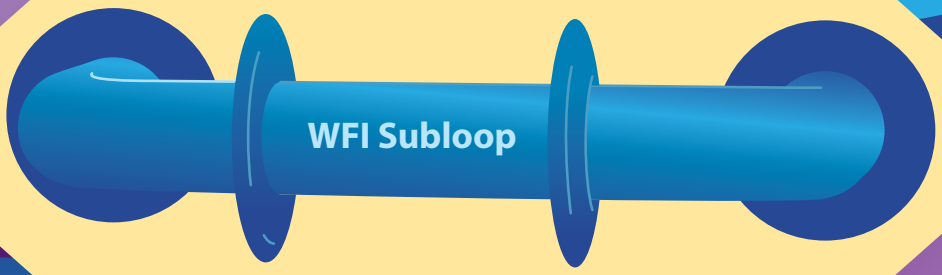
In Week 4 of validation testing, out-of-trend microbial counts were detected.

The counts continued to go up, in spite of hot water sanitization, increasing after each treatment of hot water.

The Findings

Investigators found that some cold coolant remained at the bottom of the shell holding the coolant. This led to cooling of the hot WFI flowing through tubes during the one-hour sanitization cycle.

Surviving cells used dead cell mass as food, resulting in growth of biofilm.



Lesson Learned: Once established, biofilm can be hard to get rid of, even with runs of hot water.

The Response

CAPAs consisted of longer heating times for sanitization, a higher sanitization cycle start temperature, and an air vent at the topmost section of the heat exchanger cell to release trapped air.

The Results

Microbial counts remained undetectable for the remainder of the yearlong Performance Qualification period.

Find out the latest information on microbial control in session A1 at the *12th Annual PDA Global Conference on Pharmaceutical Microbiology.*

Source

PDA Technical Report No. 69 (2015): Bioburden and Biofilm Management in Pharmaceutical Manufacturing Operations

PDA
Parenteral Drug Association

PDA: Taking the Lead on Post-Approval Changes

PDA's Post Approval Change: Innovation for Availability of Medicines (PAC iAM℠) program strives to identify, assess and address current barriers to implementation of post-approval changes to promote continued operations and to drive innovation and continual improvement.

Addressing these barriers will better ensure and sustain reliable global supply and availability of product to patients through the entire commercial lifecycle of a product.

Through the PAC iAM℠ initiative, PDA has available a number of valuable resources for the industry, including:

- Points to Consider Papers
- A Call to Action
- Informational Articles
- Webinar/Presentations
- 2017 PAC iAM Workshop, Sept. 13-14, 2017 Washington, DC

To access these important tools, visit www.pda.org/pac

SNAPShot

PDA Contributes to EMA Shared Facilities Discussion

Ester Lovsin Barle, Novartis, and Igor Gorsky, ValSource

PDA recommended using a risk-based approach to address health-based exposure limits (HBELs) in the presentation, "Key points to recognize quality in Health Based Exposure Limits (HBEL) and associated monograph" at EMA's June workshop on shared facilities ***(1).*** In particular, PDA advocated flexible approaches for products currently manufactured in shared facilities to avoid interrupting the supply of essential medicines.

Hosted by EMA's Safety Working Party (SWP), this workshop offered industry representatives a chance to discuss the Agency's Q&A concerning risk-based strategies to prevent cross-contamination in shared facilities ***(2).*** The discussions at the workshop were positive and paved the way for continued use of scientifically justified, toxicological, risk-based approaches that rely on documented rationale proportionate to the level of cross-contamination risk.

Background on Shared Facilities

Chapters 3 and 5 of the *EU EudraLex Guidelines for Medicinal Products for Human and Veterinary Use* require a toxicological evaluation to assess and control cross-contamination risks presented by drug products manufactured in shared production facilities ***(3, 4).*** On June 1, 2015, EMA's regulatory guideline setting Permitted Daily Exposure (PDE) values went into effect for all new human pharmaceutical products. The guideline for existing human pharmaceutical products then went into effect Dec. 1, 2015 ***(5).*** Previously, other methods were used to determine an acceptable level of carryover with uncertain levels of patient health protection ***(6).*** One of the most frequently used methods was 1/1000 of the minimum daily dose (MinDD). This method has many shortcomings, as has been covered in recent articles ***(7, 8).***

Following implementation of the PDE guideline, EMA issued a Q&A document in response to several open questions ***(2).*** While EMA hoped this nonmandatory document would clarify interpretation of the PDE guideline, it reintroduced two criteria that appeared to be a step back. One was the classification of products into two hazard categories; the second related to the continued use of the 1/1000 criteria for nonhazardous drugs. These two points caused significant confusion within industry, and a number of comments have been sent to EMA by industry associations, such as PDA, as well as individual experts.

In its comments, PDA's Regulatory and Quality Advisory Board (RAQAB) advocated "flexible approaches for products currently manufactured in shared facilities to avoid interruption of supply of essential medicines"***(9).*** PDA recommended use of a scientifically justified, toxicological, risk-based approach relying on a documented rationale. Further, PDA urged EMA to remove references to 1/1000 of the minimum therapeutic dose based on the approach described in the 2015 guideline.

PDA Position Discussed at Workshop

The PDA presentation at the June workshop reiterated the points made in the earlier comments. Following the presentation, attendees raised the following key points in support of PDA's position:

- Inspectors expect to see the HBEL approach to avoid redundancy of terminology such as "highly hazardous" and the use of 1/1000 MinDD
- Trained and knowledgeable individuals must complete a rigorous methodology to accurately determine a safe/acceptable exposure for a given substance
- Cross-functional users should employ a solid implementation plan to ensure consistent application of practices in complex quality risk management systems ***(10)***
- There are many factors in controlling carryover risks beyond the HBEL, which also need to be done consistently by qualified experts

The discussions at the workshop were positive and paved the way for continued use of a scientifically justified, toxicological, risk-based approach with a documented rationale. While more time is clearly needed for implementation of the PDE/HBEL concepts, future use of toxicological limits is not in dispute. During future inspections, more focus will be given this topic, as well as topics addressed in the Q&A document, such as quality of the PDE documentation, toxicological expertise, responsibilities associated with implementation, and quality of overall GMP risk assessments. A proper and consistent risk assessment of cross-contamination risks has to be available; best practices would include historical process control limits as well as proper training of personnel. The extent of the risk assessment concept must be proportional to the associated risks, which gives some additional opportunities for flexibility to small to medium-sized enterprises with lower cross-contamination risks.

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The Parenteral Drug Association presents the...

2017 PDA Visual Inspection Forum

October 23-24, 2017 | Bethesda, MD

Bethesda North Marriott Hotel & Conference Center

Exhibition: October 23-24 | Courses: October 25-26

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Photo courtesy of John Shabushnig, *Insight Pharma Consulting LLC*

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- Regulatory compendial issues
- Particle control and characterization
- Difficult-to-inspect products
- Manual inspection
- Primary packaging materials
- Automated inspection

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

Learn more and register at *pda.org/2017Visual*

Extend your learning with a two-day *Introduction to Visual Inspection* course offered by PDA Education on **October 25-26**, immediately following the Forum. Discover more about this course at ***pda.org/2017OctVi***

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Noted industry and regulatory speakers on the agenda include:

- **Ernest A. Bognar,** Vice President Operations, *Gradalis Inc.*
- **Darius Pillsbury,** Head of Validation, *Adaptimmune LLC*
- **Zenobia F. Taraporewala, PhD,** CMC (Product) Reviewer, Gene Therapies Branch, CBER, *FDA*
- **James Wilson, PhD,** Director of Gene Therapy, *University of Pennsylvania*

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Learn more and register at *pda.org/2017CellGene*

SNAPShot

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One Simple Way to Manage Aseptic Risk Assessments continued from page 20

the author's poster at the *2017 PDA Annual Meeting*.]

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About the Author

Since 2013, the microbiologist **Guenther Gapp** has been working as an independent consultant for different clients around the globe.

The Cost of Microbial Control continued from page 25

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Novel Drug Products Drive New Views on Suitability

Diane Paskiet, West, and Ronald Iacocca, PhD, Eli Lilly and Company

The drive for patient-centric solutions and the emergence of novel drug products has led to the need for early understanding of container closure and delivery system suitability. A therapeutic product is fit for use when it meets established quality criteria with appropriate correlations between drug product quality and clinical performance. But when and how should the drug delivery system or drug/device system characteristics be considered? A broad range of challenges related to safety and compatibility must be overcome when qualifying combination products associated with both drugs and devices.

What types of delivery system risks should be considered? How can they be assessed? What data is needed to qualify a combination product?

These will be among the topics of discussion at the *2017 Container Closure, Devices and Delivery Systems: Compatibility and Material Safety Workshop*. This event will focus on current topics related to container closure systems and device/drug combination products. Individual components of a system are often regulated under different FDA Centers, each having different policies, practices and timelines. As delivery technologies advance, so too does the need for inter-Center agreements, although the requirements are not clear-cut. Areas of common interest include:

- Intended use and design inputs
- Biocompatibility data
- Design outputs conforming to the design inputs
- Design verification and validation
- Translation of the design into manufacturable specifications

FDA representatives will speak to these requirements. **Jennifer Goode,** Biocompatibility Program Advisor, CDRH, will discuss biocompatibility assessments for devices. CDER's **Susan Kirshner** will address biologic compatibility. CDRH's **Nazia Rahman** and **Isabel Tejero** will speak on the impact of supplier controls on delivery system quality. And CDER's **Dan Mellon,** PhD, will review the Agency's extractables and leachables studies.

2017 PDA Container Closure, Devices and Delivery Systems: Compatibility and Material Safety Workshop

Washington, D.C.

Oct. 2–3

www.pda.org/2017CC

Visual Inspection Faces Changing Environment

John D. Ayres, MD, Eli Lilly and Company

Visual inspection of injectables has become one of the most dynamic functions in pharmaceutical manufacturing. Advances in technology have given us a remarkable ability to assess the contents of individual parenteral units with increasing sensitivity. Noninvasive technology allows us to confirm the adequacy of container closure. Enhanced orthogonal tools and techniques permit a better understanding of the characteristics of both inherent and extraneous materials.

But significant challenges persist. Difficult-to-inspect products, such as suspensions, lyophilized cakes, opaque containers, large volume parenteral flex bags and blow-fill-seal containers add significant complexity to visual inspection process design and qualification. Likewise, the increasing development of complex biotherapeutics introduces the need for added discrimination between acceptable inherent proteinaceous drug product and undesirable extraneous matter through enhanced noninvasive inspection techniques. In addition, all of this results in updated regulatory and compendial requirements.

Staying attuned to the changes in regulatory and compendial requirements, inspection process capability, advances in inspection-related technology and the impact on the ultimate recipient—the patient—is essential to address the question: *Are our visual inspection programs built to meet the litmus test of quality and capability?*

The *PDA Visual Inspection Forum* provides an unparalleled opportunity to participate in in-depth discussions of new technologies, hear insights from regulators and engage with recognized leaders in visual inspection. This year's sessions include updates on regulatory compendial issues, particle control and characterization and difficult-to-inspect products, including biopharmaceutical inspection and primary packaging material considerations—all augmented with case studies and interactive Q&A opportunities. As in past years, the meeting will feature an exhibition with multiple poster presentations and vendor booths where attendees can see the latest in commercial inspection hardware and discuss production needs with key suppliers of inspection systems and services.

2017 PDA Visual Inspection Forum and PDA Education Courses

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www.pda.org/2017visual

The Parenteral Drug Association presents...

12th Annual PDA Global Conference on Pharmaceutical Microbiology

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Network, interact, and share with industry experts and professionals at the three-day, *12th Annual PDA Global Conference on Pharmaceutical Microbiology*. At this best-in-class Conference, pharmaceutical microbiologists and interdisciplinary scientists will explore solutions to new challenges related to antimicrobial resistance and microbial control.

Take part in a combination of brand new and crowd-favorite sessions, including a U.S. FDA update on human drug compounding; U.S. Pharmacopeial Convention updates; the U.S. FDA's Mutual Reliance Initiative and its impact on pharmaceutical inspections around the world; case studies on microbial control, combination products, and environmental monitoring; and the always-popular "Ask the Regulators" panel discussion.

Don't miss out on the latest industry trends, issues, solutions, and best practices in the field of pharmaceutical microbiology! **To learn more and register, please visit *pda.org/2017Micro***

After the Conference, on **October 18-19**, PDA will host the *2017 PDA Endotoxins Workshop*, which will provide scientific understanding and real-world practices for endotoxin testing in bio/pharmaceutical production processes. **For additional information on the topics that will be covered and to register, please visit *pda.org/2017Endotoxins***

Are you looking to obtain new skills or expand your knowledge on pharmaceutical microbiology? Attend one of the five PDA Education courses comprising the *12th Annual PDA Global Conference on Pharmaceutical Microbiology Course Series*, **October 19-20. To learn more and register, please visit *pda.org/2017MicroCS***

Four Steps to Ensuring Data Integrity for BET

Jennifer Farrington, PhD, Associates of Cape Cod, Inc.

Data integrity has been well established as a fundamental regulatory expectation under cGMP. Naturally, data integrity also applies to bacterial endotoxin testing (BET).

Tests with BET products generate results in three different methodologies: (a) those that use data generated in electronic form via equipment/software combinations (e.g., chromogenic and turbidimetric products); (b) those that are documented on paper-based systems (e.g., Gel-Clot products); and (c) those that involve hybrid records. Data integrity controls are expected across the product lifecycle for all BET assays in all three formats, starting from data creation, through processing and use, to retention and retrieval. The U.S. FDA data integrity guidance issued in April 2016, along with PIC/S and MHRA documents, encourages the adoption of risk-based approaches to data integrity.

Step 1: Data Creation

Controls for electronic records include system validation, hardware and software controls, access controls, audit trails, backups and electronic signatures. Appropriate controls should be in place to ensure that changes to data records can be made only by authorized personnel and are traceable. For paper-based systems used to create data and records, master forms must be controlled and recorded, data initialed and dated by the operator, critical steps witnessed and completed with document peer review. In the case of Gel-Clot BET, the actual testing is conducted, visually read, recorded, initialed and dated by the analyst at the time results are read. All records must be retained, including those due to entry error or unexpected result.

Step 2: Data Processing

In BET electronic testing, data is analyzed to show the endotoxin concentration, which is interpolated from the standard curve using the software associated with the type of reader, and validated to 21 CFR Part 11compliance. In the case of the Gel-Clot method, the geometric mean is manually calculated from the endpoints or calculated with a validated third-party solution. All calculations should be peer-reviewed for accuracy.

Step 3: Data Review and Use

Once reported, data is reviewed by the quality assurance unit using established procedures. That data can then confidently be used to make quality decisions. The review should be based on original data, including relevant metadata and audit trails, and assessed (when appropriate) according to risk.

Step 4: Data Retention and Retrieval

Procedures should be in place to ensure all original data and records are retained securely and protected from the possibility of destruction so that they can be readily retrieved for review at any point in the defined retention period. Additionally, relevant associated metadata should be readily traceable to the original data.

Throughout these four steps, a risk-based approach to data integrity ensures that quality decisions can be made with conviction throughout the product lifecycle.

The *2017 PDA Endotoxins Workshop* following the *12th Annual PDA Global Conference on Pharmaceutical Microbiology* provides an excellent opportunity to learn how data integrity issues impact BET procedures.

About the Author

Jennifer Farrington, PhD, is the Associate Director of Regulatory Affairs at Associates of Cape Cod, Inc. She is also co-chair of the *2017 PDA Endotoxins Workshop* and will moderate the breakfast session on data integrity, Oct. 19 at 7:15 a.m.

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PDA Links Quality and Science

Barbara Allen, PhD, Eli Lilly

When you hear someone from PDA talk about "quality beyond compliance," what do they mean? Well, in the pursuit of achieving quality in manufacturing, it refers to doing more than just what is required to appease global regulators, i.e., moving past a checklist mentality by ingraining a quality mindset within an organization.

How can we as an industry address this change of mindset? Collaboration is the key to bringing about change—collaboration among manufacturers of all sizes from pharma and biopharma as well as suppliers and regulators. PDA members are working toward that goal. Volunteer groups comprising representatives from the varied factions of the industry are working together to grow an organic and holistic quality mindset across the industry. I wanted to follow up **Melissa Seymour's** excellent article from last month—covering PDA's efforts to promote quality beyond compliance with quality metrics, data integrity and post-approval changes—with some information about additional PDA efforts in this space.

One of these efforts involves quality culture, which grew out of PDA's work on quality metrics. Our Quality Culture Task Force began its work by developing and publishing a survey on the state of quality culture in the industry (this survey can be found in the *PDA Journal of Pharmaceutical Science and Technology*). From this survey, the task force developed a Quality Culture Assessment Tool that provides a more objective measure of quality culture by assessing the quality attributes most important to quality culture. This tool is also being used to support other PDA quality culture initiatives.

Then, this June, PDA hosted a workshop on quality risk management (QRM) in Chicago. This conference featured a strong lineup of speakers and breakout sessions designed to stimulate discussion about appropriate QRM practices. **Kelly Waldron,** one of the workshop speakers, along with **Emma Ramnarine** and **Jeffrey Hartman,** led the team responsible for the 2015/2016 Quality Risk Management Benchmarking Survey. The results of this survey will appear in the September/October issue of the PDA Journal. Emma Ramnarine will also be one of the instructors for a series of PDA Education courses on QRM this fall.

Of course, science is the core of quality. A strong quality culture focuses on the science of making medicine, encouraging and enabling the use of science. It is important that regulatory systems also facilitate improvement to product quality and quality assurance and foster adoption of new technology and work practices. To encourage this line of thinking, PDA will cohost a workshop with the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) this month that will explore how industry and regulators are working together to streamline and harmonize post-approval change management using science and risk-based approaches.

Science and quality is also a focus topic of sessions at PDA's signature meetings, particularly the *PDA/FDA Joint Regulatory Conference* and PDA's U.S. and European Annual Meetings. The topic is regularly discussed within PDA'S interest groups, in particular the Inspection Trends, Quality Risk Management, Quality Systems, and Regulatory Affairs Interest Groups. Make your voice heard and learn from your peers by joining one of these interest groups. PDA's team efforts have resulted in books, articles, conferences and training courses that advance these concepts, and PDA will continue to advocate for strong science, quality and regulatory connections. I encourage you to contact PDA and get involved in collaborating with other members.

PDA Bookstore New Release

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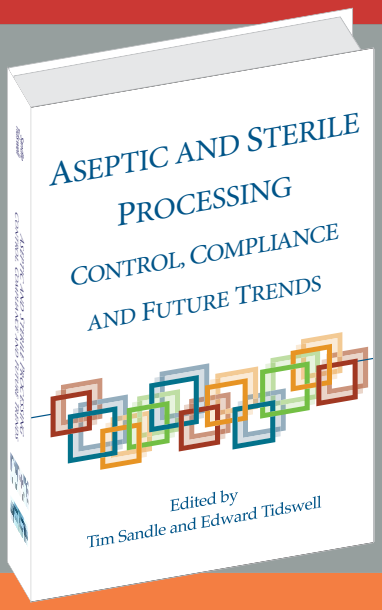

Aseptic and Sterile Processing: Control, Compliance and Future Trends

Edited by: Tim Sandle and Edward Tidswell

PDA MEMBER PRICE: ~~$260~~ $221
PDA NON-MEMBER PRICE: ~~$325~~ $276.25
HARDCOVER: ITEM NO. 17342
DIGITAL: ITEM NO. 18038

The *Aseptic and Sterile Processing: Control, Compliance and Future Trends* is the most important text discussing aseptic and sterile manufacturing that has been published in the last decade! This text looks at both today and tomorrow in regard to these two vital processing procedures.

The Editors of this book realized that there was an urgent imperative for these subjects to be reassessed and represented. To achieve this objective, along with many subject matter experts, they produced a book that is designed for those involved with aseptic and sterile processing to take away many learning points and apply these principles to aseptic and sterile processing, within the pharmaceutical and healthcare sectors.

It is the aim of the Editors to help readers reassess legacy definitions and historical understandings and move them toward concepts that will help them think in new ways about equipment and processes in order to reach the highest standards and evaluate them through science-based risk assessments.

Table of Contents:

- Sterility
- Contamination Risks and the Patient
- Current, Ideal and Anticipated Regulations for Sterile Drug Products
- Aseptic Processing
- Bioburden Control
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- Microbial and Endotoxin Control of Water Systems
- Depyrogenation, Nonpyrogenation and Repyrogenation
- Microbial Contamination Control in Cleanrooms
- Environmental Control and Environmental Monitoring in Support of Aseptic Processing
- Aseptic Process Simulations/Media Fills
- Cleaning and Sanitization for Aseptic Processing
- Cleanroom Gowning
- The Sterility Test
- Risk Assessment and Mitigation in Aseptic Processing
- The Misattribution of “Human Error” in Producing Sterile Products
- Evaluation and Improvement of Aseptic Processes
- Single-Use (Disposable) Technology
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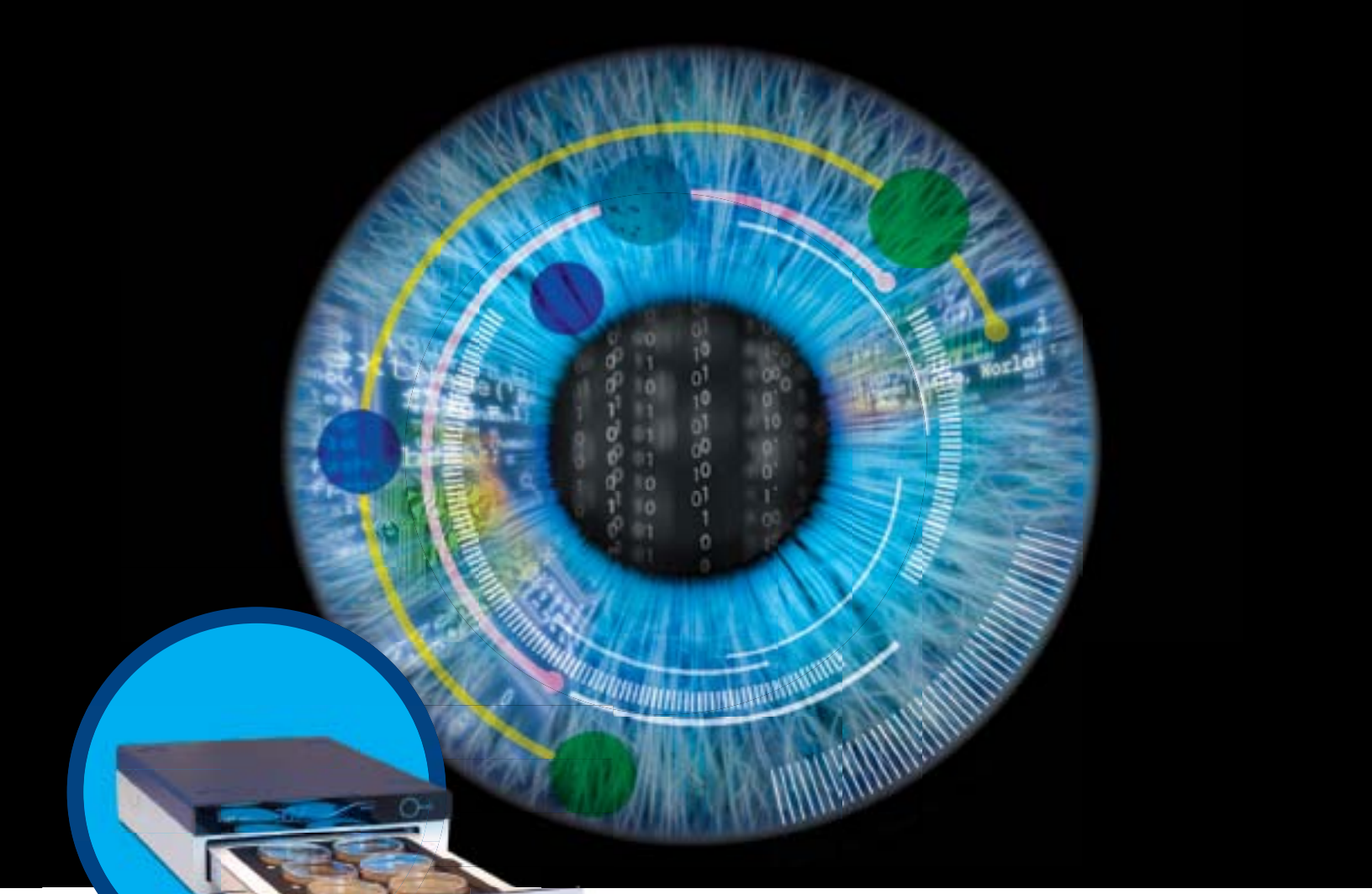

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