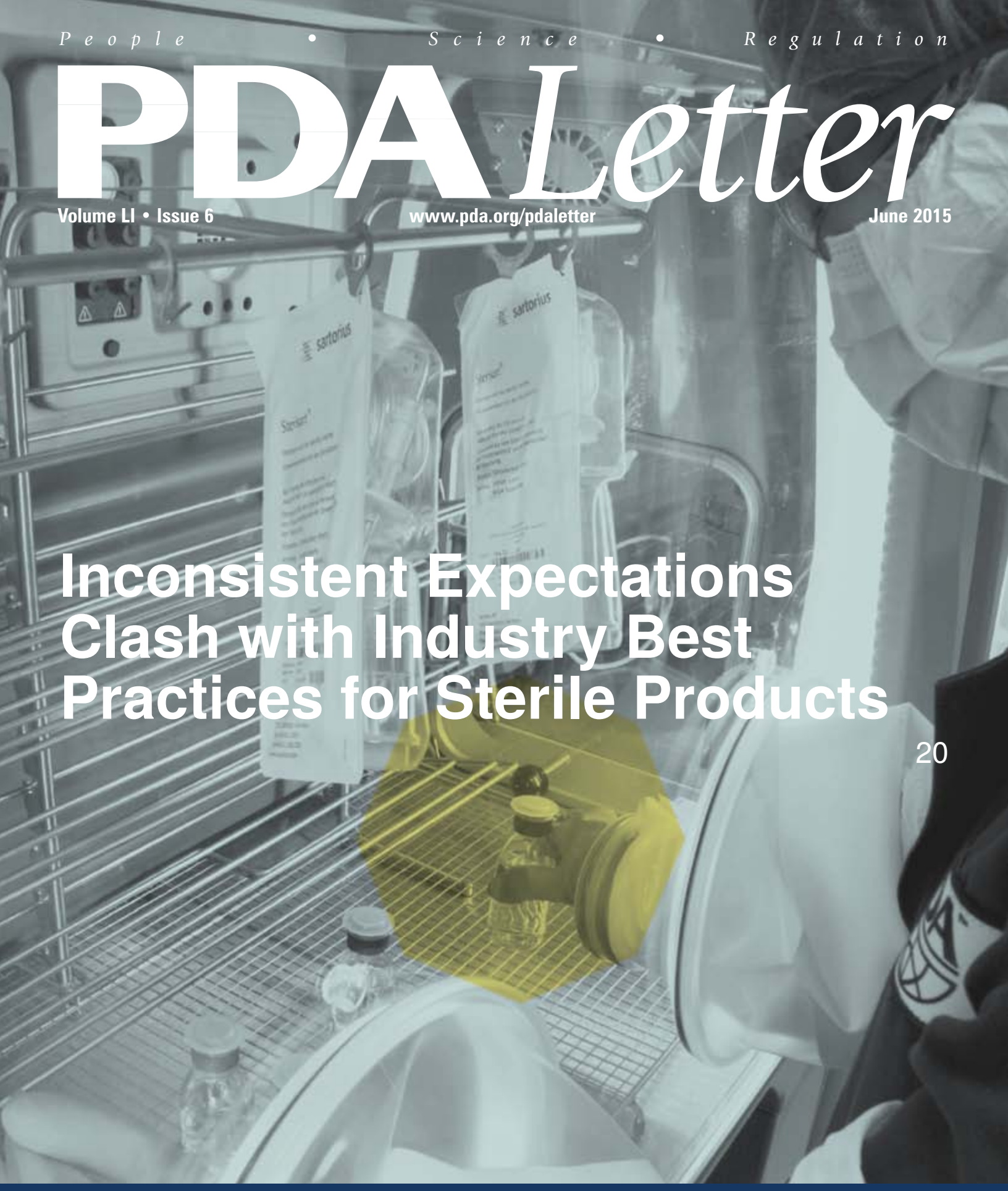
People • Science • Regulation

PDA Letter

Volume LI • Issue 6 www.pda.org/pdaletter June 2015



Inconsistent Expectations Clash with Industry Best Practices for Sterile Products

20

The Parenteral Drug Association presents...

2015 PDA Visual Inspection Forum

October 26-27, 2015 | Bethesda, MD

Bethesda North Marriott Hotel and Conference Center

Exhibition: October 26-27 | Course: October 28-29

PDA® Parenteral Drug Association

Register before August 17, 2015 and save up to $400!

The leading meeting and exhibition dedicated to quality assurance of injectable products

Join leading regulatory and industry experts at the *2015 PDA Visual Inspection Forum* to get the latest on new developments in this critical field.

FDA Presenters Just Confirmed!

- **Stephen Langille, PhD,** Branch Chief, Division of Microbiology Assessment, Branch 3, CDER, *FDA*, will discuss the risks associated with various categories of visible particulate matter, regulations and standards that apply to particulate matter limits and the elements of an effective visible particulate control program.
- **Ewa Marszal, PhD,** Chemist, CBER, *FDA*, will address the thinking, concerns and assessment expectations of the regulatory community when evaluating subvisible particle burdent that might be presented by biologics.

Additional industry experts *just* added to the program include:

- **Andreas Brutsche,** Head of Global Quality Assurance, *Sandoz*
- **Heino Prinz,** Director, Inspection Devices, *Rommelag*
- **Kevin Kerls,** Senior Manager, Inspection MSAT, *Genentech, Inc.*
- **Richard Watson,** Director, Sterile & Validation COE, *Merck Sharp & Dohme Corporation*
- **Roy McLean,** Manager, Sterile Manufacturing, *Hospira*

This meeting will present case studies, explore new USP chapters<790>, <1790> and focus on the latest developments in the field of visual inspection.

To learn more and to register, visit pda.org/visual2015

Expand your knowledge of visual inspection – stay on for the popular PDA education course, *An Introduction to Visual Inspection* (October 28-29), which will explore the fundamentals of visual inspection and their application to injectable products through a combination of lecture, discussion and hands-on laboratory exercises.

Visit pda.org/visualcourse to learn more and register.

Upcoming Laboratory and Classroom Training for Pharmaceutical and Biopharmaceutical Professionals

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PDA® Parenteral Drug Association

Educational Opportunities at PDA

SEPTEMBER 2015

Fundamentals of an Environmental Monitoring Program
September 9-10 | Bethesda, MD
pda.org/enviro

Establishment of a Risk Based Environmental Monitoring (EM) Program
September 11 | Bethesda, MD
pda.org/EMP

2015 Glass Quality, Visual Inspection and Foreign Material Identification Week
September 14-18 | Bethesda, MD
pda.org/glassqual

- Identification and Classification of Nonconformities in Molded and Tubular Glass Containers for Pharmaceutical Manufacturing (September 14)
- An Introduction to Visual Inspection (September 15-16)
- Foreign Particulate Examination, Isolation and Analysis – New Course (September 17-18)

Utilization of Statistical Methods for Production Monitoring
September 22 | Bethesda, MD
pda.org/statistics

For more information on these and other upcoming PDA courses, please visit pda.org/courses

Denotes Laboratory Course

Denotes GSA Schedule Contract

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

OCTOBER 2015

2015 Regulatory Course Series
October 1-2 | Washington, DC
pda.org/pdacourses

- Risk-Based Product Development Basics for Combination Products: Harmonizing Design Controls and Quality-by-Design in Product Development and Market Authorization Documents (October 1)
- Quality Metrics: Performance Indicators (October 1-2)
- Root Cause Investigation for CAPA (October 1-2)
- Process Validation and Verification: A Lifecycle Approach (October 1-2)
- CMC Regulatory Requirements in Drug Applications (October 2)

Filtration Week
October 12-16 | Bethesda, MD
pda.org/filtration

- Filters and Filtration in the Biopharmaceutical Industry: Basics Course (October 12-13)
- Filters and Filtration in the Biopharmaceutical Industry: Advanced Course (October 14-16)

Validation of Moist Heat Sterilization Processes
October 21-23 | Bethesda, MD
pda.org/moistheat

PDA 10th Annual Global Conference on Pharmaceutical Microbiology Course Series
October 22-23 | Bethesda, MD
pda.org/microcourses

- Investigating Microbial Data Deviations (October 22)
- Evaluation, Validation and Implementation of Alternative and Rapid Microbiological Testing Methods (October 22-23)
- Regulatory Aspects of Microbiology in a Non-Sterile Environment (October 23)

An Introduction to Visual Inspection
October 28-29 | Bethesda, MD
pda.org/visualcourse

PDA Letter

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Cover Art Illustrated by Katja Yount

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Voices of PDA

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Features

PDA Welcomes Dr. Falk Klar

PDA's Europe office welcomes **Falk Klar,** PhD, as the new Senior Director of Education. He joined the PDA family on May 26. In his new role, he will work closely with **Georg Roessling,** PhD, Senior Vice President of the Europe office, and will strengthen PDA's education portfolio in Europe as well as support other European PDA activities.

Klar has 19 years' experience in the pharmaceutical and biotech industries. His experience covers medicinal products as well as clinical research for drugs, vaccines, sterile liquids, biotech active ingredients, combination products and medical devices.

PDA is Hiring!

PDA has an immediate opening in our Education department for a Director of Education Operations. The successful candidate will have a BS/BA degree or equivalent in biological, chemical or physical science with eight–ten years' experience in the pharmaceutical industry and a demonstrated interest in education and developing educational content. Experience in sterile product operations, including aseptic processing, is required.

If you have strong interpersonal skills and good business acumen, and you enjoy working with people, this job might be right for you. To learn more, please forward your resume to hiring@pda.org.

PDA Extends Richard Johnson as President/CEO

In early May, PDA's Board of Directors finalized an agreement that allows **Richard Johnson** to continue as President and CEO through 2021.

"We are very pleased to have Richard Johnson continue as our President and CEO," said **Hal Baseman,** the Chair of the Board of Directors. "Under his leadership, PDA enjoyed significant success, performance and growth. He has led a strong staff and dedicated volunteers, hosted PDA's largest meetings, published a record number of technical reports, expanded membership and services globally and facilitated increased participation by regulators. This continuity of leadership ensures that PDA will play an ever-increasing role in providing unmatched services to its members and our industry for many years to come."

Johnson joined PDA as President in 2009 following a 30-year career in the pharmaceutical industry, which included 20 years as an active PDA volunteer and member.

Call for Volunteers

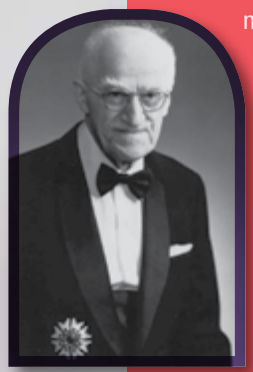
If you're planning to attend the *2015 PDA/FDA Joint Regulatory Conference* and would be interested sharing your experience with the *PDA Letter*, please contact **Rebecca Stauffer** at stauffer@pda.org.

PDA Volunteer Spotlight

Janeen Skutnik-Wilkinson

- Corporate Quality
- *Biogen*
- Member Since | 2000
- Current City | Oneco, Connecticut

As a member, I have the opportunity to work with experts from a very diverse network



Janeen is an admirer of Joseph Juran

Why did you choose to join PDA?

PDA provides a unique opportunity to work with technical experts across the industry. As a member, I have the opportunity to work with experts from a very diverse network spanning large to small companies as well as innovator firms to generic manufacturers and also regulatory authorities.

Where do you go for professional development and why?

Right now I am looking into PDA training to enhance my industry knowledge in the area of biologics.

Of your PDA volunteer experiences, which have you enjoyed the most?

Creating the first *PDA/FDA Supply Chain Workshop,* and continuing to work on subsequent workshops for several years. The issue was extremely important in terms of patient safety and this provided an opportunity for industry and regulators to align around a key topic. These workshops set the stage for many spin-off activities.

What are some topics you would like to see covered at future PDA events?

There are a few great topics I would like to see addressed, for one, regulatory convergence and the future. As various regulators begin working more closely together, what role can PDA and industry play to help support and encourage more convergence? And second, quality systems of the future. As we continue to explore scientific developments such as nanotechnology, personalized medicines, 3-D printing of medicines and maybe 3-D printing of packaging components, how do our quality systems need to shift and evolve?

What trends in your industry are you most excited about?

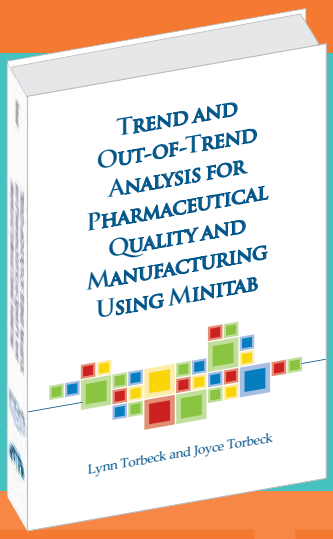
The focus on quality culture. I feel that quality culture is the foundation for success in delivering safe, high-quality products to patients.

Where are you originally from?

I don't consider myself originally from anywhere. I have moved 39 times in my life.

PDA Bookstore New Release

Pre-order and Save 15% through July 31, 2015.
Enter Campaign Code TAPQ during Checkout.



Trend and Out-of-Trend Analysis for Pharmaceutical Quality and Manufacturing Using Minitab

BY: LYNN TORBECK AND JOYCE TORBECK
PDA MEMBER PRICE: ~~$210~~
PRE-ORDER PRICE: $178.50
ITEM NO. 17330

A trend is a series of events or data collected, generally over time, that has an established and expected pattern. The trend can be observed or it can be based on theoretical models. Any departure from the trend is then an unexpected out-of-trend event. It is atypical and begs for investigation.
Trend analysis is good business and good science. The need for a trend analysis book is justified by the continued interest in presentations and discussions, both public and private, and the lack of a widely accepted, clearly defined approach by the industry that lends itself to consistent interpretation and uniform application.

Out-of-Trend Analysis for Pharmaceutical Quality and Manufacturing Using Minitab, a new publication by Lynn Torbeck and Joyce Torbeck, answers this call, contributing to an industry/regulatory dialogue and consensus that will serve and benefit all stakeholders, and patients in particular.

This book is for pharmaceutical professionals working in product discovery, development, manufacturing, quality assurance and quality control. It presents a basic introduction to data and Trend and Out-of-Trend definitions, and proposes terminology to clarify the use of the word 'control" in several contexts. Outtakes from FDA warning letters, plant audits and investigations for trend and out of trend are presented to highlight the agency's viewpoint. Helpful graphs, charts and tables are also included throughout the book and in the appendices.

go.pda.org/TAPQ

ABOUT THE AUTHORS

LYNN TORBECK AND JOYCE TORBECK, started Torbeck and Associated in 1988 providing training and consulting in applied statistics and experimental design for pharmaceutical and biopharmaceutical development, quality assurance and control. Specific effort was targeted to process and method validation under cGMP's. Publications include many journal articles, books and chapters. Specifically, *Validation by Design* and *Square Root of (N) Sampling Plans* as well as a chapter in *Pharmaceutical Quality* titled *Using Statistics to Measure and Improve Quality.*

chapter update

Missouri Valley Chapter Marks Five Years of Growth

Jeff Kisslinger, Steris

PDA's Missouri Valley Chapter hosted its annual spring meeting April 13 at Arrowhead Stadium in Kansas City, Mo. The meeting was another roaring success with 88 members, representing various segments of the industry from 20 different organizations, in attendance.

At the meeting, Chapter President **Jeff Hargroves,** announced that he has "been pleased to see the continual growth of the chapter during our first five years. The individuals and vendors of our area help us to put current, interesting topics in front of our crowds, which in turn draw more people to each meeting. It has been a great circle of success."

The chapter also announced plans for its first student chapter, which will support students at the University of Missouri-St. Louis. **Jeffrey Wiegers** will lead this new student chapter. Chapter Treasurer **Valerie Welter** then announced that the Chapter plans to offer a scholarship for students pursuing careers in pharma.

Following a behind-the-scenes tour of Arrowhead Stadium, **Gerald Bromley** kicked off the meeting by discussing the U.S. FDA's current organizational direction as well as regulatory trends he's noticed. Next, **Manuel Garza** provided a review of vendor qualification and management. He highlighted key areas of focus and concern that manufacturers should pay close attention to in their supply chain and outsourced functions, citing examples of failures that resulted in FDA warning letters. **Bob Williford,** the final speaker of the evening, discussed the importance of quality agreements, emphasizing relationship terms, practical application, adherence and what to do when things go wrong.

The evening closed with a lively panel discussion on FDA inspection trends featuring the night's speakers as well as **Gary Klaassen.**

PDA Who's Who

Gerald Bromley, U.S. FDA, Kansas City Field Office

Manuel Garza, Principal Consultant, PAREXEL

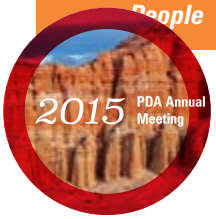
Jeff Hargroves, President and CEO, ProPharma Group

Gary Klaassen, Director of Quality, Bayer Healthcare

Valerie Welter, Sr. Director, Quality Management, Bayer Animal Health

Jeffrey Wiegers, Senior Director, Quality and Operations Integration, Mallinckrodt

Bob Williford, Lead Director of Quality Operations, Hospira



New PDA Member's First Foray to Annual Meeting

Janera Harris, Cytonet

In March, I spent a week at the *2015 PDA Annual Meeting* in Las Vegas not only learning more about the industry but also interacting and networking with other professionals in the areas of manufacturing and quality. This was my first time attending a PDA conference since joining last December. My interest in the topics covered at this meeting served as a driving force in my decision to join.

The Sunday before the meeting, I went down to the registration area following my arrival, picked up my packet and began meeting some very interesting and entertaining PDA board members during the Meet and Greet Reception. While talking with them, I learned about all the things that PDA does, how it's strongly volunteer-driven and has a deep-seated role in the regulations issued from the different governing bodies. The next morning, I attended the new member breakfast where I met other new PDA members and learned even more about the various volunteer opportunities available within PDA.

One of the sessions I looked forward to the most was the plenary session "Importance of Science & Technology to Building a Quality Culture." As Director of Quality at a small cell therapy company where everyone wears a lot of different hats, it is important to learn different ways to foster a quality culture. Another session I found beneficial explored new processes and challenges facing cell therapy products. It was interesting to hear about the different hurdles other cell therapy companies face with getting their product to market.

I also attended a couple of the breakfast sessions. At the quality metrics meeting, I learned about the quality metrics guidelines that the U.S. FDA plans to release at the end of 2015 and how that will impact the industry. At this same meeting, I also learned that the European Union now plans to focus on quality metrics during audits they perform. One of the other breakfast sessions I attended provided an update on the aging facilities task force. To hear about the different problems that companies experience when updating their facilities was eye opening.

One of the interest group sessions I attended covered management of outsourced operations. My company, Cytonet, is a contract manufacturer, but we also outsource different operations to other companies. Quality agreements

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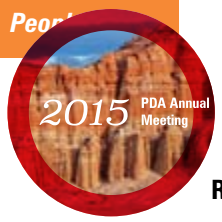

The Annual Meeting Through the Eyes of a Rookie and a Vet

Rebecca Stauffer, PDA

For the *2015 PDA Annual Meeting* in Las Vegas, the *PDA Letter* followed **Christopher Dominguez** and **Steven Mendivil** to experience the meeting through their eyes. This was Dominguez's first time attending the Annual Meeting, although he has attended other PDA conferences. For Mendivil, a long-time PDA volunteer and former board member, this was one of many Annual Meetings.

Both were happy to answer questions for **Rebecca Stauffer** over the course of the meeting.

Monday, March 16, 3:15 p.m. PST

PDA Letter: How has your first day been at the Annual Meeting?

Dominguez: I think overall I was quite pleased with the discussions, and found it to be very informative. I think it was very powerful to have the keynote speaker **Chad Juros** in the morning session. I thought that leading off with that, illustrating the patient impact, really [resonated] with the attendees, and [made] it really that much more important of what we're doing within industry overall.

Beyond that, I think probably, the other big highlight for me was the presentation by **Fran Zipp** on the cost of poor quality. I found that to be very powerful—especially with the figure of 62% of companies do not calculate the cost of poor quality. It was significant and something I would definitely bring back to the executive management of my firm.

PDA Letter: You just attended a breakout session. Can you tell us about it and what you took from it?

Dominguez: Sure, the breakout session I was in was with respect to serialization and drug diversion and counterfeiting. There [were] a couple of presentations—one from a gentleman from Johnson & Johnson and then one from Eli Lilly. And then the closing presentation that I just left was from the [U.S.] FDA office of criminal investigations—actually quite eye opening with respect to the criminal element that is present within industry with drug diversion and its potential impact to the patients. Without having that appropriate level of education and vigilance, we can do some real harm. And it's unfortunate.

PDA Letter: While this is your first Annual Meeting, you've attended other PDA meetings. How does this compare?

Dominguez: I think it's on par. I think that overall, I feel the PDA is at a very well-respected level within industry. And I think it's one of the premier associations…I'm always pleased to attend and find opportunities to catch up with past colleagues and have some very interesting dialogues and discussions and do benchmarking. So, I think they're always an excellent opportunity and I would highly encourage others within industry to attend.

Monday, March 16, 5:30 p.m. PST

PDA Letter: When did you attend your first *PDA Annual Meeting?*

Mendivil: It was about 26 years ago in San Francisco.

PDA Letter: How did your first day at this Annual Meeting go?

Mendivil: I thought it was really a great meeting. I thought it started with some fantastic presentations, especially [Chad Juros]. He was a pediatric cancer patient that's also a magician. He had a *very* inspiring story…and now he's using magic to help fellow pediatric cancer patients. He survived because of some experimental treatments and we need to continue to push the envelope and develop new experimental treatments to affect children impacted by life-threatening diseases.

PDA Letter: Tell us about the interest group session you attended.

Mendivil: I just attended the Biotechnology Interest Group meeting. I thought they gave a really great overview of the new bioburden and biofilm management technology report. This is a great example of how PDA is tackling an important issue with strong scientific understanding of both microbiology and biotech processing.

PDA Letter: So far, how has this Annual Meeting compared to others you've attended?

Mendivil: They're all really strong meetings, especially strong scientific meetings. It was great to have patients talking about their needs. So I'd say this falls within the group of best Annual Meetings that I've attended.

Tuesday, March 17, 4:30 p.m. PST

PDA Letter: What was the takeaway from Day 2 of the conference for each of you?

Dominguez: I started off by participating in the quality metrics/drug shortage breakfast session, and that turned out to be quite a hot topic for the conference overall—it was basically standing room only. I think that displays the amount of interest within that particular topic, [there was a] lot of review and healthy discussion with respect to the technical report and the output.

Following that, I think a couple of the highlights would be the process validation session, and the modular manufacturing presentation from **Michael O'Brien** that I thought was quite interesting because [with] his insights into a

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Site Visit Offers PDA Staff Holistic View of Manufacturing

Jahanvi (Janie) Miller, PDA

Last June, PDA's Scientific and Regulatory Affairs Senior Project Manager **Jahanvi (Janie) Miller** began a series of educational development activities for all PDA staff, consisting of site visits to bioprocessing and manufacturing facilities.

This year, PDA was fortunate to have **Kimberly Carnes** at GlaxoSmithKline (GSK) provide an opportunity to tour GSK's Rockville facility on April 17. PDA staff received a full circle view of the manufacturing process, from the commercial bioprocessing and manufacturing areas to the warehouse where materials are received and shipped out.

Carnes also gave PDA staff a comprehensive overview of GSK and its interdepartmental activities, along with some key functions within each department. To facilitate this discussion, some of GSK's leadership team was in attendance as well. This group consisted of: Kimberly Carnes, Manager, QA Compliance, **Jon Conary,** Director, Manufacturing, **William Jones,** Director, Validation and Metrology, **Carlos Motta,** Manager, QA Compliance, **Joan Abrams,** Site Quality Director, and **Patrick Boylan,** Manager, Manufacturing.

Once the PDA staff was brought up to speed on GSK history and internal activities, the visit began with a walking tour of the manufacturing facility led by **David Rubin.** This part of the visit included experts from the following departments: David Rubin, Manager, Manufacturing,

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The Annual Meeting Through the Eyes of a Rookie and a Vet continued from page 12

site of the future and this style of equipment, there is potential for [use] outside of solid dosages but also potentially for aseptic manufacturing eventually.

Mendivil: I thought there were a couple of really good presentations by **Martin VanTrieste** and by **Kerry Ingalls** talking about quality culture and something called Defense in Depth, and how you can use tools from other industries, in this case, the U.S. Navy, to facilitate preventative actions, and prevent human errors.

I thought there was a good discussion in the combo product area. Learning a new language and then understanding new requirements for combo products is really going to be important as we move forward with combination product development.

PDA Letter: What are you looking forward to the most tomorrow?

Dominguez: I just took a peek, and I think two things: I'll go to the breakfast session—this is a continuation of Annex 1. This one will be led by **Mike Sadowski** with **Gabriele Gori** presenting. And then the inspection trends [session] with **[Sharon Thoma]** from the FDA—that is also something that interests me quite significantly as my role is Director of Compliance for my organization.

Mendivil: I haven't looked that far ahead yet. ***[Laughs]***

After the Conference

PDA Letter: What were your takeaways from the last day of the conference?

Mendivil: Biosimilars are coming and PDA needs to take the lead in helping to understand scientific "sameness," and quality culture seems to be a common theme for many of the sites that seem to be in compliance trouble.

Dominguez: I had a very interesting final day at the conference. I found the breakfast session on sterile product manufacturing extremely valuable to understand the timing and updates with Annex 1 and the PDA's aseptic processing Points to Consider document, as well as the inspection trends discussion with **Sharon Thoma** from the FDA.

PDA Letter: What did you get out of the conference?

Dominguez: I felt that the conference went very well overall and matched my expectations with respect to the amount of information and the level of detail that was presented. It was an excellent opportunity to keep current with industry expectations.

Mendivil: I thought this year's conference had many different topics which were very important for pharmaceutical professionals to stay on top of. I found the patient presentation to be very informative and entertaining.

There were many great opportunities to network and meet new people which I really appreciate.

About the Experts

Christopher Dominguez is Director, Global Quality Compliance at Akorn Pharmaceuticals. He is a pharmaceutical professional with over 15 years of experience in a variety of pharmaceutical and biotechnology operations.

Steven Mendivil has been with Amgen for 19 years and is Senior Advisor in International Quality, External Affairs.

eye on education

New Batch Oven One of Many Changes to Depyrogenation Class

Rebecca Stauffer, PDA

Students participating in the upcoming PDA Education course, "Validation of Dry Heat Processes Used for Depyrogenation and Sterilization," this August at the Training and Research Institute (TRI) in Bethesda, Md. can look forward to using a new batch oven during lab work. Provided by Despatch, this oven offers high capacity to support the growing number of students in the course.

The *PDA Letter* interviewed renowned TRI instructor and endotoxin expert, **James Cooper,** about how the new oven will be used by students as well as current plans to update the course.

For more information about the course, please visit www.pda.org/depyro.

PDA Letter: Last year's depyrogenation course proved to be quite popular. Why? What's the draw?

Cooper: In discussing content with participants, most of them came to learn more about endotoxin, rather than just the destruction, or depyrogenation, of endotoxin. They did indeed want to know more about its behavior in different environments as well as multiple ways of depyrogenation, and like I said, they wanted to understand endotoxin—which really is one of the most amazing biological agents in nature. It takes on different forms in different circumstances and in different environments, so it is always a challenge to know how to deal with it properly, know how to measure it and, in many cases, how to destroy it or assure ourselves that it's no longer present.

PDA Letter: You plan to update the course to examine more of the science and technology behind endotoxin removal. Can you tell us more about that?

Cooper: Well, new issues have arisen regarding the nature of endotoxin. We've had the so-called Low Endotoxin Recovery, or LER, phenomenon, being discussed and it's prompted a lot of questions about what is the nature of the endotoxin that we're trying to measure, and, in most cases, trying to eliminate by some form of depyrogenation.

So, we want to spend more time helping our participants understand the different ways that endotoxin responds when it's in water as well as when it's dried on a piece of equipment. We're designing new experiments that use naturally occurring endotoxin as well as purified endotoxin known as LPS, or lipopolysaccharide. One experiment will compare the recovery of endotoxin and LPS under so-called LER conditions with citrate and polysorbate. We're excited about setting up those new experiments, and think many of our participants would enjoy the opportunity to look at endotoxin recovery differently.

PDA Letter: This must be a very hands-on course then.

Cooper: Absolutely! I would say the course is perhaps 60% hands-on. We give our participants plenty of opportunity to work in the lab, and we now have a relatively new depyrogenation oven. Although the title of the course is "Validation of Dry Heat Processes Used for Depyrogenation and Sterilization," we want to extend the experiments and look at other ways of depyrogenation—such as washing and rinsing.

PDA Letter: Tell us about this new oven. How will it be used in the course?

Cooper: We have a new batch oven with appropriate software to set up the depyrogenation cycles and we have up-to-date thermocouples and temperature measuring devices. These features allow us to describe the nature of the thermal profile very explicitly and accurately.

For endotoxin measurements, we'll be

using a kinetic chromogenic method. We feel that's perhaps the only method that we can use within the confines of the course, but we'll be using microplate readers as well as cartridge readers.

PDA Letter: How will the course address USP's changes to chapter <1228>?

Cooper: Hopefully, we'll soon see the new chapter <1228> in its final form. There are some drafts available of some of the sections of the chapter but hopefully we'll see some finished chapters, or subchapters, and we'll try to make sure that our experiments and course material is consistent with the vision of the new depyrogenation chapter. And that vision is that it may not always be necessary to have a three-log reduction of endotoxin, but be able to show that we have reduced any potential endotoxin level to well below what we would consider safe levels.

Throughout our drug processing, we have multiple and redundant depyrogenation steps. We need to have a way to recognize the cumulative effect of our depyrogenation processes so that we're not just totally reliant on one procedure or one measurement.

Interphex | New York, NY — April 21–23

Pharmaceutical Technology Interviews PDA VIPs

PDA Chair Hal Baseman (left), former Board member Susan Schniepp and President/CEO Richard Johnson answer questions about PDA's Manufacturing Science Program, aseptic processing documents, and other PDA activities for *Pharmaceutical Technology* Editorial Director Rita Peters at Interphex.

PDA President Richard Johnson was also interviewed by *Pharmaceutical Technology* at INTERPHEX.

PDA Visitors | PDA Headquarters

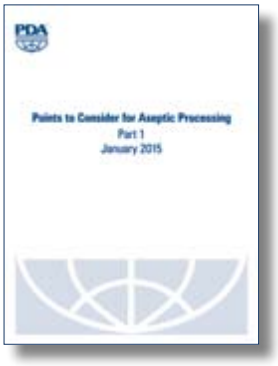
2016 PDA Annual Meeting Planning Committee

Members of the planning committee for the *2016 PDA Annual Meeting* met April 15 to begin setting an agenda for this signature event.

snapshot

PDA Looks at the Modernization of Aseptic Processing

Jahanvi (Janie) Miller, PDA



PDA continues to engage in dialogue with industry, health authorities and suppliers to stay abreast of the demands of modernization within the global sterile health care product manufacturing landscape. At the *2015 PDA Annual Meeting*, PDA announced the release of the recently revised *Points to Consider for Aseptic Processing: Part 1*. This document provides our members with insight on the future of aseptic processing. Historically, PDA has remained very active by developing both technical documents and comments to draft guidances on this topic; this is covered in Part 1 of the Points to Consider. Currently, there are two ongoing PDA initiatives further supporting the aseptic space: a sterile manufacturing GMP comparison and Part 2 of the *Points to Consider for Aseptic Processing*. The GMP Comparison project is a comprehensive gap analysis of GMP regulatory documents from the U.S. FDA, EU Annex 1 and WHO Annex 6, which will facilitate understanding the key differences in each of these documents.

The goal of the Points to Consider documents is to support harmonization of technical and regulatory language and offer a science- and risk-based perspective on aseptic processing. Part 1 issued 70 points that cover aspects of the following topics: physical environment, environmental monitoring, cleanroom personnel and behavior, material transfer, filter integrity testing and water for injection preparation. Part 2 will include some of the aforementioned topics but will also take a closer look at aseptic process simulation and validation, modern blow/fill/seal technology, RABS and isolators, cleaning, disinfection and sterilization and critical utilities.

The PDA *Points to Consider for Aseptic Processing* documents are not standards or regulatory requirements; they are consensus-based best practice guidance documents developed by subject matter experts drawn from PDA's members.

PDA's *Points to Consider for Aseptic Processing: Part 1* is currently available at the PDA Bookstore (www.pda.org/bookstore).

PDA Journal *Top 10*

PDA Papers, PQRI Content Continue to Draw Journal Readers

Below are the top ten articles from the *PDA Journal of Pharmaceutical Science and Technology* read during the month of April.

1. Conference Report
Stephan Rönninger, "Knowledge Management and ICH" March/April 2015

2. PQRI Special Section – *Research*
Dennis Jenke, et al., "Extractables Characterization for Five Materials of Construction Representative of Packaging Systems Used for Parenteral and Ophthalmic Drug Products" September/October 2013

3. PDA Paper
Steve Mendivil, et al., "PARENTERAL DRUG ASSOCIATION POINTS TO CONSIDER: Pharmaceutical Quality Metrics Updated September 2014" September/October 2014

4. PDA Paper
Stan Bukofzer, et al., "Industry Perspective on the Medical Risk of Visible Particles in Injectable Drug Products" January/February 2015

5. PQRI Special Section – *Review*
Diane Paskiet, et al., "The Product Quality Research Institute (PQRI) Leachables and Extractables Working Group Initiatives for Parenteral and Ophthalmic Drug Product (PODP)" September/October 2013

6. Proceedings of the 2013 Viral Clearance Symposium – *Conference Proceeding*
David Roush, Kurt Brorson and Rich Levy, "Proceedings of the 2013 Viral Clearance Symposium (Princeton, NJ)" January/February 2015

7. Review
Stephen E. Langille, "Particulate Matter in Injectable Drug Products" May/June 2013

8. Review
Dominick Degrazio, "Adapting to Biology: Maintaining Container–Closure System Compatibility with the Therapeutic Biologic Revolution" March/April 2015

9. Research
Emil M. Friedman, Mark Warner, Sam C. Shum and Fred Adair, "In-Process Microbial Testing: Statistical Properties of a Rapid Alternative to Compendial Enumeration Methods" March/April 2015

10. Research
Benson Gikanga, Yufei Chen, Oliver B. Stauch, and Yuh-Fun Maa, "Mixing Monoclonal Antibody Formulations Using Bottom-Mounted Mixers: Impact of Mechanism and Design on Drug Product Quality" March/April 2015

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Visible Particles: Why is This Still a Pain Point?

Deborah Shnek, PhD, Drug Product Development LLC

It is extremely difficult to deal with unwanted particle in drug product following completion of manufacturing but it's also perplexing. After all, it is required to inspect drug products 100% after they are made, so how is it even possible that there is a visible particle there at all? And as far as the recent definitions of visible particle types—inherent, intrinsic and extrinsic—which ones are the most commonly rejected?

Another pressing issue concerns the "no man's land" of particle sizes between subvisible particle measurements and visible particle detection, whether human- or machine-based. Subvisible particle size is determined by machine capability for analytical range and limit of detection, usually between 2-150 microns for commercially available technology. For visible particles, the detection limit is taken from idealized studies in glass with 150 microns ***(1)*** defined as 70% detection using trained manual inspectors and manual inspection conditions. Yet, we have seen or met people who can easily see 50 micron particles. The overlap range spans the USP <788> requirement for less than 600 particles per container for the >25 micron size range. Some of those particles above 25 microns could be visible particles.

Preventing particles from entering the process, inspecting for particles, classifying particles and developing CAPAs are all part of the quality systems developed to keep unwanted particles out of product. Therefore, strategies to develop quality systems around drug product inspection will be presented this year at the *2015 PDA Visual Inspection Forum* in October. Critical steps to qualifying the manual inspection process will be explored.

For more information, visit www.pda.org/visual2015. For information about the PDA Education course following the event, go to www.pda.org/visualcourse.

Reference

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

Rapid Micro Methods: Where Are They Now?

Kim Sobien, BD Rx, and Rebecca Stauffer, PDA

Rapid micro methods still offer the potential for faster analyses within the industry. While the past 20 years have seen greater acceptance of rapid methods by regulators, many companies have yet to adopt these strategies for a variety of reasons. Still, rapid micro tools are becoming common vendor offerings.

Sometimes it takes looking to the past to view the future. And this is often the case when it comes to technological advances, such as rapid methods, in the industry.

The first day of this year's *PDA Global Conference on Pharmaceutical Microbiology* will feature a special, retroactive "where are they now" look back at the development of rapid microbial methods over the years, including lessons learned for both the pharmaceutical microbiologist of today and tomorrow.

In fact, this year's conference is extra special as the program planning committee will recognize its 10th anniversary. This years' experience will be enhanced with new conference features, including an audience response system and an enhanced poster viewing area.

Day 2 brings thought-provoking conversations about bioburden and biofilms, the unique challenges facing biotech and the ever-popular Emerging Leaders session where the newest generation of talented leaders will showcase the possibilities of the next ten years. Day 3 focuses on USP and global agency perspectives.

The *PDA Annual Global Conference on Pharmaceutical Microbiology* was conceived in 2006 when long-time PDA members and dedicated microbiologists, **Rich Levy** and **Michael Miller,** made the case that microbiology was at the heart of pharma manufacturing and that it was a core interest and competency of many of PDA's members. Their vision of PDA's role supporting that membership included the addition of a global microbiology conference designed to specifically meet the needs of the industry and regulators. From its humble beginnings, the conference has grown over the years, becoming one of PDA's most successful signature conferences with over 400 participants.

For more information, please visit www.pda.org/microbiology2015. To learn more about PDA Education courses after the conference, visit www.pda.org/microcourses.

New PDA Member's First Foray to Annual Meeting continued from page 11

are becoming more and more important in the relationship between the contract giver and contract acceptor, and, in many instances, this is where the communication is outlined between the two. Participants in this meeting lively discussed this topic and shared viewpoints from both those who work for a contract manufacturer and those who receive the services of a contract manufacturer.

Overall, my experience at the PDA conference was very positive. I learned a lot of valuable information and appreciated the opportunity to discuss with other professionals the various problems we all face. My biggest takeaway was that no matter what size company you work for—small, midsize or large—we all face the same problems and can all learn by sharing our experiences with each other.

About the Author

Janera Harris is the Director of Quality at Cytonet, a liver cell therapy company, located in Durham, N.C. She has been with Cytonet for eight years in the areas of manufacturing and quality.

Inconsistent Expectations Clash with Industry Best Practices for Sterile Products

Paul Larocque, Acerna Inc

Article at a Glance

- USP uses a relative approach to recovery rates while regulators use an absolute approach
- There is increasing scrutiny of isolators and RABS
- Avoid using sterility test for container closure integrity testing

When it comes to manufacturing sterile drug product, discrepancies exist in the available regulatory guidances/compendial documents and industry best practices that cause tension in the industry. These divergences often affect my recommendations to clients regarding updating or adding new facilities. As examples, I discuss several of these divergent interpretations as they relate to environmental programs.

Viable Environmental Monitoring

Having spent a year working on a Warning Letter off and on, one message became clear: the USP approach to environmental monitoring **recovery rates** ***(1)*** as applied by some companies is not being accepted by inspectors in the United States and other countries. This is something my clients often struggle with. The problem lies in that USP <1116> uses a *relative* (percent excursions) approach whereas the U.S. FDA, ***(2)*** European authorities under Annex 1 ***(3),*** and Health Canada ***(4)*** all call for an *absolute* (recovery) approach. **Table 1** shows that the regulators have harmonized on the absolute values. For example, for active air samples in Grade A/ISO 5 areas, the regulators wish to see less than one cfu/m3 generally over all the samples during a shift. Thus, if hourly samples are drawn, seven zeros and one +1 cfu sample meet the regulators' guideline.

In contrast, USP suggests that less than 1% of samples be positive (in an ISO 5 area)—a relative approach. In this area, if thousands of samples are taken from multiple ISO 5 areas, percentages can mask trouble in a particular room or zone. If the 1% metric is used for each individual zone, however, then 100 of 101 samples in that zone must all be zero to meet the metric, which is perhaps what USP intends but not what all companies do.

USP <1116> goes on to suggest that no individual sample should exceed 15 cfu without investigation. Notwithstanding the rationale put forward in USP <1116>, it is my opinion that upon seeing a +15 cfu/sample result in a Grade A/ISO 5 area during active

Table 1 Active Air Sampling Levels

Grade A/ISO 5	Regulators	<1 cfu/m³
	USP	<1%
Grade B/ISO 7	Regulators	<10 cfu/m³
	USP	<5%
Grade C/ISO8	Regulators	<100 cfu/m³
	USP	<10%

processing, many inspectors are not likely to let it pass without observation, especially if it is an objectionable organism.

PDA Technical Report No. 13 notes that: "For ISO 5 [Grade A] environments, there is no difference in excursion [relative] rates and recovery [absolute] rates" ***(5).*** All major regulators emphasize the absolute approach in another way: they have all harmonized on expectations for media fills (aseptic process simulations). In short, if there is one positive in 10,001 units, an investigation is needed; two positives is a failure. In traditional cleanrooms, the USP approach based on percentages may represent reality, but it is inconsistent with the regulators' approach. The bar is being raised in favor of isolators and/or robotic designs instead of traditional cleanroom facilities. Isolators and/or robotic designs are the only types of cleanrooms we recommend now to clients planning a new or renovated facility.

Alert and Action Levels

Setting Alert and Action levels is also something clients struggle with. Clients who do not adopt meaningful Alert and Action Levels will not be forewarned of a rising level, which often becomes an exponential rise in a short time. Then the company has real—and usually expensive—problems. Many clients adopt the aseptic and sterile processing guidance values, but because most companies' environments are much better than the guidance levels, they do not normally provide the company with either an "alert" or an "actionable" trend. ➤

Table 2 Setting Alert and Action Levels – nonviables – Grade B/ISO 7

Sample #	Raw Data	Alert Level (calculated: 2SD)	Action Level (calculated: 3SD)	Guidance Level
	(Particles/m³)	(Particles/m³)	(Particles/m³)	(Particles/m³)
1	122			
2	25,444			
3	3,456			
4	167,999			
5	7,890			
Average	40,982			
Standard deviation (SD)	71,672	143,344	215,016	
Avg + SD		184,326	255,999	352,000

2015 PDA Upcoming Events

SAVE THE DATE for PDA's 2015 Events

JUNE EVENTS

23 – 24
Quality & Regulations
Brussel, Belgium
europe.pda.org/QuaReg2015

23 – 24
2015 PDA Single Use Systems Workshop
Bethesda, MD
pda.org/sus2015

25
Risk-based Prevention of Drug Shortages
Brussels, Belgium
europe.pda.org/DrugShortage2015

25 – 26
2015 PDA Single Use Systems Workshop Course Series
Bethesda, MD
pda.org/SUSCourseSeries

30 – JULY 1
Managing Risk in Aseptic Processing
Tel Aviv, Israel

JULY

2
Particle Identification in Parenterals
Tel Aviv, Israel

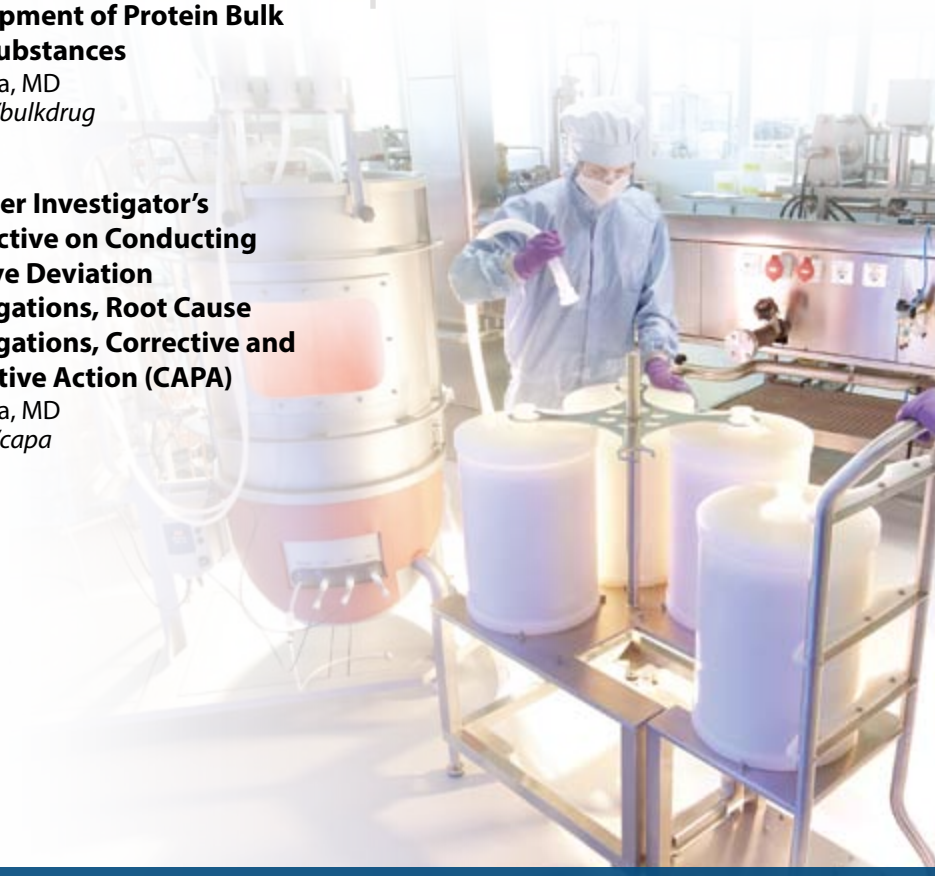
2 – 3
Cleaning and Disinfection
Tel Aviv, Israel
europe.pda.org/Cleaning&Disinfection2015

7
Application of Phase-Appropriate GMP to the Development of Protein Bulk Drug Substances
Bethesda, MD
pda.org/bulkdrug

8
A Former Investigator's Perspective on Conducting Effective Deviation Investigations, Root Cause Investigations, Corrective and Preventive Action (CAPA)
Bethesda, MD
pda.org/capa

21 – 23
Moist Heat Sterilization Week
Bethesda, MD
pda.org/moistheat

27 – 29
Risk-based Qualification of Sterile Drug Product Manufacturing Systems
Bethesda, MD
pda.org/risk



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

AUGUST

3 – 7

SOLD OUT GSA Schedule Contract GS-02F-113BA

2015 Aseptic Processing Training Program – Session 4, Week 1
(Week 2: August 24-28)
Bethesda, MD
pda.org/2015aseptic4

10 – 11

NEW COURSE

Airflow Visualization Techniques and Practices
Bethesda, MD
pda.org/air

12 – 14

GSA Schedule Contract GS-02F-113BA

Validation of Dry Heat Processes Used for Depyrogenation and Sterilization
Bethesda, MD
pda.org/depyro

17 – 19

GMP Week
Bethesda, MD
pda.org/GMP

PDA CONFERENCE RECORDINGS – Interactive Online Learning

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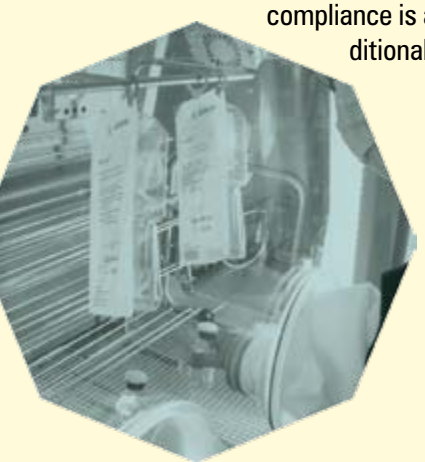
For more information on all PDA conference recordings, please visit pda.org/online-learning

Warning Letters Don't Come Out of the Blue

Common reasons we see clients receive Warning Letters:

1. A big pharma company invests in its relationship with its district office from which it has received no Form 483 for three consecutive inspections, but then a national expert from Washington, D.C. pays a visit.
2. An emerging company has its focus on the clinical trial results; chemistry, manufacturing, and compliance are secondary. They may not receive a Warning Letter but they may be refused or delayed at the preapproval inspection.
3. A virtual company that tries to outsource all responsibility.
4. Companies that think they are more important or more invincible than they really are: medically necessary product and/or product in short supply and/or a feeling that the company is so big and has so much internal expertise, the company knows best even on external matters.
5. An attitude that because few complaints or adverse events are received, compliance must be good.
6. The product has been approved in a major country; therefore, the next country should welcome it with open arms.
7. Or, my favorite, the company has an ISO 9000 certificate and thinks GMP compliance is a small additional step.



The sterility test is still with us because it remains the primary tool for analyzing sterility

For example, if we look at **Table 2,** some hypothetical raw data are presented. Using this typical data for our calculations, we find that using the two-sigma and three-sigma approach noted by PDA ***(5),*** Alert and Action Levels—well below the guidance level—are obtained. Adopting these levels will not result in a flood of deviations for the company adopting them. A three-sigma action level means that only one in a hundred samples will require some action—not a burdensome amount.

Isolators vs. RABS

I have seen a potential trend of investigators not accepting traditional cleanrooms, even tightening the use of RABS. At an ISPE meeting in 2012, an FDA expert stated: "It is supposed to be a restricted access barrier system [RABS]. That means it is restricted. If it is open, that should be an exceptional occasion," with documentation on "why it was opened, the extent of the deviation, the time of the deviation, what kind of intervention took place" ***(6).*** He also explained that the FDA definition for a closed RABS is that the doors are only open for changeover and cleaning/sanitization; otherwise they are closed throughout the run. If the door is opened, the rest of the batch should be scrubbed.

This appears to be an indication of FDA's expectations for traditional cleanrooms and RABS filling. It also suggests that the FDA is attempting to lead other regulators and the global industry in the same direction.

Container Closure Integrity and the Sterility Test

The sterility test is still with us because it remains the primary tool for analyzing sterility even though a passing result adds almost no assurance the lot is sterile. Conversely, a failing result must be taken as definitive—short of obvious contamination during the test. The probability of detecting a contaminated batch using the sterility test is expressed by the equation $p = n(1 - (1 - c))$, where p = probability of detection, c = true fraction contaminated, and n = number of units tested ***(7).***

In a typical lot, we know from media fills that the true fraction contaminated is less than one in 10,000 ($c < 0.0001$) and the number of units tested is typically 20. Thus, the probability of detecting a contaminated unit in a typical lot is less than 0.002 (0.2%). Whenever a batch release decision hangs on whether the lot is deemed sterile, the result of the sterility test is barely helpful unless it fails. Since the sterility test is so poor, using it as a container closure integrity test during stability studies is unwise and raises a number of challenges. For instance, what does a failure at 24 months mean? Is your product's package unsound? Must you withdraw product from that batch and recall everything out there? Is it wise to base such important considerations on a test that is outmoded, laborious, time consuming, prone to false positives, and expensive? Clearly, a proper container closure integrity test should be used.

My recommendation to my clients is to make sure their boss, or the Qualified Person in charge of quality, fully understands that this sterility test adds almost no assurance that the lot is actually sterile. Until a reliable test is available, the critical process parameter—ideally a closed isolator—trumps the critical quality attribute, i.e., the sterility test.

And if the client does not have a viable container closure integrity test, I recommend that one be developed and tested before implementing. If not, the client may end up working on an unexpected Warning Letter or receive other bad news from regulators (see sidebar).

In summary, companies should look at their use of percentages in their environ-

Continued on page 41

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USP <1116> and its Implications for Measuring Microbial Recovery Rates

Claudio Denoya, PhD, and Gilberto Dalmaso, PhD, Particle Measuring Systems

The recently revised United States Pharmacopoeia (USP) chapter <1116> *Microbiological Control and Monitoring of Aseptic Processing Environments* includes a thorough description, definitions and guidance on microbiological control and monitoring in aseptic processing environments ***(1).*** Chapter <1116> is arguably one of the most comprehensive informational chapters from the USP, and it is particularly challenging due to its proposal regarding measurement of microbial contamination based on Contamination Recovery Rates (CRR) rather than the conventional enumeration of colony forming units (cfu). Instead of using the microbial limits currently endorsed by aseptic guidances ***(2–4)***—which are based on cfu—<1116> proposes CRR values expressed in maximum allowed percentage of contaminated samples. The proposal is generating a broad range of discussions among pharmaceutical professionals regarding potential implications of these changes.

It is important to note that <1116> is a "general information" chapter, and as such, it "provides information and recommendations for environments where the risk of microbial contamination is controlled through aseptic processing." Therefore, the chapter in its current format provides recommendations not yet adopted and not enforceable by the U.S. FDA or any other government agency. This clarification is important because the recommendation on the adoption of CRR is generating a positive debate that will probably require further discussion and clarification before any enforcement occurs. If adopted, hopefully, a harmonized approach by U.S., European and Japanese authorities will take place to avoid disparity of values for microbial limits.

Main Changes When Compared to Previous

1. Title

The most obvious change concerns the title of the chapter. The previous title of <1116> was *Microbial Control and Monitoring Environments Used for the Manufacture of Healthcare Products* while the revised title is *Microbiological Control and Monitoring of Aseptic Processing Environments.*

2. Scope

The scope of the chapter has been narrowed to apply to the following products manufactured in an aseptic processing environment:

- Pharmaceutical sterile products
- Bulk sterile drug substances
- Sterile intermediates
- Excipients
- Some medical devices

In addition, the types of environments covered in <1116> are:

- Conventional cleanroom with unidirectional airflow
- Blow/fill/seal machines
- Restricted Access Barrier Systems (RABS)
- Isolators

3. Aseptically Filled Product

The emphasis on the word "aseptic" in the introduction implies that the chapter is not applicable to all "sterile" products. This means that terminally sterilized products are outside the scope of the chapter. By "aseptic," a low level of contamination is acknowledged: "An expectation of zero contamination at all locations during every aseptic processing operation is technically not possible and thus is unrealistic." Therefore, a low level of contamination—over a given period of time—is a good assumption and it should be accepted as a norm in operations where personnel are present.

4. Room Classes

In the revised <1116>, all old notations (e.g., M3.5) and old FDA 209E classes (e.g., Class 100) were eliminated and replaced by ISO 14644-1 classes in the operational state **(Tables 1–2).**

Table 1 Microbial Limits During Operation, According to European Union Guidelines (Annex 1) (top) and FDA Guidance (2004) (bottom)

Grade	Air Sample cfu/m^3	Settle Plates (∅ 90 mm), cfu/4 hours	Contact Plates (∅ 55 mm), cfu/plate	Glove Print 5 fingers cfu/glove
A	<1	<1	<1	<1
B	10	5	5	5
C	100	50	25	–
D	200	100	50	–

Clean Area Classification (0.5 μm particles/ft^3)	Air Sample cfu/m^3	Settle Plates (∅ 90 mm), cfu/4 hours	Glove Print 5 fingers cfu/glove
100	ISO 5	1	1
1000	ISO 6	7	3
10000	ISO 7	10	5
100000	ISO 8	100	50

5. Risk Assessment

The chapter emphasizes that even with a good total particulate monitoring program in place, "It is not possible to clearly distinguish between background particulate contamination generated… by mechanical operations and the total particulates contributed by personnel." Therefore, it is standard routine to implement both total particulate and microbiological monitoring programs. The chapter also discusses the differences between operating in conventional cleanrooms and open RABS, and more controlled environments where personnel interventions have significantly less impact on microbial contamination, such as in closed RABS and isolators. It is clear that the relative risk of microbial quality depends on the different types of aseptic barrier systems; the greater the barrier, then the lower the expected contamination risk.

6. Air Changes

As specifications for air changes per hour and air velocities were not included in ISO 16444 ***(5),*** nor in Federal Standard 209E, chapter <1116> provides the following guidance: ISO class 8 (minimum 20 air changes per hour [ac/hr]), ISO class 7 (>50 ac/hr), and ISO class 5 (>100 ac/hr). In isolators and cRABS, lower air changes and air velocities can be justified. USP <1116> emphasizes that these specifications should be used only as a general guide due to the numerous variations on designs and operational use of cleanrooms.

Table 2 <1116> Suggested Initial Contamination Recovery Rates in Aseptic Environments

Room Classification	Active Air Sample (%)	Settle Plate (9 cm) 4h Exposure (%)	Contact Plate or Swab (%)	Glove or Garment (%)
Isolator/Closed RABS (ISO 5 or better)	<0.1	<0.1	<0.1	<0.1
ISO 5	<1	<1	<1	<1
ISO 6	<3	<3	<3	<3
ISO 7	<5	<5	<5	<5
ISO 8	<10	<10	<10	<10

7. The Case for CRR

Chapter <1116> emphasizes that if human operators are present, microbial contamination at some level is inevitable. The following points on the conventional way to evaluate microbial contamination are discussed:

- Real-time active monitoring of Total Particulate, even if run continuously, ➤

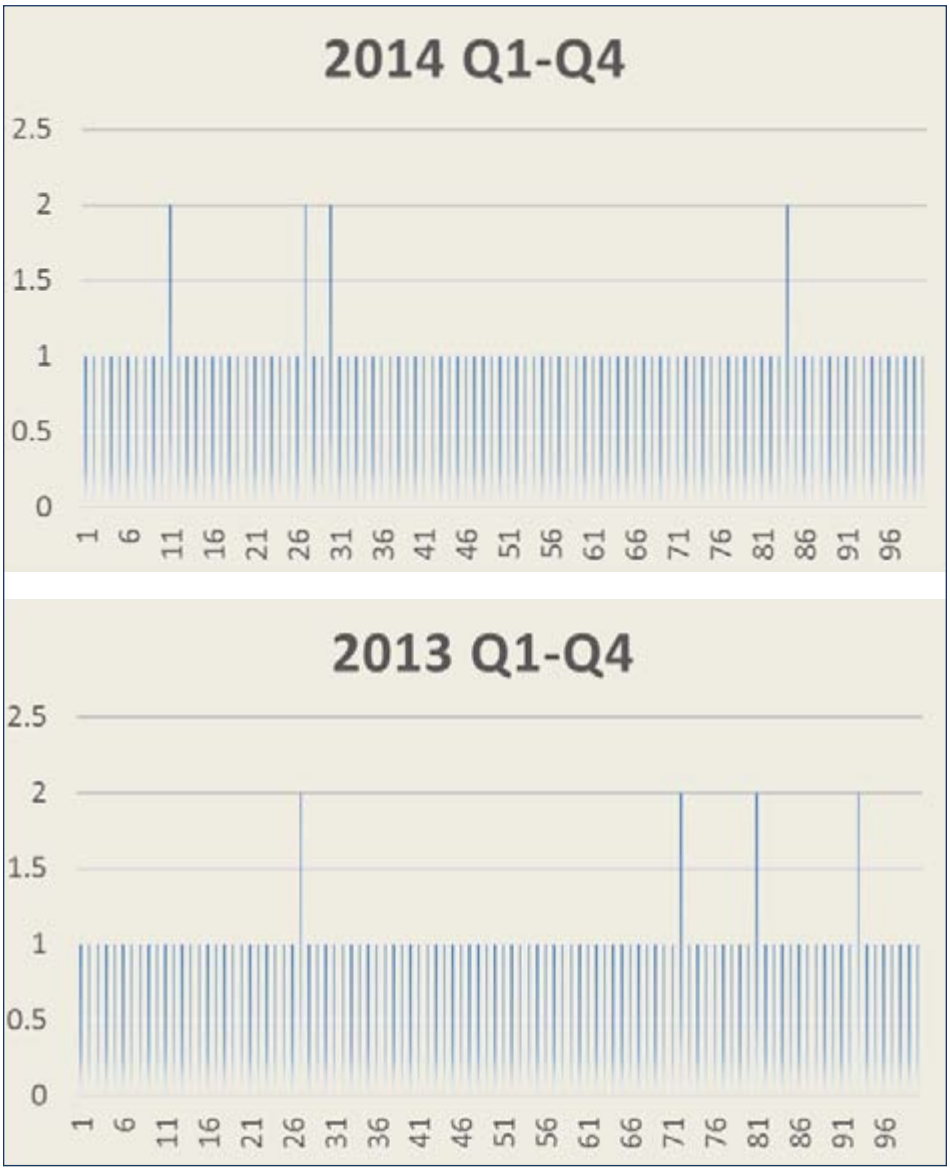
does not provide direct information on the microbiological content of the environment.

- Airborne microorganisms are enumerated as cfu, but a great diversity of physical states (single cells, aggregates associated to particles, microbial cells associated to inert particles, etc.) make the counts subject to significant variability.
- A microbial monitoring sample represents only the microorganisms captured during a narrow length of time at a particular location.
- The absence of growth on a microbiological sample means only that growth was not discovered; it does not mean that the environment is free of contamination.
- Numerical differences between Alert and Action Levels have become quite small in ISO 5 and other areas.
- Those differences are not significant considering the large variability in microbiological assay recovery (±0.5 $\log_{10}$) ***(1).***

Based in part to the above points, <1116> proposes a new perspective on environmental control relying on incident rates rather than Action/Alert Levels. Under this proposal, all contamination events (≥1 cfu, including events that exceed and events that do not exceed the level mandated by current aseptic guidance) will be considered for the trending analysis. Could this trending help to improve data analysis and help to maintain a continuous state of control? The answer will need to be tested by comparative analyses of one method versus the new alternative one.

The proposal emphasizes than *"rather than isolated events, analysis of data upon time would detect changes in the contamination recovery rate (CRR) that may be indicative of changes in the state of control within the environment."* Because of the inherent variability of microbial sampling methods and the cfu values, <1116> recommends the use of CRR as a more useful measure of trending results than the number of colonies recovered from a given sample (**Tables 1–2**). The incident rate is the rate at which environmental samples are found to contain microbial contamination (≥ 1 cfu). For example, an incident rate of 1% would mean that only 1% of the samples taken have any contamination regardless of colony number. In other words, 99% of the samples taken are completely free of contamination.

Figure 1 Garment: Microbial Monitoring, Annual Evaluation (2013 and 2014)



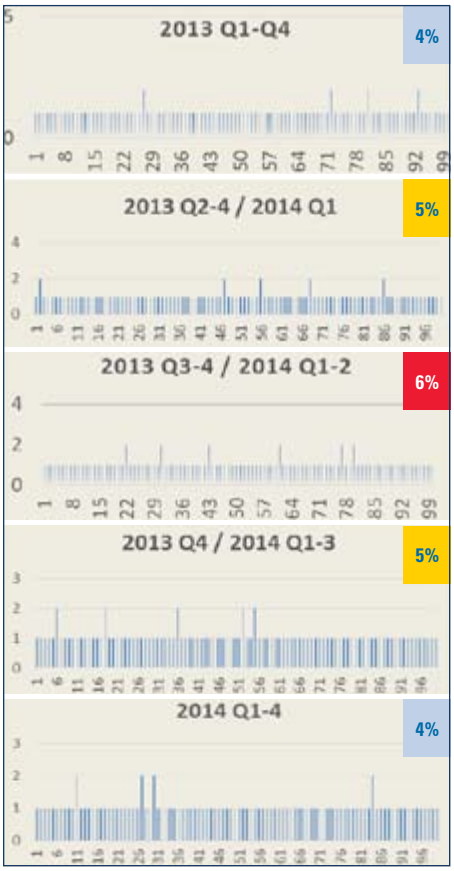
Recommendations When Using CRR

- ✓ Use frequency of contamination instead of absolute numbers detected in a sample
- ✓ Determine recovery rates for each cleanroom environment
- ✓ Detection frequency should at least be retabulated monthly
- ✓ If CRR are adopted, any single ISO 5 excursion of >15 cfu should prompt an investigation, even if CRR is <1%
- ✓ Investigate if the incident was isolated or can be correlated with other recoveries including events of 1–5 cfu that might indicate an unusual pattern

Case Study: Garment Contamination Rates

Garment samples at a large European manufacturing facility were tabulated and trended on an annual basis. There were approximately 100 samples collected per quarter (horizontal axis of **Figures 1** and

Figure 2 Rolling Contamination Rates (2013–2014, Quarterly)



2). Two annual evaluations are shown in **Figure 1** (2013 and 2014). In this example, noncontaminated samples were assigned a value of 1, and the samples that were contaminated with cfu values lower than the action limit were assigned a value of 2 (vertical axis of **Figures 1** and **2**). Samples with values equal or above the Action Level were not observed. In this study, the rate of contaminated samples for 2013 and 2014 were 4% each (**Figure 1**). It is important to consider that in terms of garment limits, for EU GMP Grade B/ISO class 7 areas, the industry understanding is often to adopt the same limits as per the limits applied to finger plates. Following this common understanding, the Action Level for gowns is ordinarily 5 cfu/25cm2, and the facility complied based on cfu results (all positives were <5 cfu/sample) (as shown in **Table 1**, top, for the European microbial limit). In addition, this facility also complied based on CRR (**Table 2**). All positives analyzed on an annual basis presented an incidence rate of 4%—which is a value complying with the <1116> recommendation of <5% limit (**Table 2**) for grade B.

If the annual CRR is updated on a quarterly basis (see **Figure 2**), however, then three of the updated trend analyses show noncompliance to the <1116> recommendations. As seen in **Figure 2,** CRR of 5% is observed for the analysis ending in Q1 of 2014, CRR of 6% is observed for the trend ending on Q2 of that year, and a 5% CRR is again observed now for the trend ending in Q3. In this case, it appears that the rolling quarterly CRR analyses brought a closer and more continuous look at the trending data and it seems to be useful to identifying some loss of control in a more sensitive way than following the more conventional data analysis approach.

Conclusions on CRR

- Current guidance on microbial limits for aseptic processing environments is based on cfu.
- Chapter <1116> proposes a new way to look at microbiological data by adopting CRR as percentage value of maximum allowed contaminated samples (those with a number of cfu equal or larger to one).
- The case study illustrates that depending on how the data is looked at (either through the current cfu-based limits or through the proposed CRR-based limits) an environment that was compliant under the first, could become noncompliant under the new limits.
- At very low recovery levels there is no way to establish Alert or Action Levels as statistically significant. Instead, emphasis should be on incidents, even those having just 1 cfu.
- Incident rates in percentage values force us to look historically at least 100 samples back, instead of focusing on just a single current incident, or only on samples showing contamination above Action Levels.
- It also helps to focus on all samples that have any contamination regardless of colony number. There could be a trend indicative of loss of control.
- Even if CRR are adopted as a way to analyze microbial contamination, <1116> emphasizes that for an ISO 5 cleanroom, any excursion of >15 cfu should also be investigated.

References

1. USP, "USP <1116> Microbiological Control and Monitoring of Aseptic Processing Environments," USP 35 vol. 1 2012a, 2012: pp. 697-707.
2. Guidance for Industry – Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice, U.S. Food and Drug Administration, 2004
3. "Manufacture of Sterile Medicinal Products" In EudraLex – The Rules Governing Medicinal Products in the European Union, Volume 4 EU Guidelines to Good Manufacturing Practice – Medicinal Products for Human and Veterinary Use – Annex 1: Manufacture of Sterile Medicinal Products, European Commission, 2008
4. Dalmaso, G., and Denoya, C. "Microbial Control and Monitoring in Aseptic Processing Cleanrooms" *Controlled Environments* (2015) http://www.cemag.us/articles/2015/01/microbial-control-and-monitoring-aseptic-processing-cleanrooms
5. ISO International Standard 14644 Part 1, International Organization for Standardization, May 1999

About the Authors

Claudio Denoya, PhD, is a Senior Applications Scientist at Particle Measuring Systems He has extensive experience in pharma and biotech companies, including Pfizer where he was a leader in bioprocess and microbiology for 23 years.

Gilberto Dalmaso, PhD, is a Global Aseptic Processes Development Manager in the Life Sciences Division, at Particle Measuring Systems.

The Future of Aseptic Processing is Now!

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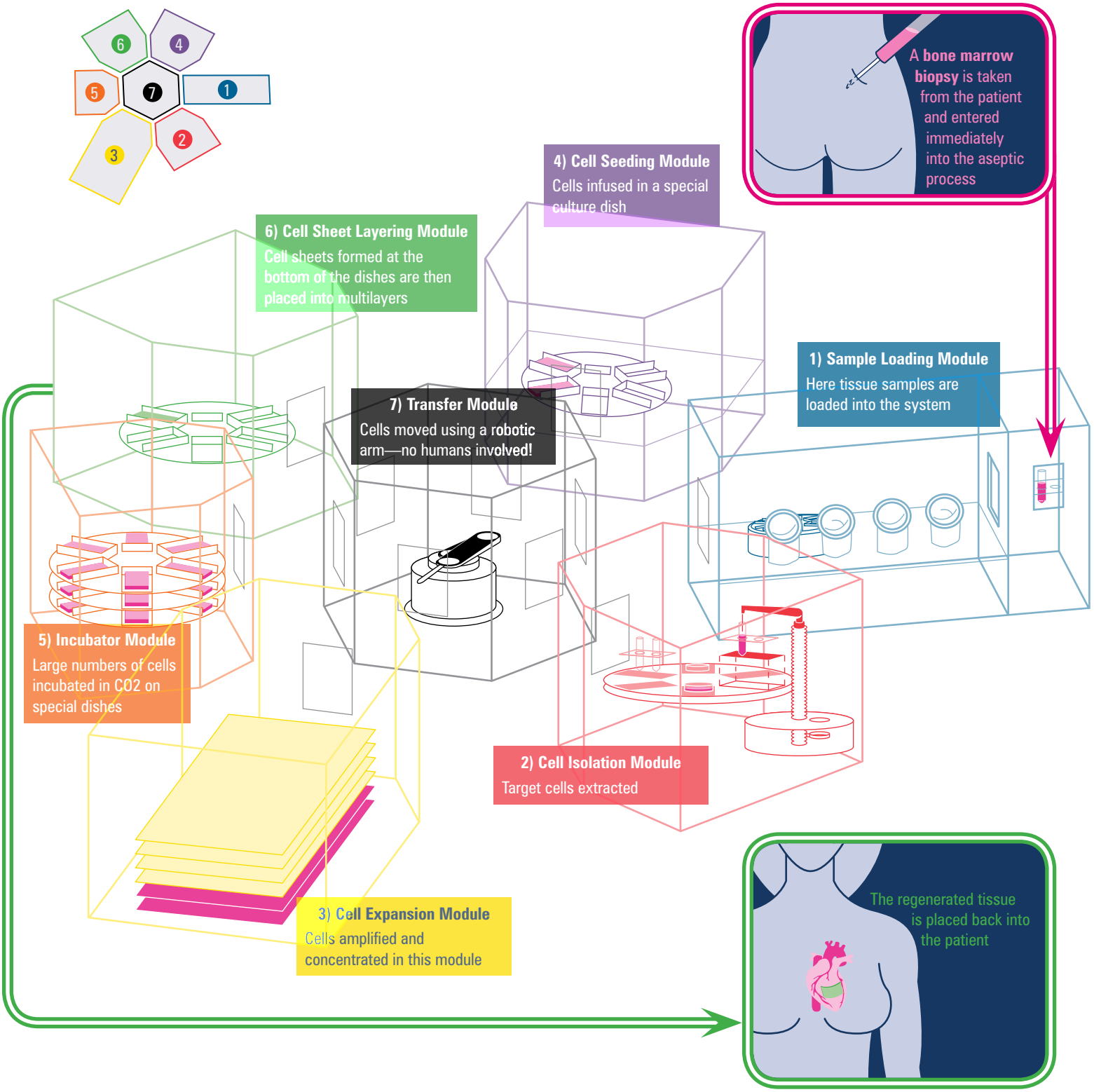

Special thanks to **James Akers,** PhD, of Akers Kennedy & Associates, and **Rich Levy,** PDA, for their assistance with this infographic.

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Teaching Compliance in Financial Terms

Jennifer Magnani, Sanofi Pasteur, and Anders Vinther, PhD, Sanofi Pasteur

In our previous article, "Quality's Role as Financial Officer – Can you speak $, €, £, ¥, CHF?" **[Editor's Note:** see story in May issue**],** we talked about adding the financial cost to investigation reports, both in terms of what the total cost of a deviation is, and what it would have cost to prevent it from happening. This is the first step in engaging with your finance department on compliance. By translating compliance topics into $, €, £, ¥, CHF, etc., there will be an appreciation of the importance of being in good compliance status across the company.

But as Quality professionals, we must go further and move from discussions about cost to conversations about value by utilizing the two ICH Q10 enablers: Quality Risk Management (QRM) and Knowledge management. These are critically important for the creation of a quality performance culture.

A traditional risk assessment will include the severity of a risk, the probability of it happening and, in many cases, how easy or difficult it is to detect. This evaluation is typically used to prioritize activities. If you go to your senior managers with the report and say, "Hey, I'd like 25 new people and $8 million to improve our risk profile," you're not really creating the basis for a good dialogue. The response might be, "Well, that's all good, but I'll give you $3 million and see what you can do with the people you have." This goes right back to a cost-based discussion. Now, imagine that for each of the risks, you added information about what the cost of the risk/failure would be if it happened, and what it would cost to mitigate it/prevent it from happening. One way to do this is by calculating the Cost Risk Benefit Index (CRB Index) for each risk as the probability of the risk multiplied by the cost of it happening and divided by cost of prevention (hence, the higher the CRB Index, the higher the financial incentive to mitigate the risk). All of a sudden, you have equipped them with a much better foundation for sound decisionmaking. They would not only have a catalogue of risks, including severity and probability, but also information about where the business might be at the highest risk financially. Many times you hear the dialogue between Quality and the CEO go something like this:

Barbara, Head of Quality: *"But I told you that the risk of this equipment breakdown was high and it would result in interrupted supply. Now it happened—and the impact is just as I said, supply is interrupted."*

Paul, CEO, responds: "*We talk about risks all the time, but I've never been provided information about the financial consequences."*

By adding financial numbers to your risks, you not only stimulate fruitful dialogue—you also bring visibility to compliance and operational-related risks in a more meaningful way. This leads to discussion about everyone's level of comfort for living with a risk vs. spending the money to avoid it. We believe it is Quality's responsibility to ensure financial information is added to your risk control strategies. This enables your company's senior managers to discuss risks in the same way they talk about product pipeline, competitor analysis, etc. This automatically drives the organization in the direction of quality performance as more thoughtful decisions are made about risks.

Sometimes companies wait to start cGMP compliance and quality performance improvement investments until Health Authorities make them aware of an issue through an inspection observation. The sad part of this is that often Quality had pointed out the risk/issue to upper management and a choice was made to "ignore" it. But perhaps Quality failed to articulate well enough in the appropriate language. Anyone who has experienced a Warning Letter, Consent Decree or other legal action knows that the cost of preventing the issues would have been much cheaper than the cost of fixing them. In addition, negative publicity, loss of reputation and potentially interrupted product supply would have been avoided. Speaking of the latter, by having solid, end-to-end risk assessments and control plans in place with financial values showing the cost of potential stock-outs, a company can at the same time prevent a potential drug shortage and maximize sales. Sometimes decisions are easier when prevention investment is negligible compared to the cost of a high probability risk occurring.

Many companies focus almost entirely on meeting departmental budgets. At the end of the day, however, what matters is the overall financial result of the company. When we follow the former, we risk becoming cost-focused instead of value-focused. As a quality professional, you should drive the discussion toward value creation. We often talk about the cost of poor quality, but wouldn't it be great if we could turn the discussion to the benefits of good quality, which implies a higher investment in proactive activities and less on reactive activities?

The Value of Knowledge

Knowledge management, if ingrained into your quality processes, can be a great financial benefit. Documenting knowledge gained during product development or a project and in our daily operations assists in institutionalizing the knowledge long into the future and helps drive expertise across an organization. Applying knowledge management principles helps in the elimination of repeat

Continued on page 42

The Parenteral Drug Association presents the...

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The *2015 PDA Pharmaceutical Quality Metrics Conference* will continue the discussion on the U.S. FDA's utilization of quality metrics, case studies on metrics that have been most valuable for raising quality and how best to measure and assess a site's quality culture.

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Experts from FDA will also share the latest on their plans for gathering quality metrics and how these metrics will be used in their inspectional risk model, to prevent drug shortages and potentially reduce post approval change submissions. The discussion will include both short- and long-term vision for metrics as the program evolves over time.

Take advantage of this unique opportunity to interact directly with regulatory and industry experts.

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Following the conference, on November 11, PDA will be hosting a course on *The Quality Culture and its Measurement*. This course will help participants select appropriate metrics to measure quality and determine how best to collect and use the data to improve the Quality System. The types of processes to be discussed include the production process; supporting processes, such as change control, training, and validation; supplier processes; and materials management.

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PDA Points to Consider on Quality Culture

PDA Quality Metrics Task Force

Linking an organization's quality culture to the success of its manufacturing operations is not new; in fact, some of the first manufacturing lines, notably **Henry Ford's** Model T production line, culminated from a careful analysis of how quality culture can drive an effective manufacturing operation to produce high quality products. Yet since the emergence of quality culture as a distinct attribute, quantifying it has proved elusive across many industries (***1-2***), including pharma. The U.S. FDA currently seeks to develop a set of metrics to measure quality within the industry. PDA supports the Agency's efforts and continues to recommend quality metrics be complimented by establishing and maintaining a strong quality culture. Just as measuring and evaluating a company's safety culture presents significant challenges, so too does measuring and evaluating a company's quality culture as it involves the beliefs and attitudes inherent within an organization.

This FDA quality metrics journey began in 2013 when the Agency reached out to industry for input on defining a set of metrics to evaluate quality. Over time, the discussion expanded from defining a set of quality metrics to include ones more focused on quality culture. Last year, the FDA outlined some early thoughts being developed on quality culture and quality culture metrics. Members of PDA's quality metrics task force continue to believe in the importance of evaluating quality culture, and would like to offer an alternative approach to quality culture metrics based on survey data and discussion at the *2014 PDA Pharmaceutical Quality Metrics Conference.* The task force strongly believes this approach provides a better, more effective method of driving the quality culture environment within a company.

This summary discusses PDA's efforts to assess and measure quality culture and should be considered as an extension, or annex, of the previously published pharmaceutical quality metrics Points to Consider document ***(3).***

Quality Culture Survey Data

In the fall of 2014, PDA conducted a survey on quality culture metrics. Respondents were asked to select quality culture behaviors and mature quality attributes that they currently observe, and to rate the quality culture at their local manufacturing site. Results were compared from more than 130 PDA members and nonmembers. Respondents from numerous global manufacturing sites completed all sections of the survey, representing perspectives from large to small companies, innovator firms to generics manufacturers as well as CMOs. Respondents' sites manufactured small molecule and biotech drug products and API in sterile and nonsterile presentations. The survey results were then presented for further discussion during the *2014 PDA Pharmaceutical Quality Metrics Conference* in December. The data provided some valuable insight into specific behaviors identified as having a positive impact on quality culture. A detailed explanation of the survey methodology, including results and analysis, will be published in the *PDA Journal of Pharmaceutical Science and Technology* later this year. From the survey, the 15 most frequently identified quality culture behaviors were:

1. Established company values that include quality
2. Actively listen and engage in two-way communication
3. Hire individuals and leaders with appropriate technical expertise for their role
4. Review quality issues that include executive level and/or CEO level staff
5. Facilitating escalation of issues
6. Encourage honest dialog
7. Promoting continuous improvement
8. Questioning or challenging non-value added activities
9. Share information on product quality performance with employees and partners
10. An eagerness to share knowledge and expertise to solve problems
11. Putting patients ahead of everything else
12. Put "quality is everyone's responsibility" in practice
13. Promote individuals based on performance and technical expertise
14. Taking personal/individual accountability
15. Communicate on as needed basis

An initial statistical analysis of the results suggests a correlation between a greater number of positive quality culture behaviors observed and the presence of specific Mature Quality Attributes. These consisted of:

1. Participation at conferences to stay current
2. Collecting error prevention metrics
3. Management communication that quality is everyone's responsibility
4. Utilization of new proven technologies
5. Clear performance criteria for feedback and coaching
6. EH&S environmental program with trained staff (risk assessments, emission controls, spill prevention and response)
7. Site has formal quality improvement objectives and targets
8. Quality topics included in at least half of all hands meetings
9. Collecting management review metrics
10. Collecting turn over rate metrics

The survey results are important in that they reinforce that there are specific

Mature Quality Attributes that, if present within an organization, may drive strong quality culture behaviors.

Quality Culture as a Program

The topic of how companies within the industry approach developing, measuring and maintaining a strong quality culture served as a focal point of interest during the December conference. Presentations from senior quality leaders at several companies provided specific examples of programs in place to improve and/or maintain their organizations' quality cultures. The actions discussed were similar in many respects, but different in that the specific actions were tailored to each organization's strengths, weaknesses and background. Two common program elements throughout these presentations were visible management and employee engagement.

Just as the program examples offered varying viewpoints, diversity also became apparent during breakout sessions where participants engaged in discussions on the organizational attributes and behaviors important enough to ensure an organization's strong quality culture. These sessions featured different and robust views as to the importance of each attribute and its impact on quality culture. Each session concluded with participants voting on the list of behaviors and attributes that best define a world-class quality culture. While there were similarities between sessions, no universally set of common attributes or behaviors were selected; this in itself provides another good illustration as to the complexity of the issue.

Building on Past Successes

A retrospective look into the industry's quality journey shows there have been several key developments resulting in a prolonged and lasting positive impact. Two examples of these are:

- The development of the quality systems approach (Quality Systems Inspection Technique) that changed the way regulators and industry viewed the role of quality and the types of quality systems needed. This led to the development of formalized programs within companies to develop and maintain quality systems as well as global efforts to define common expectations such as ICH Q10.

- The development and expected use of Quality Risk Management (QRM) to support and identify areas for added focus in manufacturing operations resulted in the development of formalized programs within companies to implement QRM as well as globally harmonized regulatory guidance in ICH Q9.

Both of these resulted in long-term changes to how the industry operates and regulators inspect. While the specific implementation steps vary among companies (based on each company's unique differences), the long-term goal of consistent product quality and effective patient outcomes remains quite similar.

If quality culture is the next logical area of focus for improving product quality and patient outcomes, it follows that the next step is establishing expectations regarding quality culture, taking into account the key organizational behaviors and attributes (some of which have been discussed above) that result in a strong quality culture. As the quality culture of a company improves, so will its quality and operational metrics.

Metrics for Quality Culture

At the December conference, FDA took the opportunity to engage with attendees on some early thoughts being developed on quality culture and quality cultural metrics of potential interest. PDA thanks FDA for the open discussion and opportunity to collaborate firsthand with a diverse group of industry and regulatory representatives on effective ways to measure quality culture. It must be noted that the metrics presented were conceptual. Participants expressed concerns mainly around the potential of some of these cultural metrics of potential interest (APR on time rate, level of management signing an APR, and number of CAPAs generated per APR) to incent the wrong behaviors as well as the lack of clarity of what constitutes a positive or negative result. There was clear agreement, however, that the quality culture of an organization is a critical factor in ensuring its operations are appropriate for producing high quality products.

While the intent to develop these types of metrics is commendable, measuring the quality culture of an organization (company or site) is, in many ways, as challenging as measuring the safety culture of an organization. Although it is possible to establish quality or safety metrics to understand how the organization performs against a specific quality or safety standard at any given time, the ability to measure the behaviors and attitudes of an organization (and its members) toward safety or quality is much more challenging. Looking specifically at safety as an example of a cultural area with decades of significant focus, there is evidence that programs to change underlying behaviors and attitudes toward safety are far more critical in reducing the accident rate rather than measuring a specific metric such as the lost time accident rate. In fact, collecting a specific metric without changing the underlying behaviors and attitudes can drive the behaviors and attitudes in the opposite direction (i.e., underreporting of minor accidents that result in corrective actions not being taken to prevent future more serious accidents). In the case of both safety and quality culture, the programs—not the metrics—should drive the desired state.

Evaluating a company's quality culture (just like evaluating safety and other areas of company culture), requires assessing the effectiveness of the programs developed to ensure underlying behaviors and attitudes support a strong culture. These effectiveness checks often involve an evaluation of the program's implementation, use of tools developed as part of the program, and employee interviews (at all levels) and surveys.

PDA's Recommendation on Quality Culture

The importance of a strong quality culture for the long-term production of high-quality products of any type is without debate. The development of formal programs to drive behaviors and attitudes that positively impact an organization's quality culture should be routinely assessed within the pharmaceutical industry. Based on the difficulty in measuring the quality culture of an organization, the emphasis should be to ensure each manufacturing site has programs in place to support development of a positive quality culture with mechanisms available to assess the effectiveness of these programs. The ability to evaluate program effectiveness then becomes the surrogate measurement for quality culture within an organization and could potentially be used as an input to risk-based decisions regarding audit frequency both internally and externally.

PDA recommends the list of Mature Quality Attributes identified through the survey, focusing on the top five voted on by the 250 attendees at the conference and the additional top five Mature Quality Attributes that conference participants developed and voted on during the breakout sessions. These should be a starting point to develop a formal assessment tool (i.e., maturity matrix) to gauge the robustness and use of these mature attributes in strong quality culture program. Some of the recommendations that came out of the conference need further development; attributes must be measurable, or verifiable, in order to be useful for assessing quality culture during an inspection.

The top five Mature Quality Attributes from the PDA survey are:

1. Management communication that quality is everyone's responsibility
2. Formal site quality improvement objectives and targets
3. Clear performance criteria for feedback and coaching staff
4. Quality topics are included in at least half of "all hands" meetings
5. Collecting error prevention metrics

Additional top five Mature Quality Attributes developed and identified as important by conference participants are:

1. Every employee understands the quality goals of the company and how their specific quality goals and their performance assessment contribute to the overall common quality goal
2. A product's quality performance and improvement is measured, shared and discussed frequently at the shop floor and throughout the business
3. Active support by CEO, Corporate Management and Site Management of QMS and continuous improvement plans
4. An established quality system maturity model and an action plan for moving to higher maturity levels and tracking this to measure progress
5. An internal survey measuring and providing feedback on the company's quality culture

PDA plans to continue to hold open forums to discuss best practices for assessing maturity levels of quality culture programs and how these can be developed into effective measures.

PDA Quality Metrics Task Force

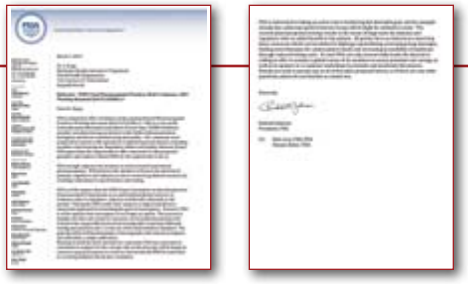
Steven Mendivil, Amgen (chair)
Glenn Wright, Eli Lilly and Company
Anders Vinther, PhD, Sanofi Pasteur
Cylia Chen-Ooi, Amgen
Gabriele Gori, GSK Vaccines
Joyce Bloomfield, Merck
Marty Nealey, Hospira
Robert Kieffer, PhD, RGK Consulting
Anil Sawant, PhD, Johnson & Johnson
Veronique Davoust, PhD, Pfizer
Susan Schniepp, Regulatory Compliance Associates
Pritesh Patel, Allergan

References

1. Srinivasan, A., and Kurey, B. 2014. Creating a Culture of Quality: Financial incentives don't reduce errors. *Harvard Business Review* 97, https://hbr.org/2014/04/creating-a-culture-of-quality
2. Hankel, A. 2014. Clues about Culture: Research findings offer insight into building and sustaining a culture of quality. *Quality Progress* 47: 18-23, http://hankel.weebly.com/uploads/1/7/8/5/17857035/clues-about-culture.pdf
3. Mendivil. S., et al. "PARENTERAL DRUG ASSOCIATION POINTS TO CONSIDER: Pharmaceutical Quality Metrics Updated September 2014." *PDA Journal of Pharmaceutical Science and Technology* 68 (2014): 535-545.

PDA Recommends WHO Look at Harmonization for GPPs

For the comments grid, visit www.pda.org/regulatorycomments



March 1, 2015

Dr. S. Kopp
Medicines Quality Assurance Programme
World Health Organization
1211 Geneva 27, Switzerland

kopps@who.int

Reference: WHO Good Pharmacopoeial Practices, Draft 14 January, 2015 Working document QAS/13.526/Rev.5

Dear Dr. Kopp,

PDA is pleased to offer comments on the proposed Good Pharmacopoeial Practices Working document QAS/13.526/Rev.5. PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by experts with experience in pharmacopoeial matters, including members representing our Regulatory Affairs and Quality Advisory Board. PDA appreciates the opportunity to offer comments on this proposed guidance and wishes to thank WHO for the opportunity to do so.

PDA strongly supports the initiative to work towards harmonized pharmacopoeias. PDA believes this initiative will serve the interests of patients, regulators and industry as one in conserving limited resources by avoiding redundancy in specifications and testing.

PDA is of the opinion that the WHO Expert Committee on Specifications for Pharmaceutical Preparations is an underutilized global resource of immense value to regulators, industry and thereby ultimately to the patient. Placing the GPPs under their auspices is logical and allows a structured approach to forwarding the goal of convergence. However, PDA is of the opinion that convergence is no longer an option. The process is lengthy and does not conserve resources, as local pharmacopoeias still interpret the supposedly harmonized monographs requiring additional testing and practices and / or the use of the local reference standard. The goal should be full harmonization of monographs with mutual acceptance and ultimately a single publication.

Bearing in mind the short timeline for comments, PDA has restricted its comments to support for the concept only at this time but will be happy to convene a group of experts to work on content should WHO be interested in receiving detailed, line by line comments.

PDA is interested in taking an active role in furthering this desirable goal, and for example already has a pharmacopoeial Interest Group which might be enlisted to assist. The current pharmacopoeial overlap results in the waste of huge sums by industry and regulators with no added benefit to the patient. All parties have an interest in conserving those resources which can be utilized in fighting counterfeiting, preventing drug shortages, finding novel therapies for unmet patient needs and increasing accessibility of medicines through reduced testing costs. As such PDA not only unreservedly backs the idea but is willing to offer to conduct a global survey of its members to assess potential cost savings as well as to sponsor or co-sponsor workshops to promote and accelerate the process.

Should you wish to pursue any or all of the ideas proposed herein, or if there are any other questions, please do not hesitate to contact me.

Sincerely,

Richard Johnson
President, PDA

CC: Rich Levy, PhD, PDA

Denyse Baker, PDA

PDA Commenting Task Force

Karen Ginsbury, PCI Consulting (Lead)

Stephan Roenninger, PhD, Amgen

Susan Schniepp, Regulatory Compliance Associates

Janeen Skutnik-Wilkinson, Biogen

So Many Reg Questions, So Many Answers

Maria Guazzaroni Jacobs, PhD, Pfizer, and Susan Schniepp, Regulatory Compliance Associates

Have you ever asked yourself, is my audit program effective, are my excipients of high quality, or what's the environmental impact of my product and how can it be minimized? These and other questions are shared by many in the biopharmaceutical industry and are the focus of U.S. FDA regulators as they emphasize quality over compliance and work with manufacturers to increase quality rather than depending on inspection findings to improve processes

Most companies, whether they are large or small, traditional or biotech, proprietary or contract manufacturing organizations, have an established auditing program for their suppliers but not all of these programs are effective. Often times these audits fail to identify crucial noncompliant issues before they manifest into serious compliance concerns.

The quality of excipients is also critical to assuring the safety, quality and efficacy of medicines. Excipients have a wide range of applications and are essential components of the drug product formulation. Characteristics that excipients impart to formulated drug products include aesthetic appearance, stability and delivery of the active ingredient. Therefore, applying appropriate GMP principles to excipients is essential.

The responsibility of assessing environmental impact of regulated biologics spans regulatory agencies and even internal divisions, such as CBER and CVM. Pharmaceuticals residues have been detected in surface waters, drinking water and soil environments. FDA is required to assess potential environmental impacts, including ecological impacts of drug residues in the environment and to ensure that the public is informed of the environmental analyses. The medical products industry is required to submit environmental assessments as part of the regulatory submission review process. In addition, the Environmental Protection Agency (EPA) is committed to investigating pharmaceuticals as environmental pollutants and to develop strategies to help protect the health of both the environment and the public.

The *2015 PDA/FDA Joint Regulatory Conference* will feature dedicated sessions focused on audits, excipients and environmental impact. Two sessions will explore the latter, one even features an EPA representative.

For the complete program and to register to the conference, go to www.pda.org/pdafda2015. For information on PDA Education courses after the even, visit www.pda.org/pdacourses.

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Breakout sessions will focus on topics related to Technology, Contamination Control, Biopharmaceutical and Quality.

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Recently Confirmed Speakers:

- **Luciana Borio, MD,** Assistant Commissioner, Counterterrorism Policy and Acting Deputy Chief Scientist, Office of Counterterrorism and Emerging Threats, OC, *FDA*
- **Joseph Chen, PhD,** Director, QC Microbiology, *Genentech, Inc.*
- **Alan Dobson, PhD,** Director, Environmental Research Institute and Professor, Environmental Microbiology, *University College Cork Ireland*
- **Dennis Guilfoyle, PhD,** Senior Director, Microbiology and Analytical Regulatory Compliance, *Johnson & Johnson*
- **Patricia Hughes, PhD,** Team Leader, Biotech Manufacturing, CDER, *FDA*
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Following the conference, attend *PDA's 10th Annual Global Conference on Pharmaceutical Microbiology Course Series*. Over two days (October 22-23), PDA Education will host three courses on topics of the utmost importance to pharmaceutical microbiology.

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Another layer of PDA leadership resides at the grassroots level in the Chapter organizations. Regional PDA Chapters provide local services to the membership, including translations of PDA publications, networking social events, student scholarship and annual regulatory and technical conferences. Each Chapter is managed by volunteer leaders.

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Cold Chain, Supply Chain Face Changing World

Rafik Bishara, PhD, and Erik van Asselt, PhD, Merck Sharp & Dohme

The biopharma and pharma industries must constantly manage global changes in the regulations and standards covering temperature-controlled distribution for both domestic and global supply chains, along with ensuring product quality and integrity during handling, storage and transportation of medical products. In addition, the security of cargo and its protection from tampering, diversion and the introduction of counterfeited products present new challenges that require the management of logistics for the cold and supply chain.

Specifically, there are new trends in GDP inspections as well as a new GDP guidance for APIs in Europe. The Falsified Medicines Directive continues to have global impact. Those involved with supply chain logistics now juggle many tasks, including managing the stability budget and excursions; overseeing mapping studies; implementing RFID, serialization and other security measures; handling practices for air, road and ocean shipments; overseeing risk management; monitoring temperatures and analyzing data, among many others.

This year, the PDA *Pharmaceutical Cold & Supply Chain Logistics* conference in Amsterdam will not only address these topics but also offer exciting, one-of-a-kind offerings. First, there is a preconference visit to Amsterdam's Schiphol airport, where attendees will visit the cargo handling area. Second, there is also an experiential learning visit to the site of the TOPA Institute, a testing laboratory focused on load distribution, for a hands-on experience covering the design and qualification of containers, preparation of packouts and gel packs, documentation and climate chambers, distribution testing for shock and vibration and a tour of the mechanical laboratory. And finally, there will be a first-time overview of the PDA Technical Report covering qualification and operational guidance of passive thermal protection systems used for global distribution of product

For more information about this event, please visit https://europe.pda.org/coldchain2015.

Inconsistent Expectations Clash with Industry Best Practices for Sterile Products continued from page 24

mental monitoring program and ensure that, if used, the percentages measure the average trend in one area, and not, for example, all Grade A zones in the building. They should also ensure they have established historically based Alert and Action Levels so there are no surprises. If your company still uses a traditional cleanroom with curtains or Plexiglas shields, consider upgrading to isolators as soon as possible. You and your executive suite should understand the weakness of the sterility test before the next lot is in question for microbiological reasons. If you are using the sterility test as a container closure integrity test during your stability program, develop a more meaningful container closure integrity test and submit it for approval prior to implementation. Do not be lulled into a false sense of compliance by a few good inspections. Those inspectors did not look at everything—and even if they looked at something, their expertise in that subject may be limited.

References

1. USP, "USP <1116> Microbiological Control and Monitoring of Aseptic Processing Environments," USP 35 vol. 1 2012a, 2012: pp. 697-707.
2. Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice, U.S. Food and Drug Administration: September 2004 http://www.fda.gov/downloads/Drugs/…/Guidances/ucm070342.pdf
3. EudraLex, The Rules Governing Medicinal Products in the European Union, Volume 4: EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Annex 1, Manufacture of Sterile Medicinal Products, November 2008 http://ec.europa.eu/health/files/eudralex/vol-4/2008_11_25_gmp-an1_en.pdf
4. Good Manufacturing Practices (GMP) Guidelines - 2009 Edition, Version 2 (GUI-0001), Sterile Products, Health Canada, March 2011 http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0001-eng.php#sterprod
5. PDA *Technical Report No. 13 (Revised): Fundamentals of an Environmental Monitoring Program*. PDA: 2014.
6. Friedman, R. "Barrier Isolation." Presented at the 2012 ISPE Aseptic Conference, Tampa, FL, February 29
7. PDA *Technical Report No. 30 (Revised): Parametric Release of Pharmaceutical and Medical Device Products Terminally Sterilized by Moist Heat*. PDA: 2012.

About the Author

Paul Larocque is the President of Acerna Inc., a biological, pharmaceutical, and medical device consulting firm specializing in aseptic processing and GMP services.

Teaching Compliance in Financial Terms continued from page 32

mistakes and increases right first time delivery of projects or processes which always benefits the financial bottom line.

We all learn in our jobs every day. When an employee leaves the company, he or she takes a lot of knowledge with them. If a company, however, could capture this knowledge on an ongoing basis, the loss to the company is then minimal when an employee leaves. Quality's role in this respect is to lead the introduction of systems and activities that foster the institutionalization of knowledge. This can be done by having great feedback systems, or by conducting and documenting a "lessons learned" exercise after a project or during process development (just make sure it is not a check-the-box exercise). It needs to be done thoroughly and with all the people involved (including Finance). It is the data and knowledge collected that should be used to justify the next project or process improvement expenses and resources. This requires demonstrating that with the right resources, projects will be executed thoroughly and with a higher likelihood of success resulting in delivery of a higher quality product.

How many times have you found yourself having a hallway conversation with a colleague about an issue with Product X that you have been dealing with for several weeks? As you explain the situation, your colleague says, "We had that same issue three years ago with Product Y, did you try removing the ZZ?" Now, if you hadn't met that colleague in the hall, how long would you have continued to search for a solution? How many wasted hours, resources, etc., did you spend? We believe that by financially quantifying reduced repeat failures, wasted rework and opportunity loss, the value of the development and use of a knowledge management system can be easily justified.

Conclusion

While it is important that those of us in Quality learn to discuss compliance in financial terms, at the same time, we must avoid diluting the message by making it *entirely* about cost. But cost should certainly be a part of the decisionmaking process. This starts with bringing visibility to where the money goes by establishing a Cost of Quality Model. The next step is tying financial numbers to investigations and other quality system elements to show actual failure costs and what it would have cost to avoid the failure. When QRM activities include the financial cost of a risk actually occurring vs. being mitigated (using the CRB Index), Quality creates a forum for meaningful dialogue, enabling the company to make an informed decision on where to close compliance gaps, avoid drug shortages, and invest in improved quality. Not until a quality dialogue happens in financial terms between Quality and the rest of the organization will a company be able to fully move from the mindset of meeting minimum compliance standards to truly creating an environment of quality performance from senior management to the shop floor.

In the final part of this series, we will discuss rewards and recognition of all employees in the July/August *PDA Letter.*

About the Authors

Jennifer Magnani's experience includes establishing and continually improving quality systems across varying countries and cultures, portfolio management, communication, and employee development. She is currently Head of Sanofi Pasteur Quality Academy (learning and education.

Anders Vinther, is Chief Quality Officer, Sanofi Pasteur. His experience includes QC, QA, executive and strategic management in a variety of cultures and a number of companies ranging from start-ups to large biologics companies.

Site Visit Offers PDA Staff Holistic View of Manufacturing continued from page 13

Markus Buergin, QC Supervisor, **Sharvari Bhatt,** QC Micro Lead, **Thuytien Pham,** QC Manager, and **Lauren Markley,** Manager, Materials Operations

This was the first time PDA staff were given an opportunity to visit all areas of a manufacturing facility. As part of this tour, PDA staff also observed firsthand the freezing processes for bulk API as well as the new technologies used to facilitate these processes.

PDA would like to thank all of the experts at GSK for their time and providing detailed overviews in their areas of expertise and related functions. PDA would especially like to thank Kimberly Carnes, who worked closely with PDA to make this site visit possible and in making it a very educational experience for PDA staff.

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Michael Sadowski, Baxter Healthcare

PDA Stresses the Science of Sterile Product Manufacturing

"How do you know that your products are sterile?"

A quick but not well thought out answer to this question might be, "All of our products must pass the sterility test prior to being released as sterile."

But what does passing a sterility test really tell us about product sterility?

As a result of discussions centered on parametric release, the shortcomings of the sterility test have been quantified. This has served to dispel longstanding myths about the test's effectiveness by exposing the true sensitivity of the sterility test. For example, if a batch of product had an issue and was contaminated to a level of one nonsterile unit out of a 100 units (10^{-2} Probability of a Nonsterile Unit, or PNSU), a 20 sample sterility test would only detect this level of commination 18% of the time. Since terminally sterilized products must meet a PNSU of $\leq 10^{-6}$, that means 82% of the time, the product sterility test does not detect a positive even when the contamination rate is *four orders of magnitude* above/worse than what is required to label that product as sterile! In addition to this statistical shortcoming, the product sterility test is also limited in which organisms it can detect based on its culturing conditions.

So, if the product sterility test is not the answer, how do we know that a product is sterile? The central pillar of PDA's mission is *Science* which serves as the foundation in demonstrating and supporting product sterility. In fact, the following definition from PDA *Technical Report No. 30 (Revised 2012): Parametric Release of Pharmaceutical and Medical Device Products Terminally Sterilized by Moist Heat* describes a parametric release program which uses a scientifically meaningful approach for supporting product sterility: *A sterility release program that is based on effective control, monitoring and documentation of a validated sterile-product manufacturing process where sterility release is based on demonstrated achievement of critical operational parameters in lieu of end-product sterility testing.*

There are many variables and risks that must be properly considered, addressed and controlled to ensure the consistent production of sterile product. Unfortunately, there is no single "cookbook" document or approach that can be applied to each and every situation; this is where PDA's technical reports represent the ultimate value proposition. In addition to Technical Report No. 30, PDA offers a wide range of technical reports and other publications covering many topics essential to manufacturing sterile product: moist heat sterilization systems, moist heat sterilization, dry heat sterilization, steam in place, filtration, aseptic processing, environmental monitoring and control, package integrity, quality risk management, biological indicators and single-use systems.

PDA's Points to Consider (PtC) documents are another resource that provide timely highlights of best demonstrated scientific practice on contemporary topics. PDA's 2003 *Points to Consider for Aseptic Processing* document is currently undergoing major revision. Part 1 was recently released and Part 2 is expected to be released in the third quarter of 2015. Part I is currently available at the PDA Bookstore (www.pda.org/bookstore) and Part 2 will be available once it is published.

As illustrated by the PDA motto, Connecting People, Science and Regulation™, PDA also actively comments on global regulations impacting sterile manufacturing. PDA comments are founded on best demonstrated scientific practice and developed by task forces containing distinguished subject matter experts and approved by the Board of Directors and the various advisory boards.

In 2012, PDA commissioned a conference devoted specifically to sterile manufacturing. The fourth *PDA Aseptic Processing – Sterilization Conference* will be held this year in San Diego, June 9–10. Subjects to be addressed include: the updated *Points to Consider for Aseptic Processing* document, single-use systems, novel sterilization technologies, aging facilities, alternate sterility assurance levels, parametric release, compounding and discussion of current sterile product regulatory trends by regulators from across the globe. In addition to these sessions, PDA Education courses following the conference will feature various sterile product themes. At the initial time of publication of this article, there is still opportunity to register for this conference—I hope to see you there!

As you can see, PDA actively strives to be the premier global leader for the advancement of science, manufacturing, quality and innovation in sterile product manufacturing.

Diversity of Issues Addressed in an Issue

This issue of the *PDA Letter* truly encapsulates the diversity of PDA's membership and the Association's areas of expertise. The feature stories and infographic cover PDA's primary area of expertise: the manufacture of sterile drug products.

The cover story points out inconsistencies in regulatory expectations and industry best practices. The issue's second feature looks at USP <1116>, and the infographic depicts the future of aseptic processing. In the Science Snapshot, we place the spotlight on the recently published PDA *Points to Consider for Aseptic Processing.* And the Voices of the Board explains how PDA promotes the science of sterile product manufacturing.

These are articles one would expect to see in an issue of the *PDA Letter.* The Association was formed in 1946, after all, to help manufacturers develop standards and best practices for sterile products; our reputation for doing so continues to this day.

But then other articles in this same issue show how diverse and how much more dynamic PDA has become. Just looking at the PDA Journal Top 10 (p. 16), I see articles published in the *PDA Journal of Pharmaceutical Science and Technology* covering knowledge management, quality metrics, viral clearance, extractables and leachables, and container closures for biologics.

This issue also has articles on quality culture, which is part of the PDA Quality Metrics effort. This initiative grew out of PDA's response to the U.S. FDA's call for assistance in developing a plan to use manufacturing quality metrics in its GMP enforcement program. PDA's rapid response to the call has resulted in two FDA/industry workshops, two points to consider articles published in the PDA Journal, the quality culture article in this issue of the Letter (p. 34), and a completed survey on quality culture that will publish in an upcoming issue of the Journal.

PDA can credit the diversity and initiative of its members for operating in such diverse fields. While all our offerings from training courses to conferences often shed light on this diversity, the *PDA Letter* provides each member ten reminders (ten issues) each year to keep you up to date with the dizzying number of highly important PDA initiatives.

PDA Letter

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PDA Global Headquarters — Bethesda Towers

4350 East West Hwy., Suite 200
Bethesda, MD 20814 USA
Tel: +1 (301) 656-5900 Fax: +1 (301) 986-0296
info@pda.org
www.pda.org

PDA Europe — Adalbertstr. 9

16548 Glienicke/Berlin Germany
Tel: +49 33056 23 770 Fax: +49 33056 23 7777
petzholdt@pda.org

PDA Training & Research Institute

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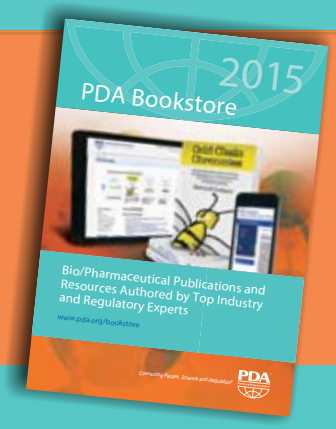

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