People • Science • Regulation

PDA Letter

Volume LIII • Issue 9 www.pda.org/pdaletter October 2017

Prefilled Syringe Manufacturing Moves Away from Hands-On Approach 28

The Parenteral Drug Association Education Department presents the...

2018 Annual Meeting Course Series

March 22-23, 2018 | Orlando, FL

Loews Sapphire Falls Resort

#PDAAnnual

Take advantage of PDA's industry-leading education course offerings at the *2018 PDA Annual Meeting Course Series*!

PDA will hold six courses specially designed to further your knowledge!

Specific course offerings include:

- *Recommended Practices for Manual Aseptic Processes* (**March 22**)
- *Container Closure Systems and Integrity Testing* (**March 22-23**)
- *Sterile Pharmaceutical Dosage Forms: Basic Principles* (**March 22-23**)
- *Cleanroom Management* (**March 22-23**)
- *Process Simulation Testing for Aseptically Filled Products* (**March 23**)
- *Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Validation and Ongoing Control* (**March 23**)

Learn more and register at *pda.org/2018AnnualCourses.*

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

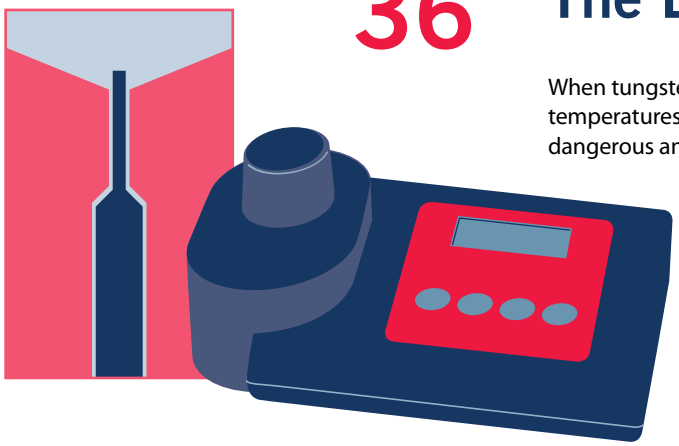
Receive the same training regulators receive when you attend a PDA course. PDA is accredited by ACPE and offers continuing education for professional engineers. Visit PDAtraining.org for a comprehensive list of all course offerings.

October 2017 PDA Letter

The Universe of Pre-filled Syringes and Injection Devices

Check out the latest advancements in prefilled syringes at the *Universe of Pre-filled Syringes and Injection Devices* in Vienna. For a preview of the sessions and exhibits at the meeting, look for articles with this banner at the top of the page.

Cover Photo Courtesy of Bosch GmbH



PDA Letter

Volume LIII • Issue 9 www.pda.org/pdaletter

The PDA Letter is published 10 times per year, exclusively for PDA members.

Articles published in the PDA Letter do not represent the official positions of PDA, Inc., but are the opinions of the authors submitting the articles.

Subscriptions are not available.

Departments

News & Notes

People

Science

Regulatory

Voices of PDA

Digital Exclusives

> **On the Issue** | Flexibility by Design
NNE's Alex Severin discusses how to design for flexible engineering at the 2nd PDA Europe Annual Meeting in Berlin

> The QC Lab of the Future
Find out what happened when a biologics manufacturer upgraded its laboratory asset management system

pda.org/letter

PDA GLOBAL HEADQUARTERS
4350 East West Hwy., Suite 600
Bethesda, MD 20814 USA
Tel: +1 (301) 656-5900
Fax: +1 (301) 986-0296
info@pda.org
www.pda.org

PDA EUROPE — AM BORSIGTURM 60
Am Borsigturm 60
13507 Berlin, Germany
Tel: 49 30 4365508-0
Fax: +49 30 4365508-66
info-europe@pda.org

PDA TRAINING & RESEARCH INSTITUTE
4350 East West Hwy., Suite 600
Bethesda, MD 20814 USA
Tel: +1 (301) 656-5900
Fax: +1 (240) 482-1659
info-tri@pda.org

Calling All Active PDA Members – Vote Now!

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

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

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

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

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

Instructions for Voting:

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

pda.org/vote

Exciting Times for Prefilled Product

The market for prefilled syringes is expected to reach $22.5 billion by the year 2025—that's eight years away, believe it or not ***(1)***—and the advancements in this area of pharma continue to grow. While glass remains the predominant packaging material, progress is being made in polymer syringes. Autoinjectors are now commonplace, and new types of delivery systems are under development.

I want to talk more about these new delivery systems because they are a sign of things to come. In 2015, University of North Carolina and North Carolina State University researchers developed a patch consisting of 121 microneedles. These microneedles contained specialized nanoparticles that release insulin in patients with diabetes experiencing high glucose levels ***(2).*** Other automatic insulin delivery systems are available, but this is the first to combine a microneedle patch with a biochemical reaction for controlling the release of insulin. This year, Kaleo reintroduced its AUVI-Q® autoinjector to the market. This product delivers epinephrine to patients suffering severe allergic reactions with an autoretractable needle. It also features voice instructions. Kaleo discussed this innovative product at the *2013 PDA/FDA Container Closure Components and Systems Workshop*.

Smart injection devices that connect with smartphone apps are also part of this new wave of technology. Bayer's BetaConnect® autoinjector delivers treatments for multiple sclerosis; it can also be synced with the myBETAapp to upload a patient's data to their smartphone or computer ***(3).*** The app can send reminder alerts for injections and includes an injection history that the patient can email their doctor ***(3).***

This all sounds pretty cool, but there will be challenges. This is all new territory and the growth of smart devices brings with it concerns about information security. Manufacturing systems will need to be adapted to these newer types of devices. In fact, the AUVI-Q® product was initially pulled from the market due to manufacturing issues. This spurred the company to move to a "100% automated production line" ***(4).***

All of this will be discussed at the upcoming *Universe of Pre-filled Syringes and Injection Devices* conference in the lovely city of Vienna. I will be there as well if you want to discuss these latest developments, the need for flexibility in manufacturing or just how to find the best *Mozartkugel* chocolates!

Rebecca Stauffer

References

1. "Prefilled Syringes Market Size To Reach USD 22.5 Billion By 2025." *Grand View Research.* (December 2016) http://www.grandviewresearch.com/press-release/global-prefilled-syringes-market (accessed Sept. 14, 2017).
2. Keener, A.B. "Next Generation: Smart Insulin Patch." *The Scientist* (June 22, 2015) http://www.the-scientist.com/?articles.view/articleNo/43355/title/Next-Generation--Smart-Insulin-Patch/ (accessed Sept. 14, 2017).
3. Allan, S. "ADVANCED DELIVERY DEVICES - How Data Hubs & Smart Devices Are Enabling the Rise of Therapeutic Ecosystems." *Drug Development and Delivery* (2016) http://drug-dev.com/Main/Back-Issues/ADVANCED-DELIVERY-DEVICES-How-Data-Hubs-Smart-Devi-1049.aspx (accessed Sept. 14, 2017).
4. Scutti, S. "EpiPen competitor alternative Auvi-Q returning soon." *CNN.com* (Oct. 27, 2016) http://www.cnn.com/2016/10/26/health/auvi-q-epinephrine-autoinjector-returns/index.html (accessed Sept. 14, 2017).

FDA Delays Quality Metrics Portal

The U.S. FDA continues to work on its quality metrics portal, though it will not be completed by the anticipated January date. **Tara Gooen Bizjak,** Senior Science Policy Advisor for Pharmaceutical Quality, CDER, FDA, made the announcement on Sept. 12 at the *2017 PDA/FDA Joint Regulatory Conference* during the "Quality Metrics" session, moderated by Amgen's **Steven Mendivil,** Senior Advisor, International Quality External Affairs.

Bizjak went on to explain that the Agency is seeking volunteers to test the portal prior to launch. Inquiries can be made to OPQ-OS-QualityMetrics@fda.hhs.gov.

The session also featured **Valerie Whelan,** Vice President, Corporate Quality, Amgen, who discussed Amgen's metrics journey. Following the presentation was a panel discussion featuring Bizjak, **Alex Viehmann** (CDER, FDA), **Barbara Allen,** PhD (Eli Lilly), **Deborah Autor** (Mylan), **Harry Jeffreys** (Catalent Pharma Solutions) and **Susan Schniepp** (Regulatory Compliance Associates).

PDA Publishes PtC on Aging Facilities

This summer, PDA published its *Points to Consider for Aging Facilities* document as part of an ongoing focus on manufacturing improvements. In some cases, noncompliant, aging facilities are a reason companies cease manufacturing, which may exacerbate drug shortages.

Points to Consider for Aging Facilities reflects the general thoughts of the pharmaceutical manufacturing industry on how to identify and modernize aging facilities. It covers eight critical areas to help companies avoid the traps encountered by other companies: Recognizing an Aging Facility, Impediments to Modernization, Business Case for Modernization, Impact of Changing Standards, Slowing the Aging Process and Regulations.

A team of industry experts developed this document based on responses to a PDA workshop held in March 2015 and a survey of PDA members conducted later that year. This team consisted of:

- **Ghada Haddad,** Merck & Co./Merck, Sharp & Dohme, Co-Chair
- **Maik Jornitz,** G-CON Manufacturing, Inc., Co-Chair
- **Glenn Wright,** Eli Lilly and Company, Inc., Co-Chair
- **James Butler,** Cimetrics
- **Jette Christensen,** PhD, Novo Nordisk A/S
- **Phil DeSantis,** DeSantis Consulting Associates
- **Robert Dream,** PhD, HDR Company, LLC
- **John Lewis,** DPS Consulting
- **Anette Marcussen,** Novo Nordisk A/S
- **Morten Munk,** NNE
- **Shelley Preslar,** Azzur Group, LLC
- **Susan Schniepp,** Regulatory Compliance Associates Inc.
- **Chris Smalley,** PhD, ValSource
- **Matthew Taylor,** Eli Lilly and Company
- **George Wiker,** AES Clean Technology

The document can be purchased at the PDA Bookstore (store.pda.org/ProductCatalog/Product.aspx?ID=3853).

PDA Volunteer Spotlight

Yves Mayeresse

- **Director, MSAT**
- ***GSK***
- Member Since | **2004**
- Current City | **Hermée, Belgium**
- Originally From | **Liège, Belgium**

PDA creates the perfect framework for sharing knowledge

Why did you decide to volunteer for PDA?
I first discovered PDA through publications and technical reports, and I then soon became a member. After participating in a few conferences as a speaker, I decided to try my hand at organizing different events as a planning committee member. I also helped PDA as an instructor for courses on risk analysis as applied to lyophilization. Additionally, I volunteered for the role of the Europe leader of PDA's Lyophilization Interest Group.

What have been some of your most memorable experiences at PDA to date?
There are plenty of memorable experiences, for example, when the session you moderate is so interesting that participants cannot stop debating the topic, making it difficult to keep the session on time.

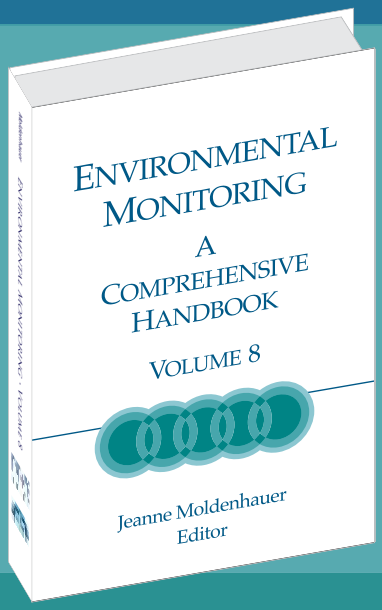
For me, my most memorable experience was receiving the Frederick D. Simon Award for the best paper published in the *PDA Journal of Pharmaceutical Science and Technology* in 2007. When I received this award, I gained further awareness of the extent of PDA's reach around the world and I was proud to be nominated.

What are some topics you would like to see covered at future PDA events?
I would like to see more coverage of primary technology in terms of upstream and downstream. Also, I would enjoy seeing more coverage of vaccine-related topics. Of course, this may be influenced by my background in vaccines!

How did your career aspirations as a child inspire you?
At the age of six, I wanted to become an engineer or a firefighter. My parents were impressed that I knew at this young age what I wanted to do. As you can imagine, I studied engineering. In school, I vacillated between electronics and biochemistry as career paths. But my work on embryogenesis during my high school degree was so fascinating that I chose an option linked to the life sciences.

PDA Bookstore New Release

Pre-order and Save 15% through **October 20, 2017**
Enter campaign code **EM8** during Checkout.



Environmental Monitoring: A Comprehensive Handbook, Volume 8

Edited by: Jeanne Moldenhauer

PDA MEMBER PRICE: ~~$260~~ $221
PDA NON-MEMBER PRICE: ~~$325~~ $276.25
HARDCOVER: ITEM NO. 17343
DIGITAL: ITEM NO. 18039

Volume 8 of the Environmental Monitoring Handbook series is a mixture of new topics and takes on previously discussed topics. In this volume, you will find information about regulatory/compendial updates, testing methods, risk methods and tools, and routine (and non-routine) monitoring.

This volume is a must have for anyone involved with environmental monitoring!

Table of Contents:

- Application of ISO 14644 Parts 1 and 2 For Cleanroom Contamination Control
- Microbial Monitoring in Cleanrooms: Use of Contamination Recovery Rates (USP <1116>), Real Time Monitoring, and the State of Contamination Control
- Environmental Monitoring for Sterile Compounding
- The Changing Expectations for Microbiological Testing of Pharmaceutical Products
- Particle Counting and Environmental Monitoring
- Contamination Control Using a Risk-Based, Automated Cleaning Validation Software System
- A Practical Approach to Investigating Environmental Excursions
- Environmental Monitoring: Taboos, Investigations, and Impact Analysis
- Environmental Monitoring and Its Impact on Assurance of Sterility
- Changing the Paradigm of Cleaning and Disinfection of Cleanrooms
- Aging Facilities and Modernizing Aseptic Processes
- Pros and Cons of Using MALDI-TOF MS for Microbiological Identification
- Environmental Monitoring Methods for Production Isolators

go.pda.org/EM8

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

Ireland Chapter Provides Once in a Lifetime Trip

Shane Costigan

My name is **Shane Costigan.** I recently graduated from University College in Dublin with a degree in microbiology and have been accepted in a master's program in biotechnology and business. At an event sponsored by PDA's Ireland Chapter, I saw a poster advertising a grant the chapter would award for students interested in attending the *2nd PDA Europe Annual Meeting* in Berlin. I applied and, thankfully, was chosen as one of the students afforded the opportunity to participate. As a result, I am now a member of the Ireland Chapter as a Young Professional member.

Arriving in Berlin ahead of the conference, I had no idea what to expect. I wondered if I would have sufficient background knowledge to follow the talks and even take something from them. Fortunately, the greeting I received upon registration was a sign of things to come. Here, representatives of the Irish Chapter recognized us students and gave us as warm a welcome as one could receive. **Mike Morris**, head of the chapter, **Declan Quinlan** and **Catriona Murphy** went out of their way to make us feel not only at ease but an important part of the conference.

It would be close to impossible to provide an in-depth analysis of each talk, so I will focus solely on the ones that resonated with me. First, **Falk Klar** opened the conference by providing a breakdown of the conference. He then introduced a series of speakers who focused on the topic of vaccines. This was of particular interest to me as, throughout my college life, I had always wondered if the pharmaceutical industry was doing all it could in providing those less fortunate with the medicines they need. WHO's **Emer Cooke** talked about what she deemed to be the biggest obstacles: access and availability. She also highlighted a critical problem for the industry: counterfeit drugs. Street vendors are selling vaccines, or products labeled as vaccines, at a much lower cost but of questionable quality. Recently, measures have been put in place to counteract this. But challenges remain given the criminal elements involved. She also commented that, as an industry, pharma has been slow to respond to counterfeiting as compated to other industries. The blame must be a shared by industry and regulators.

The conference attendees not only listened intently but asked specific questions about what needs to improve, which really struck me. There is a true desire from the industry to listen to the WHO and help in any way possible. One delegate

summed it up for me when he said, "the pharmaceutical industry should be about doing well by doing good."

Having worked in the quality function of a pharmaceutical company during one summer, I was excited at the prospect of attending a later presentation based on growing a culture of quality. The perception of quality within industry seems to be an issue. The old methods of policing and punishing are dead. There is now a need to look ahead and train our teams. A holistic approach backed by strong leadership is required to build an ethos that promotes accountability. The industry needs to reward individuals who raise issues rather than sustain an environment that creates a fear of mistakes. **Frederik Asell** proposed a new standard where the culture of quality grows from the bottom up. In this system, friends and colleagues push each other to promote quality and reward accountability. This system really did seem to me like the way forward. But these things are much easier said than done and implementing this new culture over the old one will be no easy feat. Still, I aspire to be a part of it in the future.

On Tuesday evening, we were all invited to attend a networking event in Berlin at Pier 13, a restaurant down by the river, where we enjoyed food and drinks and a spectacular performance from the PDA Europe Band. Everyone was in great spirits and it was a fantastic opportunity to network in a relaxed setting.

Overall, the conference was without doubt the most rewarding experience of my career so far. In college you are surrounded by a bubble: learn this and understand that. But there is no significant background as to why you learn what you do on a daily basis. It is very hard to look to the future and see where the educational path you are on will eventually take you. The *2nd PDA Europe Annual Meeting* gave me the opportunity to see where this path may eventually lead. It has provided me with a unique insight into the inner workings of the pharmaceutical industry. In addition to this, PDA Europe has shown the willingness of everyone involved to work together and build a better future—a future built around quality of life, transparency and harmonization.

Again, many thanks to the PDA Ireland Chapter for this memorable opportunity.

[Editor's Note: For a summary of the Annex 1 workshop preceding this meeting, see p. 43.**]**

PDA Who's Who

Frederik Asell, AstraZeneca

Emer Cooke, Head of Regulation of Medicines and other Health Technologies, WHO

Falk Klar, PhD, General Manager, Vice President PDA Europe

Mike Morris, formerly Irish Health Products Regulatory Authority

Catriona Murphy, EU Qualified Person, Eli Lilly

Declan Quinlan, Operations Director, MSD Ireland

The Top Three Things Holding You Back From a Promotion

Roberta Chinsky Matuson, Matuson Consulting

You work really hard, perhaps too hard. And you're doing what you believe are the right things in order to advance your career. Yet, here you are. In the very same role where you started. The word "frustrated" cannot begin to describe what it feels like to be in this position.

In my work as an executive coach and job search mentor, I have seen this scenario countless times. In particular, I see three things holding people back from being promoted.

Failure to self-promote | Early in my career, I daydreamed about receiving calls from headhunters near and far asking me to consider new opportunities. In retrospect, my time would have been better spent letting my boss and her colleagues know about all the great work I was doing, as my daydreams never did come true.

In today's workplace, there is much competition for attention. As I wrote in my book, *Suddenly in Charge,* you have to pump up the volume and make enough noise so people in the organization know who you are and what you are accomplishing. You do not want to be obnoxious in promoting yourself, but others in the organization need to know your value; they are not likely to find out unless you make them aware.

Think about one or two things you are most proud of and be sure to weave these accomplishments into your everyday conversation with your boss and their peers. Do not worry about sounding boastful. People will see you as a person of interest, which is exactly how you want to be seen in order to get noticed.

Lack of confidence | Imagine you are the boss and have to decide who to promote into a leadership position. You have one employee who is confident and rarely reorts to second-guessing and another employee who is always looking to you for validation. If you are like most people, you choose the candidate exuding confidence.

If you are more like the candidate with a lot of self-doubt, you need to work on increasing your confidence level. This starts with a new mindset: You have to believe you are in your job because someone thought you had what it takes to do the job. Otherwise, they would have hired someone else. You also have to believe you deserve the promotion you seek.

You can hire a coach to help you work on boosting your confidence. If that's not in your budget, then consider asking a trusted work colleague to signal when you are sliding back into self-doubting behavior. You can also work on increasing your skill level by reading books or taking online courses in areas where you want to improve.

Not asking for a promotion | It is certainly nice to be tapped on the shoulder and asked to take on more responsibility at work. But that is not always how promotions occur. Sometimes the person who asks for the job is the one who actually gets it.

You may be thinking, "How do I ask for a job that I don't even know is available?" Well, you do not have to ask for a specific promotion; you can simply tell your boss you are interested in taking on more responsibility and that you would like to be considered for a promotion the next time a position opens up. A reminder every now and again will be helpful as well, to ensure you stay on top of mind.

About the Author

Roberta Chinsky Matuson, The Talent Maximizer® and President of Matuson Consulting, helps organizations achieve dramatic growth and market leadership through the maximization of talent. She is the author of four books including the newly released, *The Magnetic Leader.*

PDA Photostream www.flickr.com/parenteral-drug

2017 PDA/FDA Biosimilars Conference

June 26–27 | Bethesda, Md.

(l-r) Steven Kozlowski, MD, CDER, U.S. FDA; Niklas Ekman, PhD, Finnish Medicines Agency; Birgit Schmauser, PhD, German Federal Institute for Drugs and Medical Devices; Sarah B. Kennett, PhD, CDER; Stephan Krause, AstraZeneca Biologics

(l-r) Alla Polozova, PhD, Amgen; Laurent Chevalet, PhD, Merck Biosimilars; Michael VanDerWerf, Halozyme Therapeutics, Inc.

(l-r) Birgit Schmauser, PhD, German Federal Institute for Drugs and Medical Devices; Patrick J. Lynch, PhD, CDER; Jeff Yant, PhD, Amgen; Emily Shacter, PhD, ThinkFDA; Jens Schletter, PhD, Sandoz; Marjorie A. Shapiro, PhD, CDER

The Universe of Pre-filled Syringes and Injection Devices

Course Sheds Light on Prefilled Manufacturing

Interaction between drug delivery system and drug product. Quality Control. Stability. These are some of the extra concerns that pharmaceutical manufacturers face when producing prefilled syringes. Sterile products have always presented challenges but prefilled syringes amplify these challenges.

In light of this, PDA Europe is offering a new, two-day course on prefilled syringe manufacturing following the *Universe of Pre-filled Syringes and Injection Devices.* The *PDA Letter* spoke with instructor **Egmont Semmler,** PhD, Director R&D Pharmaceutical Fill and Finish, Groninger, about the new course.

What spurred the development of this new course?

The course, "Development and Manufacturing of Pre-filled Syringes,"covers the latest trends in prefilled syringes, aseptic manufacturing and drug delivery. We have been working on this course with several partners to deliver a complete picture of the manufacturing process from forming to nested objects, testing and visual inspection, container closure, regulatory aspects and, finally, insertion into drug delivery devices. We especially focused on practical, hands-on applications so that students will have the opportunity to perform and understand key aspects (particles, siliconization, elastomers for closures, plunger testing, filling) around prefilled syringes.

Will the course address some of the newer, more flexible technologies available for prefilled syringe manufacturing, such as robotic filling lines, compartmentalized isolators, etc.?

Yes, the course will also address these emerging technologies and their benefits to the manufacturing process for prefilled nested components. Where applicable, we will go in depth and discuss the risks and benefits.

How will the course address manufacturing in an aseptic environment?

It will address aseptic manufacturing throughout the entire prefilled syringe product lifecycle, starting with the glass forming/injection molding process for a glass/plastic syringe and the requirements to control particle load and microbial ingress, continuing to aseptic processing in filling to insertion into drug delivery devices. The most important aseptic concepts, e.g., RABS and isolators, will be discussed with a focus on prefilled syringe production.

What technologies and equipment will students be using in the hands-on sessions?

The students be able to turn lecture contents directly into practical experience using our trial equipment. We will have equipment for siliconization, filling, stoppering, qualitative function testing and quantitative particle/siliconization testing. Furthermore, we will have a number of samples of prefilled syringes from different manufacturing steps, from raw materials to a fully integrated device, so the students can experience the look and feel to enhance their understanding.

Who would benefit from this course?

This course would be of value to pharmacists, engineers and anyone dealing with prefilled syringes on a daily basis who wants to understand them more in depth and how they differ from traditional parenteral products.

I also welcome professionals from adjacent fields who want to broaden their perspective on prefilled syringe manufacturing.

As an instructor, what is your main goal for this course? What do you want students to take away from it?

I sincerely hope that students will enhance their understanding of prefilled syringes as a primary container for their drug and drug delivery systems. Students should be able to evaluate and determine root causes of potential failures around prefilled syringes. Additionally, they will have the tools to prevent these issues by choosing the right delivery system and closure upfront along with awareness of the detailed interactions between prefilled syringes and drugs.

Development and Manufacturing of Pre-filled Syringes

Vienna

Nov. 9–10

www.pda.org/EU/WSPrefilled2017

The Parenteral Drug Association presents the...

2017 PDA Cell and Gene Therapy Conference

December 5-6, 2017 | San Diego, CA

Manchester Grand Hyatt San Diego

Exhibition: December 5-6

#2017CGT

The Journey of Cell and Gene Therapy – Bringing Science to Reality

Discover best practices and novel approaches for the development and commercialization of pharmaceutical and biopharmaceutical products at the *2017 PDA Cell and Gene Therapy Conference*.

The Conference will feature presentations from leading pioneer academic researchers and industry experts on topics carefully chosen to meet the needs of this fast growing and ever-changing industry.

This Conference highlights current and future applications for emerging therapeutic entities such as the inventive field of immunotherapy – gene- and cell-based therapies. Hear directly from the experts about the science and technology needed to bring these innovative products to market.

Plenary sessions will also focus on topics regarding process development and manufacturing, including:

- Next-generation approaches in gene and cell therapies
- Leveraging big data to speed cell and gene therapy product development
- Development of a process control strategy

Gain more insight about this exciting and rapidly growing field and the tools necessary to keep pace with the latest developments!

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

SNAPShot

A Handy Guide to Preventing Contamination

Andrew Dick, Johnson & Johnson, and Marilyn Foster, PDA

The prevention of microbiological contamination in the nonsterile manufacture of drugs and consumer products is paramount to maintaining a robust supply chain and ensuring consumer safety. Consequently, the importance of understanding, practicing and maintaining control of sanitation in a manufacturing plant cannot be emphasized enough.

For these reasons, the upcoming PDA book, *Handbook on Contamination Prevention for Nonsterile Pharmaceutical Manufacturing,* will provide solutions to ongoing contamination events. Chapters will cover:

- Facility Layout
- Equipment Design, Components, and Maintenance
- Cleaning and Sanitization Practices
- Purified Water System and Microbiological Controls
- Hygienic Manufacturing Practices (Raw Materials and Sampling)
- Personnel
- Plant Microbiological Risk Assessment and Qualification Checklist

Handbook on Contamination Prevention for Nonsterile Pharmaceutical Manufacturing will be available shortly for purchase in the PDA Bookstore (www.pda.org/bookstore).

Journal *Top10*

PDA Papers on Particulates and PACs and PQRI Papers on Extractables Popular Reads

Below are the top ten articles from the *PDA Journal of Pharmaceutical Science and Technology* (journal.pda.org) for the month of August.

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

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

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

4. PDA Paper
Emma Ramnarine, et al. "PDA Points to Consider: Technical Product Lifecycle Management. Pharmaceutical Quality System Effectiveness for Managing Post-approval Changes" May/June 2017

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

6. Review
James Agalloco "Increasing Patient Safety by Closing the Sterile Production Gap—Part 1. Introduction" July/August 2017

7. Review
Robert A. Schaut and W. Porter Weeks "Historical Review of Glasses Used for Parenteral Packaging" July/August 2017

8. Review
James Agalloco "Increasing Patient Safety by Closing the Sterile Production Gap—Part 2. Implementation" July/August 2017

9. Review
James Agalloco "Increasing Patient Safety by Closing the Sterile Production Gap—Part 3—Moist Heat Resistance of Bioburden" July/August 2017

10. Research
Dennis Jenke, et al. "Simulated Leaching (Migration) Study for a Model Container-Closure System Applicable to Parenteral and Ophthalmic Drug Products" March/April 2017

One Company's Approach to Rapid Micro Methods

The Vision and Experience at Merck, Sharp and Dohme Corp.

Mousumi Paul and Scott Hooper, Merck Sharp and Dohme Corp.

Microbiology is a relatively old science. Many of the microbiological techniques in use today were developed over a century ago. These techniques include growth-based methods, which assume culturability of organisms, require days of incubation for adequate growth, and depend on visual examination for growth. Rapid Microbiological Methods (RMM) offer answers to a number of business drivers and improvements to existing technologies. At MSD, there is an effort to accelerate innovation through migration of conventional microbiological methods to RMM. Some of the drivers and benefits of the rapid methods we are targeting include:

- significantly reduced time to result (TTR) to support earlier release of product,
- automation and efficiency to reduce lab costs,
- improvements in process control with frequent or real-time monitoring, increasing the possibility to intervene earlier in a contamination event, and
- bringing technology to the shop floor for troubleshooting and aid decision-making

Despite these benefits, deploying RMM present unique challenges and requires strategic effort for broader engagement with stakeholders both internally and externally. In sharing an overview of our implementation process, MSD hopes to increase industry-wide acceptance for adoption of RMM.

RMM fall into three categories: growth-based, indirect and direct detection methods. Growth-based methods are comparable to the compendial methods; the difference is earlier detection of growth. In contrast, indirect and direct detection methods produce results in nontraditional units such as fluorescence units, and can detect viable non-culturable organisms. As such, their reads are sometimes more sensitive than traditional methods. Therefore, these methods require more intensive validation approaches to establish correlations and define new thresholds.

Two-Prong Deployment Strategy

At MSD, our approach to RMM development and deployment includes both new and existing products/processes.

For in-line/existing products, the value proposition of switching to RMM is defined, engaging with sites/business units prior to the migration process. Since ➤

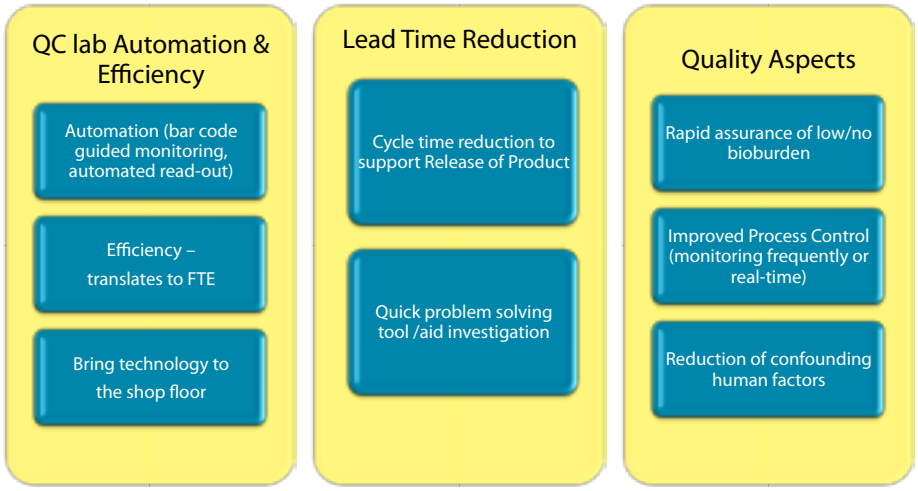


Figure 1 RMM as an Enabler for World Class Supplier Vision

there will likely be a change in regulatory filings for these products, this necessitates a compelling business case for making this change, such as a comparison of RMM with the conventional method along different dimensions (cost, resources, cycle time, validation, industry use and experience, etc.). The second step is the selection of the right technology and deployment to a targeted site for strategic deployment, where the RMM has high value and limited scope or proceed with multi-site/multi-product implementation.

For new products and processes, Merck's intent is to develop guidance that will outline how research labs and product development teams can adopt RMM during development and commercialization. Throughout process and product development, RMM will be a standard testing method, moving the company in the direction where RMM is a standard for microbiological testing of new products prior to reaching commercialization.

Implementation Occurs in Phases

The first of many phases in implementing RMM is a design phase. Here a critical point in a process is selected and requirements are evaluated. Next, a research on commercially available RMM for compatibility and robustness is done. This is not a one-size-fits-all approach; even applications using the same compendial method may require a different RMM to suit their needs. During the design phase, relevant regulatory and compliance standards, such as data integrity need consideration. In all circumstances, the RMM must have a clear advantage over the traditional method before implementation.

Development consists of a proof of concept (POC) studies in one or more of our research labs. Data is collected to ensure the ability of the RMM in question to meet microbiological testing compendial requirements, as well as internal requirements. These requirements include suitability of the instrument for its intended use, its accuracy, precision, ease of use, feasibility for implementation, and overall business benefit. Once the POC is executed, there is close collaboration with the internal statistical group to assess the POC data to develop a validation model.

Implementation is comprised of equipment qualification, method validation, and method transfer. This starts with installation, operational, and performance qualifications of the equipment at the pilot site. During validation, samples are tested in parallel using the rapid and conventional methods. Validation ensures that the robustness, specificity, accuracy, and precision of the rapid method are equivalent or better than the compendial method. Next, method suitability testing is performed to establish how the technology will be used when the RMM is in operation. Once the RMM is qualified, we are able to implement it for use at the pilot site. This site's use of the technology then becomes the model for implementation at other sites across the MSD network.

Globally, there are protocols for method transfer across sites, which enable standardized implementation of RMM once the process is completed at a single site. Figure 2, illustrates this global implementation strategy. In Phase 1, the RMM is impemented at a single site as described above, and in Phase 2, the methods are transferred globally from the initial validation site.

Example of RMM deployment: BacT/ALERT for Rapid Sterility Testing

One of the RMM that Merck has implemented is the BacT/ALERT by BioMérieux **(Figure 3),** which is a rapid method for sterility testing. The BacT/Alert system is comprised of liquid culture media bottles and a computerized system that reads the bottles for samples and alerts the user for positive results. Fluid samples under 10 mL in volume are injected into the media bottles, and an indicator in the bottle turns yellow in the presence of

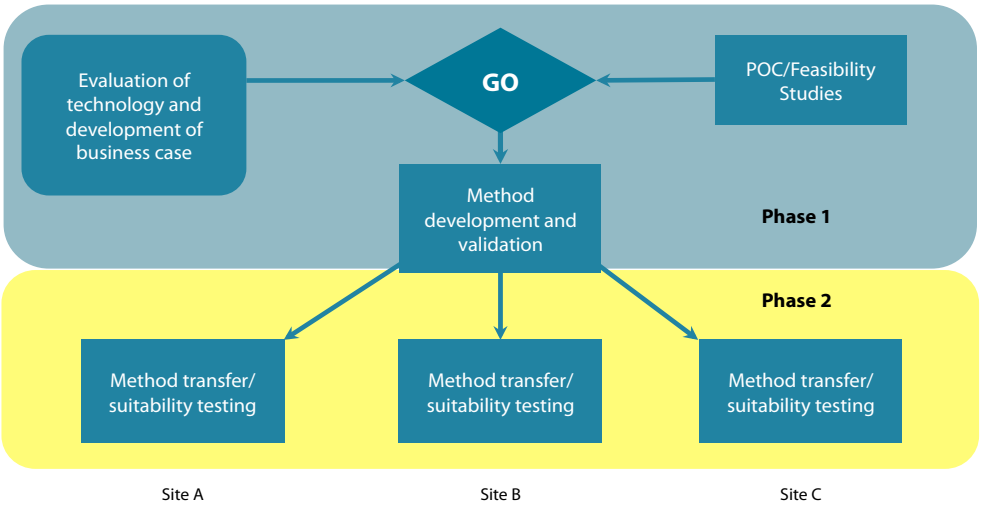


Figure 2 Global Implementation Strategy for RMM

carbon dioxide. An LED shines on the indicator region of the bottle, and the machine detects the reflected light using a photodiode.

The BacT/ALERT presents a number of advantages over conventional sterility tests. It is suitable for suspension products, processes containing antimicrobials, and for non-filterable low volume samples. Sterility testing via the BacT/ALERT system can done on the shop floor, saving time, and energy. By performing 20-25°C incubation at the same time as 30-35°C anaerobic incubation, the system significantly reduces cycle time. It also increases process efficiency by interfacing directly with LIMS and providing automatic readouts and alerts. Automation improves data integrity and efficiency gains greater focus on other parts of the process.

The implementation process for the BacT/Alert system is well underway. The BacT/Alert system was validated at a single site, where the Microbiology Center of Expertise developed and validated the method. At MSD we have implemented this technology at a number of sites and continue to expand.

Example of RMM deployment: MuScan for Rapid Bioburden Testing

Another example of an RMM currently moving through the implemenation process is theMuScan by Innosieve Diagnostics. In some of our downstream biologics purification columns, current sanitization methods are aggressive to ensure there is no microbial contamination in the biologics processes. These sanitization methods, however, lower the lifecycle of the purification columns. As these columns are costly and microbial proliferation must be prevented, this is a strategic point for a high-value RMM to be introduced. Our main criterion for the RMM was the ability to measure bioburden without incubation and with higher sensitivity than traditional bioburden methods, resulting in a sanitization program based on action and alert limits rather than regular intervals of sanitization. This led to establishment of a decision tree **(Figure 4),** where low bioburden triggers less aggressive sanitization and high bioburden triggers more aggressive sanitization. A lighter sanitization regimen will extend the lifecycle of the columns reducing the frequency of costly replacement.

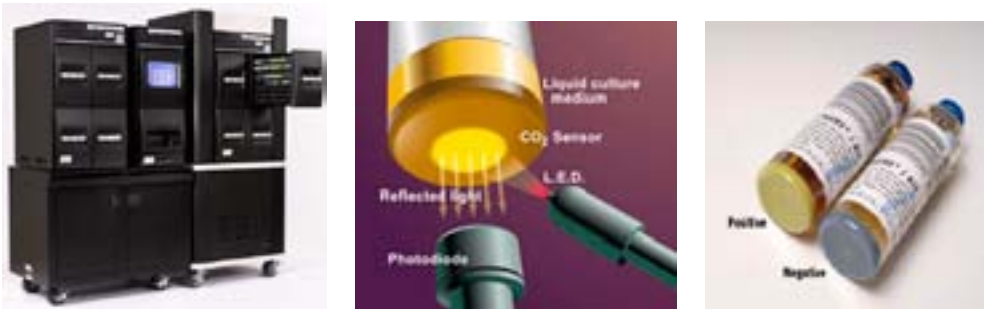


Figure 3 The BacT/ALERT system

A number of technologies were evaluated, and the company settled on MuScan, a direct detection method for detecting bioburden in samples where the sample is filter-retained, stained, and read. It has a time-to-result of one hour with no incubation, and can detect viable, non-culturable contaminants. Therefore, the MuScan is more sensitive and has a TTR advantage over traditional bioburden testing, which requires up to five days of incubation.

We are in the early stages of evaluating the MuScan. POC studies have commenced to characterize the performance of the MuScan technology to develop a sensible monitoring strategy using the MuScan technology (FFU) instead of the compendial method (CFU).

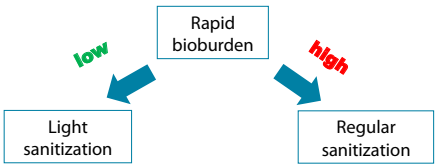


Figure 4 Decision Tree

Adoption of the MuScan along with a portfolio of other RMM allows MSD to respond better to business and quality needs. With plans to further global implementation of RMM, we envision having shorter lead times, better detection for product and facility protection, improvements in sensitivity and benefits gained in automation. The business and quality drivers that have led MSD to use RMM are not unique to the company, but rather are industry-wide challenges and desires. By sharing this information about MSD RMM implementation strategy, the company hopes to see broader collaboration within the industry for development of automated and reliable RMM accepted by regulators.

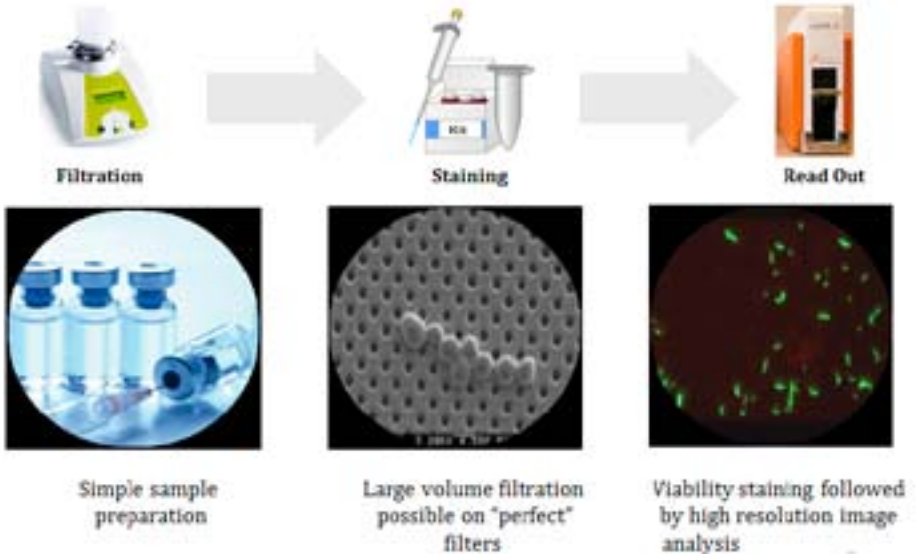


Figure 5 MuScan technology

Continued at bottom of page 43

PDA
Parenteral Drug Association

The Parenteral Drug Association presents:

PDA Europe Conference, Exhibition

Pharmacopoeia Conference

Convergence, Harmonization & The Future Direction of Pharmacopoeias

MARK YOUR CALENDAR!

28-29 May 2018

Vienna, Austria

pda.org/eu-pharma2018

The Universe of Pre-filled Syringes and Injection Devices

Two Views on Packaging from Prefilled Exhibitors

Packaging-related topics will be a focus of numerous sessions and demonstrations at the upcoming Universe of Pre-filled Syringes and Injection Devices *conference and exhibition. Below are articles from two of the companies that will be exhibiting.*

How to Evaluate Packaging Options for Parenteral Drug Products

Crystal Kraft, PhD, West Pharmaceutical Services, Inc.

Drug packaging is an integral part of the safety and efficacy of a drug product. Despite this fact, the intricacies of primary packaging often are not considered until late in the drug development process, or worse, until there is an issue with the final packaged product. A relationship between suppliers and drug manufacturers that enables technical and scientific conversations as early in the process as possible ensures that packaging will best meet the needs of both the patient and the drug product.

In order to evaluate the chemistry, safety and performance of container and delivery systems (e.g., prefilled syringes), supplier labs employ a number of analytical and compendial methods (e.g., USP, ISO, Ph. Eur., etc.). These test methods are important to ensure regulatory compliance, confirm basic fitness for purpose and inform drug manufacturers of the best packaging for their drug products. There are numerous potential failure modes for containers and delivery devices, some overlapping and some unique (see **Figure 1).**

The key to preserving the safety and efficacy of a drug product is to consider and evaluate these failure modes early and often. From a supplier perspective, materials should be tested to their extreme limits in order to generate useful data to inform optimal design. From a drug manufacturer perspective, while accelerated testing conditions and supplier testing data can support in-house regulatory qualifications, the most important information comes from evaluating the packaging under conditions of use. Conditions of use comprise containment of the drug product in the actual environmental conditions in which the drug product will be handled and stored (e.g., in cold rooms undergoing end-over-end rotation or at cryogenic temperatures) to determine physicochemical compatibility with container materials, stability and shelf life. If these tests are performed early in the pack-

Continued on page 24

Extractables Profile of Aluminosilicate Glass Prior to Chemical Treatments

Claudia Heinl, PhD, Schott AG

As the complexity of modern drug products grows from a chemical and physical point of view, packaging and storing these products safely against environmental influences is ever more challenging. Therefore, possible drug/container interactions are an increasing focus in primary packaging development.

These interactions mainly depend on three factors: the chemical composition of the glass packaging material, the conversion process (i.e., the transformation of glass tubing into containers), including any additional surface treatments and, finally, the drug product itself. Regarding the first aspect, the composition of glass varies among different glass types as well as among different manufacturers. In consequence, the composition of a glass gives first indications for potential sources of extractables.

Glass, in general, consists of so-called network formers, such as silicon, boron and aluminium, as well as network modifiers like alkaline metals (e.g., sodium, potassium) and alkaline earth metals (e.g., calcium, magnesium). In this case study, the number of components, which are extracted from the inner surface of two different glass types, namely a borosilicate and an aluminosilicate glass (see **Table 1),** are compared.

This study used untreated glass tube sections of the different glass types in order to exclude the influence of the converting process. These tube sections were closed in a suitable manner, filled with ultrapure water and autoclaved for one hour at 121 °C according to ISO 4802-2 ***(1).*** Due to the harsh conditions, this method is suitable to quickly reveal the chemical stability of the inner surface of the glass. The analysis of the extracted elements was performed by means of inductively coupled plasma mass spectrometry and inductively coupled plasma-optical emission spectrometry, respectively. The exemplary results are given as their oxides and displayed in **Figure 1.**

This study shows that the total amount of extractables from the borosilicate glass

	Network Formers			Network Modifiers			
	Si	Al	B	Na	K	Ca	Mg
Borosilicate Glass	✓	✓	✓	✓	–	✓	–
Aluminosilicate Glass	✓	✓	–	✓	✓	✓	✓

Table 1 Elements in the Composition of the Glass Types Tested

Continued on page 25

How to Evaluate Packaging Options for Parenteral Drug Products continued from page 23

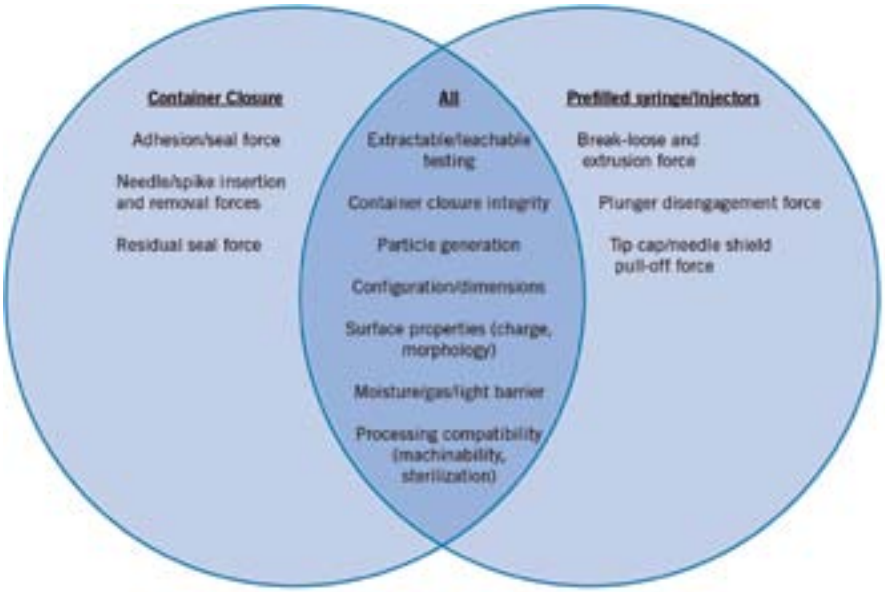


Figure 1 Potential Failure modes for Containers and Delivery Devices

age design and drug development phases, and a packaging component or system fails a test, adjustments to the controls, processes or packaging can be made with less impact to the drug's supporting regulatory files. To prevent costly changes and ensure the highest level of quality—based on robust science and risk management—the ICH Quality by Design (QbD) approach should be employed in packaging development, and packaging should, in turn, be included in the drug development QbD process.

Use of QbD principles at each step builds product and process understanding that can enable minimization of the risk of failures throughout the parenteral drug product lifecycle.

About the Author

Crystal Kraft, PhD, is a Manager of Scientific Affairs at West Pharmaceutical Services, Inc., where she serves as an industry liaison and provides cross-functional scientific support.

Extractables Profile of Aluminosilicate Glass Prior to Chemical Treatments continued from page 23

is ~60% lower compared to the aluminosilicate glass type. Tests of the hydrolytic resistance as described in current regulations do not include all these elements, but rather focus mainly on the extraction of sodium oxide ***(2,3).*** As can be seen in **Figure 1**, sodium oxide exhibited the largest difference (0.5 mg/L vs. 2.2 mg/L, respectively) in extractables between these two glass types. Furthermore, the study also revealed that the major proportion of the extractables can be attributed to silicon (2.8 mg/L vs. 6.5 mg/L, respectively) as it represents the major component of both glass types. These exemplary results indicate a weaker glass attack and a higher stability toward water for the borosilicate glass type.

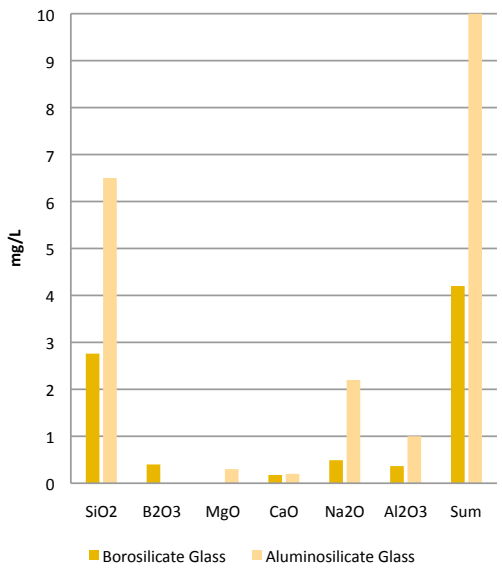


Figure 1 Extractables from Borosilicate and Aluminosilicate Glass Tubing after Autoclaving with Ultrapure Water (1 h, 121°C)

In conclusion, this case study demonstrates that the amount of extractables significantly differs between different glass types, not only in the level of network modifiers, such as sodium, but also network formers such as silicon.

Taking into account that the converting process tends to negatively, rather than positively, affect the extractables profile, there is a risk that without complex chemical treatment of the inner contact surface of an aluminosilicate glass container, certain standards expectations and requirements for today's parenteral primary packaging might not be achieved. Subsequently, a stringent incoming inspection would need to be implemented to unambiguously avoid intermixture with potentially untreated containers.

References

1. ISO 4802-2:2016, *Glassware – Hydrolytic resistance of the interior surfaces of glass containers*, ISO, 2016.
2. Ph. Eur. 9.2, *Chapter 3.2.1 Glass containers for pharmaceutical use*, European Pharmacopeia, 2017.
3. USP 40, NF 35, *Chapter <660> Containers – Glass, United States Pharmacopeia*, 2017.

About the Author

Claudia Heinl is a Product Manager for SCHOTT Pharmaceutical Tubing.

2017 PDA Upcoming Events

SAVE THE DATE for PDA's 2017 Events

OCTOBER

16-18
12th Annual PDA Global Conference on Pharmaceutical Microbiology
Bethesda, MD
pda.org/2017Micro

18-19
Best Practices for Glass Primary Containers
Mainz, Germany
pda.org/EU/GPC2017

18-19
2017 PDA Endotoxins Workshop
Bethesda, MD
pda.org/2017Endotoxins

19-20
12th Annual PDA Global Conference on Pharmaceutical Microbiology Course Series
Bethesda, MD
pda.org/2017MicroCS

23-24
2017 PDA Visual Inspection Forum
Bethesda, MD
pda.org/2017Visual

25-26
An Introduction to Visual Inspection
Bethesda, MD
pda.org/2017OctVI

25-26
NEW COURSE
Temperature Sensitive Packaging and Distribution for Biopharmaceuticals
Franklin, MA
pda.org/2017Temp

NOVEMBER

1
Training Effectiveness: What's Your Design Strategy?
Bethesda, MD
pda.org/2017TE

1-3
Environmental Monitoring Course Series
Bethesda, MD
pda.org/2017NovEM

2
Strategies for Reducing Human Error Nonconformances
Bethesda, MD
pda.org/2017HE

6
Pre-Conference Workshop: Connected Health & Drug Delivery – Improved Patient Convenience and Adherence Through New Technnologies
Vienna, Austria
pda.org/EU/CONNECTED

6
Pre-Conference Workshop: Impact of Pre-filled Syringe Packaging Components on Biopharmaceuticals
Vienna, Austria
pda.org/EU/PSPC-UPS2017

6
Pre-Conference Workshop: Innovative Drug Delivery Systems/ Combination Products
Vienna, Austria
pda.org/Eu/DDS-UPS2017

7-8
The Universe of Pre-filled Syringes and Injection Devices Conference
Vienna, Austria
pda.org/EU/UPS2017

9
Container Closure Development
Vienna, Austria
pda.org/EU/CCD2017

Denotes Laboratory Courses | Denotes Lecture Courses

PDA®
Parenteral Drug Association

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

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

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

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

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

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

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

14-17
Facilities and Engineering Course Series
Bethesda, MD
pda.org/2017FacilitiesCS

15-16
COURSE IN GERMAN LANGUAGE
Track und Trace – Implementierung von Serialisisierung, Fälschungssicherheit und Verifizierung
Leipzig, Deutschland
pda.org/EU/TRACK-UND-TRACE2017

21-22
Outsourcing & Contract Manufacturing Conference
Munich, Germany
pda.org/EU/Outsourcing2017

23-24
Outsourcing, Technology Transfer, and CMO-Client Relationships
Munich, Germany
pda.org/EU/cmo-tt-17

23-24
Practical Guide for Root Cause Investigations – Methodology and Tool Kit
Munich, Germany
pda.org/EU/RootCause2017

23-24
Risk Management in Technology Transfer
Munich, Germany
pda.org/EU/RM2017

28-29
2017 PDA Modern Biopharmaceutical Processing Conference
Singapore
pda.org/2017BiopharmSingapore

DECEMBER

4-7
Fundamentals of Aseptic Processing
Bethesda, MD
pda.org/2017DecFundAP

5-6
2017 PDA Cell and Gene Therapy Conference
San Diego, CA
pda.org/2017CellGene

7-8
Evaluation, Validation and Implementation of Alternative and Rapid Microbiological Testing Methods
Bethesda, MD
pda.org/2017Rapid

11-14
PDA Quality Risk Management Certificate Program
Bethesda, MD
pda.org/2017QRMTP

Prefilled Syringe Manufacturing Moves Away from Hands-On Approach

J. Martin Bultmann

When talking about production of sterile dosage forms, the term *manufacturing* is still commonly used. But when one breaks up the word according to its Latin origin (*manu* = hand, *facere* = make), meaning to create something with ones' own hands, a dichotomy emerges when referencing manufacturing of sterile product, including prefilled syringes. In actuality, isolators and RABS provide a boundary between the product and the operator. Due to the requirements of high throughput, time-consuming manual operations have already been replaced by automation. But is this status quo still sufficient, or is greater flexibility required?

The most widely used systems currently employed consist of highly automated processes comprising conveyor belts, handling stations, concealed gears and drives and sensors in a aseptic environment. The typical design of such a machine is a sequential layout engineered for a specific type of primary packaging material, usually optimized for high throughput—and very often of just one single product.

This design has proven to be very valuable throughout the last two decades and will continue to work in the future for mass produced medications, but will mass production still prevail as *the* model for the future?

Article at a Glance

- Smaller, personalized batch sizes necessitate more flexible systems
- Future systems will need to accommodate different types and numbers of products
- Robotic systems offer advantages

Better is the Enemy of Good

Meanwhile, things are changing. The preeminence of high-volume blockbusters is likely decreasing for most therapeutic areas. Additionally, the more specific a disease is treated, the more specific the medication needs to be. This results in smaller markets, smaller demands and, consequently, smaller batch sizes and/or fewer batches per year. On the other hand, by refraining from the one-size-fits-all shotgun approach, the aim is to ultimately treat more diseases in total.

Hence, the future calls for machines capable of handling smaller batch sizes and newer types of primary packaging material while high machine throughput becomes less important. Instead, the emphasis is on short changeover time between highly differing batches. In other words, flexibility is key (**Table 1**).

Flexibility in Action

Consequently, existing quasi-static line layouts with sequential processing, sometimes even dedicated to a single product, will no longer satisfy the needs of industry. Changing gears on the fly to accommodate small and totally different batches with different workflows becomes crucial. For example, changing the setup from a 20 ml freeze-dried vial to a 2.25 ml syringe batch or a dual-chamber syringe requiring dual-filling, lyophilization and dual-stoppering steps should be feasible with the least interruption to production. Changeover time, therefore, becomes a bottleneck that has to be solved; format parts need to be changed fast in a plug-and-play manner without any adjustment needed. Also, relying on ready-to-use primary packaging material and disposables will speed up the process. The sterilization step for the primary packaging material before production can be eliminated as well as the cleaning step afterwards. Also, the need for cleaning validation/verification of product contact parts to avoid cross-contamination disappears. Extractables and leachables still have to be assessed as before, but this should not affect the process or changeover anyway.

> **The future calls for machines capable of handling smaller batch sizes**

If the product is to be lyophilized, then the freeze-drying cycle becomes long compared to the filling time required for small quantities. Smart solutions for feeding a third batch into another (third) lyophilizer while the previous batch is lyophilized in the second lyo and the first batch is being unloaded from the first lyo—all without infringing line clearance and segregation of products—can help here, too.

Upcoming concepts will require flexibility on the machine vendor side as well. Simply plugging together some traditional building blocks in a new manner will not be sufficient. This applies to both hardware and software. In particular, implementation of new primary packaging material must be carried out easily by the end user and not require the vendor to come in to adapt the specific software accordingly.

The above principle works fine as long as the critical parts are already available. But for new formats, this might become time-critical. First, the *primary packaging vendor* must provide the final drawings of the primary packaging material itself, plus its nesting configuration in the tub. Then, the *machine vendor* needs to engineer and manufacture the format parts accordingly. Next, the corresponding layout and movements have to be programmed into the machine (ideally, by the *operators*). Additionally, the questions of *qualification* and necessity of one (or more) *media fills* to validate the aseptic processing have to be answered. The times required for all the above can easily stretch to about six months. This amount of time seems long

Table 1 Current Versus Future Manufacturing Lines

Current lines	Future lines
High volume	Small volumes (units per batch)
Large batches	Small batches
Parallel filling stations	Single filling station
Campaign production	One off projects or once in a while products
Sometimes lines dedicated to specific product	Various projects on single line
Little to no changeovers (change of format parts)	High number of (fast!) changeovers
Absolute line losses high, but low compared to overall batch size	Very low line losses to keep relative loss as small as possible
Cleaning validation efforts low compared to high number of batches	Disposables to a) speed up cleaning and change over and b) to reduce cleaning verification workload
Single type of packaging material (e.g. vials only or syringes only)	Various types of packaging materials to be handled on the same line
One primary packaging material (e.g. glass)	Suitable for existing and new primary packaging materials (glass, hard plastic, foil bags…, and combinations thereof)
If packaging material comes nested in tubs: Machine requires specific nesting configuration	Suitable for various existing nest configurations and even suitable of handling not yet known future configurations
Predefined, sequential workflow	Variable to accommodate various primary packaging materials and workflows

at first glance, but it is still fast compared to the old approach of implementing a new line, especially for new packaging material, which would have consumed years. Nevertheless, in the future, machine vendors will be required to speed up engineering and manufacture to less than one week. Industry and regulators will also have to work together to expand smart media fill, line clearance and qualification concepts.

The Many Benefits of Robotics

The key to flexible manufacturing ultimately lies in robotic systems. The benefits of robotic systems compared to established systems are adaptability to new materials, designs of innovative primary packaging materials and flexibility in using production lines in a multiproduct manner to easily switch from one product or format to another. The use of disposables and ready-to-use primary packaging materials eliminates process steps and can be paired with line loss reduction, which becomes especially important for greater numbers of smaller batches. One additional fact is worth mentioning: With robotic arms handling the highest critical process steps of aseptic handling and filling, the worst enemy of aseptic processing is eliminated—human involvement.

For example, robot arms can grab any single unit from any nesting geometry without additional teaching efforts. Gracefully built robotic fingers in conjunction with camera-assisted systems should do the trick and, perhaps, even achieve self-training status. On the other hand, one must not forget that the more complex a system, the higher the propensity for errors. Qualification will also be more complicated. And the price tag of such machines will be high.

Such systems would allow very high flexibility and, potentially, could handle, track and document each single unit produced so that a product could be tailored to the needs of a specific patient—individualized, on demand and on time. This would truly personalize medicine. But such a goal requires flexibility and even the further removal of the human element from the manufacturing process itself.

[Editor's Note: Hear the author speak on this at the *Universe of Pre-filled Syringes and Injection Devices* in Session 2: "Manufacturing and Technology" on Nov. 7 at 4:55 p.m.**]**

About the Author

J. Martin Bultmann heads the NBE Process Engineering Sciences group for AbbVie in Ludwigshafen. When Abbott separated in 2013, he became part of AbbVie and soon after he took over responsibility for the clinical supply of parenterals and became head of the parenteral pilot plants. He is also a pharmacist by training.

Five Keys to Manufacturing Success

R. J. Filannino, Alice Redmond, and Richard Tree, Commissioning Agents

Commercializing GMP products requires tremendous organizational learning. This conflicts with the regulatory and business drivers that force product development down a fast-paced, restrictive path. Knowledge transfer is rarely a priority. Short-term motivators end up taking precedence over long-term organizational development. As a result, manufacturers find themselves without sufficient knowledge to consistently supply quality product. Organizations that are functionally balanced and can transform knowledge into organizational learning will be the ultimate winners in achieving greater manufacturing flexibility ***(1).***

Product commercialization presents a significant opportunity for organizational development. At the point of commercialization, decisions must be finalized on where and how to manufacture for mass market consumption. New and/or expanded organizational capabilities will be required to achieve manufacturing success at full-scale, within market appropriate regulations and business parameters. Capabilities required may include manufacturing, warehousing and storage facilities, testing laboratories, supplier relationships, quality systems and qualified personnel. Some of these capabilities will require large capital investment while others may be outsourced via agreements with external partners. At product commercialization, organizations must make a series of strategic decisions which will have a large impact on the success of the product and, quite possibly, the overall organization.

Addressing Biz, Reg Challenges

One of the challenges to developing organizational ability is the quickly shifting business environment. The business landscape for each organization, and even for each product, is unique. As the industry shifts from blockbuster drugs to more specialized and personalized treatments, speed to market remains a strategic priority. When a product enters development, clinical development is the resource priority. Here, process scale-up and development may not receive the full attention that is necessary. But when clinical development nears completion, manufacturing becomes center stage in the product lifecycle. Then, when initial market penetration is complete, a desire to cut costs while maintaining quality and increasing supply becomes the new strategic priority. Enterprises without sufficient organizational ability find it difficult to make this transition quickly and sustainably.

When it comes to regulations, there are further challenges. Achieving consistent product quality in manufacturing has long been recognized as the primary means to protect consumers. Over time, regulatory guidance and expectations have changed as new approaches to safely manufacture product have become available ***(2).*** For example, it used to be thought that production controls, good documentation practices and rigid process validation were the answer to product quality issues. In response to the U.S. FDA's 1987 process validation guidance, the industry as a whole tended to treat the manufacturing process as static—run three batches, prove it worked and then minimize future changes. Process and product knowledge essentially froze once commercialization was approved. Strict process change policies greatly inhibited the continuous improvement. Instead of investing in understanding the process to minimize product quality risk, manufacturers began overengineering facilities to control the process. Accompanying these expensive facilities were wide-sweeping and nonvalue-added commissioning and qualification efforts conducted without regard to the actual impact on the process. Since the arrival of ICH Q8, Q9, Q10 and the 2011 FDA Process Validation Guidance, expectations on how to achieve consistent product quality have started to shift, enabling greater organizational capability ***(3–5).***

Product quality is a function of process performance, and process performance is a function of organizational performance. Organizational development is about expanding the knowledge of an organization in order to accomplish more innovative change and achieve higher levels of operational performance.

Although improving process performance for GMP manufacturers is only part of the focus on organizational development, it tends to drive the whole organization. This focus has driven the industry to take a more holistic process management approach for achieving product quality. True organizational development, however, should go one step further to understand the root causes of where variation enters organizational systems. Until this occurs, change is likely to be gradual, resulting in unintended consequences.

Consider a laboratory. There may be little to no concern around the procurement and control of a process reagent used for a series of experiments because the reagent may be sampled once to ensure quality. In fact, it is likely that one laboratory technician is performing the same dispensing method and using the reagent in the same process experiment with a highly controlled piece of bench-top equipment. When this process scales up, however, the opportunity for variation to enter the process increases significantly. This reagent will likely need to be procured in bulk volume from different vendors, distributed through multiple facilities, dispensed by many operators and used in several differeing pieces of process equipment. The opportunity and magnitude of variation should not be ignored.

In plotting how an organization can achieve full-scale manufacturing in line with current regulations and industry best practices, a pattern emerges, and analysis of this pattern shows that there are five dominant management systems required to achieve manufacturing performance **(Figure 1).** According to this pattern, organizations should implement the following strategies sufficiently.

- Manage the **project** (or business) pressures that preserve financial and strategically driven organizational ➤

MOVE PRODUCTS NOT CONTAMINATION

ELIMINATE CART WHEEL DISINFECTION

- Reduces safety concerns with cleaning.
- Provides the ability to steam sterilize bases & wheels.
- Eliminates the over use of disinfectants, reducing corrosion and pitting.
- Reduces garment contamination and gloves ripping.
- Available in 3 styles: Mircro Cart, Can & Bottle Cart, and Tray Cart. **Custom Built Carts also available.**

For more information visit: **sterile.com/cart2core**

vai

Veltek Associates, Inc.
15 Lee Boulevard
Malvern, PA 19355
Patents: sterile.com/patents

STERILE.COM

goals. Every capital project has to work within the confines of scope, schedule and budget. And every ongoing manufacturing operation has to balance the priorities of quality, time and cost.

- Manage the **people** who execute both physical and quality systems. Even in highly automated processes, humans are required to use judgment to handle and inspect materials, maintain equipment, develop production schedules and test samples, etc.

- Manage the **process,** understanding the parameters, materials and conditions the result in quality product of predetermined specification. The process should be managed in a lifecycle manner in which initial developmental knowledge expands during the commercial manufacturing phase. This knowledge can then be used to constantly improve the process, which will need to consider both known and unknown variations that can impact product quality.

- Manage the **facility,** which includes all of the systems, equipment and environmentally controlled areas required to manipulate resources. Systems and equipment convert air, water and other process-specific materials into intermediates and, eventually, the final packaged product. Systems and equipment are expected to perform their intended function in a reliable manner. Careful design, qualification and maintenance of these features enables a high-performance process.

- Manage the **quality** of the product by means of an independent and cross-functional organizational quality system. The quality function includes organizational controls, such as investigations, CAPAs, internal auditing and change controls, which should promote the sharing of knowledge in order to continue creating consistent product quality.

Organizations must be maintained with an appropriate blend of these organizational elements in order to achieve operational performance. Each element drives an important priority within the organization. An imbalance in any direction will create a gap and introduce unnecessary organizational variation, impacting product quality. For example, a well-designed facility without a capable staff can lead to product quality issues. A well-qualified staff and facility running up against unrealistic project timelines may lead to human fatigue and poorly maintained equipment, creating a hazard for product quality.

Knowledge management is one of the best underlying mechanisms helping organizations achieve advanced levels of development ***(6).*** For example, if a product quality out-of-specification report results in learning about opportunities to improve the process, this type of knowledge should be shared across the organization leading to retool equipment, supplement staff training and, possibly, change production scheduling and/or operating budgets. This knowledge needs to flow across the organization without difficulty. One of the best ways to accomplish this is building the practice into each organizational management system that supports the project, staff, process, facility and quality.

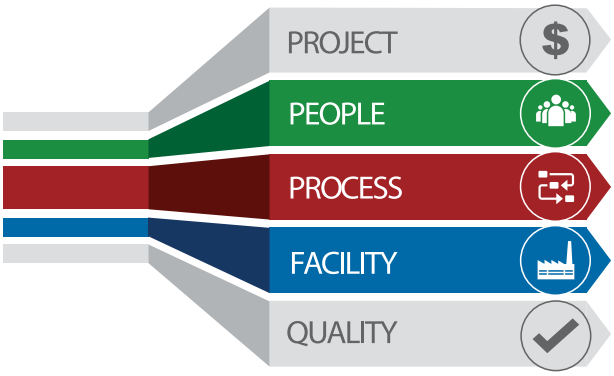


Figure 1 Five Elements of Manufacturing Organizations

An organization that focuses on capturing, retaining and using knowledge will be able to weather dynamic market conditions, benefitting process and operational performance.

Manufacturing flexibility and operational performance is a competitive advantage in the pharmaceutical marketplace ***(7).*** An organization that achieves this by means of organizational development and knowledge management practices not only realizes the gains of technology adoption and reduction in risk but garners significant intellectual capital that increases the value of the enterprise.

References

1. Lipa, M., Bruno, S., Thien, M., and Guenard, R. "A Practical Approach to Knowledge Mangement - A Case Study of the Evolution of Knowledge Management (KM) at Merck." *Pharmaceutical Engineering* 33 (2013): 94–105.
2. "Pharmaceutical CMGPs for the 21st Century - A Risk-Based Approach." 2004, U.S. Food and Drug Administration.
3. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). 2009. "Q8(R2) Pharmaceutical Development." Harmonised Tripartite Guideline.
4. —. 2005. "Q9 Quality Risk Management." Harmonised Tripartite Guideline.
5. —. 2008. "Q10 Pharmaceutical Quality System." Harmonised Tripartite Guideline.
6. Greene, A., and O'Donnell, K. "From Science to Knowledge: An Overview of the Evolution of Knowledge Management in Regulatory Guidance." Supplement. *Pharmaceutical Engineering* 34 (2014) S44–49.
7. Gonce, A., and Schrader, U., *Plantopia? A mandate for innovation in pharma manufacturing.* McKinsey.

About the Authors

R. J. Filannino is the Manager of Technical Services, Mid-Atlantic Region for Commissioning Agents, Inc. (CAI).

Alice Redmond is the Vice President of European Operations for Commissioning Agents, Inc. (CAI), where she challenges clients on how they develop their GMP manufacturing organizations to achieve success.

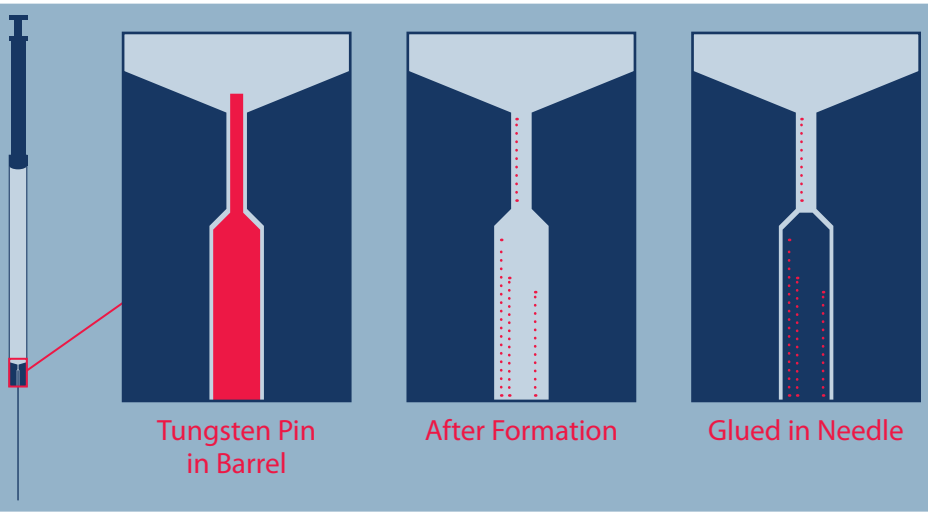
Richard Tree is the Vice President of Strategy & Development for Commissioning Agents, Inc. (CAI), where he challenges clients on how they manage the lifecycle performance of their assets.

The Danger of Tungsten Leaching

What is it?

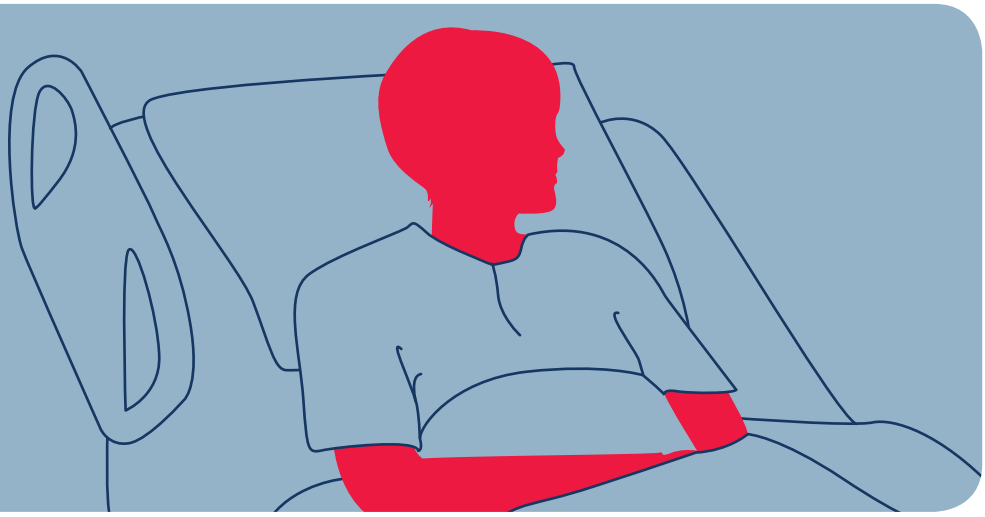
When tungsten pins used in manufacturing prefilled syringes are heated to very high temperatures, the tungstate can leach onto the drug product

…And tungsten pins are commonly used for making glass syringe tips



Why is it dangerous?

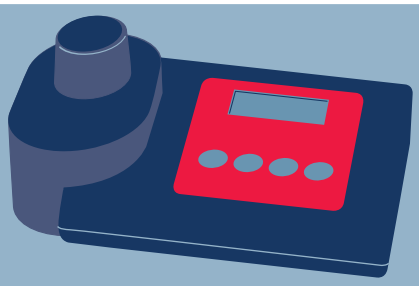
This leaching can lead to formation of protein particles—something that can potentially cause immune reactions in patients



How can this be prevented?

Size Exclusion Chromatography and turbidity meters offer some potential ways to assess the risk of protein aggregation.

Also, consider attending the 2017 *Universe of Pre-filled Syringes and Injection Devices* to learn what your colleagues are doing to prevent tungsten leaching!



Sources

1. Ronk, M., Lee, H., Fujimori, K., Yeh, P., and Nashed-Samuel, Y. "Characterization of Protein Aggregating Tungstates: Electrospray Mass Spectrometry Analysis of Extracts from Prefilled Syringes and from Tungsten Pins Used in the Manufacture of Syringes." *PDA Journal of Pharmaceutical Science and Technology* 70 (2016): 51–61.
2. Waxman, L., Steeley, T., and Vilivalam, V. "Protein Sensitivity to Tungsten." *Pharmaceutical Technology* (Nov. 1, 2011).

The Parenteral Drug Association presents the...

2017 PDA Visual Inspection Forum

October 23-24, 2017 | Bethesda, MD

Bethesda North Marriott Hotel & Conference Center

Exhibition: October 23-24

#PDAVisual

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

Explore the newest and most innovative topics in visual inspection with industry experts and professionals at the two-day, *2017 PDA Visual Inspection Forum*.

Through plenary sessions, panel discussions, presentations, and networking opportunities, discover the latest trends and advancements in the field of visual inspection. The Forum will provide case studies, examine new USP chapters<790> and <1790>, and discuss new developments in the field of visual inspection.

Additional topics will cover:

- Regulatory Compendial Issues
- Particle Control and Characterization
- Managing Product Appearance Challenges
- Biopharmaceutical Inspection
- Manual Inspection

Don't miss the exhibition featuring the latest in commercial inspection hardware. Take the chance to discuss your production needs with key suppliers of inspection systems and services.

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

Following the Forum, PDA Education will hold a two-day Introduction to Visual Inspection course, **Oct. 25-26**, where you can explore the fundamentals of visual inspection and their application to injectable products.

Discover more about this course at pda.org/2017OctVi

The Parenteral Drug Association presents the...

2017 PDA Modern Biopharmaceutical Processing Conference

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


Image supplied courtesy of Pall Corporation

From Facility Design to Product Distribution

Sessions at the *2017 PDA Modern Biopharmaceutical Processing Conference* will include a case study of a new Singapore facility for biopharmaceuticals manufacturing, details on experiences with process, regulatory agencies, and business-related advantages as well as a technology update session that will showcase new trends in technologies for the pharmaceutical industry.

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

Hear about:

- Regulatory Updates
- Facility Design, Single-Use Systems, and Cleaning Requirements
- Single-Use Systems
- Continuous Processing
- Technology Transfer
- Good Distribution Practice: Temperature-Controlled Distribution of Biopharmaceuticals

There will be plenty of time for dialogue and questions during the panel discussions and networking opportunities with your peers.

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

Learn more and register today at **pda.org/2017SingaporeConference**

SNAPShot

Gain Proficiency in Quality Risk Management

PDA's New Role-based QRM Certificate Program Offers Courses for all Levels of QRM Involvement

Emma Ramnarine, Genentech/Roche, and Stephanie Ko, PDA

Risk management may not be in your official job description, but do you find yourself assessing risks when making decisions in your day-to-day activities, even if you do not document it formally? Have you participated in a risk assessment and want to improve? Would you like to learn when, where and how to apply quality risk management (QRM)? Are you interested in understanding what good risk-based decision-making means and how it can be achieved?

If you answered "yes" to any of these questions, you will certainly want to take advantage of PDA's new, first-of-its-kind, role-based "QRM Certificate Program" developed by leaders in QRM. This certificate program is accredited by the Accreditation Council for Pharmacy Education (ACPE) and will be accredited by the Dublin Institute of Technology (DIT).

ICH Q9, *Quality Risk Management* has been effective since November 2005, yet industry and regulators have still not fully realized its vision and value. While there are various reasons, one foundational explanation is the gap in QRM skills. Since ICH Q9 was published, the primary focus has been on the QRM process and risk assessment tools, while very little attention has been paid to the various roles in the QRM process or developing the skills for each of these roles. Just like different actors have distinct parts in a play, there are different roles in the QRM process, so the program has been designed with this in mind.

This certificate program is a modular training course with tiered tracks **(Figure 1).** The first series of classes is being offered Dec. 11–14 at PDA TRI.

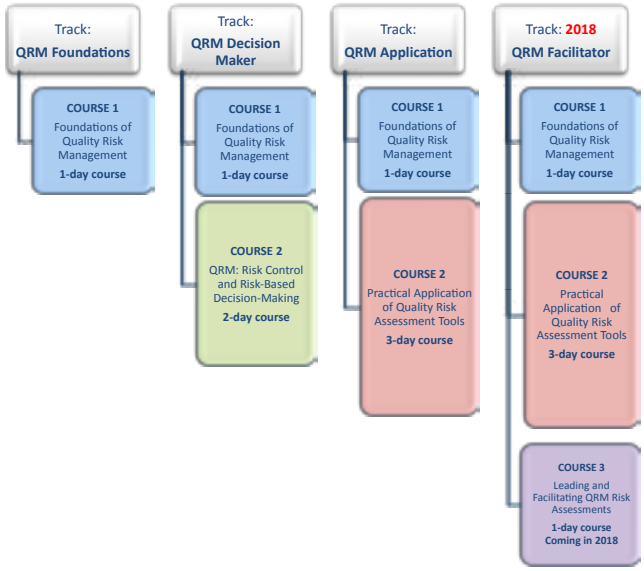


Figure 1 Foundations for QRM Course

- **QRM Foundations Track**: This track is designed for all personnel involved in QRM as a participant in risk assessments, QRM facilitator or decision-maker, such as personnel from QA, QC, engineering, validation, production and technical services who are involved in QRM activities. This course is a prerequisite for the tracks listed below.
- **QRM Decision Maker Track:** This track is applicable to supervisors, managers and directors from disciplines such as QA, QC, engineering, validation, production and technical services, who often make decisions based on the outcomes of risk assessments for their areas of responsibility.
- **QRM Application Track:** This track is applicable to pharmaceutical professionals engaged in QRM application activities related to CMC for pharmaceutical/biotechnology processes, such as manufacturing supervisors, managers and directors; process development biochemists; microbiologists; cell biologists and molecular biologists; etc.
- **QRM Facilitator Track:** This track, to be offered in 2018, will be the most comprehensive of the four tracks. It is applicable to individuals expected to be highly skilled and proficient in the entire QRM process and its application, including the use of various QRM tools. QRM facilitators may be involved in various functions across an organization including project management, operational excellence and technical functions.

The benefits that companies can expect to get from this program include:
- Increased alignment in QRM application across the industry
- Reduced internal QRM training efforts
- Improved sharing of QRM application knowledge between companies
- Fully realized QRM application for companies with QRM programs at all maturity levels

For more information, contact **Stephanie Ko** (ko@pda.org) or **David Talmage** (talmage@pda.org).

The Parenteral Drug Association presents:

2017 PDA Europe Conference, Exhibition, Education

The Universe of Pre-filled S

Improving Patient

DOWNLOAD THE EVENT APP FOR DIRECT PROGRAM UPDATES ON THE CONFERENCE WEEK!

pda2017.com

7-8 November 2017

Austria Center

Vienna | Austria

yringes & Injection Devices

Outcomes with Innovative Drug Delivery

Pre-Conference-Workshops

6 November
Impact of Pre-filled Syringe Packaging Components on Biopharmaceuticals

6 November
Innovative Drug Delivery Systems | Combination Products

6 November
Connected Health & Drug Delivery – Improved patient convenience and adherence through new technologies

Education Program

9-10 November
Development and Manufacturing of Pre-filled Syringes

9-10 November
Container Closure Integrity Testing

9-10 November
Container Closure Development

9-10 November
Best Practices and Points to Consider in Aseptic Processing

9-10 November
Drug Delivery Systems: Global Technical, Regulatory and Quality Challenges

9-10 November
Rapid Microbiological Methods

PDA®
Parenteral Drug Association

pda.org/EU-UPS2017

PQS: An Effective Lever for Managing PACs

Anders Vinther, Sanofi Pasteur, Emma Ramnarine, Genentech/Roche, and Kevin O'Donnell, Irish HPRA

Implementation of an effective pharmaceutical quality system (PQS) is essential for a company to achieve product realization, establish and maintain a state of control, and facilitate continual improvement ***(1).***

According to ICH Quality Guideline Q10: *Pharmaceutical Quality System,* companies that apply the principles and concepts of ICH Q8: *Pharmaceutical Development,* ICH Q9: *Quality Risk Management* or ICH Q10 should be eligible for reduced regulatory oversight once they have demonstrated that a PQS is in place. In this regard, ICH Q10 makes specific reference to changes made during the commercial lifecycle of a product (i.e., post-approval changes or PACs) ***(1).*** With sufficient product and process understanding and the use of quality risk management (QRM), certain PACs should be covered in the PQS (or only as a regulatory notification) with little to no prior approval by regulators. This should be the case as long as a comprehensive risk assessment concludes that a proposed change introduces no additional risk to patient safety, product quality or product efficacy. This includes downgrading the reporting category for established conditions (ECs) on a case-by-case basis as supported by the risk assessment.

Elements for Effective PAC Management

At the time of first license or approval, manufacturing process knowledge is limited. The regulatory framework should facilitate timely improvements to manufacturing processes and controls as commercial production experience and knowledge grows. Regulators should accept that the PQS is capable of an appropriate degree of self-governance in ensuring product quality and safety. Building an effective PQS is the responsibility of the company—one that extends beyond having a license or a GMP certificate to manufacture medicines. Essential elements of a PQS for effective PAC management include the following:

Management Responsibilities | Senior management is ultimately responsible for ensuring that an effective PQS is in place for managing PACs. This includes defining and communicating roles and responsibilities, providing adequate resources and ensuring a comprehensive and objective science- and risk-based approach to decision-making. Internal audit and self-audit mechanisms should enable proactive assessment and mitigation of compliance risks in the PQS, including any issues that might be introduced by a PAC. Management is also responsible for developing the desired quality culture at all levels throughout the company.

Process Performance and Product Quality Monitoring (PPPQM) | Systems should be in place for the early detection of process drifts and unexpected variability and trends, as well as for the effective handling of adverse events, complaints and defects. Systems should identify PACs needed to ensure an ongoing state of control and product availability that drives continuous improvement.

Change Management | An effective change management system for internal as well as outsourced operations is characterized by a data-driven, science- and risk-based approach to the assessment and management of changes that takes into account the potential impact on all relevant aspects of the product and process, established conditions and any unintended consequences. It ensures improved product quality, process performance and a state of control and/or product availability, and it lowers residual risks. Changes should be managed in keeping with the product lifecycle management strategy (with plans and protocols).

Corrective and Preventive Actions (CAPA) | An effective CAPA program monitors and manages unintended risks and consequences of PACs for internal and outsourced operations and should enable identification of root cause(s) so that appropriate actions can be taken to correct problems and prevent their recurrence. The program should also monitor and verify the effectiveness of any CAPAs associated with PAC initiatives.

Knowledge Management (PQS Enabler) | An effective knowledge management system leverages existing and newly achieved or newly identified product and process knowledge, including innovation and technology advancements, as well as knowledge gained from PPPQM, deviations, trends, complaints, recalls, annual product/product quality review and management reviews. Effective knowledge management ensures that the right knowledge is used by the right people at the right time, allowing for effective decision-making.

Quality Risk Management (PQS Enabler) | An effective QRM system provides a risk-based decision-making framework and ensures that systematic and proactive risk-based and data-driven decision-making is used for all PACs. Such a system should facilitate faster implementation of changes that reduce the risk of quality failures and manufacturing problems and improve process capability. It should also be used to determine the appropriate level of regulatory oversight, i.e., distinguish changes that require regulatory reporting or notification from changes (ECs as well as non-ECs) that can be managed solely within the PQS.

Demonstrating PQS Effectiveness

The effectiveness of a PQS can be demonstrated by management review activities that monitor the performance of the key elements outlined above. Appropriate performance indicators, based on the use of data and trends, should be in place for each of those elements; they should be meaningful and simple, and should not be subject to interpretation ***(2).***

Management review activities should also include a review of all PAC initiatives, their intended objectives, their implementation, and a verification of their expected outcomes. Where the objectives of PAC initiatives are not achieved, formal

Continued at bottom of page 44

Industry Awaits Annex 1 Revision

Four Months After PDA EU Annex 1 Workshop, Revision Still Eagerly Anticipated

Walter Morris, PDA

At the *2017 PDA Europe Revision of Annex 1* workshop, European regulators estimated a summer release of the long-awaited draft revision of the EMA guidance on GMPs for the manufacture of sterile drug products, now delayed for a later date. **Andrew Hopkins,** MHRA, and **Beate Reutter,** Landesamt fur Soziale Dienste (Germany), spoke on behalf of the EMA, providing glimpses into areas of the guidance that are being updated. The workshop took place on June 12 in Berlin and was a preconference session to the *2nd PDA Europe Annual Meeting.* **[Editor's Note:** For more about the Europe Annual Meeting, see p. 12**.]**

The European regulators said the revision is necessary after years of piecemeal changes to the 40-year-old guidance. The revised guidance will emphasize the need for manufacturers of sterile drug products (which also include vaccines and most other biologics) to adopt modern manufacturing tools like isolators and single-use systems. The revised guidance will also emphasize use of quality risk management (QRM) in sterile processing.

Hopkins stressed that outdated methods that require operators in a Grade A room to reach over product are not acceptable modern processes, even if the guidance will not specifically forbid the practice. He warned, however, that modern single-use closed systems are not a panacea.

Additionally, the revision will not remove pre-use, post-sterilization integrity testing, commonly referred to in the industry as "PUPSIT." Hopkins indicated that the EMA still has concerns about filter failure and that it is a "genuine issue." Arguments for keeping the requirements included the aggressive nature of sterilization and inconsistent manufacturing among filter producers. The arguments against PUPSIT boil down to firms not liking the requirement and finding it difficult, he said.

Hopkins also received a number of audience questions regarding new language in the draft on container closure integrity and environmental monitoring.

The remainder of the workshop addressed some of the issues discussed in the opening plenary session. **Kelly Waldron,** ValSource, and **Geert Vandenbossche,** Novartis, provided informative lectures on the application of QRM to aseptic processing control and sterile suspension process design. Next, **Johannes Rauschnabel,** Robert Bosch GmbH, discussed contamination control. **Derek Duncan,** Lighthouse, closed out the presentations with a discussion of a control strategy for container closure integrity.

PDA President **Richard Johnson** also announced that PDA was conducting a survey on sterile product manufacturing, which recently closed. PDA received 304 responses. Questions covered:

- Technologies
- Physical Environment
- Environmental Monitoring
- Aseptic Process Simulation
- Personnel
- Material and Material Transfer
- Cleaning, Disinfection and Sterilization
- Container Closure Integrity Inspection
- Single-Use Systems
- Terminal Sterilization
- Lyophilization
- Blow-Fill-Seal

PDA will publish the results of the survey before the end of 2017. PDA members will have another opportunity to hear Hopkins on the Annex 1 revision at the *2017 PDA Annex 1 Workshop* in Washington, DC, Oct. 2–3.

PDA's Annex 1 task force is prepared to analyze and submit comments to the revision once it is published for public review.

One Company's Approach to Rapid Methods continued from page 21

Disclaimer: Commercial products featured in this paper are examples and not to be interpreted as endorsements by MSD.

*[The author(s) wish to acknowledge the efforts of **Geert Verdonk,** Director Quality, Micro COE lead, and **Jessica Long,** Scientist II, PSCS Analytical Sciences.]*

About the Authors

Mousumi Paul, Director Manufacturing and Quality, Center Of Expertise Microbiology at Merck, Sharp and Dohme Corp. is responsible for developing and managing the Quality and Compliance initiatives within COE-Micro. She leads the Global deployment of Rapid Micro projects for manufacturing as well as for micro labs. Mousumi has over seventeen years of diverse experience from development through technology transfer, manufacturing and quality support for vaccines and biologics. She holds a Master's Degree in Pharmacology and in Microbiology and a Master of Business Administration degree in Management.

Scott Hooper, PhD, is Associate Director of Preclinical Development and Head of Microbiology at MSD Werthenstein BioPharma GmbH, a Swiss unit of Merck, Sharp and Dohme Corp. He has over 30 years' experience in research, development, technology transfer, and technical, quality and operations support of microbially-derived APIs, biologics and vaccines.

The Universe of Pre-filled Syringes and Injection Devices

New Realities for Prefilled Syringes

Mathias Romacker, Pfizer, Conference Scientific Program Planning Committee, with Rebecca Stauffer, PDA

The new business reality for prefilled syringes centers on self-injection delivery systems adapted to the needs of individual patients. This will certainly have a clear impact on the pharmaceutical market. At the same time, these new products will require new approaches to addressing the needs of regulators. The U.S. FDA has in recent years expressed concerns about errors related to self-administration by patients, necessitating more attention to human factors analysis during the development cycle ***(1).***

Lifecycle management during manufacturing will be critical to the success of self-administered injection devices. But how can manufacturers of prefilled products learn more about the latest developments in this area as well as gain a sense for the larger business and regulatory environment?

This year's *Universe of Pre-filled Syringes and Injection Devices* will examine these issues. In the opening keynote presentation, Pfizer's **Simon Wilson** and Amgen's **Sheldon Moberg** will look at the issues of evolving perspectives on connectivity and patient-centered solutions, respectively. The talks in this session will cover outcome-based adaptive reimbursement. Such arrangements between payers and pharma have been made for multiple self-injected drugs. The subsequent drug delivery implications will also be discussed.

The conference will be split into three tracks: Patient-Device Interface, Manufacturing and Technology and Marketing and Business Development. The first session in the Marketing and Business Development track will cover lifecycle management, featuring a case study on how an off-patent IV drug was filled in a subcutaneous version using a patch pump. A second case study from Japan will describe the impact of a third-generation digital autoinjector for a growth hormone franchise.

The second day of the Marketing and Business Development track starts with a session on market trends and reimbursement. Attendees will receive an update on the latest overall market trends followed by presentations on reimbursement. The final presentation of the session will review evolving payer perspectives on the value of drug delivery devices. Results from conversations with payer executives will be presented on how to improve population health with the assistance of drug delivery technology.

The last session focuses on business strategies. The first talk will review lifecycle management for devices. Case studies will be presented, including one showing how to convert an off-patent heart failure drug from IV administration in a clinical setting to subcutaneous delivery at home using a patch pump.

Reference

1. Baker, J. "Educating patients on self-administered drug injections." *Pharmaceutical Online*. (January 20, 2014) http://pharmaceuticalcommerce.com/manufacturing-and-packaging/educating-patients-on-self-administered-drug-injections/ (accessed Aug. 30, 2017)

The Universe of Pre-filled Syringes and Injection Devices

Vienna

Nov. 7–8

www.pda.org/EU-UPS2017

PQS: An Effective Lever for Managing PACs continued from page 42

CAPA plans should be developed and implemented, and lessons learned should be captured and incorporated into future PAC activities.

For sustained effectiveness, the PQS needs to be embedded within the company's quality culture—a set of shared values, beliefs and behaviors that support product quality- and patient-centric decision-making. Senior management should demonstrate and communicate to the entire organization their commitment to achieving and maintaining an effective PQS. It should also share a common vision, fostering transparent, open and "no-blame" communication throughout the company based on trust and investing in employee education and training to ensure a proficient and knowledgeable workforce.

References

1. ICH Q10: Pharmaceutical Quality System, International Conference on Harmonisation, 2008 tinyurl.com/65e2yjf (accessed Aug. 22, 2017)
2. Ramnarine, E., et al. "PDA Points to Consider: Technical Product Lifecycle Management-Pharmaceutical Quality System Effectiveness for Managing Post-Approval Changes." *PDA Journal of Pharmaceutical Science and Technology* 71 (2017):252–258.

The Parenteral Drug Association presents:

2017 PDA Europe Conference, Exhibition

Outsourcing & Contract Manufacturing

Getting it Right Throughout the Manufacturing Lifecycle

EDUCATION PROGRAM

23-24 Nov
Risk Management in Technology Transfer

23-24 Nov
Practical Guide for Root Cause Investigations - Methodology & Tool Kit

21–22 November 2017

Roomers Design Hotel
Munich | Germany

pda.org/EU-Outsourcing2017

Building on the Principles of TR-54

Ghada Haddad, Merck

Over the course of the past two years, I have had the privilege of working with a dedicated team of Quality Risk Management (QRM) professionals to develop another annex to *Technical Report No. 54 (2012): Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations.* Like most PDA members, I strongly believe in the value our technical reports bring to the scientific community.

Hal Baseman, **Dave Calvaresi**, **Liza Lamb**, **Lori Richter**, **Chris Smalley**, **Bill Stelzenmuller**, **Kelly Waldron**, **Steve Wisniewski**, and I collaborated to create a best practices annex, *Technical Report No. 54-5 (2017): Quality Risk Management for the Design, Qualification, and Operation of Manufacturing Systems.*

Although ICH Q9, *Quality Risk Management* presents general QRM principles and examples of various risk management tools and potential areas where risk management may be applied, it does not provide details on how to use QRM principles to manage risks throughout the design, qualification and operation of manufacturing systems. In applying QRM to the design, it is possible to determine potential causes of process failure and identify control elements to manage failure modes/hazards to an acceptable level of risk.

TR-54-5 provides a practical guide on how to manage quality risks throughout the manufacturing lifecycle and illustrates concepts through two case studies, thereby bridging the gap. In the writing process, the team ensured that the concepts in the technical report applied to both new and existing manufacturing systems for clinical and commercial drug substances or products, packaging, warehousing and critical utility systems, with a focus on manufacturing systems that impact product quality. The inherent assumption is that each firm will adapt the content according to specific needs.

On the heels of the approval of TR-54-5, the technical report team led a two-day workshop on QRM this past June in Chicago, attended by representatives from over 30 companies. The value and evolving role of QRM on the manufacturing lifecycle was discussed by **Kevin O'Donnell**, HPRA, and **Elizabeth Zybcynski**, Baxter International Inc. Lamb, Richter and Waldron discussed risk-based approaches to characterizing system design as covered in TR-54-5. Baseman, along with members of the task force, led an interactive breakout session, allowing participants to practice risk-based approaches to characterizing system design. **Jason F. Chancey**, U.S. FDA, and Kevin O'Donnell shared with participants their views on the practical implementation of QRM for the manufacturing system lifecycle, focusing on the use of risk-based thinking to promote the use of modern technology and PIC/S inspector training initiatives on advanced QRM, respectively. Stelzenmuller moderated a session on QRM approaches for designing a more effective pharmaceutical quality system. Wisniewski spoke about the use of risk-based approaches for performing commissioning, qualification and validation of critical systems. And Smalley discussed linkage between product quality and process requirements, while Richter shared with participants the "how-to" of building a more effective quality system.

TR-54-5 is really a one-of-a-kind, "out-of-the-box" document and is not to be missed. I encourage you to read it and apply its principles to improve operations within your company. Finally, stay tuned for an announcement on when PDA Education will offer training courses focused on TR-54-5. These courses, like all other PDA courses, provide members with a unique opportunity to enhance their learning so all can stay current on the latest industry best practices.

The Parenteral Drug Association presents the...

2018 PDA Annual Meeting

March 19-21, 2018 | Orlando, Florida

Loews Sapphire Falls

Exhibition: March 19-20 | Post-Workshop: March 21-22 | Courses: March 22-23

#PDAAnnual

Register by January 8, 2018 and save up to $600!

Agile Manufacturing Strategies: Driving Change to Meet Evolving Needs

Join us in Orlando, FL for the *2018 PDA Annual Meeting* for the opportunity to gain best practices and learn how industry is applying novel approaches for development and commercialization of pharmaceutical and biopharmaceutical products.

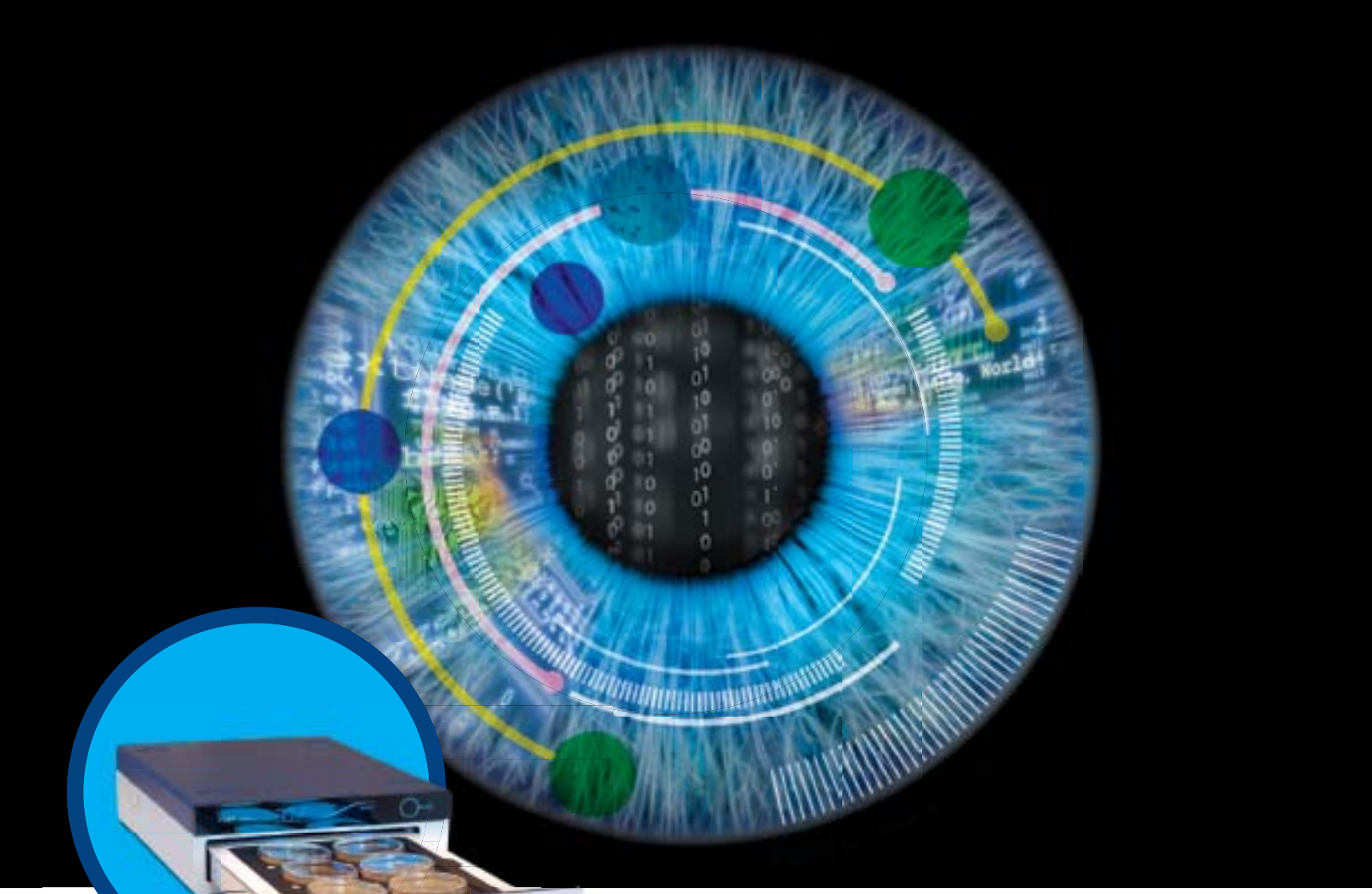
Plenary sessions at the *2018 PDA Annual Meeting* will focus on patient perspective and future visions, genomic profiling, and a new topic – *Disruptive Technologies*. Additional plenary sessions will further explore current and future trends in process development and manufacturing, including next-generation processing and facilities, the application of big data for process design and optimization, and accelerating the industry response to healthcare needs.

Concurrent session tracks will offer you a closer look at continuous processing, patient centricity, and complexities in the product value chain.

Take advantage of networking opportunities to observe the latest technology in action in the Exhibit Hall.

Be a part of this exciting meeting filled with novel approaches and strategies for bringing products to market! Learn more and register at pda.org/2018Annual

Following the Annual Meeting, PDA Education will be hosting seven courses, **March 22-23**, as part of the *2018 PDA Annual Meeting Course Series* to help you further advance your knowledge. Learn more and register at **pda.org/2018AnnualCourses**



THERA

EviSight™ Compact

CREATING A CULTURE OF DATA INTEGRITY

INTELLIGENT INCUBATOR AND COLONY COUNTER

BIOMÉRIEUX INDUSTRY

PIONEERING DIAGNOSTICS

www.biomerieux-industry.com