People • Science • Regulation

PDA Letter

Volume LV • Issue 8 www.pda.org/pdaletter September 2019

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September 2019 PDA Letter

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Lifecycle Approach Wipes Away Cleaning Validation Concerns

Raji Vathyam

Cleaning validation is a perpetual undertaking for multiproduct drug manufacturing companies, particularly those with dynamic product profiles and frequently changing commercial needs. With rising demands for complex molecules or highly potent drugs, manufacturers now must continuously invest in new technologies such as containment systems, which offer protection to both operators and finished products.

Cover Photo by Katja Yount

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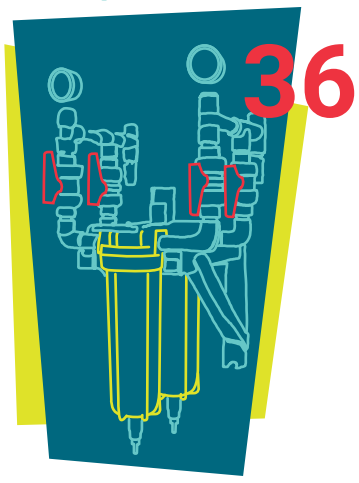
Human Error Causes OOS Investigation

One Company's Experience with Determining Root Cause for an Endotoxin Testing Failure

Rebecca Stauffer and Madeline Cusick, PDA

Testing failures are not unheard of in the industry. Routine samples that normally pass specification can, out of the blue, suddenly fail.

InfoGraphic



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Endotoxin Control in Another Industry

Find Out How an Operating Room Improved Their Endotoxin Control

Endotoxin control is a major concern for pharmaceutical microbiologists. Did you know it is also an issue in operating theaters? A ten-year study of endotoxin-retentive ultrafilters used for reverse osmosis (RO) plants in an operating theater was highlighted last year in the *PDA Journal of Pharmaceutical Science and Technology.*

PDA Letter

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> **On the Issue** | Here They Come: Pharma Young Professionals
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> Another Perspective on rFC
Lonza's **Allen Burgenson** comments on recent coverage of alternative endotoxin testing technologies.

> SE Chapter Helps Students Build Bridge to Future
Learn more about the new student chapter affiliated with the Southeast Chapter!

pda.org/letter

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Author Thomas Stanton and *U.S. FDA's* Janet Woodcock, MD, to Present Keynote Addresses!

Other noted experts throughout the week include:

- **H. Gregg Claycamp, PhD,** Biologist, CVM, *U.S. FDA*
- **Anne Greene,** Professor, Lecturer, and Pharmaceutical Project Manager, *TU Dublin, School of Chemical and Pharmaceutical Sciences*
- **Anil Sawant, MSc, PhD,** Senior Vice President, Global Quality Compliance, *Merck & Co., Inc.*

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OPTIMIZING QUALITY RISK MANAGEMENT CONFERENCE: DEC. 12-13

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2020 PDA Annual Meeting

SUBMIT YOUR ABSTRACT BY SEPT. 30

Call for Abstracts is now open!

The *2020 PDA Annual Meeting* Program Planning Committee encourages you to submit an abstract for a podium or poster presentation.

Suggested topics for **podium presentations** include, but are not limited to:

- Modernizing Older Facilities vs. New Facilities of the Future
- Supply Chain Security (Serialization, Track and Trace, Counterfeit)
- Practical Applications of Artificial Intelligence (AI) and/or Machine Learning (ML)

Suggested topics for **poster presentations** include, but are not limited to:

- Single-Use Bioprocess Technology and Validation
- Combination Products
- Microbial Control Program Cell Culture Systems and Expression Rates

We highly encourage the participation of young professionals and students.

Ready to submit an abstract? Visit *pda.org/2020AnnualCFA* today!

MARCH 30-APRIL 1 | RALEIGH, NC

EXHIBITION: MARCH 30-APRIL 1
WORKSHOP: APRIL 1-2
TRAINING COURSES: APRIL 3
#PDAAnnual

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PDA Contaminates Podcast Scene

Rebecca Stauffer @RebeccaStauPDA

Contamination control is a major concern for readers of the *PDA Letter.* Recent news articles in the *news uPDAte* show this concern is valid. In July alone, the U.S. FDA cited a number of companies for inadequate contamination control. A nonsterile drug manufacturer was warned about ineffective cleaning processes to prevent cross-contamination ***(1).*** FDA told another manufacturer it failed to follow procedures for cleaning and disinfection ***(2).*** And a manufacturer in India was cited for, again, inadequate cleaning practices (with some data integrity violations thrown in as well) ***(3).***

Naturally, articles and videos on prevention of contamination, particularly microbial control, are some of the most-read articles in the *PDA Letter.* PDA's annual *Global Conference on Pharmaceutical Microbiology* remains one of our more popular meetings, having grown in significantly in little more than a decade.

For this reason, we want to continue providing our readers with the latest information on this important topic. As part of this effort, we are working on a new *PDA Letter* podcast that will focus on contamination events and other GMP stories from the industry. Since *Serial* hit the scene in 2014, podcasts have become a medium to be reckoned with. Shows cover everything from sports to true crime to news analysis. Considering that the Letter provides both written articles and videos, it made sense to also join the ever-growing ranks of podcasters. Our first episode will launch this fall, so stay tuned!

Also, if you plan to attend the *14th Annual PDA Global Conference on Pharmaceutical Microbiology* in October (and I highly recommend you do so), feel free to stop me and let me know what you think of this and other Letter content!

Also, I want to thank our summer intern **Madeline Cusic**k for coming up with the witty title for this Editor's Message. She has now resumed her journalism studies at Georgetown University. An upcoming issue will feature Madeline's summary of her summer at PDA.

References

1. "Non-Sterile Drugmaker Hit for Inadequate Cleaning." *Drug Industry Daily* (July 18, 2019).)
2. "Connecticut Manufacturer Gets FDA Warning Letter." *Pharmaceutical Technology* (July 17, 2019). www.pharmtech.com/connecticut-manufacturer-gets-fda-warning-letter
3. Palmer, E. "Indoco caught in maelstrom of FDA concerns as plant hit with warning letter." *FiercePharma* (July 15, 2019). www.fiercepharma.com/manufacturing/indoco-caught-maelstrom-fda-concerns-as-plants-hit-warning-letter-other-citations

Help Shape the Future of Your Association

Vote for the 2020 PDA Officers and Board of Directors

Once again, you as a member have an opportunity to shape the strategic direction of PDA. How? By voting for Officer and Board of Directors candidates.

This year, there are three open Officer seats (Chair-Elect, Treasurer and Secretary) and three open Director positions. Due to the change in PDA's bylaws, three Directors will be elected by members with a fourth appointed by the Board.

The election is open until Nov. 15; members in good standing as of Aug. 23, 2019 can vote online or at conferences held before Nov. 15 in the United States and Europe.

Officer Candidates

Susan Schniepp (Chair-Elect)

Glenn Wright (Treasurer)

Melissa Seymour (Secretary)

Director Candidates

Barbara Allen

Jeffrey Broadfoot

Tia Bush

Ghada Haddad

Ivy Louis

Steven Lynn

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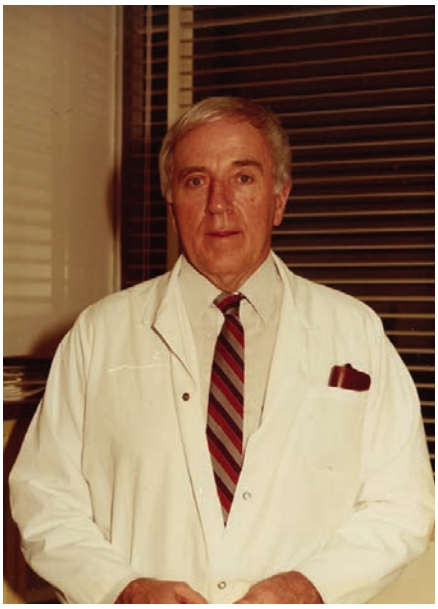
www.pda.org/vote

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

PDA Remembers Edmund "Ed" Fitzgerald



PDA was saddened to learn of the passing of longtime volunteer **Edmund "Ed" Fitzgerald** on April 11. He was 96 years old.

Ed made significant contributions to PDA during his time as a volunteer. He was a member for more than 25 years, served on committees and presented papers. In 1988, he helped spread the reach of PDA by founding the Canada Chapter, the Association's first chapter outside the United States. In his memoirs, penned in 2010, he wrote: "I organized a committee with representation from Toronto and Montreal and held a number of planning meetings in both cities. I visited a number of companies in Montreal and spoke to many groups about a first ever chapter in Canada. I kept in touch with the PDA on our progress. Within six months we pulled it off with the first meeting and attendance of over 200 people." He supported the new chapter by serving as Director-at-Large.

In 2001, Ed received the Distinguished Service Award from PDA. In his retirement, he spoke of his pride in PDA and its contributions to the pharmaceutical industry by connecting industry professionals around the world.

Ed retired following a distinguished career as a Microbiologist (Quality Control) at Ayerst Laboratories (later Wyeth, Pfizer) in Montreal. Ed also served in the Canadian military in World War II, participating in the liberation of the Netherlands.

PDA Volunteer Spotlight

Kir Henrici

- **CEO and Principal Consultant**
- ***The Henrici Group***
- Member Since | **2015**
- Current City | **New York, New York**

I have had amazing mentors in PDA

How did you hear about PDA and why did you join?
I joined PDA in 2015. I was introduced initially by a colleague with whom I collaborated with on presentations for PDA conferences. The conference vibe hooked me immediately—the interactions with regulators and industry leaders, the sessions and the overall fellowship. All of this offered a link to staying current on the side of progress.

What are some of the volunteer projects you have been involved with?
I have been fortunate to serve on the PDA task force collaborating on technical reports addressing data integrity within laboratories, manufacturing and the quality management system. The team has been highly engaged, supportive and draws from diverse experiences.

What challenges do you see facing the industry?
The sweeping impact of big data and artificial intelligence has completely disrupted the data integrity regulatory paradigm, which is my area of expertise. I am fascinated and intrigued by this technology, and, equally so by all the collaborative work to define regulations, including data integrity requirements.

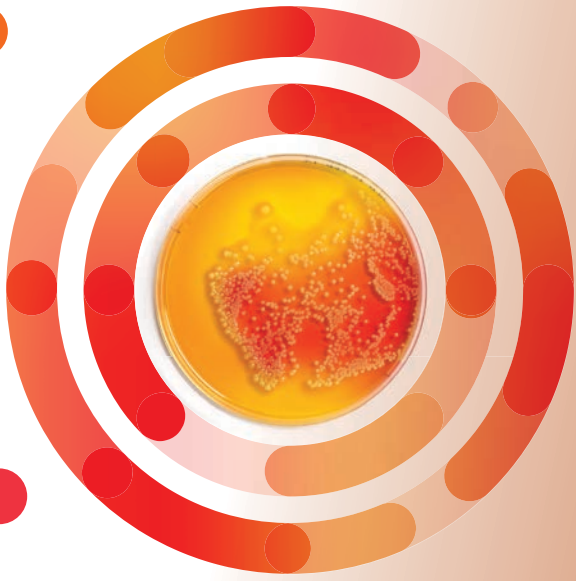
Who is your personal hero?
My father was a veteran. He was fierce on integrity. Character was everything. He was genteel but demanding of goodness, courage, humility and trust. If I fell short, he never raised his voice but would get a look of disappointment that could crush an army. A day does not go by that I do not reflect and draw upon his teachings.

What has been your once-in-a-lifetime experience?
When I was 38, I took a year off from my career and essentially went to live on an ashram. To partake in the community you must also serve, so I was the head of the kitchen. For the first six weeks I practiced Ashtanga yoga, meditated and studied Sanskrit from 4 a.m. to 9 p.m. I also cooked breakfast, lunch and dinner for the community in between programs.

The ashram received guests from all over the world, and for the remainder of the year, I taught yoga and cooked meals for these amazing people. Everyone was seeking mindfulness and working to align themselves with the principles of absolute love. It was a total awakening for me.

pda.org/2019Micro

14th Annual PDA Global Conference on Pharmaceutical Microbiology



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OCTOBER 21-23 | ROCKVILLE, MD

EXHIBITION: OCT. 21-22
2019 PDA RAPID MICROBIOLOGICAL METHODS WORKSHOP: OCT. 23-24
TRAINING COURSES: OCT. 25
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Chapter Update

Published online first

Ireland Chapter Addresses Annex 1 Revision

PDA Ireland Chapter

The draft Annex 1 revision remains much discussed and much debated. On May 3, the PDA Ireland Chapter hosted an all-day conference in Dublin on the revision and its potential impact. This event provided an opportunity for attendees to comment on the revisions and gain clarity on specific parts of Annex 1. Below are some key takeaways from the discussion.

First, contamination control strategies and quality risk management (QRM) emerged as some of the most important themes regarding updates to the original document. For example, the original document only had 21 mentions of QRM. Now, the term is referenced 132 *times* in the draft.

The aim of a contamination control strategy is to define the ethos of a site's approach to contamination control. How are existing controls defined? How will they be enhanced? How frequently will they be reevaluated? And how will QRM be integrated into the strategy, proving there is less reliance on end testing? Every area should be involved in generating a contamination control strategy for a site (with the exception perhaps of HR and Finance!).

The Annex 1 revision has been developed with innovation in mind. If QRM is done well, it can be used as a tool to drive innovation and continuous improvement, however, the industry needs a mature QRM process if we are going to deal with all the risk management expectations in this revision. At the same time, the biggest challenge for Annex 1 implementation is the execution of risk management and incorporating risk culture into organizations—an indicator of maturity of a QRM program is the people involved in performing risk assessments.

When it comes to risk, we must ask ourselves, are we translating our risk information and data into true knowledge management? Are operators and analysts gaining the true knowledge during training of the "why" we do things in procedures to mitigate risk? After all, knowing your risks is a good thing—organizations should not be afraid to speak to regulators about their risks and how they are managing them.

In the opinion of regulator **Ciara Turley** of the Irish Health Products Regulatory Authority, the revised Annex 1 should result in fewer deviations and better supply chain integrity. In fact, she highlighted that Ireland has embraced the revised Annex 1 and most companies are in a very good position regarding the draft revision due in part to HPRA's strong expectation.

The comments received on the Annex 1 draft have been reviewed. it was stated that there will not be a second consultation period for the updated document. Due to constraints, the final version may not be issued by the European Commission until 2020. Still, the regulators urged companies not to wait for the final publication as there may only be a minimal grace period before regulatory observations will be received. In fact, it was suggested it could be as little as three months. It is important that companies read the draft, carry out a detailed gap analysis and embrace the changes. PDA's Ireland Chapter will continue to provide information to its members about the Annex 1 revision as it becomes available.

What do you think of the proposed Annex 1 changes? Email the PDA Letter Managing Editor stauffer@pda.org.

PDA Who's Who

Ciara Turley, Inspector, Irish Health Products Regulatory Authority

Barricade

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pda.org/2019RapidMicro

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Volunteer Opportunities Abound!

Lend Your Expertise to PDA for a Slate of Exciting Projects

PDA is always looking for volunteers to help advance the science of sterile manufacturing. Below is a sampling of opportunities.

For more information about each opportunity and to apply, visit www.pda.org/membership/upcoming-volunteer-opportunities.

Scientific/Regulatory Affairs

PDA Good Distribution Practices Team

Apply by Oct. 1

PDA is working to assemble a team of subject matter experts to address issues of downstream drug distribution as they arise. This might include commenting on regulations and guidances relating to distribution issues, reviewing our current technical reports on distribution to identify any necessary updates and assisting other PDA teams when particular insight in this area is needed.

PDA Education

Course Instructors

Apply by Jan. 1, 2020

PDA Education is looking for individuals with appropriate experience and expertise to serve as **course instructors.** Course areas include microbiology, aseptic processing, isolator technology, filtration, biotechnology and combination products.

Publishing

Authors and Reviewers Apply Anytime!

PDA Journal of Pharmaceutical Science and Technology

The PDA Journal is looking for **authors** to write commentaries, reviews, original research and technology/applications (e.g., case studies) on a variety of topics related to pharmaceutical science.

In addition, the **PDA Journal seeks reviewers** to evaluate manuscript submissions for quality and relevance.

PDA Letter

The *PDA Letter* is looking for authors to submit content on aseptic processing, pharmaceutical quality, microbiology, data integrity, global regulations and visual inspection.

The Letter also has openings on its Editorial Committee for the 2020–2021 term. The Committee reviews Letter submissions to ensure relevance to the *PDA Letter* community.

pda.org/2019Quality

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DECEMBER 9-13, 2019 | WASHINGTON, DC
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Students Enthused About PDA Courses in India

B. V. Krishnakumar, EduOriens Skill Development LLP

If you have been following the *PDA Letter*, you are probably aware that PDA began offering a series of PDA Education courses through its partner company, EduOriens Skill Development, in India this year ***(1).*** In March, PDA offered the first course in the series which covered basic aseptic technique. This course set the stage for the entire program with 57 students in attendance.

The majority of these students hailed from leading Indian pharma/biopharma manufacturers and most worked in operations, plant management and quality functions. Their enthusiasm was infectious, and all were excited to learn about the latest in aseptic processing. All found this progressive learning program to be engaging.

During classroom sessions and in the corridors during breaks, students participated in group discussions, shared experiences and exchanged viewpoints. Many were excited to see how they could apply lessons learned from the course to make procedures easier to follow at their companies.

One student expressed: "I was impressed by the quality of the trainers and also the fact that the attendees were from a variety of companies representing a range of functions. It was also a good platform to network with the other students."

Another student said, "for me, with my vast role and responsibilities, learning about the basics of aseptic processing was very useful."

PDA Education offered more advanced courses in India in August. For more information, visit www.pda.org/courses/about-pda-education.

[Editor's Note: For a perspective from three of the course instructors, see "PDA Aseptic Processing Course Instructors Go Global," in the July/August issue**.]**

Reference

1. "PDA Expands Course Offerings in India." *PDA Letter* 54 (May 2019) 17.

About the Author

B. V. Krishnakumar is Chief Business Officer for Eduoriens. He has over five decades of experience in sales, marketing and business enterprise management combined with an education in science.

PDA Photostream www.flickr.com/parenteral-drug

4th PDA Europe Annual Meeting

June 25–26 | Amsterdam

The *4th PDA Europe Annual Meeting* provided not only opportunities to learn about the past developments in the industry but also extensive networking where participants could enjoy the start of summer and make new connections.

(l-r) Valerio di Giovanni, Altran; Martin Düblin, One One Eleven

PDA Board member Veronique Davoust (fifth from left) bid on a guitar auctioned by the PDA Band. Proceeds supported the Sonnenhof children's hospice.
(l-r)Juha Mattila (aka Speed King); Roland Zeller (aka Stick Machine); Horst Koller (aka Metal Head); Oliver Valet (Bass Oli); Veronique Davoust; and Holger Krenz (aka KeyMinator)

PDA

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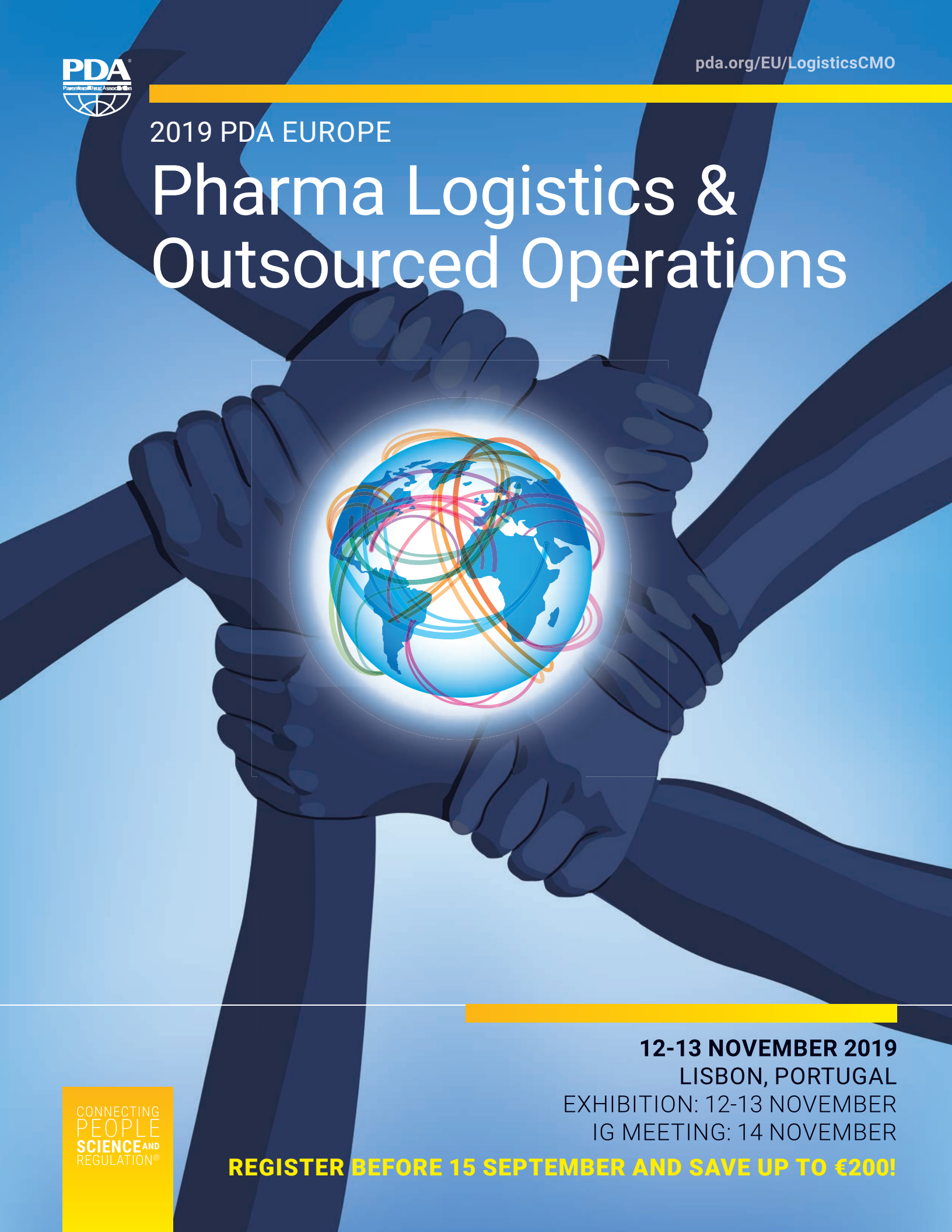
2019 PDA EUROPE

Pharma Logistics & Outsourced Operations



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SNAPShot

In *Print*

Validation Requirements for Cleaning and Sanitization Practices

The following is excerpted from the chapter, "Cleaning and Sanitization Practices," in the book, Contamination Prevention for Nonsterile Manufacturing, *by* ***Andrew Dick.*** *The book can be purchased at the PDA Bookstore (www.pda.org/bookstore).*

Validation Requirements

- Include identification and classification of equipment (by type) in the validation.
- Identify the strategy by which product(s) and/or equipment are grouped in the validation. Use the hardest-to-clean products and hardest-to-clean equipment for the validation study and supply a rationale (e.g., why one piece of equipment is used rather than another).
- Be prepared to demonstrate reproducibility of the resultant cleaning; in most cases, three executions are sufficient to demonstrate reproducibility.
- Identify or define the specific cleaning procedure that will be used to clean the equipment (i.e., in an SOP), including reference to a change control document, as well as validation frequency.
- Ensure the results meet the "reasonable" industry standard of 1/1000 of the active ingredient level dose or no more than 10 ppm of any previous product.
- Conduct residue studies to ensure elimination of product, detergent, and chemical sanitizer. The detergent manufacturer should list the specific composition of the chemical so that the site can test for the composition recovery after cleaning. Two methods are commonly used:
  - **Direct Surface Sampling:** Measures the actual equipment surface being cleaned. Determine the type of sampling material used and its impact on the test data as the sampling material may interfere with the test. For example, the adhesive used in swabs has been found to interfere with analysis of samples. Therefore, early in the validation program, ensure that the sampling medium and solvent (used for extraction from the medium) are satisfactory and can be used readily.
  - **Rinse Samples:** Tests for contaminants remaining in rinse water. There are two advantages of using rinse samples: a larger surface area can be sampled and inaccessible systems, or those that cannot be routinely disassembled, can be sampled and evaluated. One disadvantage of rinse samples is that the residue or contaminant may not be

Continued on page 27

Journal *Preview*

More on Low Endotoxin Recovery in the September/October PDA Journal!

Cannot get enough of the latest on low endotoxin recovery? Check out a research article on the topic in the September/October *PDA Journal of Pharmaceutical Science and Technology* (journal.pda.org)!

Research

"Development of Protein-Like Reference Material for Semi-Quantitatively Monitoring Visible Proteinaceous Particles in Biotherapeutics," Srivalli N. Telikepalli, et al.

"Sample Treatment that Solve Low Endotoxin Recovery Issues," Masakazu Tsuuchiya

"Vapor Phase Hydrogen Peroxide Uptake by Silicone Tubing and Primary Packaging Components during Protein Drug Product Aseptic Filling: Impact by Pre-treatment and Sterilization Process," Yuh-Fun Maa, et al.

Technology/Application

"Charting and evaluation of real-time continuous monitoring water bioburden," Raphy Bar

"Single-Use Container Closure Integrity I: Using Microbial Ingress Test Method to Determine the Maximum Allowable Leakage Limit (MALL)," Saeedeh Aliaskarisohi, et al.

"Retrospective evaluation of cycled resin in viral clearance studies – A multiple company collaboration," Louise Bennett, et al.

"Preventing Cross-Contamination During Lyophilization. GMP and Occupational Cleaning Requirements for Nonproduct and Indirect Product Contact Parts," Richard Denk, et al.

Commentary

"The Bugs Don't Lie," James Agalloco

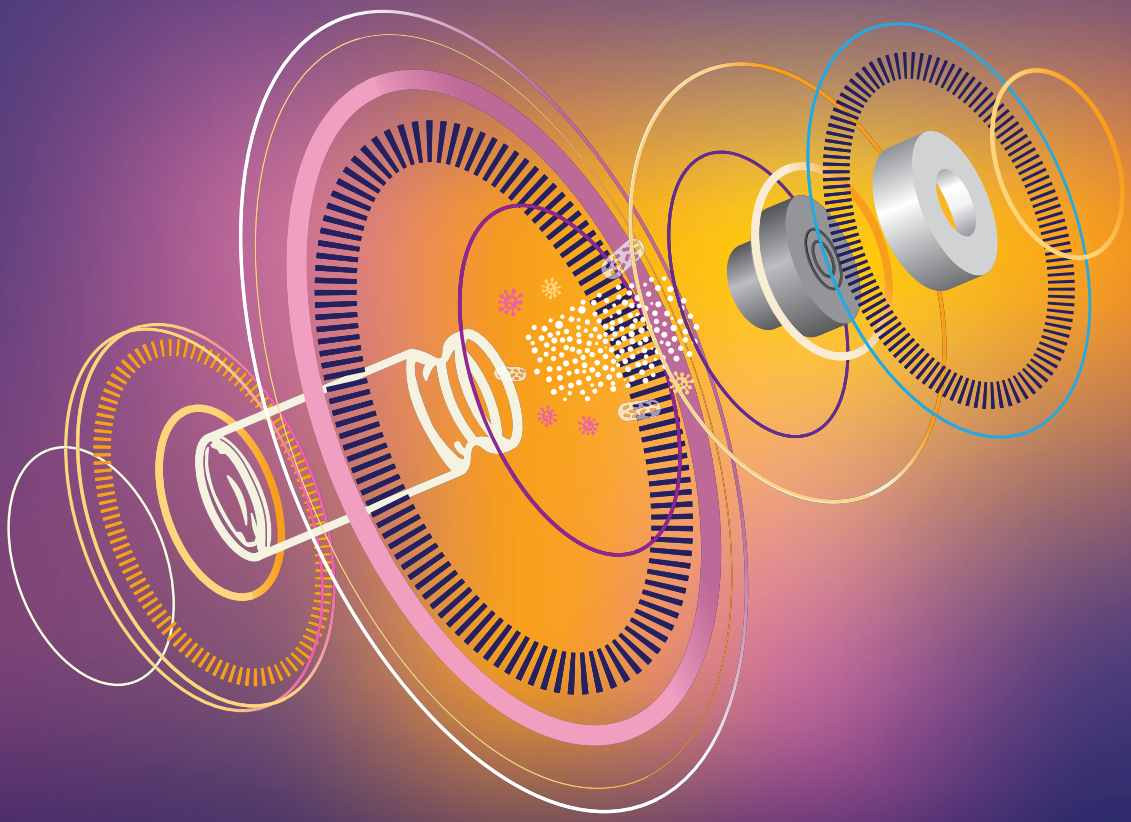
"Fidelity to Science & Correct Scientific Vocabulary – Microbial Control Versus Contamination Control," Ed Tidswell, et al.

PDA
Parenteral Drug Association

pda.org/EU/ParPack2020

2020 PDA EUROPE

Parenteral Packaging



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ISO 22519: A Flawed and Counterproductive Standard

Igor Gorsky, et al.

The article "New ISO Standard Available for Water Systems," was published in the June *PDA Letter*. In our view, this article erroneously "promotes" the ISO 22519: Purified water and water for injection pre-treatment and production systems standard released that month.

In response, our team of recognized pharmaceutical water industry leaders encourages the prompt repeal of ISO 22519 based on technical criticism. Below is an outline of our criticism with information pulled from both the ISO 22519 standard and the *PDA Letter* article. This article highlights several critical technical inaccuracies and biases in the standard which render it unusable and irrelevant. Only the most serious flaws in the standard are discussed, although there are numerous other points of concern.

From the outset ISO 22519 claims: "This document provides a standard benchmark that can be used by the industries that use PW and/or WFI, national governments, state authorities and regulatory bodies to evaluate PW/WFI systems." The meaning of this excerpt is clear: it is suggested that regulatory bodies use this standard as a benchmark by which to evaluate/audit water systems.

In general, the standard is heavy-handed in its use of prescriptive language ("shall" as opposed to "should" or "may"). Below are more specific criticisms that must be addressed.

Improvement in Water Quality

In the section on Design and Practices the standard states:

> ***4.2.3*** *The PW/WFI Pre-treatment and Production water quality shall show improvement in all quality parameters as the water advances through the system.*
>
> ***4.2.4*** *The following parameters shall be steadily reduced at each stage in the system:*
> — microbial total count;
> — conductivity and;
> — *TOC.*
>
> ***4.2.5*** *PW/WFI quality shall be according to the last revision of the local/national/relevant Pharmacopoeia. Table 1 provides recommended water quality.*

There are several problems with these statements and **Table 1.** The purpose of each purification step, and the order of the steps, is to control specific types of impurities, i.e., ions, organics, organisms, particles, etc. Some treatment steps could result in an increase in some attributes while achieving their primary purpose. Adherence to this requirement could also preclude the use of some innovative future technology that does not meet this arbitrary requirement yet could be of great value.

1. Sections 4.2.3 and 4.2.4 implicitly forbid cation exchange softening, which is one of the most commonly used unit operation for the prevention of hardness scaling of reverse osmosis membranes:
   a. There is a slight increase in the conductivity of the water due to the higher equivalent conductance of sodium compared to hardness elements such as calcium and magnesium.

   b. On very microbially pristine feedwater, it is expected that there may be a slight increase in microbial load due to the large surface area of resin in water ion exchange (IX) softeners.

   c. IX water softening is a proven technology that is widely used in compendial water treatment and is in use in thousands of water treatment systems worldwide.

   d. Currently, more than 99% of all pharma systems worldwide do not meet these requirements, especially the prescription for "improvement in all quality parameters" for each unit operation. It is necessary to first condition feedwater before the real purification process starts. This ensures that downstream unit operations l function without being damaged and that water recovery can be optimized. For preconditioning of the water, it is acceptable to refrain from purifying the water with each treatment step.

2. Sections 4.2.3 and 4.2.4 implicitly forbid the use of activated carbon, which is primarily and extensively used for neutralizing chlorine and chloramines:
   a. It is virtually inevitable that when using activated carbon for chlorine (and, more importantly, chloramine) removal, that microbial counts increase as a result of the removal of

Table 1 Recommended Water Quality

#	Parameter	RO feed	After RO	PW	WFI
1	Hardness (ppm $CaCO_3$)	≤ feed water	<1	<1	<1
2	Total Organic Carbon (ppb)	≤ feed water	<500	<500 (online)	<500 (online)
3	Endotoxin (EU/ml)	NA	NA	NA	< 0.25
4	Microbial total count (cfu/ml)	<500	<200	<100	< 10 cfu/100 ml
5	Free chlorine (ppm)	<0.05	<0.05	<0.05	<0.05
6	*Pseudomonas* (cfu/100ml)	<1	<1	<1	<1
7	*E. coli* (cfu/100ml)	<1	<1	<1	<1
8	Total coliforms, fungus, (cfu/100ml)	<1	<1	<1	<1
9	Conductivity (µS/cm)	Like feed water	<10	<1.3 (online)	<1.3 (online)
Conductivity shall be measured uncompensated at 25 °C, according to USP					

disinfection chemicals and the large surface area of activated carbon.

i. The standard later indicates that the preferred method (but due to this section the only viable method) for chlorine removal is ultraviolet light treatment. While ultraviolet light is a viable technology for chlorine and chloramine removal, it is often not the best application choice for practical and financial reasons. Activated carbon has been used in thousands of systems successfully with suitable control strategies to ensure reliability.

3. Sections 4.2.3 and 4.2.4 implicitly forbid the use of sodium bisulphite addition and caustic addition whose functions are to neutralize chlorine and to adjust pH respectively.
   a. The addition of either of these chemicals will increase conductivity and are therefore forbidden.
      i. As in the case of activated carbon, this treatment option for chlorine removal is forbidden and has been used in hundreds of systems successfully.

      ii. pH adjustment is often utilized in reverse osmosis pretreatment systems to optimize the CO_2-CO_3^{2+} and NH_3-NH_4^+ equilibria. Precluding the use of this NaOH addition for pH adjustment would virtually mandate that the removal of these ionizing dissolved gases may only be done with membrane degassing.

4. Section 4.2.5 mandates that specific water quality limits be met in the pretreatment, which will also likely result in an excessive amount of pretreatment sampling. Sampling is needed to show adherence to the reduction of each parameter cited by each production module. According to industry standards for microbial sampling, each sample costs U.S. $250 for sampling, containers, single-use, inoculation, incubation, labor, and analysis. Thus, minimum daily sampling at three pretreatment modules would cost an additional USD $273,750 per year (i.e., 750 × 365) with no additional compliance to the pharmacopoeia which is mandated.

USP <1231> Water for Pharmaceutical and Analytics Purposes states:

"6.4.2 PRETREATMENT AND PURIFICATION SYSTEM SAMPLING

The location and frequency of sampling from ports within the pretreatment and purification systems may be selected based on a risk analysis of unit operation purpose. The purpose of this sampling is primarily for PC (Process Control), for example, to ensure maintenance of acceptable unit operation performance, to assess maintenance procedure efficacy, and to investigate the need for remedial action. ***Quality deviations in the early portions of the purification process can affect unit operation efficiency but usually do not impact the finished water quality or acceptable use."*** (**Bold** added for emphasis.)

Specifically, USP <1231> states that early portions of the purification process can affect unit operation efficiency, but rarely does it affect the finished water quality or its accepted use. The directive of ISO 22519 to sample each pretreatment module for microbial reduction or ionic reduction places an onerous burden in cost, labor, laboratory personnel and laboratory equipment on all biopharmaceutical manufacturers without any compendial mandate.

5. Section 4.2.5, **Table 1** also misrepresents certain USP requirements:
   a. The table mandates that conductivity shall be measured at 25°C, while USP allows for uncompensated measurement to be performed at any temperature from 0-100 °C. Compensated temperature readings are permissible at 25° C according to USP <645> and Eur. Ph. 2.2.38

   b. **Table 1** mandates that total organic carbon be measured online. While it is agreed this is a best practice, it is not a requirement of USP or any other pharmacopeia. See USP <643> Total Organic Carbon and Eur. Ph. 2.2.44 where online or laboratory analysis of the sample is permissible.

   c. The table implies that *E.coli.*, and fecal coliforms are allowed up to 1 cfu/100 ml in purified water and water for injection. The presence of any *E.coli.* or fecal coliforms is forbidden in the compendial water. USP <1231> states:

"8.2.2 NON-BIOFILM-FORMING BACTERIA IN WATER SYSTEMS

Other types of non-pseudomonad Gram-negative bacteria are generally non-aquatic by nature. They include coliforms from the genera Escherichia, Salmonella, Shigella, Serratia, Proteus, Enterobacter, and Klebsiella, which are used as indicators of fecal contamination. Although some of these bacteria can be human enteric pathogens, these non-pseudomonads are not suited to colonizing or surviving in pharmaceutical water systems owing to the water's chemical purity. In fact, non-pseudomonad enteric bacteria are extremely unlikely contaminants of pharmaceutical water systems unless local sewage and source water controls are not in place. Such controls are required in order to comply with the source water requirements for making USP-grade waters as described in their respective monographs."

Read More!

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2019 PDA Upcoming Events

SEPTEMBER

19-20 Quality Culture Assessment Tool and Training – Option 2
Bethesda, MD | *pda.org/2019SeptQCT*

20 Regulatory Training Course Series
Washington, DC | *pda.org/2019RegulatoryTCS*
- CMC Regulatory Requirements in Drug Applications
- Root Cause Investigation for CAPA
- Global Regulatory and CGMPs for Sterile Manufacturing
- Quality and Compliance Management for Virtual Companies
- Cybersecurity Risk Management for Drug Delivery Combination Products
- Change Management – A Practical Workshop – Option 2

23-27 PDA Aseptic Processing – Option 5 Week 1 ■
Week 2: October 21-25 [SOLD OUT]
Bethesda, MD | *pda.org/2019Aseptic5*

24-25 PDA Exchange Series – Pharmaceutical Freeze Drying Technology Particles in Injectables
Berlin, Germany | *pda.org/EU/exchange19*
- 26 Freeze Drying for Advanced Users – A Risk-Based Approach
- 26-27 Development of a Freeze Drying Process
- 26-27 Mastering Automated Visual Inspection
- 26-27 An Introduction to Visual Inspection: A hands-on course

30 Designing a Risk-Based Cleaning and Disinfection Program
Incheon, South Korea | *pda.org/2019koreatraining*

30 Extractables and Leachables for Parenteral Applications
Incheon, South Korea | *pda.org/2019koreatraining*

30-OCT. 3 Filtration Processes in the Pharmaceutical and Biopharmaceutical Industry ■
Bethesda, MD | *pda.org/2019filtration*

30-OCT. 4 Sterilization Training Course Series
Bethesda, MD | *pda.org/2019STCS*
- 30 Radiation Sterilization
- 30 Validation of Dry Heat Processes
- 10/1 Modern Thermal Validation Using Real Time Wireless Dataloggers ■
- 10/1 Steam Sterilizers: Getting it Right from the Beginning
- 10/2-4 Validation of Moist Heat Sterilization Processes – Option 2 ■

OCTOBER

1-2 2019 PDA Aseptic Manufacturing of Biopharmaceuticals Conference
Incheon, South Korea | *pda.org/2019korea*

7-10 Fundamentals of Aseptic Processing – Option 5 ■
Bethesda, MD | *pda.org/2019OctFundAP*

9-10 Best Practices for Glass Primary Containers
Mainz, Germany | *pda.org/EU/GPC2019*

14-18 Visual Inspection Training Course Series
Bethesda, MD | *pda.org/2019VisualTCS*
- 14-15 An Introduction to Visual Inspection – Option 2 ■
- 16 An Introduction to Automated Visual Inspection
- 17-18 Foreign Particulate Examination, Isolation, and Analysis ■

15-16 Mastering Environmental Monitoring
Wattwil, Switzerland | *pda.org/EU/EM2019*

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

21 Impact of Pre-Filled Syringe Components on Biopharmaceuticals Workshop
Gothenburg, Sweden | *pda.org/eu-ups/IPSB19*

21 Innovating the Journey from Manufacturing to the Patient Workshop
Gothenburg, Sweden | *pda.org/eu-ups/IJ19*

21 Innovative Drug Delivery Systems/Combination Products Workshop
Gothenburg, Sweden | *pda.org/eu-ups/DDSCP19*

22-23 The Universe of Pre-Filled Syringes and Injection Devices
Gothenburg, Sweden | *pda.org/EU/UPS2019*

24-25 All about Pre-Filled Syringe Systems – From Initial Development to Final Fill Finish
Gothenburg, Sweden | *pda.org/EU/TC_PFS19*

24-25 Extractables and Leachables – Fall Edition
Gothenburg, Sweden | *pda.org/EU/E-and-L2019-fall-edition*

24-25 Container Closure Integrity Testing – Fall Edition
Gothenburg, Sweden | *pda.org/EU/CCIT2019-fall-edition*

24-25 Measuring Quality Culture Maturity? Learn How!
Gothenburg, Sweden | *pda.org/EU/TC-MQCM19*

24-25 Test Methods for Pre-Filled Syringe Systems – Fall Edition
Gothenburg, Sweden | *pda.org/EU/TMPFS2019-fall-edition*

28-29 Cleaning Training Course Series – Option 1
Bethesda, MD | *pda.org/2019CleaningTCS1*

- 28 Addresssing Biofilm and Other Non-Routine Microbial Events
- 29 Shutdown Recovery and Disinfectant Effectiveness Studies for Controlled Environments

28-30 Airflow Visualization Techniques and Practices ■
Bethesda, MD | *pda.org/2019airflow*

29-30 PDA Pharmaceutical Product Quality Testing Conference
Tokyo, Japan | *pda.org/2019japan*

OCTOBER SPOTLIGHT ON:

14TH ANNUAL PDA GLOBAL CONFERENCE ON PHARMACEUTICAL MICROBIOLOGY
OCTOBER 21-23 | Rockville, MD | *pda.org/2019Micro*

23-24 2019 PDA Rapid Microbiological Methods Workshop
Rockville, MD | *pda.org/2019rapidmicro*

25 PDA Global Conference on Pharmaceutical Microbiology Training Course Series
Rockville, MD | *pda.org/2019MicroTCS*

- Exclusion of Objectionable Microorganisms from Pharmaceutical and OTC Drug Products
- Establishment of a Risk-Based Environmental Monitoring Program
- Contamination Control, Clean Room Design, and Environmental Monitoring for Controlled Environments – Option 2
- Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Validation, and Ongoing Control
- Application of Quality by Design and ICH Q9 Rules to Aseptic Processes and their Impact to Sterility Assurance
- Developing a Microbial Monitoring Plan and Leveraging New Technologies for Effective Sterility Assurance in Aseptic Processes
- The Microbiology of Water in a GMP Environment
- Identification of Fungi for Quality Control

■ This course is taught in PDA's U.S. Manufacturing Training Facility.

Ready for the Pharma of Tomorrow?

Melissa Seymour, Biogen, and Aaron Goerke, PhD, Roche

We live in an era where medical advancements are revolutionizing treatments and driving our industry to innovate quicker than ever. New ways of manufacturing are fast becoming a reality. We must not take this progress for granted; instead, we must work collaboratively to ensure both new and existing medicines are provided in a safe and compliant manner

Today's pharmaceutical industry is constantly challenged to fast track innovation and introduce new drugs to market in ever shorter timeframes.

PDA has always followed the important issues facing the pharmaceutical and biopharmaceutical community by delivering high-quality, relevant education to the industry and offering a broad range of conferences and workshops. In particular, through its flagship Annual Meeting, PDA provides a venue for trending topics related to innovative manufacturing and supply chain technologies. The core purpose of this meeting is to drive innovation by bringing the industry together to provide practical solutions to the future challenges.

The *2020 PDA Annual Meeting* will be dedicated to providing continued guidance for manufacturing processes and growing our understanding of new technologies. The opening plenary session will focus on the patient and the criticality of delivering innovative medicines.

As in the past, concurrent sessions will support the conference theme. Topics within these sessions will be wide-ranging with emphasis on technology, science and processing. Each of these sessions will take a closer look at topics such as artificial intelligence, machine learning, continuous processing, regulatory complexity and supply chain security to name a few. There are many challenges and these sessions will provide access to industry experts as well as allowing for open discussion as a way to increase learning among participants.

Continuing on from the last year's meeting, the *2020 PDA Annual Meeting* will continue its focus on young professionals, offering networking opportunities and sessions designed for this segment of our membership.

2020 PDA Annual Meeting

Raleigh, N.C.
March 30–April 1, 2020
www.pda.org/2020annual

In Print continued from page 20

soluble or may be physically occluded in the equipment, giving a false negative result. (Rinse water samples taken may pass; however, when opened, residue is evident indicating that water did not rinse the surface.)

An analogy that can be used for rinse samples is the "dirty pot." In evaluating the cleaning of a dirty pot, particularly one with dried-out residue, observe the interior of the pot to see that it is clean, rather than observing the rinse water.

- Check to see that a direct measurement of the residue or contaminant has been made for the rinse water when it is used to validate the cleaning process. In other words, the rinse water cannot simply be tested to see that its quality meets pharmacopeial standards; it must also be tested for potential contaminates and TOC.
- Identify the times, locations, and number of replications for equipment sampling, including "worst-case" scenarios. Include which equipment must be dismantled for sampling and inspection.
- Identify the people responsible for cleaning and sanitizing equipment.
- Provide validation activity summaries as indicated in the validation protocol. Testing should demonstrate the ability of the cleaning procedure to adequately meet the criteria for success. Any test results exceeding the criteria for success must be addressed, the risk assessed, and corrective action implemented.
- Include digital photographs of the equipment that requires cleaning and sanitizing in the master validation report and validation implementation. Take photos both before cleaning and after sanitization to demonstrate what is expected.

Author Andrew Dick will speak in session "B5: Microbial Control," Oct. 22, 2:15 p.m. at the *14th Annual PDA Global Conference on Pharmaceutical Microbiology.*

Learn more: www.pda.org/2019micro

LIFECYCLE APPROACH WIPES AWAY CLEANING VALIDATION CONCERNS

Raji Vathyam

Cleaning validation is a perpetual undertaking for multiproduct drug manufacturing companies, particularly those with dynamic product profiles and frequently changing commercial needs. With rising demands for complex molecules and highly potent drugs, manufacturers now must continuously invest in new technologies such as containment systems, which offer protection to both operators and finished product ***(1).*** This results in manufacturers relying on multiple types of production equipment and manufacturing lines, ranging from production facilities with antiquated technologies (i.e., legacy equipment) to facilities with newer technologies, e.g., isolators or restricted access barrier systems (RABS).

Naturally, using different types of equipment presents a challenge when it comes to successful cleaning validation. One multiproduct manufacturer of generic injectables took a lifecycle approach to cleaning validation, resulting in a cleaning validation program tailored to each specific production line.

Multiple Lines, Multiple Reqs

The manufacturer's four production lines and their differing requirements for product-based contamination control are summarized in **Table 1.**

Equipment in all manufacturing facilities is classified as direct, indirect or nonproduct contact. Direct product contact equipment, such as formulation tanks are cleaned using semiautomated procedures, as shown in Lines B and C, whereas, in Lines A and D, formulation tanks are cleaned manually. Similarly, filling equipment is cleaned using automated washers for Lines B and C, and manually for other lines. Isolators are cleaned manually in each line.

As the company expanded, new state-of-the-art production Lines B and C

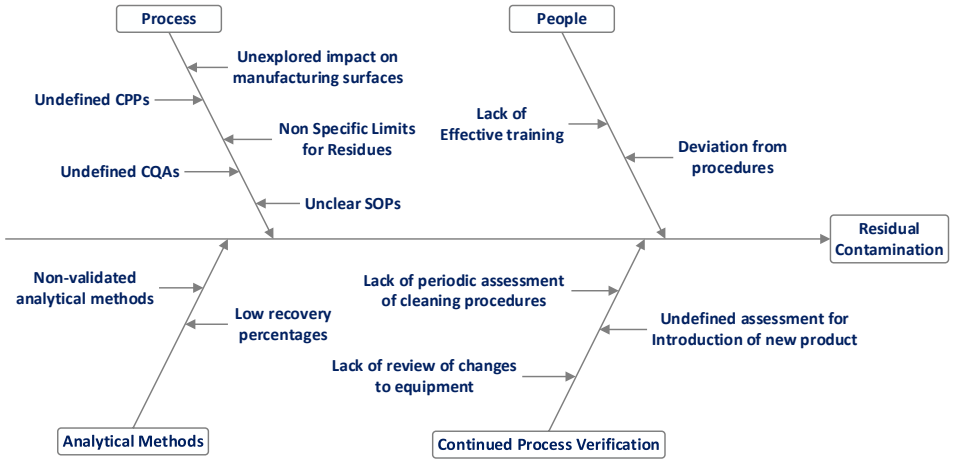
Table 1 Production Lines Profile

Variable	Line A (Legacy Aseptic Fill Line)	Line B (Isolator Line)	Line C (Isolator Line)	Line D (RABS Line)
Established	2005	2012	2012	2016
Line Description	Bosch TL Filler with Aseptic Laminar Flow and Curtain Barriers	Bosch MLF Filler with Isolator Containment System	Bosch MLF Filler with Isolator Containment System	Marchesini High Speed Filler with RABS Containment System
Cleaning Procedure	Manual	Semiautomated	Semiautomated	Manual
Product Profile	Liquid Drugs • Noncytotoxic • Hormones • Suspensions	Liquid or Lyophilized Drugs • Noncytotoxic	Liquid or Lyophilized Drugs • Cytotoxic	Liquid Drugs • Noncytotoxic • Hormones • Suspensions
Manufacturing Equipment	Dedicated and Shared	Shared	Dedicated	Dedicated and shared

were added, dedicated to noncytotoxic and cytotoxic products respectively. Each line is equipped with a dedicated clean-in-place (CIP) skid and a parts washer for automated cleaning to prevent cross-contamination by actives from other production lines. Lines B and C are also equipped with formulation and filling isolators which are critical to contamination prevention of the finished product.

A sitewide cleaning validation program was developed and implemented in phases, beginning with Lines B and C, followed by Line D. The program was then extended to dedicated equipment on Line A, the legacy aseptic fill line. The program was designed to follow a three-stage lifecycle approach consisting of **1)** Process Design, **2)** Process Qualification and **3)** Continued Process Verification ***(2,3).***

Figure 1 Cause and Effect Diagram for Residual Contamination



Stage 1 – Process Design

The design space for the cleaning validation program included risk factors associated with products and cleaning procedure variability as this could lead to residual contamination between subsequent batches. A cause-and-effect diagram, highlighting potential causes of failure in the cleaning procedure, is shown in **Figure 1.**

A cleaning validation masterplan was developed, recognizing the risk factors shown in **Figure 1** along with accompanying procedures to adequately mitigate these risks, while defining relevant critical process parameters and critical quality attributes ***(3,4).*** The masterplan included establishment of a cleaning validation committee with defined responsibilities for each participating department and cleaning validation program deliverables, leading up to the continuous process verification program stage.

Lines B and C contain portable process equipment cleaned in dedicated cleaning areas using CIP skids for manufacturing tanks and a parts washer for smaller equipment. Operations, such as equipment disassembly and loading parts in the parts washer, are limited to the cleaning area; cleaned and dried equipment is stored in a separate area to avoid any possible cross-contamination between unclean and cleaned parts.

Cleaning cycles developed for CIP skid(s) and parts washer(s) consist of three phases: prewash, cleaning and drying.

Article at a Glance

- Facility produced multiple product types with a variety of cleaning requirements
- Cleaning validation program used three-stage lifecycle approach
- Risk assessments critical to cross-contamination prevention

The cleaning process for every product is evaluated for effectiveness through visual inspection of product contact areas and testing of rinse and swab samples at the end of the cleaning cycle.

Specific analytical methods such as high performance liquid chromatography or ion chromatography are used to detect residues from production equipment. Swab samples are collected from locations that are either difficult to clean or critical for ➤

production. Riboflavin studies determine areas which might be harder to clean than others. Residual limits for swab samples are derived via therapeutic dosages or Acceptable Daily Exposures/Permitted Daily Exposures and calculating Maximum Allowable Carryover (mg) and Surface Area Limit (SAL, µg/cm^2) between two batches ***(5).*** Recovery factors obtained from method validation studies are also considered for setting product limits.

Additional nonspecific analytical tests such as conductivity and total organic carbon (TOC) are also executed on rinse samples. These provide comprehensive evaluation of tank cleanliness for residues otherwise not analyzed by HPLC/IC, etc. Microbial contamination is assessed through bioburden and endotoxin testing.

The dynamic product profile of the company includes products of varying solubilities, pH levels and toxicities. All products are evaluated for their cleanability by the current cleaning cycle, and, if need be, a newer cycle may be developed to clean a product which cannot be grouped with existing products.

Products filled in Lines B and C are grouped by shared equipment. These products are then ranked based on SAL **µg/cm^2** between subsequent batches in any possible combination of production schedule.

In addition to product ranking, a cross-contamination assessment is done for products, as shown in **Figure 2,** before introducing a product into an existing matrix. Through this cross-contamination assessment, conclusions are drawn regarding whether equipment may be shared, or whether dedicated or disposable equipment should be used. In addition, cleaning validation approaches for direct contact parts and verification and monitoring requirements for indirect and non-product contact surfaces are determined.

> **“At least one cleaning verification run is executed on each product”**

Coupon studies are executed as a part of cross-contamination assessment for all new products to evaluate product cleanability as well as potential product impact on the intended manufacturing equipment surface. Typically, coupons are soiled with a product and dried in air for a minimum of 72 hours before proceeding with cleanability assessment. Products with low pH are particularly susceptible to rouging. When this occurs, a requirement to clean equipment immediately postproduction or use disposable equipment is considered.

Stage 2 – Process Qualification

Cleaning validation runs are routinely scheduled to coincide with production runs. If necessary, equipment may also be soiled artificially and dried for a cleaning validation run. At least one cleaning verification run is executed on each product, depending on its risk profile and studies executed during the process design stage ***(6).*** If warranted, a minimum of three cleaning validation runs are performed on high-risk products.

Validation runs are executed on both shared and dedicated equipment. For shared equipment, limits are calculated for all products manufactured using the equipment and the cleaning process is validated for the lowest limit.

Stage 3 – Continuous Process Verification

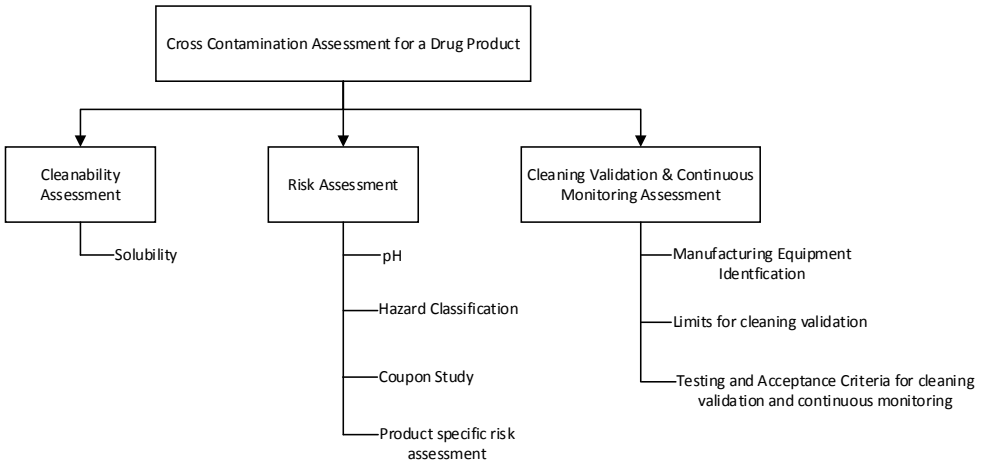
Risk factors associated with continuous process verification can be seen in **Figure 2.** A multifold approach is implemented to ensure that the cleaning process remains in validated state.

1. Automated cleaning processes are verified periodically through a cleaning verification run. Visual inspection and inline rinse monitoring are performed at the end of each cleaning event.

2. For manual cleaning processes (i.e., dedicated or nondedicated equipment) at the end of each cleaning event, cleaning is verified through visual inspection and rinse sampling for TOC to ensure there are no anomalies in the cleaning process.

3. All changes to equipment or manufacturing process flow are assessed for their potential to impact the cleaning process and these assessments are captured through change controls to ensure traceability. If cleaning validation/verification is to be executed on new equipment, a worst-case product and manufacturing condition that applies to the equipment is chosen, and the run is executed with rinse sampling for residual and microbial assessment and swab sampling for product specific residual assessment.

Figure 2 Cross-Contamination Assessment for a new Product



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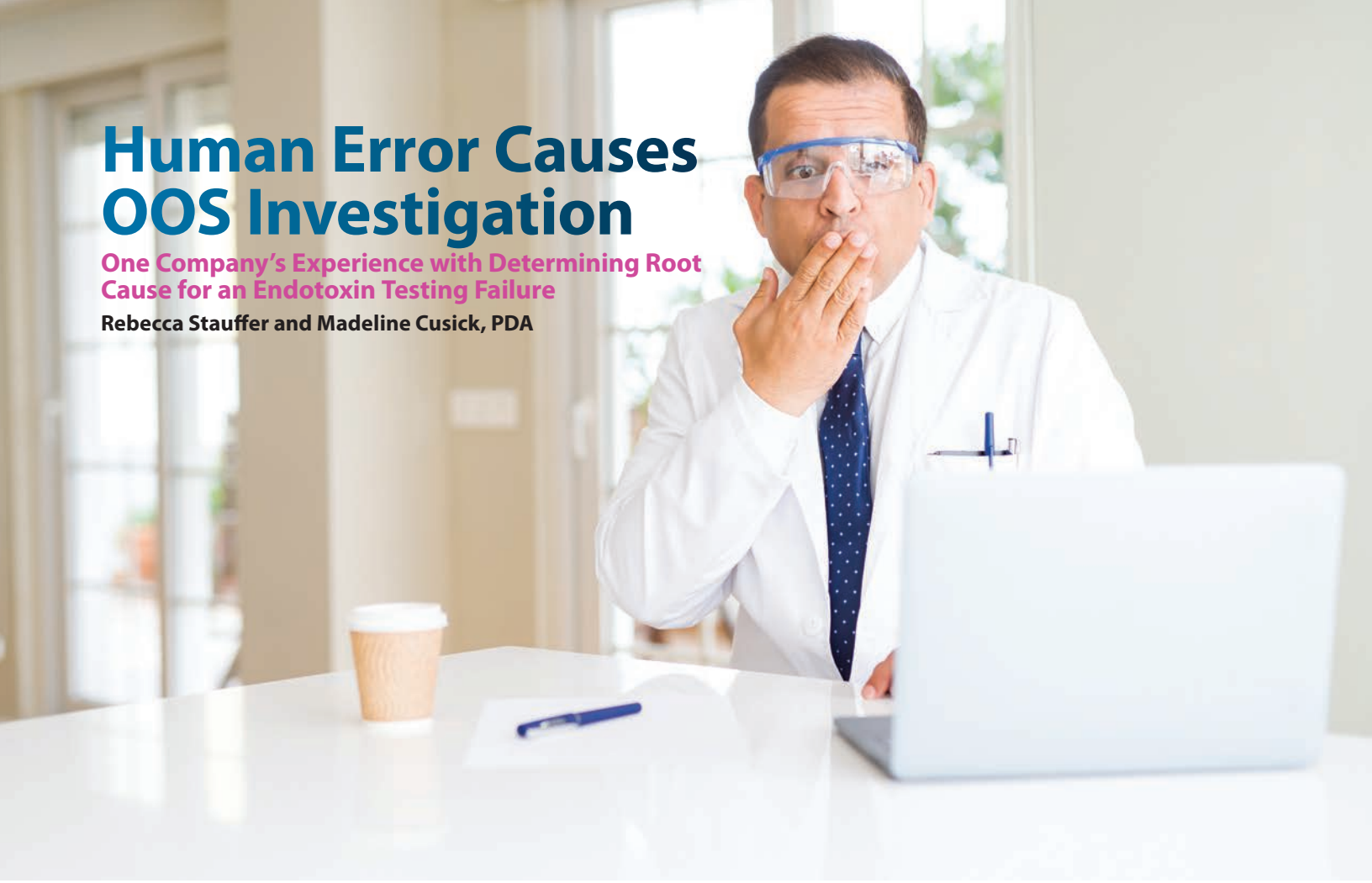

Human Error Causes OOS Investigation

One Company's Experience with Determining Root Cause for an Endotoxin Testing Failure

Rebecca Stauffer and Madeline Cusick, PDA

Testing failures are not unheard of in the industry. Routine samples that normally pass specification can, out of the blue, suddenly fail.

More often than not, the laboratory is cited as the cause of the failure. Yet sometimes these testing failures can be the result of a chain of simple human errors that do not even involve the lab at all.

Crystal Booth, Southeast Regional Manager for PSC Biotech, a consulting firm in the life sciences sector, saw just such an occurrence at a previous employer. The situation opened her eyes to how a set of human errors on the manufacturing floor led to a root cause investigation due to an out-of-specification (OOS) investigation involving routine endotoxin testing. She will describe this experience in more detail Oct. 21 at the *14th Annual PDA Global Conference on Pharmaceutical Microbiology* in Rockville, Md. ("Session B1: Solving Endotoxin Challenges – From Assay to Process Control Strategies," 10:15 a.m.).

For her, the experience highlighted the role of human error in endotoxin testing.

"With endotoxin assays, the two most common causes of invalidity are negative control and standard curve failures," she explained. "These can be lumped into a human error category most of the time. Failures come from dilution errors, pipetting errors, air bubbles in a pipette tip or testing well, selecting the wrong wells on the software, incorrectly making the standard curves, contaminated wells, contaminated supplies or contaminated reagents."

In this situation, a manufacturer used a raw material containing endotoxin. During production, an ultrapurification filter was supposed to remove the endotoxin in upstream manufacturing. Immediately after filtration, the microbiology lab would test a product sample for endotoxin.

"For the laboratory, it was a routine sample they had to test," Booth said. Once this result was reported, production would move to the next phase.

The testing always passed specification. Until one day it failed, triggering a multi-department investigation.

"In the end, it was simple root cause," she said. "A person made a mistake during maintenance and installed the filters incorrectly. Luckily, this was caught in-house, corrected and preventative actions were put in place."

The Person Behind the Machine

While the root cause might have been "simple," the implications to this unanticipated discovery were a bit more complex.

"We were fortunate to find the root cause so quickly and then realized how lucky we had been that it had never happened before," said Booth. "The filter housing had an arrow that showed where the product was supposed to run through the filter. But this was never explained or shown in any SOPs. One could assume the arrow should point with the flow of the product stream (which was the correct way) or point against the product stream." ➤

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Catching the reason behind the testing failures brought relief.

"When it's not a laboratory problem, the root cause becomes more difficult to find. So, when production actually found the problem, the atmosphere lightened and the attention turned toward fixing the issue," she explained.

The event also shed light on other ways that the risk of human error can be reduced with regard to testing failures.

"I think training and technique is always a good fix, but now they are coming out with better technology like portable test systems. These systems use cartridges where all of your standards are already loaded and ready to use. All you really need to do is dilute your sample and add it to the cartridge. But you need to be careful not to add air bubbles," Booth said.

Additionally, the issue with the inadequate SOP was addressed. One of the resulting CAPAs required updated SOPs that include drawings showing which way the filter is supposed to go—this is in line with current trends toward more visual, even multimedia, SOPs ***(1).***

Still, there were some surprises in the investigation, notably, what Booth termed "wacky" results from the portable test system and kinetic systems.

"The endotoxin was so high, it was difficult for the equipment to determine the positive product control percent recoveries," She pointed out. "We had to resolve this by dilution. Normally, endotoxin results pass specifications. We were also thankful to have a validated gel-clot method on hand to use and a trained analyst."

Want to learn more about endotoxin testing, OOS investigations and other critical aspects of microbiology? Attend the *14th Annual PDA Global Conference on Pharmaceutical Microbiology*, Oct. 21–23, in Rockville, Md.

www.pda.org/2019micro

> **"There has been a push for microbiologists to get out of the lab and spend more time on the floor"**

For root case analysis, she used an Ishikawa Diagram and the 5 Whys. Both were selected for three reasons: 1) to meet internal SOPs, 2) the complex nature of the investigation and 3) the ease of use of these tools for this investigation. The Ishikawa Diagram narrowed the root cause down to the machine (e.g., the filters were incorrectly installed). The 5 Whys tool, an iterative method that explores cause-and-effect relationships by repeating the question "Why?" five times, narrowed that root cause down even further to the maintenance technician who did not receive proper training.

Microbiologists Must Leave the Lab

As far as routine endotoxin testing, Booth stated that the laboratory used the kinetic turbidimetric assay to test multiple lots of product at one time. During the investigation, the portable test system was used to quickly screen product at multiple locations along the manufacturing product pathway. This system was not routinely used to test product in the laboratory because more lots could be tested simultaneously on the standard kinetic endotoxin machine.

"Due to the high volume of endotoxin present, kinetic and gel-clot assays were performed to confirm the results with multiple analysts repeating the test," she said.

Overall, this case served as a reminder that problems can arise from sources outside the laboratory. In recent years, there has been a push for microbiologists to get out of the lab and spend more time on the floor to hopefully catch such events earlier before they reach the stage of a testing failure ***(2).***

Booth agrees with this push. Visiting the shop floor is helpful for her as it allows her to see "what could go wrong, how to fix it and how to prevent it."

Overall, the investigation presented a number of key "lessons learned."

"The lessons that I learned were really how to properly investigate failures and the things that you need to look at other than the typical laboratory causes. When you explore the entire manufacturing process, it really opens up your eyes to how many things could cause failures. Those were some of my takeaways. Look at the holistic process including manufacturing equipment and maintenance operations. Do not just focus on the technique of laboratory technicians."

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1. Walson-Billin, C. "Leveraging Video to Improve Operations." *PDA Letter* 53 (March 2017) 30-33, 41.
2. Sykes-Winstead, L. "Aseptic Observation Program: A Shop Floor Program that Engages Quality and Operations to Assure Good Aseptic Technique." Presented at the 12th Annual PDA Global Conference on Pharmaceutical Microbiology, Oct. 17, 2017, Bethesda, MD.

About the Expert

Crystal Booth has over 20 years of experience in pharmaceutical microbiology, environmental monitoring and quality assurance. She has worked in microbiology, consulting, quality assurance, CDMOs, R&D and quality control laboratories.

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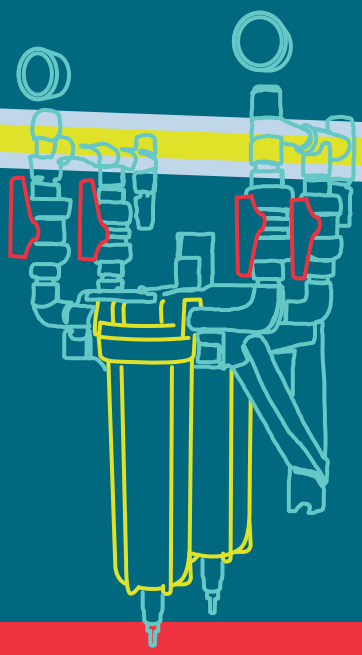
Endotoxin Control in Another Industry

Find Out How an Operating Room Improved Their Endotoxin Control

Endotoxin control is a major concern for pharmaceutical microbiologists. Did you know it is also an issue in operating theaters? A ten-year study of endotoxin-retentive ultrafilters used for reverse osmosis (RO) plants in an operating theater was highlighted last year in the *PDA Journal of Pharmaceutical Science and Technology*.

In March 2006, RO plants A and B were installed

In 2009, following a move of the alarming system, endotoxin increased by **0.301 mL in RO A** and by **1.446 in RO B**.



In March 2010, endotoxin retentive ultrafilters were installed on the two plants. By April of that year, endotoxin levels for both plants were below **0.025 mL**.

As of Sept. 2016, endotoxin levels remain low

Source

1. Uetera, Y., et al. "The Role of Heat-Tolerant Endotoxin-Retentive Ultrafilters (UFs) for the Remediation of Reverse Osmosis (RO) Plants Employed for Surgical Hand Antisepsis Using Periodic Thermal Disinfection—A Ten Year Longitudinal Experience Study in the Operating Theater." *PDA Journal of Pharmaceutical Science and Technology* 72 (2018) 420–437.

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Concerns About USP <1235> Revision

May 31, 2019

Dibyendu Saha, Ph.D.
12601 Twinbrook Parkway
Rockville, MD 20852-1790, USA

Reference to Correspondence Number – C204656
Proposed <1235> Vaccines for Human Use – General Considerations
USP 41 page 7795

Dear Dr. Saha:

PDA is pleased to have the opportunity to provide comments on the revised USP Informational Chapter <1235>, released for public comment on January 4, 2019. We recognize that the purpose of the proposed revision is to provide guidance on commonalities throughout the vaccine manufacturing process and have provided comments in line with the stated intent.

Our comments were prepared by an international group of expert volunteers with experience in vaccine regulation, development, and manufacture. The following pages present some concerns with the proposed revision overall, as well as a number of technical comments. These specific technical comments are organized by the draft update's section headings.

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. These comments were prepared by a committee of experts with experience in the practice of pharmacy and pharmaceutical manufacturing including members representing our Board of Directors, our Science Advisory Board, and our Regulatory Affairs and Quality Advisory Board.

If there are any questions, please do not hesitate to contact me.

Sincerely,
Richard Johnson
President, PDA
CC: Tina Morris, PDA; Joshua Eaton, PDA

PDA thanks the coleaders of the Vaccines Interest Group for working with the interest group on this set of comments

Jane Halpern, PhD, Independent Consultant

Sabrina Restrepo, PhD, Merck & Company

Lifecycle Approach Wipes Away Cleaning Validation Concerns continued from page 30

Conclusion

Aimed at robust product quality, safety and patient protection, a successful cleaning validation program requires a lifecycle approach. Multiple processes, tailored to suit facility design, technological opportunities available in each production line and variability of the product profiles are required to support an expanding product portfolio in a multiproduct facility. Risk assessments evaluate the cleanability and detectability of the product, leading to procedures that prevent cross-contamination among batches.

[Editor's Note: The online version has additional content**.]**

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3. Snee, R.D. "Building Blocks of Quality by Design." *IVT Network* (Jan. 24, 2013)
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5. *Technical Report No. 29 (Revised 2012): Points to Consider for Cleaning Validation*
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About the Author

Raji Vathyam has nearly ten years' experience in aseptic processing in pharmaceutical manufacturing including sterile injectable and medical devices.

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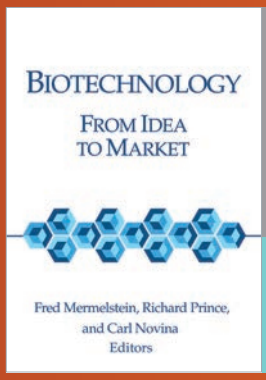

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Editors: Fred Mermelstein, Richard Prince, Carl Novina

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Why is the EU Medical Device Regulation So Critical?

Olivia Henderson, PhD, and Kesley Gallagher, Amgen

The new EU Medical Device Regulation (MDR) will impact not just CE-marked medical devices in the European Union but also drug/device combination products. Implementation of the MDR began in May 2017, with a three-year transition period ending May 26, 2020. All MDR CE-marked medical devices require recertification under the Regulation by May 2024. MDR has resulted in the reclassification of many medical devices and narrowing of the number of designated Notified Bodies (NBs) within the European Union. But how does this impact prefilled syringes and autoinjectors? Previously, these were never regulated as medical devices, per se. With MDR, the rules have changed, causing enormous concern within pharma.

Article 117 introduces extensive documentation content requirements for drug/device combination product marketing applications. Many applicants will need to retain an NB for the first time. Effected products include prefilled syringes, autoinjectors and needle safety devices. Given the widespread use of these products, this change will impact the submission approval process for new products along with currently marketed products that undergo any design change of the device constituent part.

Article 117 of the MDR will go into full effect May 2020 in the European Union. It is anticipated that the NB opinion will be based on a review of technical documentation maintained by the marketing authorization holder. The NB will review the device data and provide a Notified Body Opinion (NBOp) regarding the conformity of the device part with the relevant general safety and performance requirements set out in Annex I of the new MDR. What does this mean? For most pharmaceutical/biotechnology companies using these injection devices, this means hiring an NB to review device technical documentation *before submission to EMA.* The additional time required to obtain an NBOp has not been established.

But wait! There is more!

Under the MDR, all NBs are required to be redesignated under the stricter regulation. Fewer than expected NBs have applied for MDR designation, and, of those who have, many have withdrawn their applications. Essentially, there are far fewer NBs to do more work in the European Union.

This leaves many areas of uncertainty for the applicant. Who are the NBs? How will their opinions be communicated? How will

changes to combination products be evaluated? This topic will be discussed in greater detail at the *2019 Universe of Pre-Filled Syringes and Injection Devices.*

Disclaimer: The views expressed herein represent those of the authors and do not necessarily represent the views or practices of the authors' employer or any other party.

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Supporting the Quality Risk Management Framework

Active Learning, Key Opinion Leaders Highlight PDA Quality Week

Denyse Baker, AstraZeneca, and Steven Mendivil, Quality Beyond Compliance

Are you looking to learn the latest in quality risk management (QRM)? Do you want to know more about the role of quality culture in applying QRM?

The *2019 PDA Quality Week* will consist of three meetings that build on each other so that participants bring home a range of QRM knowledge. The first conference, *Risk Management in the Regulatory Landscape,* will provide a foundation on the role of quality culture in supporting QRM. This conference will be followed by the one-day workshop, *Building a Foundation and Culture for Quality Risk Management Integration.* The final two-day conference, *Optimizing Quality Risk Management,* will focus on implementing QRM programs within a quality management system.

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In addition to U.S. FDA CDER Director **Janet Woodcock,** who will kick off Quality Week, the program planning committee has invited a representative from the FDA's Office of Pharmaceutical Quality (OPQ) for updates on CDER's quality metrics program, the Inspectional Risk Program and how FDA uses QRM principles to prioritize patient safety. This will be an opportunity to hear about any outcomes from the two quality metrics feedback programs announced a year ago and what FDA has learned from them.

The second day of Quality Week will prioritize ICH Q9: *Quality Risk Management,* the foundation of the QRM systems used today. **Greg Claycamp** (formerly of FDA) and **Stephan Roenninger** (Amgen) have been invited to speak on the ten-year impact of ICH Q9 and discuss any plans to update it. Both were on the original ICH Q9 Expert Working Group and are knowledgeable about the latest plans for this important ICH guideline.

You will also have an opportunity to hear from key industry leaders on QRM. **Guy Villax,** CEO, Hovione, has been invited to kick off Wednesday's workshop with a talk on how to integrate QRM into assessing the broader risks a company faces.

Make your plans now to join us for an exciting week of learning and networking.

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Regulators, Compendia Eye Components

Rebecca Stauffer, PDA

Cathy Zhao, *PhD, Director of the Scientific Insights Lab, West Pharma, presented, "The Advantages of Considering Primary Container Systems as an Excipient During Formulation Development," on March 19, at the* Parenteral Packaging *conference in Venice earlier this year. The* PDA Letter *asked her a few questions about current regulations guiding packaging components.*

PDA Letter: What are the main regulatory and compendial concerns around packaging innovations? Are these holding companies back from implementation?

Zhao: The main regulatory and compendial concerns around injectable drug packaging innovations are the same as with general packaging. They include the suitability of protection, compatibility, safety, performance/drug delivery or any specific performance function built into the drug product for its intended use.

Regulatory guidance and compendial requirements should not hold companies back from implementation of innovations. The fundamental function of packaging is to ensure that medicines arrive safely in the hands of the patients for whom they are prescribed. The regulatory guidelines and compendial requirements set checkpoints that serve the same purpose. Protection, compatibility, safety and performance/delivery are the basic deliverables for packaging to accomplish its mission. A package cannot serve its purpose if it misses any of those four elements. Packaging innovations should include the regulatory guidelines and compendial requirements in design input from the beginning and use compendial tests as tools to check if the innovation is on the right track. In this case, regulatory guidelines and compendial requirements should be built-in characteristics of packaging innovations.

Want to learn more about regulatory and compendial requirements for packaging components? Consider attending the 2019 *Universe of Prefilled Syringes and Injection Devices*. To learn more and to register, visit www.pda.org/ups2019.

PDA Letter: Are there any major differences in the U.S. and EU compendial requirements for packaging?

Zhao: The differences between the U.S. and EU requirements for packaging are big questions. I can only try my best to address some major differences to the best of my knowledge. As I understand it, we are only talking about primary packaging for injectable drugs here. One point to note is that many current U.S. and EU chapters are under revision.

Starting from elastomeric closure components, the biggest difference is that USP <381> Elastomeric Closure for Injections requires USP <87> Biological Reactivity Tests, In Vitro and <88> Biological Reactivity Tests, In Vivo, as biocompatibility tests while neither Ph. Eur. 3.2.9 nor ISO 8871 covers biocompatibility. Although USP <381> and <382> Elastomeric Closure Functionality in Injectable Pharmaceutical Packaging/Delivery Systems and Ph. Eur. 3.2.9 share the same specifications on chemical/physical compendial testing, the specific testing methods are different. The proposed USP <381> includes elemental impurities testing; the proposed USP <382> requires testing for the fitness of intended use functionality requirements. With the anticipated changes that will occur with these chapters, as well as with their corresponding guidance chapters—<1381> Elastomeric Evaluation of Elastomeric Components Used in Pharmaceutical Packaging/Delivery Systems and <1382> Assessment of Elastomeric Closure Functionality in Injectable Pharmaceutical Packaging/Delivery Systems—we expect there will be an even greater difference from the European Pharmacopoeia.

For glass components, the major difference currently between USP <660> Containers—Glass and Ph. Eur. 3.2.1 is that the latter requires testing of hydrolytic resistance by flame atomic absorption spectrometry while USP <660> does not. USP <660> has been under major revision since 2016.

USP <1207> Sterile Product—Packaging Integrity Evaluation, provides guidance on container closure integrity leak test methods and qualification. Ph. Eur. does not address container closure integrity. Most of the global industry seems to now use USP <1207> Package Integrity Evaluation—Sterile Products as the standard.

PDA Letter: Is there a sense that regulators are willing to work with companies and suppliers to address concerns?

Zhao: Yes. I have been to conferences in which regulators are invited to present. They have explained the review process and strategies. U.S. FDA regulators usually encourage companies and suppliers to communicate with them as early as possible in the filing process.

About the Expert

Cathy Xia Zhao, PhD, has over 15 years of experience in the medical/pharmaceutical industry. She is currently the Director of Scientific Insights Lab in West Pharmaceutical Services, Inc.

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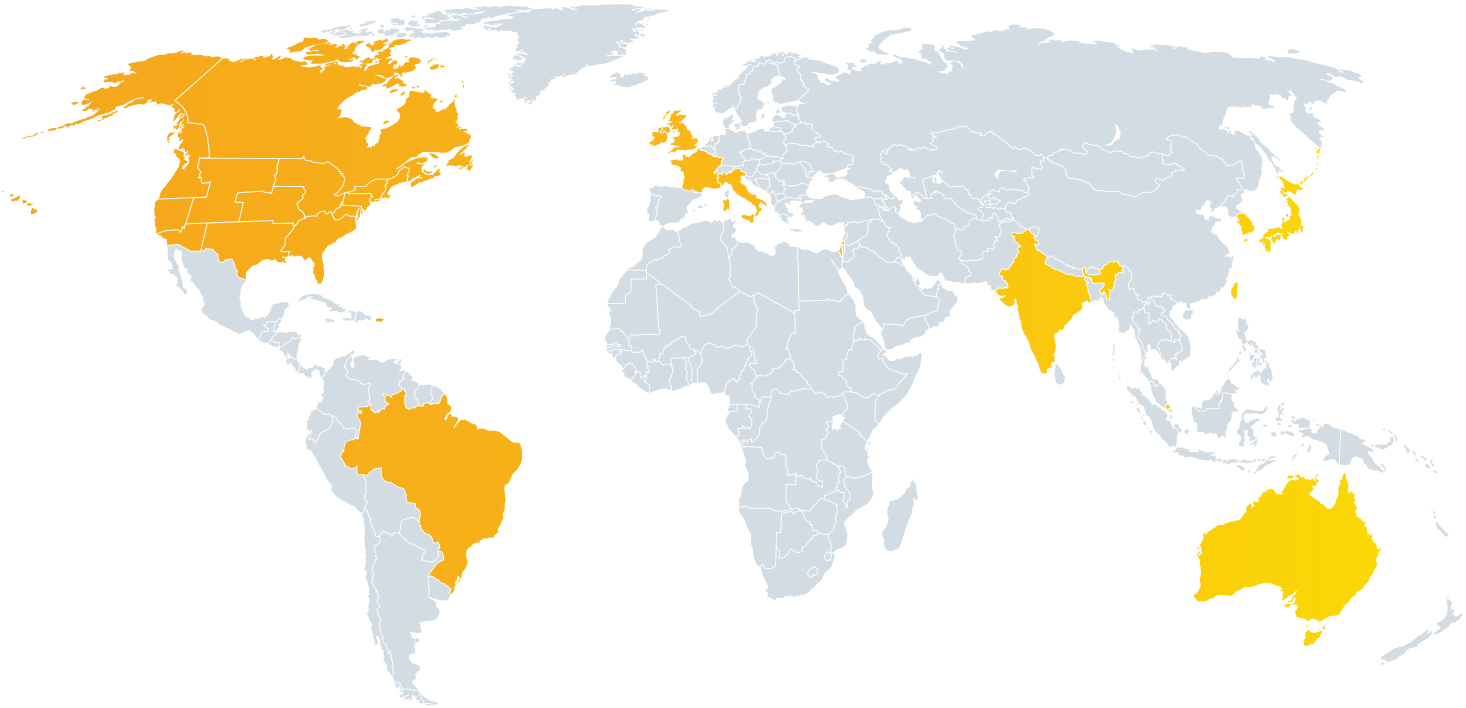
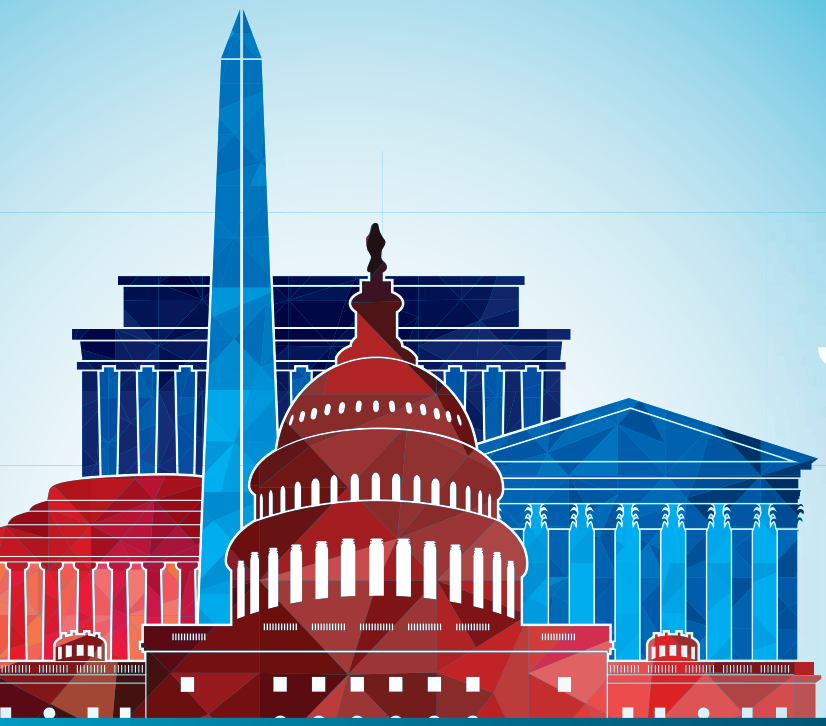
Each of the chapters is led by a locally elected Board of Directors who follow PDA's chapter handbook. This handbook also contains a helpful summary of recommendations based on lessons learned over the years. The president of each chapter is a member of the Chapter Council which meets monthly and is chaired by **Trevor Swan**, PDA's Director of Membership, who has done a fantastic job strengthening collaboration to drive success across the chapter network. I have been fortunate to participate with the council and am truly inspired by this exceptional group of leaders with their strong dedication to PDA's mission and to providing value to members.

Chapters host a wide variety of regular events that include opportunities for networking. The most common format is a dinner meeting featuring a speaker or panel, although all-day events focused on a specific topic, such as pharmaceutical microbiology, occur as well. Other chapter events are devoted exclusively to "kicking back" with industry colleagues in comfortable settings (e.g., picnics, sporting events, dinner cruises, etc.).

I strongly encourage all PDA members to take full advantage of the benefits offered by participating in their local chapters. If you are interested in learning more about your local PDA chapter or how to get involved, visit www.pda.org/pda-chapters.





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