People • Science • Regulation

PDA Letter

Volume LIII • Issue 2 www.pda.org/pdaletter February 2017

Changing Currents

26

The Parenteral Drug Association presents the...

2017 PDA Pharmaceutical Quality Metrics and Quality Culture Conference

February 21-22, 2017 | Bethesda, MD

Bethesda North Marriott Hotel & Conference Center

#2017Metrics

REGISTER NOW!

Next Steps: Using Quality Metrics to Advance Quality Culture

The U.S. FDA recently released its revised Quality Metrics draft guidance. The *2017 PDA Pharmaceutical Quality Metrics and Quality Culture Conference* provides the *first opportunity* to hear directly from the FDA about the changes to and implications of the revised guidance as the collection and use of metrics to enhance pharmaceutical product quality moves from theory to practice.

Industry and regulatory experts will take an in-depth look at the new guidance, the benefits to industry and patients and potential challenges to implementation across various segments of the pharmaceutical industry. Key topics to be addressed include:

- FDA Update on the Reissued Quality Metrics Draft Guideline
- Analytical Approaches
- Implementation Approaches
- Quality Culture and What We Are Learning as an Industry
- What Moves the Needle for Maturing Quality Culture?
- Assessing Quality Systems and Quality Culture

Don't miss out on this unique opportunity to join the conversation on the latest developments in quality metrics and quality culture!

Be one of the first to secure your spot –

Register now at pda.org/2017Metrics

February 2017 PDA Letter

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InfoGraphic

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Departments

Digital Exclusives

> China FDA Taking Closer Look at Clinical Trial Data
In November, the Chinese FDA announced plans to inspect clinical trial sites for 30 products. What does this mean for data integrity in the country?

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The Parenteral Drug Association presents the...

2017 PDA Annual Meeting

Innovation in Manufacturing Science and Technology

April 3-5, 2017 | Anaheim, California

Anaheim Marriott

Exhibition: April 3-4 | 2017 Cell and Gene Therapy Workshop: April 5-6 | Courses: April 6-7

#PDAAnnual

Register by February 17 and save up to $200!

Conference Theme: *Manufacturing Innovation: The Next Wave of Sterile and Biopharmaceutical Science, Technologies and Processing*

In the age of personalization, the emerging fields of immunotherapy and gene- and cell-based therapies offer considerable promise in bringing personalized treatments to the forefront of medicine. At the *2017 PDA Annual Meeting*, a number of presentations will address how the industry can bring these innovative treatments to patients.

Hear from a mix of industry and regulatory experts, including:

- **Ursula Busse, PhD,** Quality Intelligence & External Relations, *Novartis*
- **Patricia Hughes Troost, PhD,** Team Leader, Biotech Manufacturing, *FDA*
- **Sau Lee, PhD,** Deputy Director (Acting), Emerging Technology Team Chair, OPQ, *FDA*
- **Emma Ramnarine,** Head, Global Biologics Quality Control, *Genentech, A member of the Roche Group*
- **Karen Walker,** Global Head of Technical Development & Manufacturing, Cell and Gene Therapies Unit, *Novartis Pharma Corp.*

And don't miss the Exhibit Hall, where participants can meet one-on-one with service providers and vendors showcasing the latest in services and technologies in this emerging field.

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

Following the Meeting, on **April 5-6**, PDA will offer the *2017 PDA Cell and Gene Therapy Workshop* to provide a more in-depth look at how these new therapies will impact the industry. Learn more and register at ***pda.org/2017CGT.***

On **April 6-7**, PDA Education will be hosting five courses as part of the *2017 PDA Annual Meeting Course Series* to help you further advance your knowledge. Learn more and register at ***pda.org/2017AnnualCourses.***

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PDA EUROPE INTEREST GROUP MEETING
13 March 2017
PRE-FILLED SYRINGES

The Parenteral Drug Association presents:

PDA Europe Conference, Exhibition

Parenteral Packaging

13 March
Secondary Packaging

13 March
Elastomers

16 March
Container Closure Development

16-17 March
Container Closure Integrity

16-17 March
Extractables and Leachables

16-17 March
Track and Trace – How to implement Pharma Serialization, Tamper Evidence and the EU-Falsified Medicines Directive

Register by 14 Feb 2017 and SAVE!

14-15 March 2017

Barcelona | Spain

pda.org/eu-parpack-2017

PDA and *PDA Letter* uPDAtes

First, the changes at PDA. The "News and Notes" section of this issue (p. 9) highlights the recently completed expansion of PDA Education's Bethesda-based Training and Research Institute (TRI). As the article notes, this expansion adds capacity to provide more hands-on training for those students participating in PDA's aseptic processing courses. PDA Education's popular "Aseptic Processing Training Program" launched in the 1990s when TRI was first founded at the University of Maryland, Baltimore County. The demand for this two-week, hands-on training has only grown since then, and the new 400 ft^2 ISO 8 cleanroom will help PDA meet that demand.

The *PDA Letter* starts the year with a big change as well. **Rebecca Stauffer** is now the *PDA Letter's* Managing Editor. Over the past 4+ years, Rebecca has steadily taken over a large part of the responsibility for acquiring content for each issue. She has not only managed the entire editorial process, including working directly with all volunteer and PDA staff authors, but she has also overseen the *PDA Letter* Editorial Committee (PLEC), the all-volunteer group responsible for reviewing article submissions and developing the editorial calendar. Her hard work and strong skills as an editor have allowed me to focus on other responsibilities involving our technical reports, books and press relations without worrying about a decline in the Letter's quality.

In addition, the PLEC has new faces as several of our members' terms expired in 2016. We extend our thanks to **Anne Connors, Sy Gebrekidan, Youwen Pan, Cecilia Turoff,** and **Tricia Vail** for their two years of service to the community. We also look forward to the contributions of **Sharon Ayd, Claire Briglia, Christine Bui, Valeria Frigerio-Regazzoni, Stephan Krause, Mina Mitry,** and **Lan Zhang** who join the PLEC for the next two years.

If that's not enough change, PDA's editorial team will also be overseeing a new electronic news feed, the "news uPDAte," generated by our new partner, InLoop. We began work with InLoop in the fall, with staff developing a beta website and helping train the system to gather the news most relevant to the PDA community. We welcome all PDA members and nonmembers to check out the beta website and read news stories of importance to them (keep in mind that the look and feel of the site will change as we move to the final version):

www.pda.myindustrytracker.com/en/top

Very soon, readers will be able to customize the newsfeed into categories by creating an account with InLoop. In addition, a weekly news email will go out later this year. The service also includes an electronic buyer's guide which features listings of over 500 vendors relevant to PDA's community.

2017 will be an exciting year of expansion and change for PDA and the *PDA Letter*!

Walter Morris

FDA Extends Metrics Deadline Per PDA Request

The U.S. FDA announced in January it is extending the commenting period for the revised guidance document, *Submission of Quality Metrics Data*. Originally, the commenting period was slated to close Jan. 24; now it closes March 27.

PDA was one of several organizations urging FDA to extend the deadline for comments. Currently, a PDA commenting task force is drafting a set of official PDA comments on the revised guidance.

To offer your input on the guidance, consider attending the *2017 PDA Pharmaceutical Metrics and Quality Culture Conference,* Feb. 21–22, in Bethesda, Md. Those planning to attend can also submit questions for discussion via the website for the meeting: www.pda.org/2017metrics.

Call for Volunteers

PDA is looking for volunteers fluent in Danish and Hungarian to translate a 30-question site survey as part of PDA's Quality Culture Assessment Pilot. The survey will be distributed to international manufacturing sites. If you're interested, email PDA's volunteer coordinator at volunteer@pda.org.

PDA Adds ISO Class 8 Cleanroom to TRI

Expansion Includes Additional Classrooms, Larger Gowning Room, and Modular Cleanroom

PDA has completed a six-month expansion of its Training and Research Institute (TRI) in Bethesda. The expansion will permit PDA Education to increase its capacity for hands-on aseptic processing and lecture-based training at TRI.

The centerpiece of the buildout is a new 400 ft^2 ISO Class 8 cleanroom that will house an isolator filling system. The cleanroom is enclosed by modular walls from Servicor and the air is processed with a HEPA air system.

"The hands-on aseptic processing instruction offered in an industrial setting at the Training and Research Institute is a critical component of PDA's educational program," said **Craig Elliott,** PDA Vice President of Education. "PDA Education's 'Aseptic Processing Training Program' provides an in-depth experience with the technologies associated with the manufacture of aseptically produced products, and now we have the capacity to train even more professionals each year."

PDA's aseptic processing program is highly valued and effective. "We've seen a dramatic increase in training demand recently, particularly from US regulators. Last year PDA trained over 300 U.S. FDA personnel, but could not keep up with the increasing demand. This new capacity will allow us to meet the needs of the industry and the demand from regulators around the world," said Elliott.

PDA leads the pharmaceutical/biopharmaceutical industry in developing technical information and training in the areas of sterile drug manufacturing, aseptic processing, and other areas related to the manufacture and distribution of parenteral drug products.

PDA Volunteer Spotlight

Bettine Boltres, PhD

- Product Manager, Pharmaceutical Tubing
- *SCHOTT AG*
- Member Since | **2011**
- Current City | **Mainz, Germany**
- Originally From | **Frankfurt, Germany**

Go out and get to know as many people as you can

Bettine received the PDA Distinguished Service Award last year

What is it like to teach a PDA Education course?
I naturally enjoy teaching, so this has been a great experience. I enjoy exchanging knowledge with my audience and giving them something they can then use in their daily work life. I always try to create an atmosphere for mutual discussion where people feel free to share their experiences and find out that they are not alone.

How has PDA contributed to your career?
It led to USP inviting me to join its Expert Committee responsible for general chapters on packaging and distribution. PDA gave me the connections to get onto this committee. So far, this has been my biggest success!

What is the most valuable professional advice that someone has given you?
Go out and get to know as many people as you can. Exchange experiences and knowledge with anyone who crosses your path. Build relationships with your industry colleagues. This brings you a long way, and PDA's conferences create the perfect platform for this!

What current industry topic interests you?
Coming from the materials side, I am interested in the different materials being used for primary packaging and how they are developing.

What do you expect from the industry in the next few years?
I expect to see a more intensive relationship between pharmaceutical companies and their suppliers. I also think the trend is moving away from statistical quality control to a more trusting relationship based on process capabilities.

What are a few of your favorite ways to pass time?
I love travelling. I am fortunate enough to travel for my job. But I also love to travel the world on my own vacation time to see and get to know different places, people, and cultures.

Tell us a surprising fact about you.
Once, I went cage-diving and found myself eye-to-eye with a great white shark!

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2017 PDA Europe Training Course

An Introduction to Visual Inspection

– A Hands-on Course

22 – 23 March 2017

Berlin Marriott Hotel

Berlin | Germany

pda.org/EU/tcvisual2017

Chapter Gets Hands-On Cold Chain Experience

Rebecca Stauffer, PDA

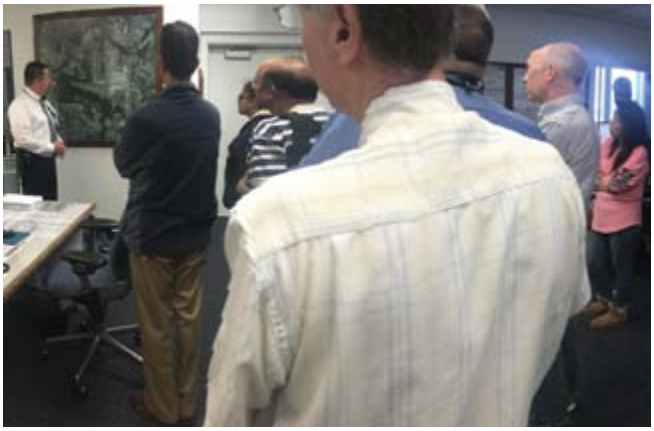
On Oct. 4, 23 members of PDA's Capital Area Chapter visited Dulles International Airport near Washington, D.C., to tour United Cargo's cold chain facilities. There, they learned first-hand from representatives of United Cargo and temperature-controlled container supplier, Envirotainer, how pharmaceuticals are managed in transit.

First, attendees were guided through airport operations, visiting the ramp tower for an aerial view of the airport, followed by hands-on experience preparing a pharmaceutical cold chain shipment for a Washington-to-Tokyo flight. As part of the exercise, everyone had a chance to climb into the cargo pit of a United 777 aircraft.

After a tour of United Cargo's warehouse and TempControl Center, the participants sat down to view presentations. **Mary Tussing** discussed United Cargo's TempControl service. This is a global network of facilities and monitoring systems specifically for temperature-controlled products. The network maintains hubs across the United States; the facility at Dulles features a dedicated control tower with 24/7 oversight and end-to-end management of all pharmaceutical shipments. All TempControl shipments have an individual SOP overseen by United's TempControl Tower. Next, Dulles' **Joe Maly** discussed airport cold chain operations.

And finally, Envirotainer's **Stephen Winyard** presented on the data requirements for GDPs.

All of the participants enjoyed the opportunity to learn more about cold chain operations at Dulles, and even had fun in the process, as evidenced by photos from the event! **[**For more photos of the event, visit the PDA flickr page: www.flickr.com/photos/parenteral-drug/albums/72157674354836051**.]**



Chapter members eagerly learn about temperature control processes for pharmaceuticals at Dulles International Airport

"Washington Dulles International Airport was very happy to host PDA's Capital Area Chapter and provide a behind-the-scenes look at airport and cargo operations. In cooperation with our strong airline partner, United Cargo, we demonstrated the cargo operations at an international airport and showcased the handling of temperature-controlled commodities," said Maly. "In the past few years, pharmaceutical products have become the largest valued imported commodity at…Dulles …and much of this is due to the success of our partner, United Cargo."

"We were thrilled PDA invited us to host this day of learning for the local pharmaceutical community," added United's **Krisha Kucharski.** "The guests seemed to enjoy the day from beginning to end with many pictures taken to document the behind-the-scenes tour. United would love to continue our engagement with the PDA Capital Chapter and we look forward to participating in future events."

The Capital Area Chapter is planning similar events in the future. Many thanks to United Cargo, Envirotainer, and the Metropolitan Washington Airports Authority for their support of this event.

Members of the Capital Area Chapter pose in front of a Boeing 777

PDA Who's Who

Krisha Kucharski, Manager, Product Development and Marketing, United Cargo

Joe Maly, Head of Air Cargo, Metropolitan Washington Airports Authority

Mary Tussing, Manager, Specialty Sales & Business Development, Cargo, United Cargo

Stephen Winyard, Industry Expert, Pharma Cold Chain, Envirotainer

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2nd PDA Europe Annual Meeting

Education Program

12 June
Cleaning & Disinfection

12 June
Supply Chain Strategies for API and Drug Product

12 June
Quality by Design for Biopharmaceuticals

15-16 June
Introduction to Aseptic Processing Principles

Register by 13 May 2017 and SAVE!

13-14 June 2017

Hilton Berlin

Berlin | Germany

pda.org/eu-AnnualMeeting2017

Chapter's Media Fill Workshops a Resounding Success

Ivy Louis, Vienni Training and Consulting LLP, and India Chapter President-Elect

Since its inception, the PDA India Chapter has been a leading facilitator of science, technology and regulatory information for the Indian pharmaceutical community, relentlessly creating awareness and understanding of the important issues facing this market. In 2016, the chapter expanded these efforts with three workshops on media fills, an important topic for members.

The chapter organized the workshops in different cities/regions to ensure representation across the country. The primary purpose of these workshops was to introduce participants to the basics of media fills, with the goal of enabling them to evaluate and design a media fill strategy. The chapter also wanted to bring together professionals associated with the pharmaceutical and biopharmaceutical industry, including service providers, suppliers, and regulators, for in-depth discussions. All in all, participants learned different ways from each other to deal with the challenges of conducting media fill runs.

The panelists in Pune take questions from attendees

(l-r) Deepak Kasbi, Lupin Pharma Limited; Kumar Nanavati, Sun Pharmaceuticals; K. Anand, Qualiminds Corporate Services; Pinkal Dave, Sun Pharmaceuticals; Vishal Sharma, VIENNI Training & Consulting LLP

The first workshop was held May 6 in the southern Indian city of Visakhapatnam with 45 participants. Interestingly, the participants for this workshop were nearly evenly split between those working with traditional parenteral products and those working with biotech products. The second workshop occurred on Aug. 30 in Pune—India's pharma-dense western region. Again, 45 participated in the workshop, including participants from the cities of Mumbai and Aurangabad. The final media fill workshop was held Nov. 29 in New Delhi with 60 attending, including representatives from India's Central Drug Standard Control Organization (CDSCO).

The highlight of the final event was the participation of senior management personnel and leadership from various organizations.

The participation of the CDSCO staff in attendance added a whole new dimension to the event. Of the three workshops, this one truly helped the India Chapter reach a wide variety of participants. Due to the large number of attendees, participants had to be placed in clusters of small groups to ensure that all involved participated in discussions.

Ultimately, participants enjoyed the small size of the workshops, which enabled livelier discussions and ensured everyone's questions were addressed. Participants also expressed that the format is a good platform for cross-organizational learning.

Buoyed by the enthusiasm and level of discussion expressed in these workshops, the India Chapter plans to host a similar workshop series directed at those working with vaccines and biologics, beginning with a two-day workshop this March in Pune.

The chapter thanks the following sponsors for supporting the media fill workshops: Becton Dickinson India, Aptar Pharma, West Pharma, Grover International, and Merck Life Sciences Pvt Ltd.

PDA Photostream www.flickr.com/parenteral-drug

Post-Approval Change: Innovation for Availability of Medicines (PAC iAM) Technical Report Team

January 5 | PDA

PDA's Post-Approval Change: Innovation for Availability of Medicines (PAC iAM) technical report team met to further hone the upcoming PDA technical report covering post-approval changes. During this all-day meeting, the group broke off into subgroups to brainstorm and discuss specialized sections of the document.

(Back l-r) Joseph McCall, Bausch & Lomb; Walter Chambliss, University of Mississippi; Morten Munk, NNE Pharmaplan; Anders Vinther, PhD, Sanofi; Kassidy Polk Good, Mylan; José C. Menezes, 4Tune Engineering; Mihaela Simianu, PhD Pharmatech Associates ; Gresham Weatherly, AbbVie; Karolyn Gale, Emergent BioSolutions; Kara Follmann, Pfizer
(Front l-r) Marazban Sarkari; Teva; Chandra Kasireddy, Pharmaceutics International; Jyoti Sachdeva, Mylan; Lois Atkins, Eli Lilly; Emma Ramnarine, Genentech/Roche; Shishir Gadam, Genentech; Denyse Baker, PDA; Gopi Vudathala, GlaxoSmithKline; Beatrix Metzner, Boehringer-Ingelheim; Kim Wolfram, Biogen; Suzanne Kiani, Mylan

Team members responsible for the materials portion of the technical report met separately (l-r) Kara Follmann; Gopi Vudathala; Walter Chambliss; Jyoti Sachdeva

The members responsible for the Equipment section discuss their part of the document (l-r) Karolyn Gale; Suzanne Kiani; Joseph McCall; Gresham Weatherly, Chandra Kasireddy; Maik Jornitz; Shishir Gadam

Team members responsible for the narrative of the technical report listen intently to Mihaela Simianu while Morten Munk (standing) looks on

(l-r) Morten Munk, Mihaela Simianu; Marazban Sarkari; Lois Atkins; Beatrix Metzner; José C. Menezes

Not Pictured: Barbara Jentges; Rebecca Devine; Lisa Skeens; Srinivasan Raman; Lou Zaczkiewicz; Brian Mullan; Lorenz Liesum; Mike Yelvigi; Amanda Bishop McFarland; Marcello Colao; Karen Zimm; James Sayer

Three Surefire Ways to Impress a Hiring Manager

Joshua Waldman, Career Enlightenment

I'm learning how to hire. My business is growing and I recently needed to hire a new customer service rep. So, I got a book on interviews and read some articles online.

Every HR expert seems to have their own strongly-held-to opinion about the best questions to ask, and what to look for in a candidate.

So I tried out three of these "must-ask" questions that I read about for my series of interviews. After the third interview, I realized that the questions I was asking weren't as important as simply knowing three important things about a candidate.

When going into a job interview, make it your No. 1 goal to be sure your interviewer knows these three things about you, even if they don't ask directly.

1 Can You Be Trained To Do the Job?

I am building a new process for handling clients. My new customer service rep will be part of developing that new process. So I can't just ask them, "Can you do this?"

I really need to know if they can learn my way of doing things using my software.

The best answer I received was from my second candidate who recounted a story from her last job. There, she'd observed the chaotic nature of her boss. After a few weeks of chaos, she built a system to help keep him, and the business, more organized.

I'd rather hire that experience than someone who simply knows how to handle an angry customer (which is also important, but can also be trained). I needed someone trainable and flexible.

2 Do I Even Like You?

One of the must-ask questions I read about was, "If you had a superpower, what would it be? Why?"

I asked all of my candidates. Many of them wanted to be invisible. Not a fan!

One laughed at my question (good sign!) and then asked me the question back (another good sign!).

I told her I would like the ability to fly. She said, "That's a good one. I think I would teleport. I like to travel but don't like waiting for visas."

This one conversation stood out to me because it wasn't a one-word answer. There was some humor and character. She showed personality and I like that.

If I were to hire her, I'd have to get along with her. I'd also rely on her to give me feedback I might not want to hear.

3 What Really Motivates You?

Anyone can BS a job interview. I know. I've done it many times!

What happens six or 12 months later? Are you still as peppy as you seemed that first day?

In my recent interviews, I distinctly looked for candidates who could show me they liked what they did and had every intention of keeping up that energy for a long time. Sure, I'm just offering them a job. They don't have to live and die for it, but some amount of interest would be nice!

One candidate's passion for building desktop computers alone was a red flag. He spends his free time at a very individual task. Even as an introvert myself, I still like to be with people, be it friends or family.

Another candidate, on the other hand, showed excitement when talking about interesting conversations he'd struck with random people during his vacation holidays.

I'd definitely go for the person excited about random conversations for my customer service job!

Answer These and Ace the Interview!

Keeping these three questions in mind and trying to answer them during a job interview is going to help you land meaningful work.

But, if you can answer these questions BEFORE you sit down for an interview, you're one step ahead. Not only will you land more interviews, but your interviewer will be more at ease with you. The trick is to make sure your LinkedIn profile and other social networks also answer these questions.

About the Author

Joshua Waldman, author of *Job Searching with Social Media for Dummies,* is the founder of Career Enlightenment, which offers professional LinkedIn profile writing services and career advice for the modern jobseeker.

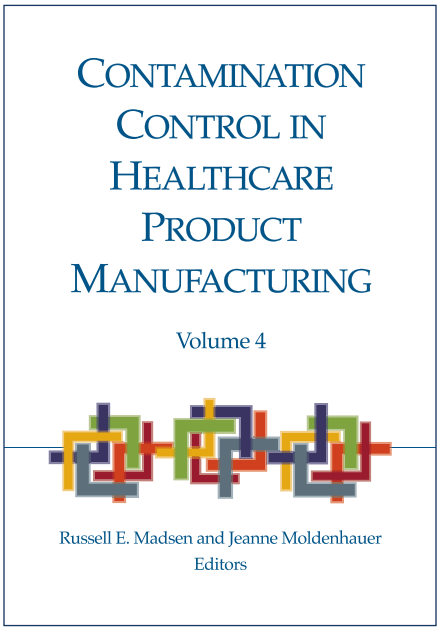
SNAPShot

InPrint

Water Types and Microbial Contamination/Biofilm Generation

Walid El Azab, STERIS

The following is excerpted from the chapter, "Investigation of Microbiological Contamination in Water Systems: A Case Study," from the PDA/DHI book, Contamination Control in Healthcare Product Manufacturing, Volume 4, *edited by* ***Russell E. Madsen*** *and* ***Jeanne Moldenhauer.***



Water Types

Different types of water are used in pharmaceutical, medical device and cosmetic manufacturing. The water type depends on the process and product quality steps. Water used as an excipient should meet the final product quality specifications. Water quality used in the final rinse steps of the cleaning process should be at least equivalent to the quality of water used for production. Therefore, for non-sterile products, the water quality at the rinse step will vary from potable to highly purified water

(HPW) quality. For sterile products, the water will be at least "water for injection" (WFI) or sterile WFI.

The United States Pharmacopeia (USP) identifies eight types of pharmaceutical grade water. The European (EP) and Japanese (JP) pharmacopeia identify five types of pharmaceutical grade waters.

The quality of pharmaceutical grade water will depend on the water system design. To achieve purified water grade, the design of the water system can include some of the following modules: a pre-filtration system with activated carbon, a filtration membrane with porosity >10 µm, a softener, a reverse osmosis process, an Ultra Violet (UV) lamp, a filtration membrane with porosity between 1 to 0.2 µm, a UV lamp and/or microfiltration. Depending on the country regulation, if the manufacturer wants to achieve the quality level of "water for injection," the design will have to include a distillation unit, reverse osmosis or an ultrafiltration module coupled with a filter.

Microbiological Contamination and Biofilm Generation

Poor design or maintenance of water systems can ultimately lead to the water quality attribute not conforming to specifications. There are two sources of microbial water contaminations — intrinsic and extrinsic:

- Intrinsic contamination examples:
  - system design such as the presence of dead leg, high surface roughness, and inadequate slope
  - high bioburden level present in the water system

- Extrinsic contamination examples:
  - intervention methods or changes or addition of a module to the current system
  - sampling methods
  - preventive maintenance leading to rouge or module inefficiencies
  - sanitization/sterilization procedure in place and in use

Detection of microbes in the water may be acceptable depending on the species found and the product quality specification and administration route for the final dosage form. Pharmacopeia specification limits are available for various dosage forms. Therefore, the water system must be designed and maintained to keep cells in a planktonic state and to avoid cell surface agglomeration to form biofilm.

Biofilm generation can be influenced by several factors. Biofilms are considered as a surface aggregation of microorganism surrounded by an extracellular polymeric substance (EPS) in surface contact water. The initial EPS is created by the "pioneer" bacteria fixed to a surface (Stainless steel, glass, plastic, etc.). The EPS developed by the microorganisms will trap nutrients, other microorganisms, and protect the bacteria from biocides. One of many types of ways biofilm can spread is by releasing new "pioneer" cells to colonize downstream sections of piping. Biofilm is generally associated with Gram-negative bacteria. However, some Gram-positive microbes, yeast, mold, mycoplasma and bacterial endospores can also be trapped in the biofilm matrix. Microbiological contamination above internal manufacturer alert limits can reflect the presence of biofilm in the water system due to a release or desorption from the biofilm matrix.

Really Get to Know Your Water System

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Journal TOC

January/February Issue of PDA Journal Includes Commentary on Disinfectant Testing

David Shields, Carol Bartnett, and **James N. Polarine, Jr.,** offer their perspective on the challenges of testing disinfectant effectiveness in the latest issue of the *PDA Journal of Pharmaceutical Science and Technology* (journal.pda.org).

Research

Alberto Biavati, et al., "Complexing Agents and pH Influence on Chemical Durability of Type I Molded Glass Containers"

Tobias Werk, et al., "A Method To Determine the Kinetics of Solute Mixing in Liquid/Liquid Formulation Dual-Chamber Syringes"

Bryan L. Yu, et al., "Kinetic Modeling of the Release of Ethylene Oxide from Sterilized Plastic Containers and Its Interaction with Monoclonal Antibodies"

Steven J. Novick, Wei Zhao, Harry Yang, "Setting Alert and Action Limits in the Presence of Significant Amounts of Censoring in Data"

Marcel Goverde, Julian Willrodt, Alexandra Staerk, "Evaluation of the Recovery Rate of Different Swabs for Microbial Environmental Monitoring"

Peter Stärtzel, "The Application of Amino Acids in Freeze-Dried Protein Formulations"

Roland Guinet, et al., "Multicenter Study on Incubation Conditions for Environmental Monitoring and Aseptic Process Simulation"

Technology/Application

Yasser Nashed-Samuel, et al., "Development of Conductivity Method as an Alternative to Titration for Hydrolytic Resistance Testing used for Evaluation of Glass Vials Used in Pharmaceutical Industry"

Commentary

David J. Shields, Carol Bartnett, James N. Polarine, Jr., "Disinfectant Effectiveness Testing Challenges"

2016 Universe of Prefilled Syringes

A New Process for Reducing Glass Breakage

Mads Reedtz Espersen, Novo Nordisk

Glass breakage is commonly acknowledged as a major nuisance in parenteral manufacturing. Depending on when it occurs in the glass lifecycle, it causes a plethora of problems, such as disruption of production flow, particle contamination and loss of sterility, to name a few.

Even though glass is a material known since ancient times, it still puzzles people, giving rise to erroneous theories and stances—everybody has an opinion on glass breakage!

Contrary to popular belief, glass does not accumulate stress. Stress arises in the glass when it is subjected to external loads and disappears again immediately when the external load is removed. Glass breakage always requires both the presence of a flaw and tensile stress.

And glass strength is determined by the properties of its flaws only—it is not a material constant. Flaws in glass are intrinsic and inherent from the manufacturing process as well as extrinsic—acquired during the entire lifecycle—primarily due to glass-to-glass contact. In other words, glass is weakened throughout the manufacturing processes due to infliction of new flaws. If a glass container is subjected to a load outside the normal load range, or the container is significantly weakened by a defect, it will break and a root cause can be assigned, and is, therefore, "special cause" and the outcome of a deterministic model.

If the load is within the normal load range and the container strength is within the Weibull Modulus (a parameter used to measure variation in the strength of brittle materials), breakage can appear where there is an overlap between the two (see **Figure 1**), and therefore "normal variation breakage" and the outcome of a probabilistic model.

It helps to characterize and rank all the manufacturing processes one-by-one on how much each contributes to the risk of glass breakage. **Figures 2–3** illustrate how Statistical Analysis Software (SAS) can calculate the differences between the two populations (before the process and after the process). The example is generic and can be applied to all glass breakage events.

A Review of Deming

First, understanding glass breakage requires a review of Deming, who said that the key to knowing variation lies in understanding that everything that is measured includes **normal** variation from a

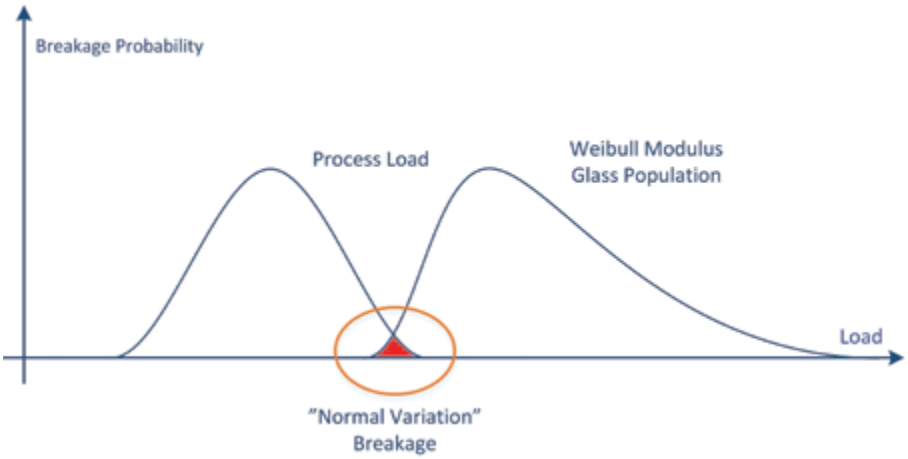

Figure 1 Overlap of Process Load and Weibull Modulus Creating Normal Variation Breakage

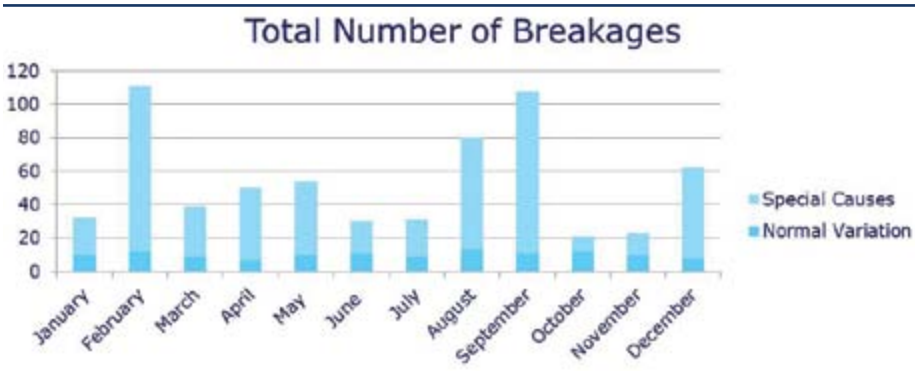

Figure 2 Aggregated Number of Breakages

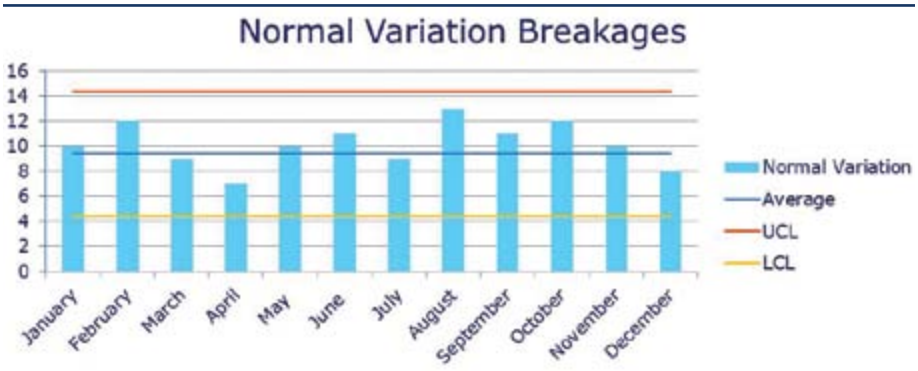

Figure 3 Normal Variation Breakages Shewhart Control Chart

system's flexibility as well as **special causes** that result in defects. Achieving quality requires eliminating **special causes** while controlling **normal** variation. Making changes in response to normal variations just makes the system worse ***(1).***

Glass breakage events can, at the outset, be considered as quality variations—a **normal** variation superposed with a **special cause** variation. In order to control variations in a given process, the nature of the variations must be known. See **Figures 1** and **2**.

The ratio between **normal** and **special cause** breakage in any process depends on the load characteristics applied by the process and the glass strength variation (Weibull Modulus). If the process loads are significantly below the glass strength, only **special cause** breakages occur.

Establishing a Shewhart process control chart on **normal** variation breakage is beneficial for the individual process steps as well as for the entire process. The Shewhart control chart can be used for monitoring the processes for verification of process improvements. See **Figure 3.**

Glass breakage can be described mathematically as a mix of deterministic and probabilistic models. In a deterministic model, it is always possible to predict the output of a process when the inputs are given. In a probabilistic model, the output of a process is always associated with probability or risk, also when the inputs are given.

As glass acquires more flaws during the entire lifecycle, the strength is irreversibly reduced and the probability of breakage increases.

Glass fractography is an essential tool in any glass breakage reduction campaign, as it enables the investigator to distinguish between **normal** variation breakages and **special cause** breakages. Glass breakage can further be divided into two subcategories: breakage caused by manual handling and breakage caused by automated process handling. Manual handling breakage can be addressed via behavioral programs (do's and don'ts) and controlled by "go-look-see" process confirmations. Glass breakage caused by automated processes is handled differently, depending on the nature of the breakage.

Special cause breakages are addressed with commonly known methodologies like Spark Plasma Sintering, a low voltage, pulsed direct current sintering technique.

Normal variation breakages can only be reduced by:

- Increasing the glass strength (and durability)
- Reducing the loads to the glass
- A combination of these two

Reducing the loads to the glass to reduce the **normal** variation breakage requires that the culprit be known. A simple approach can be counting the piles of broken glass along the process flow; however, most of these breakages are likely to be **special cause** breakages or "delayed" breakage of glass that is weakened in upstream processes by infliction of flaws, making it too weak to withstand loads within the normal range.

A better approach is to measure the relative strength reduction of the glass population in the different subprocess steps. By ranking the relative strength reduction in all subprocesses, a prioritized list of improvements can be established.

Consider the following methodology for an automated process variation. First, determine the most common breakage morphology for the **normal** variation breakages by fractography; second, establish a glass breakage method and use equipment that emulates the most common **normal** variation breakage morphology with a quantifiable, calibrated output of the breakage strength. Third, sample immediately before and immediately after pertinent, critical process steps; then, establish the Weibull Modulus for the two samples. And finally, compare the two Weibull Moduli using statistics. Here is an example of such a methodology.

Parameters:

- Sample size 150 items
- 10% quantile
- Nonparametric quantile regression tests (Wald and Likelihood Ratio)
- Estimated difference between 10% quantiles with 95% confidence limits

"Old" filling line infeed

- 12% strength reduction of 10% quantile
- Wald Test: H_0 : $Ref_{0.1}$= $Scroll_{0.1,}$ p < 0.0082
- Likelihood Ratio: H_0 : $Ref_{0.1}$= $Scroll_{0.1,}$ p < 0.0007
- $Scroll_{0.1}$ – $Ref_{0.1}$ = -8.93, [-15.581;-2.278]
- There is a **significant** difference

New, improved filling line infeed

- No strength reduction of 10% quantile
- Wald Test: H_0 : $Ref_{0.1}$= $Scroll_{0.1,}$ p < 0.8265
- Likelihood Ratio: H_0 : $Ref_{0.1}$= $Scroll_{0.1,}$ p < 0.7195
- $Scroll_{0.1}$ – $Ref_{0.1}$ = -0.320, [-3.192;2.552]
- **No** significant difference

As **normal** variation breakage is probabilistic by nature; it is not possible to predict a quantifiable effect of improvements in the process. If a Shewhart chart is established for the process as recommended, however, the effect of the improvement can be measured as a downward shift in average value or a reduction of standard deviation.

This approach to glass breakage offers a systematic and practical approach to an often misunderstood problem. Glass breakage is a challenge that will always be present, so using an effective tool to manage process variations is key.

[Editor's Note: The article is based on the author's talk, "Case Study: Reduction of Glass Breakage in Pharmaceutical Process, a Systematic and Practical Approach," delivered at the *2016 PDA Universe of Pre-filled Syringes and Injection Devices*.**]**

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About the Author

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Requirements after "Opening" a Water System

The following blinded, unedited remarks are taken from PDA Connect℠, an online forum that allows PDA members to share some of the most challenging issues confronting the pharmaceutical industry. The discussions on PDA Connect℠ do not represent the official views of PDA, PDA's Board of Directors, or PDA members. The following is taken from the Pharmaceutical Water Interest Group forum.

Questioner

Hello — I am looking for any regulations/guidance (global) regarding if SIP is required after "opening" the water system — this would be both for WFI and Water for Pharmaceutical use (used for Solid oral Dosage Forms) — or is it just a "best industry practice" to perform SIP after the system is breached... any thoughts feedback/information is appreciated.

Respondent 1

I am not sure where you have read "it is best industry practice to SIP" a water system after opening it. It is common practice to sanitize the water system after opening it — according to your sanitization practices — whether by chemicals, steam, hot water, ozone, etc... I have never seen a document stipulating Steam-in-place is required.

Respondent 2

I agree with [redacted]. In fact, WFI systems are typically not designed for SIP as they are not properly vented for the cooldown. As the steam collapses upon cooling without venting, a significant vacuum may be produced, possibly aspirating external contamination through fittings. I have never actually seen this but was warned of the phenomenon many years ago by an astute FDA investigator who said he had. Of course, you could vent with filtered air, as in an autoclave, but I am not aware of this being a practice. As [redacted] says, WFI systems need sanitization, not sterilization, and hot water does this quite well.

Respondent 3

I have never seen anything written that requires it. WFI if distilled and maintained above 80°C is pretty self-regulating but after a real breach – if the system is opened to the atmosphere, it is good practice to passivate which tends to remove almost any possible contamination so that if followed by going back to 80°C would probably take care of anything. This is also the case for purified water if there is provision for heat sanitization.

I don't know if that helps – some WFI systems have provision for sanitization at 100°C in which case, recommended after a major breach.

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23
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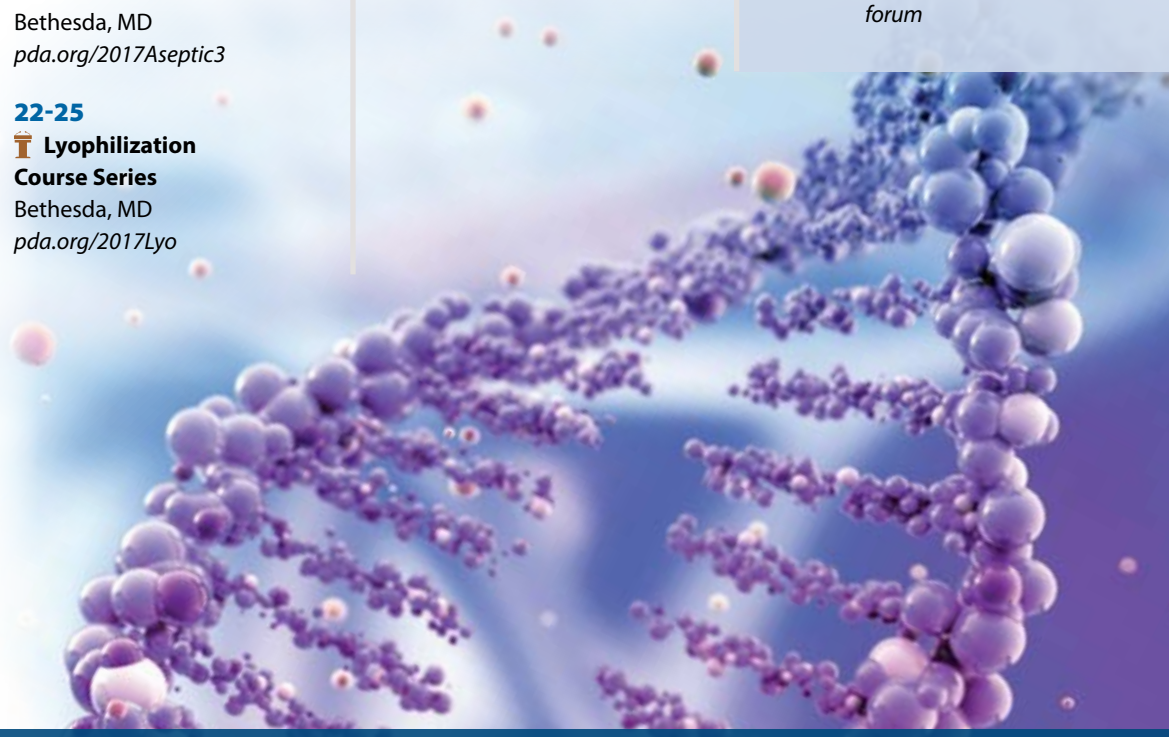

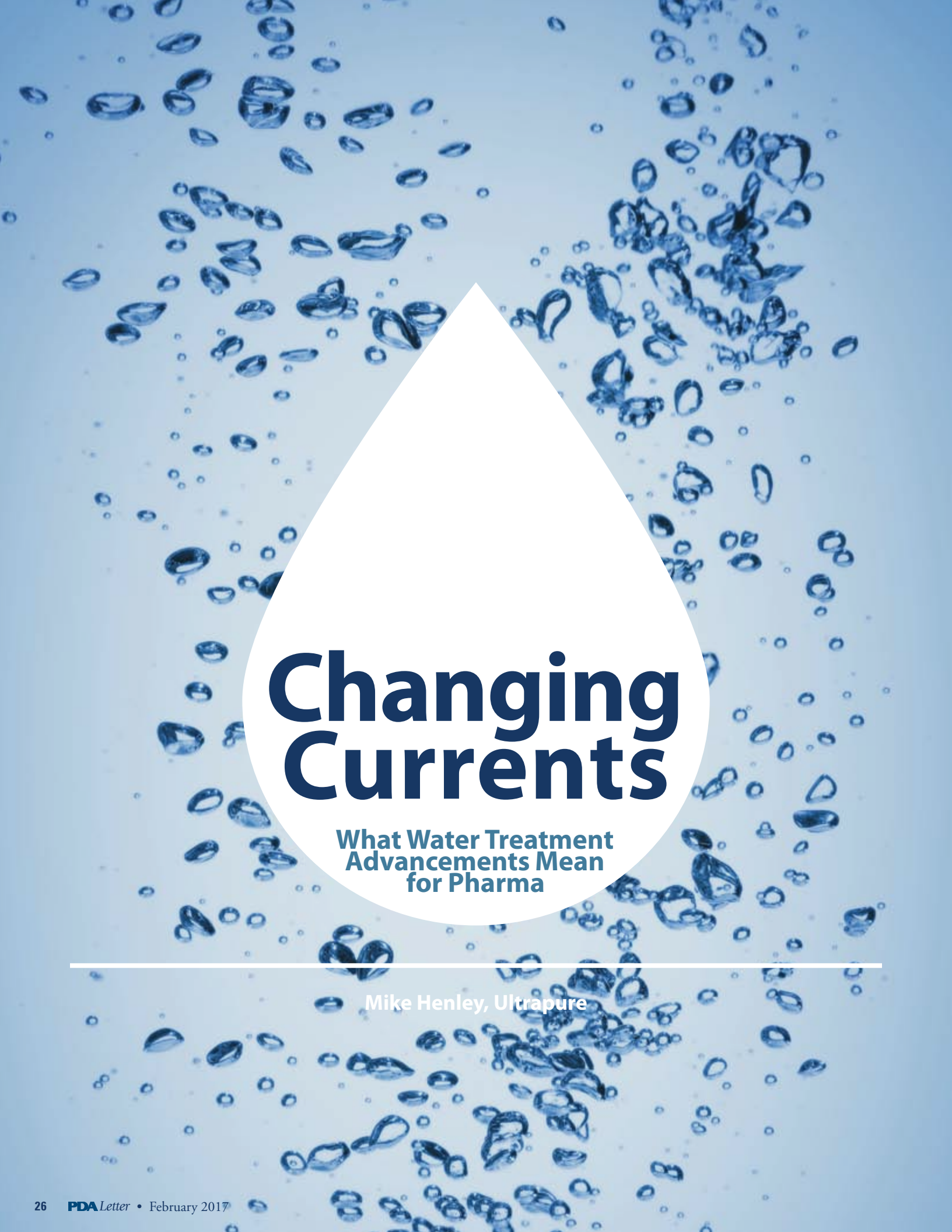

Changing Currents

What Water Treatment Advancements Mean for Pharma

Mike Henley, Ultrapure

Article at a Glance

- Water treatment guidelines based around compendial requirements
- Innovation often driven by regulation instead of need to adapt
- EP allowance for non-distillation tech an example of harmonization

Pharmaceutical water is key to the production of pharmaceutical drug products, many of which require high-purity water. This is water purified according to guidelines as defined by the USP or other pharmacopeias.

There have been a number of technological advancements in high-purity pharmaceutical-grade water. Unlike other industries, however, changes in the use of high-purity water systems have often been in response to compendial and regulatory changes rather than a desire to innovate.

To start, it's useful to provide some context about pharmaceutical water's place in the larger water world. The category known as ultrapure water (UPW) itself is used by end users in four main industries: life sciences, microelectronics, power generation, and specialty applications. Each industry's definition of UPW is unique and their methods to produce this water, and requirements for materials of construction (piping, valves, storage tanks, etc.), vary. Treated UPW that meets requirements for a power station would be unacceptable for a pharmaceutical plant. And purified water meeting pharma plant quality standards does not meet the stricter requirements found in the microelectronics industry.

For pharma, the water treatment guidelines are based around pharmacopeias, of which the USP, European Pharmacopeia (EP), and Japanese Pharmacopeia (JP) are among the most influential. The Indian Pharmacopeia and Chinese Pharmacopeia are also growing in importance. Of course, facilities providing products to other regions follow the pharmacopeias applicable for those markets they sell into. For example, an Indian plant supplying the European market follows EP guidelines when purifying water used to make products sold in that market.

On the regulatory side, the U.S. FDA administers the USP treatment guidelines through inspections to validate system performance, as well as by taking enforcement action when problems are found. Because pharma is a global industry, the FDA sends its staff internationally to nations like India to inspect and validate a treatment system when the plant's products are sold into the U.S. market.

Water Flows Throughout Pharma

Pharmaceutical water falls under several classifications, based on the final application. Examples include bacteriostatic water for injection, purified water, sterile purified water, and water for injection (WFI). Other examples are listed in **Table 1,** which also provides an overview of the concerns and uses for pharmaceutical-grade waters. Outside of being used as an ingredient, pharmaceutical water has multiple other applications, including container and equipment cleaning, intravenous fluids, product contact of ingredient, product contact of medical device (cleaning), and reagent or solvent in drug manufacturing (but not in final product).

Specific water treatment concerns within pharma include chemical/microbial/ endotoxin contamination and case-specific controls for certain types of pharmaceutical water (i.e., aluminum for water for hemodialysis). Life science facilities, including pharma plants, are required to use feedwater that meets drinking water standards as set forth by the U.S. EPA, similar agencies in the country the plant is located, or WHO. Since incoming water is already clean, water pretreatment generally focuses around chlorine removal to protect reverse osmosis (RO) membranes. Common technologies may be activated carbon or metabisulfite.

The main treatment system may include ion exchange (IX), electrodeionization (EDI), RO, distillation, ultrafiltration (UF), microfiltration (MF), ultraviolet (UV), and ozone. The most common material of construction for distribution systems and storage tanks is stainless steel, which can be heat sanitized and carry

Table 1 Overview of Pharmaceutical Water and Concerns

Industrial End User	*Types of Water*	*Treated Water Uses*	*Treated Water Concerns**	*Primary Guidelines/ Standards***
Pharmaceuticals***	Bacteriostatic Water for Injection, Purified Water, Sterile Purified Water, Sterile Water for Inhalation, Sterile Water for Injection, Sterile Water for Irrigation, and Water for Injection, Water for Hemodialysis, Pure Steam, and Highly Purified Water	Container and equipment cleaning, product ingredient; intravenous fluids; some consumer products; product contact of ingredient; product contact of medical device (cleaning); reagent or solvent in drug manufacturing (but not in final product)	1. Chemical, microbial, and endotoxin contamination 2. In some cases, specific controls are additionally needed (i.e., aluminum for Water for Hemodialysis)	USP, EP, JP, WHO

Source: Compiled by M. Henley, Media Analytics Ltd. (©2016).

Notes:

* The examples listed are commonly associated with these areas of pharmaceutical water treatment.

** These are examples of the principal sources for high-purity water treatment standards and guidelines for the pharmaceutical and life sciences industries.

***Besides pharmaceuticals and biopharmaceuticals, other end users that strive for these grades of water would include medical device manufacturers and consumer goods (e.g., cosmetics) that must meet USP quality water for their products.

hot water. Common instruments used to measure water quality are total organic carbon (TOC) and conductivity.

What's Driving New Water Treatments?

One key factor that drives the choice of water treatment technologies among pharma companies is regulation and changes in the USP guidelines over time. So, unlike other users of UPW, pharma companies tend to move slowly and carefully when adopting new treatment technologies. Many times, innovation in pharmaceutical water systems is driven because of changes in the USP chapters, not because it is the best available technology for a particular need.

One case in point is the use of on-line TOC and conductivity instruments to track water quality. Prior to USP 23, USP called for using wet chemistry testing to measure calcium, sulfate chloride, ammonia, and carbon dioxide. These wet chemistry tests were replaced by the use of conductivity instruments as outlined in USP <645> Water Conductivity ***(1, 2).*** The logic behind adopting the conductivity test was that if a plant met the conductivity requirement then it would pass the chemistry tests. Likewise, the Oxidizable Substances test was replaced by <643> on TOC ***(2).***

After implementation, the USP 23 revisions prompted a widespread move among pharmaceutical companies to buy and install TOC and conductivity instruments. For pharmaceutical companies, these new requirements led to innovation to their treatment systems.

A more recent example of how the regulatory approach impacts technology implementation by pharmaceutical companies has been the changes in the acceptable treatment technologies to produce WFI. The USP and JP have permitted the use of non-distillation technologies, while the EP has not.

In 2009, the *Japanese Pharmacopoeial Forum* recognized RO and ultrafiltration (UF) as an acceptable alternative to produce WFI from either a purified water source or water previously treated by RO or ion exchange, also pointing out that the USP defines WFI as "…water purified by distillation or a purification process that is equivalent or superior to distillation in the removal of chemicals and microorganisms" ***(3).***

While the EP has been slow to change their WFI guidelines, the pharmacopeia had previously set standards for highly purified water (EP 6.3) that actually called for treatments similar to what the USP and JP allowed in their WFI classifications ***(4).*** The EP is now prepared, however, to allow for non-distillation technologies to produce WFI **[Editor's Note:** See page 38 for PDA's comments on the EP revision**].**

In March 2016, the EP adopted a revised monograph for WFI that allows for the use of technologies equivalent to distillation, such as RO, that are "coupled with appropriate techniques" ***(5).*** Appropriate treatment technologies will now include electrodeionization (EDI), UF, or nanofiltration (NF) ***(6).*** The change will be effective this April.

The net effect of these changes is that pharmaceutical companies will have greater freedom to produce WFI by either a thermal distillation technology or with membranes. New facilities could opt for either distillation or membrane technologies, while plants with aging stills will also be able to update their plant equipment. Also, since membrane systems operate at ambient temperatures, pharmaceutical facilities opting to use non-distillation technologies could see potential energy and cost savings by changing equipment.

Another important part of this development is that pharmaceutical plants may not need to use distillation to make WFI if their products do not go into markets where the governing pharmacopeia only allows for stills. This change is a part of efforts by the EP, JP, and USP to harmonize different requirements impacting pharmaceutical-grade waters. The benefit is that it simplifies operations for pharmaceutical companies as they make products sold in different global markets.

Closing Thoughts

The adoption of new treatment technologies by pharmaceutical companies is often driven more by changes in pharmacopeia/regulatory requirements. The pending move by the EDQM to allow for non-distillation treatments will aid the continuing efforts by the EP, JP, and USP to harmonize treatment standards between these pharmacopeias.

The author thanks the following individuals for their help with ***Table 1:*** ***Slava Libman,*** *PhD, Air Liquide-Balazs NanoAnalysis;* ***Anthony Bevilacqua,*** *PhD, METTLER-TOLEDO Thornton;* ***William V. Collentro,*** *Water Consulting Specialists; and* ***Brad Buecker,*** *Kiewit Engineering and Design. The author also thanks* ***T.C. Soli,*** *PhD, of Soli Pharma Solutions, and* ***Igor Gorsky*** *of Concordia ValSource for their assistance with this article.*

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About the Author

Mike Henley is the editor of www.ultrapurewater.com, which incorporates the former bimonthly technical publications, *Ultrapure Water Journal* and *Industrial Water Treatment*. He may be contacted at: mhenley@globalwaterintel.com.

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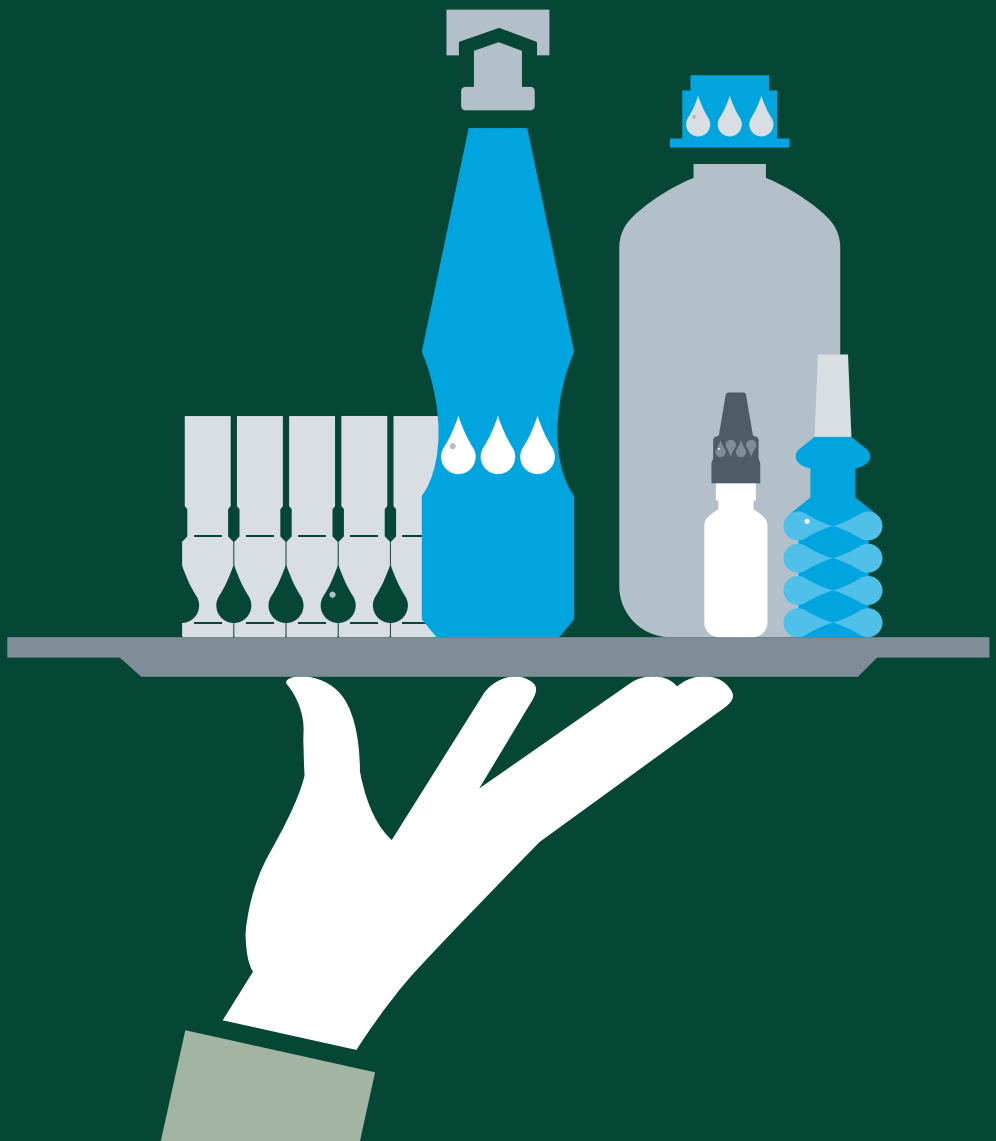

The New Annex 16 – Eight Questions for Rainer Gnibl

Sabine Paris, PhD, Maas & Peither AG

[Editor's Note: This article was originally published in the April 21, 2016 issue of Maas & Peither's cGMP newsletter. Here, Maas & Peither editor **Sabine Paris,** PhD, interviews German GMP Inspector **Rainer Gnibl,** PhD, on the Annex 16 revision, "Certification by a Qualified Person and Batch Release," that became effective last year**.]**

One objective of the revision was to more clearly define the responsibilities and accountabilities of the QP [Qualified Person]. Has this been accomplished?

Annex 16 is, in fact, very clear now with respect to what duties the Qualified Person must perform personally, and what he or she can delegate. However, there are only three rather formal aspects that the certifying QP has to personally ensure, namely:

- Certification is permitted under the terms of the manufacturing/import authorization
- Any additional duties and requirements of national legislation are complied with
- Certification is recorded in a register or equivalent document

The other 21 certification requirements given in the Annex can be delegated to appropriately trained employees or third parties. They deal with all quality-related activities involved in manufacturing and testing pharmaceuticals in the broader sense of the word. These include documentation of the supply chain, audits, specifications, OOS/OOT investigations, starting materials, changes, technical agreements or compliance with the marketing authorization.

Is the globalization of the supply chain well represented as planned?

Yes, according to the revised Annex 16, the supply chain has to be completely mapped out. This change was implemented because of the EU Anti-Falsification Directive (2011/62/EU). It makes an important contribution to blocking the intrusion of counterfeits. The supply chain has to be documented not only for active substances and medicinal products, but also for starting materials, packaging materials and other materials that are crucial to product quality. As a result, all suppliers, including subcontractors, now have to be disclosed. In the case of batch certification, GDP compliance is now advancing to take a prominent position beside GMP compliance. Meeting the GDP requirements for active substances is specifically mentioned. ➤

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> **According to the revised Annex 16, the supply chain has to be completely mapped out**

When can the QP rely on third-party audits? What does the QP have to ensure?

The QP does not have to personally audit plants that are involved in manufacturing and testing the product or in manufacturing active substances. That can be delegated internally, or an external service provider can be engaged, as long as this provider has been prospectively qualified in accordance with Chapter 7 of the EU GMP Guide, Part I, "Outsourced Activities." The new Annex 16 also defines minimum requirements audit reports must fulfill to retain their usefulness for the QP. In any case, the certifying QP must be informed about critical outcomes of audits. Audit reports must be available to the QP at all times.

The QP has to ensure that the pharmaceutical quality systems (PQS) of the plants involved in manufacturing and testing the product are in working order and in compliance with the plants' own PQS. This is especially important in those cases in which the QP relies, for the batch certification, on the QP of a contract manufacturer to verify that production is GMP compliant (Certificate of Conformance, or CoC). But this is only possible with contract manufacturing under the terms of a European manufacturing authorization.

What does the QP have to watch for in imports from third countries? Is everything different now?

The prerequisites for importation from third countries have not changed. What is new, however—and this poses a new risk—is the possibility of sampling for EU reanalysis in the third country. The previously valid Annex 16 permitted sampling only within the EU or the EEA [European Economic Area]. In third countries it was only possible to take extra samples (such as sampling during filling to test for sterility). It is true that samples taken at the manufacturing site in the third country may be drawn in accordance with a technically justified approach which is documented within the company's quality system. This includes audits of the sampling and comparative tests to ensure that the samples are fully representative. Unfortunately, however, in actual practice things are often different and the samples cannot always be proven to be fully representative. But if importers are satisfied with purely formal security to give them the advantage of time, for instance to compensate for poor internal planning for replenishments, then of course this change will offer new opportunities. As a consequence, however, the GMP principle of quality assurance and the highest measure of product safety which it strives to achieve are subordinated in this way to the new objective of "continuous supply."

Another important aspect for the QP in certifying products from third countries is that he or she absolutely cannot rely on the verifications or CoCs of other QPs—as is the case within the EU. The QP certifying the import in this case is solely (!) and fully responsible for all manufacturing and testing steps taken in third countries. Nor can the batch record review to ensure GMP compliance take place in a third country or be verified by a QP located there, no matter how qualified that person may be.

For the first time the Annex also contains requirements for certification of the parallel importation and/or distribution of products. Are these requirements reasonable and adequate?

Contrary to the earlier version of Annex 16, for the first time, the new one now includes mention of the parallel importation and/or distribution of medicinal products. However, it does not address content that is truly relevant to quality, such as proof of GMP compliance of the starting materials used. This comes as a surprise in contrast to the draft version where the QP's responsibility is clearly cut back. He or she must only verify that the repackaging took place in accordance with the marketing authorization and in conformity with GMP.

Consideration of unexpected deviations in the manufacturing process or with respect to control methods is also totally new. The already published "QP Discretion Paper" by the EMA was incorporated here. How helpful is the regulation in this format?

Including the content of the "QP Discretion Paper" in the Annex is advantageous for the GMP inspectorates, since it is now unequivocally made clear that only unplanned deviations can be accepted in batch certification. And that is true only as long as the specifications for active substances, excipients, packaging materials and finished products according to the marketing authorization have not been affected. Thus, the deviations concerned can only be miscellaneous deviations in batch production and testing.

About the Expert

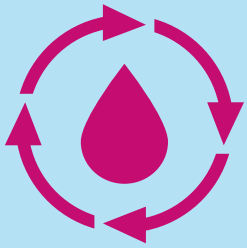
As GMP Inspector for the Government of Upper Bavaria and EMA, **Rainer Gnibl,** PhD, is responsible for carrying out national and international inspections of the manufacturers of medicinal products and active ingredients.

About the Author

Sabine Paris, PhD, joined the editorial team of Maas & Peither GMP Publishing in 2014. She is responsible for the technical content of the German and English newsletters and the creation of English-language publications. Previously, she was Head of the Medicinal Product department at the Central Authority of the Laender for Health Protection with regard to Medicinal Products and Medical Devices (ZLG) in Germany.

Know Your High-Purity Water System

There are many types of high-purity water systems used within the pharma industry. Below is a primer for some of the most commonly seen or referenced.



Purified Water

Used as an excipient in production of nonparenteral preparations and in cleaning of certain equipment. Also used for tests and assays that call for water. Susceptible to biofilm.

Water for Injection (WFI)

Used as an excipient during production of parenteral preparations. Not required to be sterile. Must have minimal microbial contamination with endotoxin removed from starting water.

Distilled Water

Produced by vaporizing liquid water, then condensing it into a purer state. Used primarily as a solvent for reagent preparation.

Reverse Osmosis

Water generated by using a membrane to separate pure water from a less pure solution to generate osmotic pressure. By applying counterpressure, the flow of water can be reversed. Membrane can be a source of contamination but has been found to be better at rejecting contamination during continuous use as opposed to intermittent. Recently accepted by European Pharmacopoeia as alternative to distillation.

Sources

1. USP <1231> *Water for Pharmaceutical Purposes*
2. U.S. FDA Inspection Technical Guide. *Reverse Osmosis*. tinyurl.com/76vyqdz
3. European Pharmacopoeia Commission adopts revised monograph on Water for Injections allowing production by non-distillation technologies. tinyurl.com/jgfc3pt

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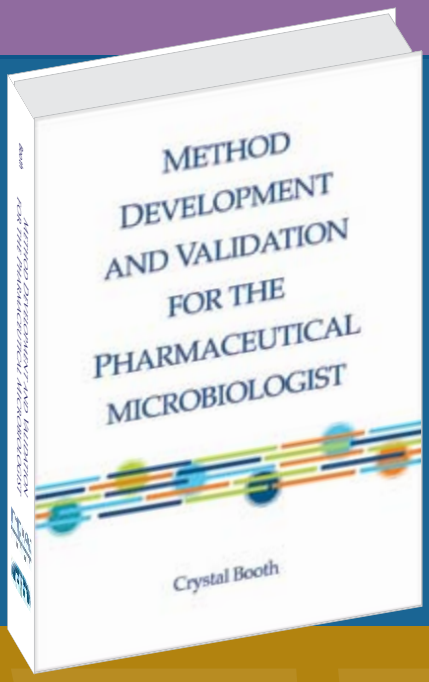

METHOD DEVELOPMENT AND VALIDATION FOR THE PHARMACEUTICAL MICROBIOLOGIST

BY: CRYSTAL BOOTH

PDA MEMBER PRICE: ~~$210~~ $178.50
PDA NON-MEMBER PRICE: ~~$259~~ $220.15
HARDCOVER: ITEM NO. 17339
DIGITAL: ITEM NO. 18022

The book primarily focuses on parenteral products and excipients, but the methodology can transfer to other areas of microbiology as well. The book also provides advice on programs and special studies that might be performed in the pharmaceutical microbiology laboratory.

The purpose of this book is to inspire ideas and provide recommendations regarding method development and validation strategies for pharmaceutical microbiologists. The book may also aid microbiologists when starting new facilities or validating equipment.

This is a must-have resource for anyone engaged in the many aspects of method development and validation in pharmaceutical microbiology.

go.pda.org/MDVPM

ABOUT THE AUTHOR

Crystal M. Booth, M.M., is an Independent Pharmaceutical Microbiology Consultant with Pharmaceutical Advisors, LLC. She earned her Bachelor's Degree in Biology from Old Dominion University and her Masters of Microbiology Degree from North Carolina State University. She has over 17 years of experience in Pharmaceutical Microbiology. She is a technical author and public speaker in the Microbiology Industry. Crystal has developed and performed numerous method validations, such as Microbial Limits Testing, Bacterial Endotoxins Testing, Particulate Testing and various equipment validations. She also teaches aseptic gowning qualification classes. Crystal has worked in both R&D and Quality Control Laboratories, including a start-up company. She also has experience working with global markets and regulatory bodies.

SNAPShot

PDA Team Addresses Q&A Doc on Non-Distillation WFI

Igor Gorsky, Concordia ValSource

Last June, EMA published the draft document, *Questions and answers on production of water for injections by non-distillation methods – reverse osmosis and biofilms and control strategies.* EMA often uses such Q&A documents to clarify the Agency's position, including possible regulatory requirements, in response to changes in directives, guidances, or in this case, a pharmacopeial monograph, specifically the European Pharmacopoeia's (EP) Water for Injections (WFI) monograph (0169).

This revision has been long-awaited. The USP has allowed purification, along with distillation methods, to be used to produce WFI for many years, while the EP only allowed the use of distillation to produce WFI. Those in the pharmaceutical water community welcomed this revision with great excitement and optimism. In response to the EMA document, PDA assembled a team of PDA water experts to review and comment on it.

In its response, PDA fully supported the implementation of non-distillation methods for WFI production into the European regulatory framework, and endorsed the premise that non-distillation technology for producing WFI should produce water equivalent in quality to that produced by distillation.

The team had concerns with many of the approaches specified in the Q&A document, however, deeming them not science- nor risk-based. In fact, the team considered some of the requirements to be above and beyond what is in the EP monograph.

PDA recommended referencing existing technical documents, such as PDA's technical reports for best practices, and allowing manufacturing firms to make risk-based decisions based on science instead of limiting firms through overly prescriptive regulations or monographs. The cited examples were rapid microbial methods and online vs. offline total organic carbon methods. The commenting team further stated that "this document should clarify monitoring methods which are reactive vs. control methods which are proactive." Additionally, the team recommended including requirements for distribution and storage systems that permit manufacturers (as long as they include appropriate documentation) a choice of routine sanitization approaches, such as steam, hot water, ozone, or other chemicals, and avoid requiring complete redundant approaches or steam in all cases.

See page 38 to read the commenting team's letter to EMA.

Enhancing GDP Compliance Through Certification

Zvonimir Majic, PhD, Teva, on behalf of the PDA Pharmaceutical Cold Chain Interest Group, (EU)

Temperature excursions and delays at airports are major concerns for companies shipping temperature-sensitive pharmaceutical products by air. In light of this, last fall, the International Air Transport Association (IATA) presented their Center of Excellence for Independent Validators (CEIV) certification program to the European steering committee of PDA's Pharmaceutical Cold Chain Interest Group. IATA represents 265 airlines that account for approximately 83% of total air traffic. The CEIV certification program was developed in 2014 as part of an effort to harmonize the air transport industry's practices for shipment of pharmaceutical product and accommodate the pharmaceutical industry's GDP expectations. This program emphasizes the importance of having defined quality and risk management systems in place to address requirements coming from global regulators. IATA intends to provide the pharmaceutical manufacturing industry a harmonized standard for handling and transporting healthcare products worldwide through a network of CEIV-certified airlines, airports, ground handling agents, trucking companies, and forwarders.

The interest group's European steering committee welcomes this initiative as a valuable effort in the joint quest of the airline and pharmaceutical industries to deliver safe healthcare products to patients. This program intends to deliver quality and risk management systems in the logistics industry designed according to mainstream GDP regulatory documents (MHRA, USP, EMA). Considering the increase in the complexity of the pharmaceutical supply chain, a network of CEIV-certified suppliers would undoubtedly enhance controls and visibility throughout the air freight industry.

More information about the program can be found at: www.iata.org/whatwedo/cargo/security/ceiv/Pages/directory.aspx.

PDA Supports Non-Distillation WFI Methods

4 November 2016

EMA
30 Churchill Place
Canary Wharf London E14 5EU
adm-gmdp@ema.europa.eu
RE: EMA/INS/GMP/489331/2016 GMP/GDP IWG

Questions and answers on production of water for injections by non-distillation methods – reverse osmosis and biofilms and control strategies

Dear Sir/Madam:

PDA appreciates the opportunity to provide feedback on this draft and fully supports the implementation of non-distillation methods for WFI production into the European regulatory framework. In addition, PDA endorses the premise that non-distillation technology for producing WFI should produce water equivalent in quality to that produced by distillation. However, PDA has concerns with many of the approaches specified in this Q&A that are not science and risk based, some of which set requirements above and beyond what is in the Pharm. Eur. Monograph.

PDA recommends referencing existing technical documents for best practices and allowing manufacturers to make science and risk based choices rather than limiting the possibilities by writing overly prescriptive regulatory guidance or monographs. In addition the requirements for distribution and storage systems should permit manufacturers a choice of routine sanitisation approaches such as steam, hot water, ozone or other chemicals and not require redundant approaches or steam in all cases.

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 a committee with expertise in pharmaceutical water systems representing the Science Advisory Board, the Board of Directors and including authors of PDA Technical Report 69 Bioburden and Biofilm Management in Pharmaceutical Manufacturing Operations.

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

Sincerely,
Georg Roessling
Vice President, PDA Europe
CC: Simona Keckesova, EMA; Richard Johnson, PDA; Denyse Baker, PDA

PDA Commenting Task Force

Igor Gorsky, ValSource (lead)
Anthony Bevilacqua, Mettler-Toledo Thornton
Scott Bozzone, Consultant
Lucia Clontz, Xellia
Mark Fornalik
David Hussong, ValSource
Anastasia Lolas, Consultant
Demetra Macheras, AbbVie
Russell Madsen, The Williamsburg Group
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Peter Noverini, Azbil
Mark Pasmore, PhD, Baxter
T.C. Soli, Consultant
George Verghese, Steris

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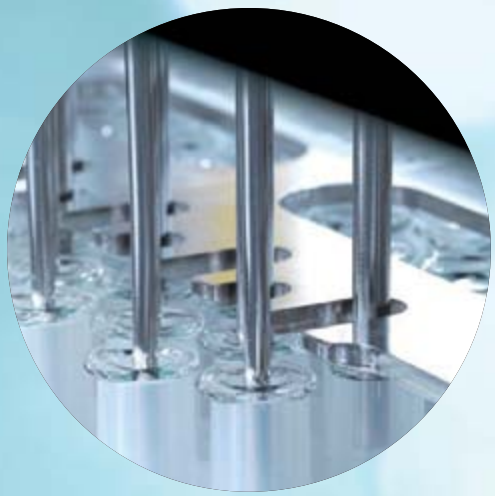

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Non-Distillation WFI Opens Door for Greater Efficiency

Andreas Gold, IMPROCESS

EDQM's decision to accept non-distillation water for injection (WFI) for pharmaceutical product manufacturing will enable manufacturers to boost their plant efficiencies, enabling continuous supply for the benefit of patients. But are manufacturers ready to upgrade to non-distillation or other WFI methods?

Most facilities still rely on conventional systems, and upgrading to more efficient ways of producing WFI is far more complex, costly, and risky in existing plants than in new plants. Therefore, inefficient systems are more or less immortal in many facilities, although a clear analysis of costs would show a solid business case for replacing these aging systems. For example, a manufacturer could improve plant efficiency by using compression distillation methods that are highly energy-efficient and reduce WFI costs by 50%.

There will, however, be some resource investment up front. Implementing a more efficient WFI system does mean that more knowledge and training has to be put into water system operator qualification schedules to ensure appropriate WFI quality, and more attention has to also be paid to microbiological risk control strategies, hygienic design, and preventive maintenance procedures. But the eventual cost savings from this initial investment in labor and training are significant.

For those companies concerned about disruption to production, keep in mind that non-distillation methods can be implemented in parallel to existing WFI supply systems. This way, a redundant WFI supply can be installed, so over time the conventional still systems can be replaced once the qualification process of the new core non-distillation WFI system has been completed. This will also lead to a significant reduction in energy consumption for WFI generation and improved energy efficiency, as non-distillation systems can be operated in standby mode and at ambient temperatures. Health and safety risks are also reduced as no hot system is used for WFI generation.

As cost pressures on biopharmaceutical manufacturing organizations increase, costs (e.g., energy, quality, maintenance, etc.) are becoming more important for manufacturing departments. An individual assessment on the best available technology for WFI generation should be made depending on the amount and quality of WFI needed for the process. In most cases, the result would be using a more efficient technology for WFI generation, be it conventional compression distillation or a non-distillation method.

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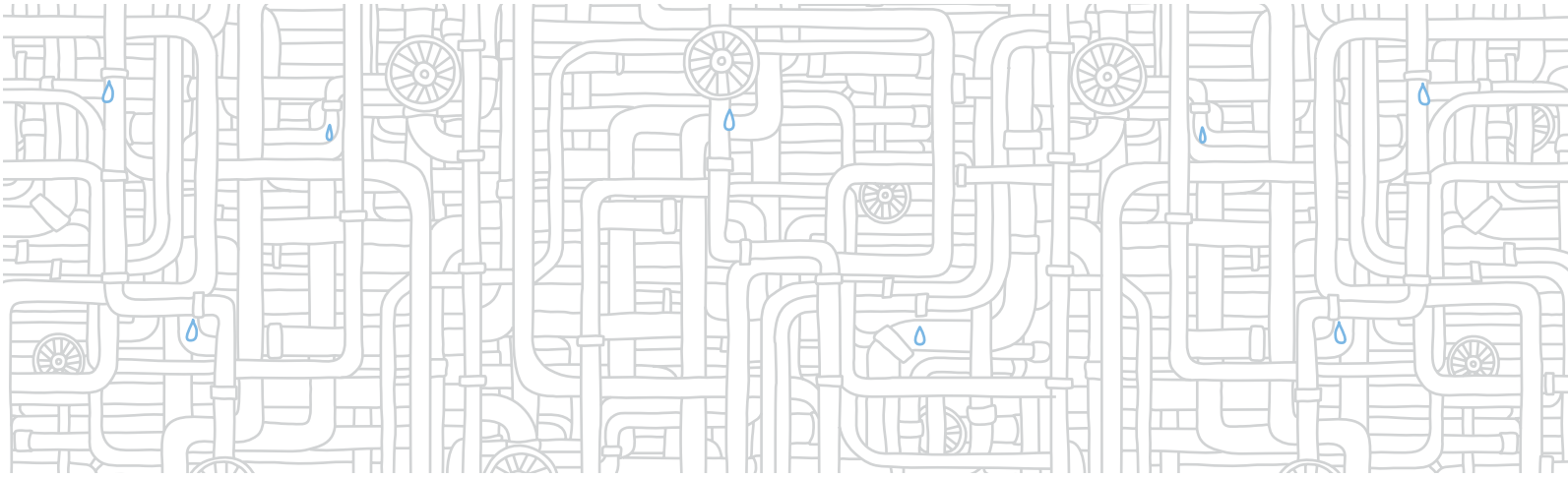

EMA has already published a draft Q&A document on the most common questions concerning this topic **[Editor's Note:** See page 37 for PDA's response to this Q&A.**]**. Before implementation of a new non-distillation WFI system, a notice has to be given to the supervisory authority of the manufacturer, so any companies planning to replace their still distillation system should plan enough time for implementation.

While implementing non-distillation WFI requires additional training and resources, the benefits outweigh the negatives. These systems are more energy-efficient and offer the potential for cost savings. In the end, it will literally pay for manufacturers to consider upgrading their WFI technology.

About the Author

Andreas Gold has spent a decade in Vaccines/Recombinant Manufacturing at Baxter/Baxalta Bioscience before starting his own company, IMPROCESS GmbH, that focuses on process improvement for biopharma operations.

Regulatory Briefs

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

North America

21st Century Cures Act Signed

On Dec. 13, U.S. President **Barack Obama** signed the 21st Century Cures Act into law. This Act creates a new pathway for regenerative medicines, requires fewer data to bring drugs and devices to market, and encourages adoption of continuous manufacturing through U.S. FDA-provided grants.

The Act also provides additional funding for research on cancer and opioid addiction.

FDA Revises Metrics Guidance

The FDA released its revised guidance on quality metrics on Nov. 23. This version includes comprehensive definitions for metrics categories as well as reporting tiers for various types of organizations. In addition, the document establishes an initial period where reporting of metrics will be voluntary.

Comments are due March 27.

Final Combo Product Guidance Out

In early January, the FDA released its final guidance on cGMPs for combination products. The finalized guidance addresses concerns industry had expressed regarding FDA communications related to combination products. In addition, the guidance discusses the role of the lead center and other Agency divisions responsible for cGMP issues for these types of products.

Owners Responsible for Quality

The FDA released a guidance for industry on Nov. 22 describing how contract manufacturing organizations can use quality agreements to delineate their manufacturing activities to ensure compliance with current GMPs. According to this document, companies outsourcing pharmaceutical operations are responsible for the quality of the final product, not the outsourcing firm.

Comments on the guidance are due at any time.

Key Regulatory Dates

Comments Due

March 27 — Submission of Quality Metrics Data: U.S. FDA Guidance for Industry

New System for U.S. Drug Imports

Effective Dec. 29, certain data on FDA-regulated products imported into the United States must be submitted through the Agency's Automated Commercial Environment (ACE) system. This more streamlined import process is expected to result in efficient use of Agency resources and more effective enforcement of FDA regulations. ACE replaces the older Automated Commercial System. The new system offers a single window for importers, eliminating the need to submit information more than once.

FDA Making Strides with MRI

The FDA recently announced that the Agency hopes to sign an agreement with the European Union soon on the Mutual Reliance Initiative (MRI). At this time, the two entities are completing assessments of drug manufacturing inspectorates for two to four EU countries. The Agency launched this initiative with the EU in 2014 to create an expanded inspectorate that enables FDA investigators and trusted EU partners to work together to avoid duplicate inspections by relying on each region's inspection information. This would allow the United States and European Union to devote more resources to regions where drug manufacturing has greatly increased, such as China and India.

Europe

EMA Launches Biosimilar Pilot

EMA will launch a biosimilar-focused pilot project this month. The Agency plans to use this pilot to provide biosimilar developers with recommendations as to what studies they should be conducting based on data from the innovator product. This program is open to all companies looking for scientific advice on developing a biosimilar product.

Asia-Pacific

Japan Seeks Collaborative API Effort

Japan's Pharmaceutical and Medical Devices Agency (PMDA) announced in December plans to join the U.S. FDA and EMA to improve the GMP inspection process for sites producing APIs through a collaborative effort. Under this agreement, PMDA will be able to share information related to GMP inspections. This information would include inspection plans and results. This is part of PMDA's International Strategy.

New Inspection Process in China

The China Food and Drug Administration has committed to adopting a "double random" approach to inspections to improve oversight. This approach involves random selection of both the inspector and the organization or process being inspected.

ICH

New Solvent Added to ICH Q3C(R6)

ICH Q3C (R6), *Impurities: Guideline for Residual Solvents*, has entered the implementation period. The most recent update revises the Permissible Daily Exposure for Methyl isobutyl ketone (MIBK) and adds Triethylamine (TEA) as a new solvent.

Keeping Our Products Sterile

Michael Sadowski, Baxter

As a major strategic imperative, PDA remains dedicated to advancing the state of its recognized core competencies, particularly aseptic processing and sterile product manufacturing, both of which are near and dear to my heart. Off the bat, I fully acknowledge my strong bias, given my professional role, but I do truly believe that the sterility of a finished product is its absolute most important attribute.

Sterility assurance is often referred to as the scientific field, or discipline, responsible for delivering, and then maintaining the sterility of our products up to (and sometimes including) administration by our customers and patients. Sterility assurance is a very specialized discipline; one of the greatest challenges we all face regarding the ongoing development and strengthening of this competency is that there are very few, if any, formal college/university programs with significant focus on this critically important area. Consequently, much of the sterility knowledge gained within our industry comes from on-the-job training. Ideally, this occurs through instruction from distinguished and competent mentors in the field. In full recognition of this industry-wide challenge, PDA plays a vital role in the ongoing development of sterility assurance expertise with an exceptional portfolio of valuable training and educational options.

First, PDA has published a multitude of valuable technical reports and Points to Consider documents on sterility assurance. Many of our technical reports address sterility assurance, and you can even find original source material on the topic by browsing the references and recommended readings located in the back of a technical report. Our technical reports and other documents also leverage the use of best practices built on a fundamentally strong foundation of science. In the case of our recent *Points to Consider for Aseptic Processing* document, those of us developing the document gained considerable practical knowledge by sharing our own experiences.

You can also read more about sterility assurance in the *PDA Letter* and *PDA Journal of Pharmaceutical Science and Technology* as well as in our technical books.

Additionally, sterility assurance is often a focus of specialized PDA conferences and workshops, such as our recent series of Annex 1 workshops. The topic is also regularly covered at dedicated sessions in our broader conferences, such as the *PDA Annual Meeting* and *Global Conference on Pharmaceutical Microbiology.*

And remember what I said about the lack of university-level courses on sterility assurance? PDA is well recognized as the leading global provider of scientific, technological, and regulatory education for the pharmaceutical and biopharmaceutical community, with many courses that support sterility assurance, including the renowned hands-on "Aseptic Processing Training Program." This training program is conducted in the aseptic processing suites and laboratories at PDA's Training and Research Institute (TRI) in Bethesda, Md.

In summary, I strongly recommend that sterility assurance professionals seeking to advance their careers make strong use of these highlighted PDA offerings to supplement their ongoing on-the-job training in support of aseptic processing and sterile product manufacturing operations.

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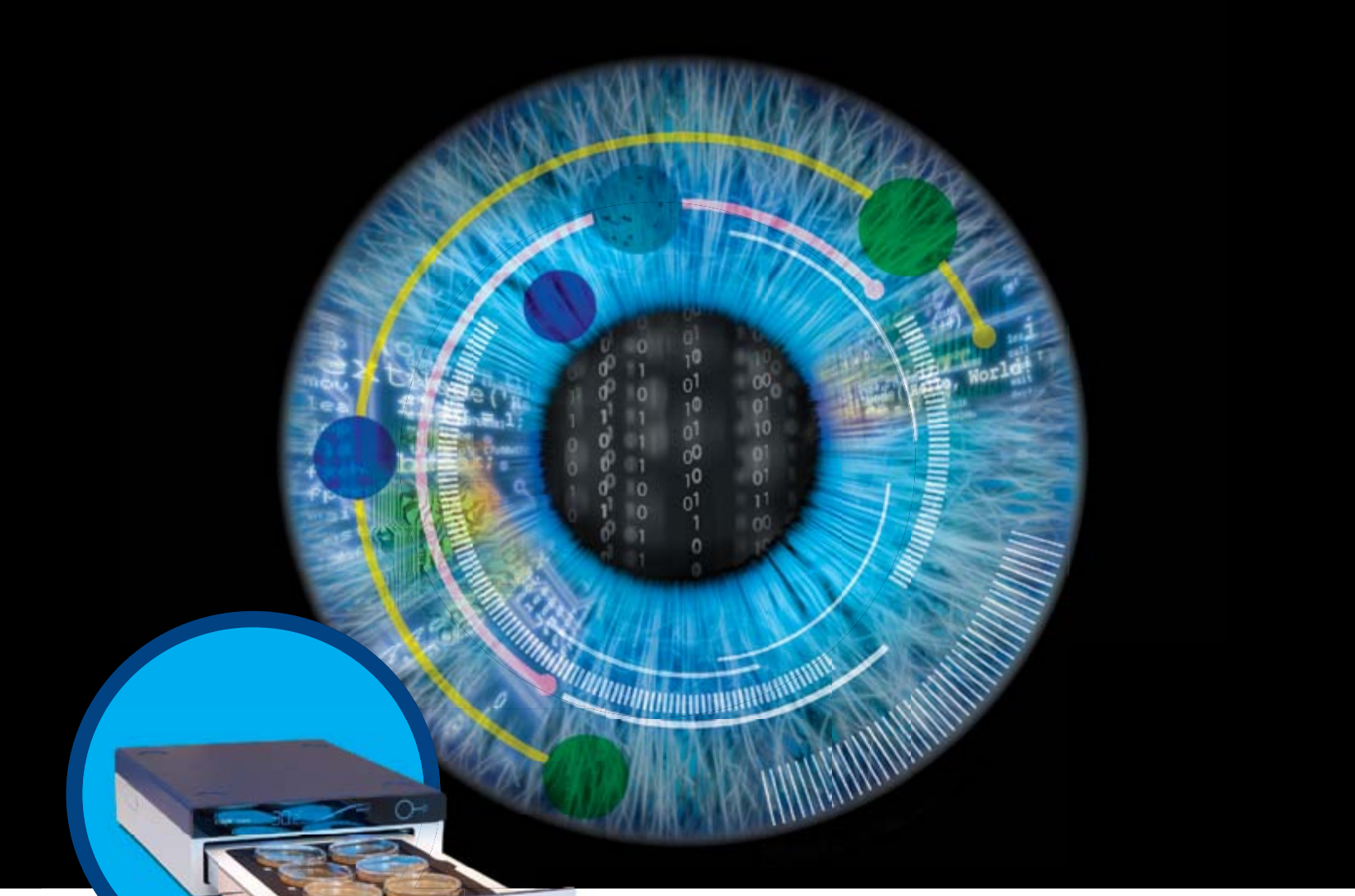

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