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PDA Letter

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May 2017 PDA Letter

2nd PDA Europe Annual Meeting

Show Issue

This year's *PDA Europe Annual Meeting* once again takes place in the city of Berlin, June 13–14. Throughout this issue are a number of articles highlighting talks, courses, and other events at this new signature PDA meeting. For a preview of the exciting sessions offered at this meeting, look for articles with this banner at the top of the page.

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Lower the H_2O_2 Concentrations in Your Isolator with One Easy Upgrade

Stefan Kleinmann, PhD, and Matthias Scheu, METALL+PLASTIC, Roland Schuhwerk, and Volker Baur, Cilag AG

In recent years, the number of protein-based biologic drug products has grown. Parallel to this, the use of filling line isolators in biopharmaceutical manufacturing plants has increased. Some of these products are extremely sensitive to oxidation. The majority of aseptic manufacturing isolators are decontaminated with H_2O_2, so potential oxidation of these sensitive products has become a concern.

Cover Art by Karol Keane, photo courtesy of Metall + Plastic

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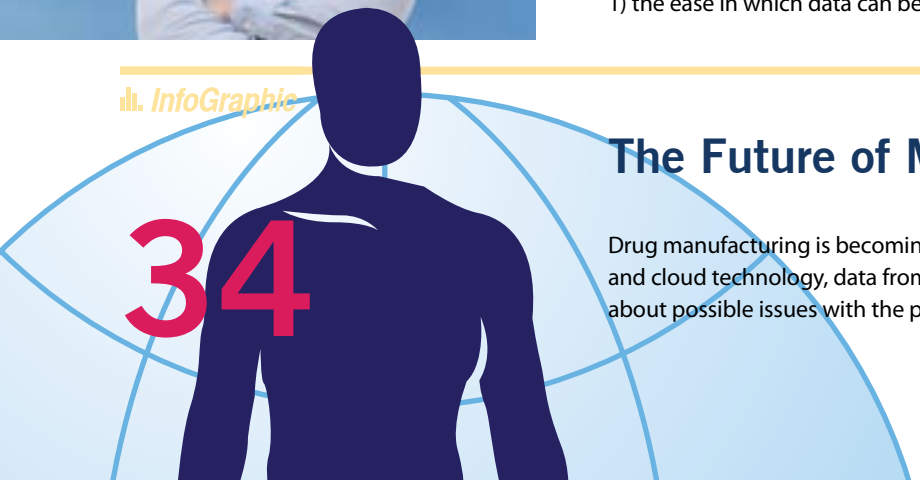
Pharma Has its Head in the Cloud

Big Data is Leading Pharma Manufacturing to Greater Maturity

Toni Manzano, bigfinite

Today, huge amounts of information are continuously being generated and stored in many different systems: external and internal hard drives, virtual disks, network storage systems, pen drives, e-drives, etc. In addition, social networks, multimedia platforms, and Internet of Things (IoT) technology contribute increasingly greater bytes of data. In fact, 2016 saw about 2.5 trillion (2.5×10^{18}) bytes of data created each month. This enormous amount of electronic information, commonly referred to as "big data," is directly related to two factors: 1) the ease in which data can be stored, and 2) the ability to connect to the internet.

InfoGraphic



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The Future of Medicine

Drug manufacturing is becoming increasingly patient-centric. Thanks to wearable devices and cloud technology, data from the drug/device provides more accurate information about possible issues with the product.

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> **Editor's Hot Seat** | *2017 PDA Annual Meeting* Poster Presenters
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Intern Offers Lessons for Industry

Having been grounded for nearly three months, my trip to Copenhagen provided an opportunity to catch up on my reading. The November/December issue of the *PDA Letter* contained several great articles—a sort of instant come-up-to-speed-on-hot-topics edition. However—and not altogether surprising, since it was written by the editor's son, **Ryan Morris** (who evidently inherited his father's writing genes)—the article I most appreciated was about Ryan's internship with PDA's Training and Research Institute (TRI) (p. 18). Apart from giving readers a glimpse into TRI from an intern's perspective, he provided some interesting learning points:

1. **Making an inventory of TRI's supplies and inputting that data into the system and organizing it into easy-to-use groups:** Vendor management learned through doing. Maybe TRI should offer a course that allows participants to handle and input stock, and think about how best to manage it for ease of use—First in, First Out (or First Expired, First Out) and supplier management?

2. **Using the autoclave:** This is an important skill, obviously, but it helped to have a fabulous mentor explain the importance of the sterilization process.

3. **Archiving:** Certainly overwhelming at first. I remember my first work assignment at a company that produced business forms and hadn't filed one in three years! Ryan took the initiative and helped with filing and scanning, so there should be less paper for the next renovation. Ryan seems resourceful and forward thinking just from how he described the experience.

4. **Biggest takeaway:** "Working is a lot different than going to school…I needed more independent thinking to complete my tasks successfully as the requirements were not as straight forward as they would be for a class project."
   Wow—food for thought for managers! Yes, you want resourceful people in positions of authority but when it comes to a production or packaging line—better ensure that the requirements *are as straightforward as for a class project.* Isn't this the reason for many of the failures, deviations, and investigations we see in the pharma industry?

Ryan, thanks for your insights. I wish you every success in your future career.

And a final thought…wouldn't resumes be a little more interesting if they included a small piece of prose about the candidate's work experience?

—Karen Ginsbury

Glimpsing the Industry's Future

I had a fantastic time at this year's *PDA Annual Meeting* in Anaheim, Calif. And not just because of the 70 degree weather! If you wanted a glimpse into the future of sterile manufacturing, this was the place to be.

In the session, "Future Facility Design," I heard **Lisa Sykes,** Director of Vaccine Operations for Merck, explain how she led the implementation of flexible manufacturing for a site in North Carolina. I found it fascinating that instead of focusing on the technology, she emphasized the importance of collaborating directly with the operators on the floor who would be using the new system. Lisa later sat down with us to film an upcoming edition of "On the Issue," which will appear in the multimedia section of the *PDA Letter* website soon.

Following Lisa's talk, US FDA CDER representative **Rapti Madurawe,** PhD, talked about CDER's position on continuous biomanufacturing. He advised companies to work with FDA to ensure implementation of continuous systems meets regulatory guidelines.

Both session talks were excellent and resulted in extensive follow-up Q&A.

All of the Annual Meeting's sessions were equally forward-thinking, and the posters were outstanding, capturing a range of topics from automated visual inspection, single-use systems, organizational ability, new microbial control strategies, next generation sequencing, PAT, and more. Four of these poster presenters have committed to submitting articles based on their topics to the *PDA Letter*—you can read the first one in this issue (p. 42). The four authors sat in the "Editor's Hot Seat" to answer a few questions about their posters and article. This new video series appears on the multimedia section of the *PDA Letter* website.

The meeting then closed with talks exploring the implications of big data for sterile manufacturing and the need to address emerging healthcare needs, including post-approval changes. **Michele D'Alessandro,** CIO, Manufacturing IT, Merck, was one of the speakers. You may remember that we profiled the talk she gave at the *2015 PDA/FDA Vaccines Conference* and even interviewed her for three "On the Issue" videos last year. Big data has proven to be a popular topic and you will continue to learn more about it at future PDA meetings, particularly the *2nd PDA Europe Annual Meeting.*

All in all, the *2017 PDA Annual Meeting* proved to be thought provoking and productive. In addition to the "Editor's Hot Seat" and Lisa Sykes videos, we also interviewed Novartis' **Karen Walker** on her company's CAR-T cell therapy for a second "On the Issue" video. Again, stay tuned!

I hope to see everyone at next year's PDA Annual Meeting in Orlando, Fla.

Rebecca Stauffer

Corrections

In the PDA Photostream on page 15 of the April issue, **Dawn Downey's** last name was incorrect. In addition, she currently works for Eli Lilly not Merck.

The quote at the end of the article on page 13 of the April issue ("Data Integrity Event Draws Largest Attendance Ever") should have been attributed to **Jim Polarine,** Board Member at Large for the PDA Missouri Valley Chapter not Chapter President **Keith Koehler.**

2nd PDA Europe Annual Meeting

Hear From Global Regulators in Berlin

Big Data, personalized medicines, and parenteral manufacturing are just a few of the topics to be discussed at the *2nd PDA Europe Annual Meeting*: *Global Healthcare of the Present & the Future,* June 13–14, in Berlin. But no meeting in this area would be complete without discussions of the continually changing regulatory environment that poses a variety of challenges for the pharmaceutical industry. The conference will include a discussion of inspection trends from the regulator and industry perspectives.

Leading global regulators will be on hand to offer their perspectives. PDA has confirmed two regulatory officials for the opening plenary session: **Paul Hargreaves,** Chair, PIC/S, and **Rassoul Dinarvand,** Head, Iran FDA. Hargreaves will speak on GMP harmonization, and Dinarvand will participate on a panel discussion of international pharmaceutical regulations.

Dinarvand has also been invited to speak in a preconference workshop, *Business Opportunities in Iran,* on June 12. At another June 12 preconference workshop, **Andrew Hopkins** of the MHRA and German GMP inspector **Beate Reutter** will speak about revisions to Annex 1.

Please visit www.pda.org/eu-AnnualMeeting2017 to learn more about other speakers and sessions at this meeting.

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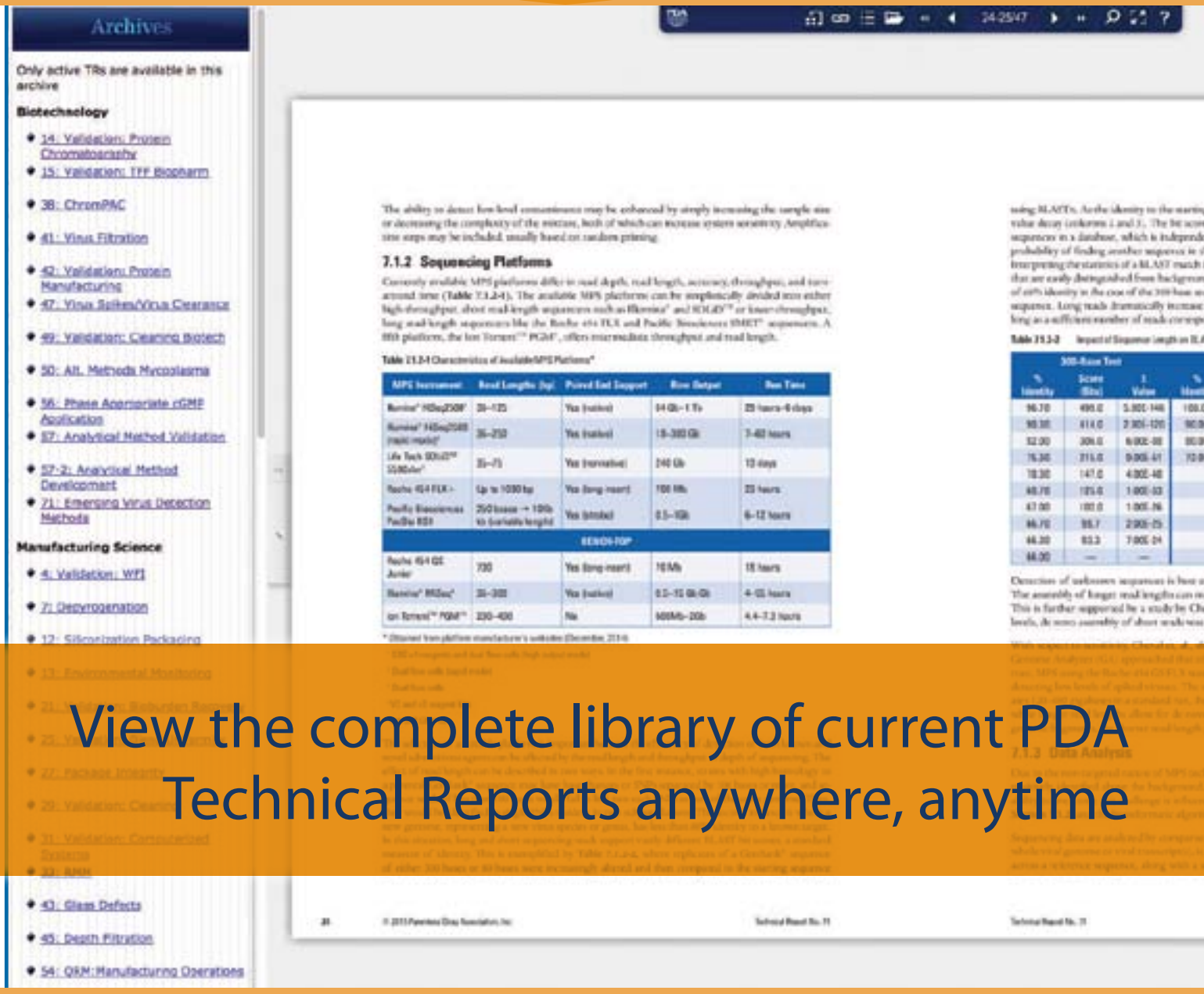

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PDA Volunteer Spotlight

Karin Baer

- **Vice President Quality-Regional Head**
- ***Teva Pharmaceuticals***
- Member Since | **1993**
- Current City | **Jerusalem, Israel**
- Originally From | **Zurich, Switzerland**

A strong chapter requires a strong team

You've been a chapter leader since the earliest days of the Israel Chapter. Why did you get involved in creating this chapter?

I felt that Israel's Ministry of Health, which regulates drugs and devices for the country, needed a platform to communicate their expectations for industry. And industry needed a platform to address their concerns to regulators. To that end, I believed (and still believe) that a PDA chapter would fulfill this need.

The Israel Chapter was founded in 1997 with ten members. Since then, the chapter has been quite active, hosting four to five activities each year.

So then, what can we expect from the Israel Chapter this year?

We plan to host events covering sterile filling technology, data integrity, and comp air/steam sampling.

You've also been part of the PDA team that commented on the US FDA's draft data integrity guidance. What was that like?

It was great to share knowledge with other professionals from different companies. This gave me new and different information to use when working on the comments.

What did you like about participating on the Combination Products Task Force?

I learned a lot about new regulatory guidances. I also enjoyed the shared experience of working with other task force members on a topic of common interest.

What inspires you?

Learning about new industry trends and regulations, and then discussing them with my colleagues to determine their added value and how to feasibly implement them.

Do you have any hobbies?

Yes, I like to run full marathons. Plus, as I am originally from Switzerland, I love skiing as well.

The Parenteral Drug Association presents the...

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In response to the industry's need for current and reliable information on this rapidly growing area of pharmaceutical manufacturing, PDA is offering the *2017 Biosimilars Conference*.

Benefit from successful case studies and practical examples illustrating how analytical similarity can be demonstrated and practical control strategies can be developed.

Hear current updates from regulatory agencies, including the U.S. FDA, EMA and Health Canada, and CMC reviewer perspectives elucidating those CMC issues that have been most challenging to approve. Attendees will have the opportunity to raise questions and concerns for discussion during the conference.

Attend this important conference to be a part of the interesting and practical discussion on this hot topic.

We look forward to seeing you in Bethesda!

Learn more and register at pda.org/2017bio

Japan Chapter Marks 25 Years at Annual Event

PDA Japan Chapter Annual Meeting Committee

In recent years, new issues related to quality assurance for pharmaceutical products have arisen. These issues have generally resulted from the progressive globalization of the pharmaceutical industry. Supply chains have been growing wider in scope. Data integrity deficiencies have ballooned around the world, resulting in US and European regulatory guidances. And the introduction of technical innovations, such as continuous manufacturing, has made new approaches to manufacturing and quality control a necessity. In light of these circumstances, PDA's Japan Chapter hosted its 23rd annual meeting with the theme: "New Trends in Quality Assurance," Nov. 29–30, in Tokyo.

Award Winners (Front row l-r) Kunio Kawamura, Katsuhide Terada, Richard Johnson, Haruhiro Okuda, Masayoshi Nishiyama (Back row l-r) Yoshihito Hashimoto, Yoshimi Urayama, Tsuguo Sasaki, Kaoru Morikawa, Hirohito Katayama, Toshiaki Nishihata, Shinji Sugaya, Yukio Hiyama, and Tsutomu Kamikukita

On the first day, following remarks from Chapter President **Katsuhide Terada** and a lecture from Chapter Chair **Haruhiro Okuda,** Japanese regulator **Yasunori Muranishi** with the Ministry of Health, Labour and Welfare (MHLW) presented, "Medical Safety Measures Related to Pharmaceuticals." Next, **Atsushi Aoyama** with Japan's Pharmaceuticals and Medical Devices Agency (PMDA) covered PMDA perspectives on continuous manufacturing. The second day saw PDA President **Richard Johnson's** presentation, "Update on PDA Global Initiatives." That same day, the chapter was honored to host a guest from the US FDA for the first time ever at the Annual Meeting, **Alicia Mozzachio.** She provided two talks: "Current GMP Issues Related to APIs" and "FDA Perspectives on the Quality of Data in the Pharmaceutical Industry."

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2017 PDA Quality Risk Management for Manufacturing Systems Workshop
June 19-20, 2017 | Chicago, IL
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Photo courtesy of Sartorius AG

The *2017 PDA Quality Risk Management for Manufacturing Systems Workshop* will inform attendees about the need for and how to integrate risk-based thinking into evolving manufacturing systems.

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In addition to these talks, the chapter's eight committees presented on the following topics: prevention of deviations, implementation of Quality Risk Management (QRM), application of cloud computing to ensure data integrity of computerized systems, risk management in design and transportation for medical products, new trends in API manufacturing, ensuring and streamlining aseptic conditions, the fusion of process design/control with method design/control, and the impact of globalization on generic manufacturers.

In conjunction with this meeting, the Japan Chapter's 25th anniversary event was held. To celebrate, the chapter presented three awards at a reception on Nov. 28. The Kawamura Award, recognizing chapter members with more than 25 years of involvement, was awarded to **Kunio Kawamura, Yoshimi Urayama, Yoshihito Hashimoto, Masayoshi Nishiyama, Tsutomu Kamikukita, Shinji Sugaya, Toshio Maeda,** and **Masahito Takeuchi.** The Aoyama Award, recognizing chapter members who have contributed to the progress of GMPs and validation, was awarded to **Kaoru Morikawa** and **Tsuguo Sasaki.** And the Terada Award for members with strong contributions to science and technology was awarded to **Toshiaki Nishihata, Yukio Hiyama,** and **Hirohito Katayama.** The Japan Chapter thanks these individuals for their years of service to the chapter.

All in all, the Annual Meeting of the PDA Japan Chapter offered a look at the latest trends in Quality Assurance for close to 500 attendees. The chapter particularly wishes to thank Alicia Mozzachio and Richard Johnson for participating in the program.

[Editor's Note: For more pictures from this event, including award winners, visit the PDA Flickr page: www.flickr.com/photos/parenteral-drug/sets.**]**

PDA Who's Who

Atsushi Aoyama, Pharmaceuticals and Medical Devices Agency (PMDA)

Yoshihito Hashimoto, Chiyoda Corporation

Yukio Hiyama, National Institute of Health Sciences (NIHS)

Richard Johnson, President, PDA

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Buddy Up in Berlin with New PDA Pals

Make friends from around the world at this year's *2nd PDA Europe Annual Meeting* in Berlin. Individuals representing different segments of the pharma industry will be on hand, learning about big data and data management, modern engineering techniques, supply chain systems, connectivity and smart devices, and more. So take some time to get acquainted with attendees from across Europe and the rest of the globe and discuss these topics of common interest.

Tuesday, June 13

Summer in Berlin

Celebrate the beginning of summer at Pier 13 in Berlin with an evening at the "beach." Switch to some more comfortable clothes and enjoy a cookout with your colleagues. PDA's very own band, the Parenteral Drug Addicts, bring down the house for everyone.

Shuttle to the venue leaves at 7 p.m. Anyone going to this event must meet in the Hilton Berlin hotel lobby.

Wednesday, June 14

Welcome Coffee

Grab some coffee or tea and discuss the second day's slate of speakers before the first sessions. 8:30 a.m.

There will also be opportunities for networking during refreshment breaks and luncheons in the Exhibition Hall both days of the conference.

(l-r) Jay Bolden, Eli Lilly and Company; and Elena Gustchina, Lonza

Anil Sawant, PhD, MSD, (far left) leads a roundtable discussion on environmental monitoring in the one of the meeting's interactive sessions.

Neil Lewis, Procter & Gamble

2017 PDA Europe Pharmaceutical Microbiology Conference

February 14–15 | Porto, Portugal

Michael Miller, PhD, Conference Chair, receives a Berlin Buddy Bear statue in recognition of his work on the conference.

2nd PDA Europe Annual Meeting

Instructor Sees Future for QbD in Biopharmaceuticals

Rebecca Stauffer, PDA

The biopharmaceutical space is facing a sea of change as new therapies enter the market, necessitating more flexible forms of manufacturing. From advanced therapy medicinal products (ATMPs) to biosimilars, this transformation brings both opportunities and challenges to the industry.

Can Quality by Design (QbD) play a role in addressing these challenges as innovative therapies come out of biopharma? PDA Education instructor **John Geigert,** PhD, President, BioPharmaceutical Quality Solutions, thinks so. He took some time to explain to the *PDA Letter* how his upcoming course, "Quality by Design (QbD) for Biopharmaceuticals," scheduled before the *2nd PDA Europe Annual Meeting,* addresses the ways QbD can help biopharmaceutical manufacturers in an era of change.

What is QbD and is it still relevant?

QbD is a systematic risk- and science-based approach to developing an effective control strategy. It was described almost a decade ago in the ICH Q8–Q11 guidances. It is still an optional strategic approach even today, yet with the challenging processes biopharmaceutical manufacturers encounter, it can be tremendously rewarding, if not a necessity. Through risk prioritization tools, limited resources focus on the areas of control with the greatest impact on product safety and quality. By relying on sound science, we gain an improved understanding of complex manufacturing processes, which should result in fewer manufacturing deviations and batch failures.

Why was the course developed?

QbD has been embraced by both global regulators and the larger biopharmaceutical companies. But many biopharmaceutical companies either have not yet visualized, or have misunderstandings about, the true value of QbD. This course was developed to address these shortcomings, and to present a practical six-step approach to implementing the core principles of QbD.

Has this course evolved over time to reflect changes in technology, particularly the growth in biosimilars and advanced therapies?

The core principles of QbD—quality target product profile (QTPP), critical quality attributes (CQAs), critical process parameters (CPPs), and control strategy (CS)—are applicable to all biopharmaceutical manufacturing processes. Those involved in recombinant protein and monoclonal antibody manufacturing have well embraced QbD, as evidenced by a quick look at the public summaries of these products being approved for the marketplace today.

Biosimilar manufacturers also fully understand the importance of QbD, especially with the need to rapidly reverse-engineer the manufacturing process of the innovator, and to adjust the CPPs to yield the desired product-related substance and product-related impurity CQA values for the required analytical comparative studies. Even those involved in advanced therapies (i.e., gene and cell therapy manufacturers) are beginning to realize the value of QbD, as judged by the number of publications on this topic, as well as by recent market-approved genetically engineered viruses and genetically engineered cells that have incorporated QbD's core principles.

What is one thing you hope students will take away from this course?

My hope is that students leave with an increased appreciation of QbD for all biopharmaceutical manufacturing processes. Yes, the investment in QbD takes place during clinical development when the product is at significant risk of not passing the threshold of the different clinical stages, but investment in sound science pays off in a fuller understanding of the manufacturing process and its proper control. I trust that the students will go back to their respective companies with this message.

Quality by Design for Biopharmaceuticals

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Journal TOC

May/June Issue of Journal Looks at Sterile Production Gap

James Agalloco looks at the latest research in how the sterile production gap impacts patient safety in the May/June issue of the *PDA Journal of Pharmaceutical Science and Technology* (journal.pda.org).

Review

James P. Agalloco, "Increasing Patient Safety by Closing the Sterile Production Gap – Part 1 - Introduction"

James P. Agalloco, "Increasing Patient Safety by Closing the Sterile Production Gap – Part 2 - Implementation"

Research

Yuh-Fun Maa, et al., "Processing Impact on Monoclonal Antibody Drug Products: Protein Subvisible Particulate Formation Induced by Grinding Stress"

Fernando A. Garcia, Michael W. Vandiver, "Throughput Optimization of Continuous Biopharmaceutical Manufacturing Facilities"

Marcel Goverde, Oliver Gordon, Alexandra Staerk, David Roesti, "Validation of Milliflex® Quantum for Bioburden Testing of Pharmaceutical Products"

Technology/Application

Ildikó Ziegler, et al., "Revision of Viable Environmental Monitoring in a Development Pilot Plant based on Quality Risk Assessment: A Case Study"

Commentary

Mostafa Essam Eissa, "Quantitative Microbial Risk Assessment of Pharmaceutical Product"

PDA Paper

Emma Ramnarine, et al., "PDA Points to Consider: Technical Product Lifecycle Management: Pharmaceutical Quality System Effectiveness For Managing Post-Approval Changes"

PDA: Enabling Pharmaceutical Manufacturing Today

Rich Levy, PDA, Debbie Goldstein, PDA

PDA has a long tradition of providing the scientific foundation to facilitate the technological developments that advance pharmaceutical and biotechnological manufacturing and, in so doing, benefit the public health.

The vocations of many of our members reflect manufacturing-related activities, such as supply chain, cleaning and disinfection, glass handling and packaging, aseptic processing and pharmaceutical microbiology, as well as biotechnological areas, such as sterile filtration, ultrafiltration, and chromatography.

For more than 70 years, PDA has been providing high-quality, expert manufacturing resources to meet the needs of our members and other industry professionals involved in these aspects of bio/pharmaceutical manufacturing. These resources include:

- Peer-reviewed technical reports offering guidance on a variety of manufacturing-related topics, such as aseptic processing, validation of dry and moist heat sterilization, steam-in-place, validation of tangential flow filtration, sterilizing filtration, virus filtration, parametric release, validation of column-based chromatography, pharmaceutical package integrity, process simulation of aseptic processing, process validation, technology transfer, single-use systems, reprocessing, and identification and classification of nonconformities in glass vials and in elastomeric closures, to name a few.

- Conferences and workshops focused specifically on trends in manufacturing, such as Quality Risk Management (QRM) for manufacturing systems, aging facilities, analytical methods, continuous manufacturing, glass quality and handling, single-use systems, lyophilization, pharmaceutical packaging, and prefilled syringes and injection devices.

- Lecture and lab-based education courses providing in-depth training and practical solutions to manufacturing challenges, including aseptic processing, bioburden and biofilm management, cleaning and disinfection, container closure and integrity testing, contamination control and environmental monitoring, cleanroom and isolator technology, facility design and operation, filtration, GMPs, moist heat sterilization, single-use systems, technology transfer, visual inspection, and multiple courses on the validation of manufacturing processes.

SNAPShot

- Subject matter expert-generated content on the latest manufacturing science covered in the *PDA Journal of Pharmaceutical Science and Technology* and *PDA Letter* magazine.

Further, we monitor and support the global regulatory interests of our members. We have frequent interactions with global regulatory authorities related to GMPs. We do this by cosponsoring meetings with regulators (FDA, EMA,PIC/S, ICH, ANVISA), and through our commenting teams, who respond to health authorities with PDA's official thoughts on proposed regulations and guidances. By doing this, we promote science-based regulations.

PDA recognizes that to better serve patients we must improve manufacturing processes and efficiencies and build quality into our products, rather than inspect after. We are committed to helping to advance technological enhancements by identifying improvement and facilitating dialogue with regulators to encourage adoption.

To that end, PDA has established a formal steering team to guide PDA's future manufacturing efforts through the Manufacturing Science and Operations Program[SM].

PDA's Manufacturing Science and Operations Program (MSOP[SM]) — Enabling Pharmaceutical Manufacturing's Future

In an effort to continue PDA's leadership position at the forefront of advances in bio/pharmaceutical manufacturing, PDA has established the Manufacturing Science and Operations Program[SM], the goal of which is to:

- Highlight the ongoing focus PDA has on pharmaceutical and biopharmaceutical manufacturing
- Strengthen and build practical solutions by filling known gaps in current manufacturing science as well as gaps that will become apparent based on ongoing developments and analyses
- Identify and encourage use of new manufacturing technology and methods

The steering team has identified several areas of interest which we are beginning to explore, which include the following:

Leveraging Technology — Leveraging technology is about delivering existing technology faster and more efficiently, this will enable suppliers to provide one best solution even if it's less expensive and deliver new technology faster

Manufacturing Organization, Culture and Process Understanding — Improving these three areas will lead to operational/technical improvements

Data on the Shop Floor — Using manufacturing data in real time on the shop floor will deliver better decisions and reduce variability

Aseptic Processing/Technology/Real-Time Release — Implementing technology advances in aseptic processing as well as real-time release will lead to improvements in pharmaceutical and biotech manufacturing as well as the quality of drug products and delivery devices

To learn more about how PDA is promoting progress in bio/pharmaceutical manufacturing, how you can benefit from the expert tools and resources available and how you can become involved in this initiative to advance bio/pharmaceutical manufacturing, please visit www.pda.org.

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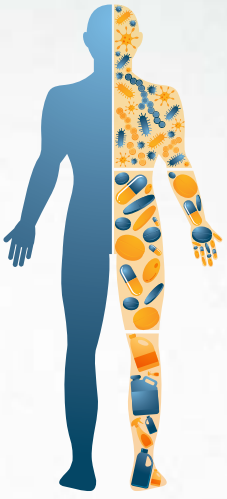

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A Case Study in Aseptic Gas Plasma Decontamination

Egmont Semmler, Groninger & Co.

Quite a few industries have adopted gas plasma technology, such as the semiconductor and lighting industries. Its use in the medical field is also growing. A recent case study that looked at gas plasma decontamination for secondary packaging components suggests it also has potential for use within aseptic manufacturing ***(1).***

For barrier systems used within a filling line in an isolator environment, the main task is getting a presterilized nested object (i.e., a "tub") into the aseptic filling area. The challenge of introducing a new technology like gas plasma decontamination in this space is twofold. First, the process and cycle development for gas plasma needs to be well understood and well controlled. Second, the technology needs to be aligned with global pharmacopeial standards and regulatory requirements, particularly for sensitive process steps such as decontamination and sterilization.

Decontamination vs. Sterilization

"Decontamination" refers to the process benchmarked by a logarithmic reduction rate of viable organisms between 4-log and 6-log (logarithm base 10). "Sterilization" refers to the proven kill efficacy achieved by a 6-log reduction of viable microorganisms plus an additional sterility assurance level of 10^{-6}, i.e., the process time for a proven 6-log reduction is doubled to ensure a safety margin of an additional 6-log reduction. This results in a 10^{-6} survivor probability, assuming linearity of the kill efficacy—a concept known as the *half-cycle approach*.

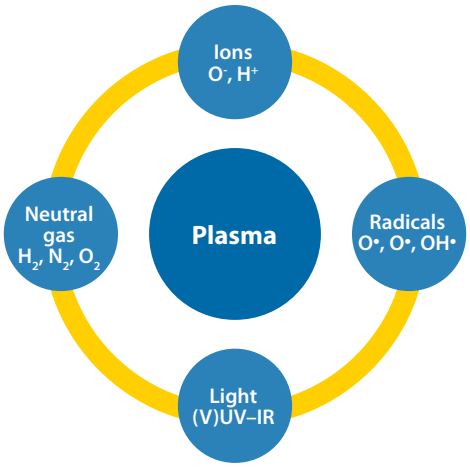

Figure 1 Gas Plasma Components

The approach chosen depends on the quality framework and regulatory guidance. Most manufacturers have experience with H_2O_2 or e-beam barriers in their aseptic filling machines. Thus, they are familiar with a 6-log reduction and half-cycle approach. When dealing with ethylene oxide (EO) presterilized nested tubs, however, a 6-log reduction is not required. The US FDA's cGMP guidance states that a proven 4-log reduction is sufficient for low bioburden (presterilized) objects ***(2).***

Before delving into the case study, the term "gas plasma" should be clarified. Gas plasma is an electrically conductive gas that always goes together with the emission of light. It also consists of properties, e.g., ions and radicals that strongly support microbial kill **(Figure 1).** These antimicrobial properties result from two forces: 1) the ions and radicals erode a spore's coat or cell membrane, and 2) in turn, the the UV-C radiation more easily penetrates into the cell to induce DNA strand breaks, inhibiting proliferation.

For aseptic decontamination, the key is developing an operating regime and gas mixture that achieves homogeneous and efficient tub decontamination by running the decontamination cycle at a low pressure. Hydrogen was chosen as the operating gas due to its well-known strong emission of UV-C light, and even shorter (higher energetic) wavelengths.

Cycle Validity

The most important information at each cycle of a production batch is how the cycle validity is ensured. Here, the gas plasma cycle was monitored by an optical spectrometer with a sensitive UV-C range and positioned at the critical worst case location that expected the least UV-C radiation.

In order to generate a dedicated number to determine cycle validity, the spectrometer spanned a wavelength range from 200 nm upward across the entire cycle time, resulting in a number equivalent to a "UV" or "plasma" dose. This was then used in conjunction with a kill efficacy study to determine the 4-log reduction validity limit of a gas plasma cycle ***(2).*** **Figure 2** shows a typical cycle run with a continuously monitored gas plasma dose and an indicated validity limit.

The main challenge in cycle development and process validation is to correlate microbial kill efficacy on all tub surfaces to the gas plasma dose. Therefore, a D-value study was performed for different spray-inoculated tub locations and linked to the spectrometer measurement at the respective positions.

The crucial part for a new decontamination concept is demonstrating process reliability. This was achieved by showing linearity between the spectrometer data and the microbial inactivation kinetics. **Figure 3** shows the good linearity achieved, and the gas plasma cycle correlates linearly well with the total gas plasma running time.

Figure 4 shows the inactivation behavior of *G. stearothermophilus* endospores on Tyvek® foil for different gas plasma cycle times. It is plotted log-linearly since the inactivation follows an exponential decrease. From the slope of the given curve, a D-Value of D_{Plasma} = 3.5 s can be estimated. This means the population of viable organisms was reduced by a factor of 10 for each 3.5 s gas plasma run time.

By linking the results from **Figure 4** to **Figure 3,** a defined gas plasma dose from **Figure 3** correlates to a defined process lethality in **Figure 4.** Furthermore, a minimum gas plasma dose limit number can be extracted, ensuring a safe 4-log reduction of viable microorganisms on the tub Tyvek®. This was also monitored and verified on each cycle by the in-process spectrometer.

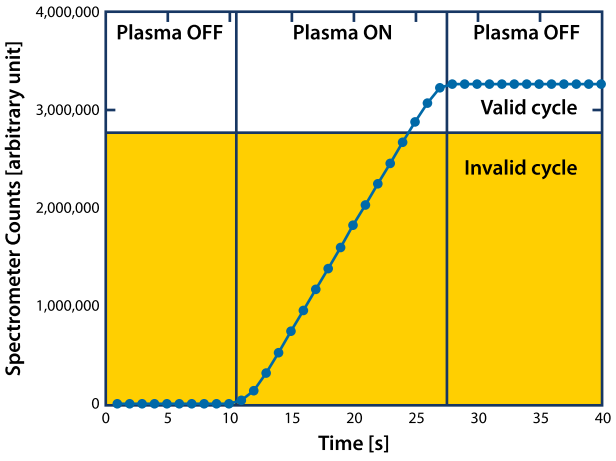

Figure 2 Cycle Validity

Since a regular (re)validation was not feasible on the basis of spray-inoculated tubs, a simple approach was developed based on standard biological indicators (BIs). Here, stainless steel BIs, known from isolator H_2O_2 validation, were used. Since the underlying carrier material is different from the polymer surface of the tub, a link needed to be established between the BI inactivation rate and the inactivation behavior from **Figure 4.** This was achieved by performing a D-Value determination of the BI on the same location (Tyvek®) as the spray-inoculation study. The resulting D-Value for the BI inactivation was D_{BI} = 1.9 s. Thus, by using the BI on the worst case location of the process, the cycle's microbial inactivation efficacy can be validated.

On the basis of the average contamination level of the BI (e.g., 4.3×10^6 colony forming units) and the D-Value D_{BI}, a minimum gas plasma cycle run time was calculated. All BI were exposed to this run time. The goal was for no BI to exhibit growth when incubated. Because the D-Value on Tyvek® (D_{Plasma}) as well as the BI's D-Value (D_{BI}) were known, a rationale was constructed linking the 6-log kill of the BI to the 4-log reduction on the Tyvek® ***(1).***

In parallel, this method was also used to determine gas plasma dose cycle validity limit. Here, the gas plasma dose number corresponding to the 4-log calculated minimum cycle time from the Tyvek® inactivation was used (e.g., D_{Plasma} × 4.0-log = 14 s). The gas plasma dose for a gas plasma cycle time of 14 s provided the cycle's validity limit. With respect to **Figure 3,** this corresponds to approximately 9 million counts as a dose value.

Conclusion

A new barrier system on the basis of low pressure gas plasma was developed for the outside decontamination of secondary packaging containers like nested objects (vials, cartridges, syringes). As shown in the study, a successful validation scheme could be developed to bring this technology to a safely controlled and verifiable operation level as governed by regulatory requirements.

The author would like to acknowledge the work and the many helpful discussions and contributions by individuals and groups fromGlaxoSmithKline (Barnard Castle site), Fraunhofer Process Engineering & Packaging, and Ruhr-University Bochum.

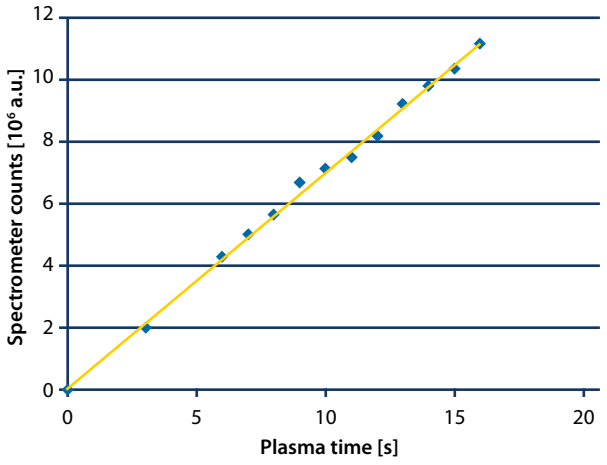

Figure 3 Gas Plasma Dose

[Editor's Note: This is an abbreviated version of the article "Plasma Decontamination: A Case Study on Kill Efficacy on Geobacillus stearothermophilus Spores on Different Carrier Materials," which appeared in the May/June 2016 issue of the *PDA Journal of Pharmaceutical Science and Technology*.**]**

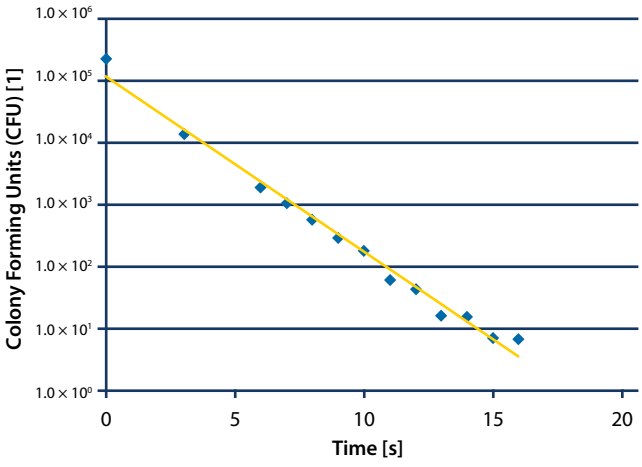

Figure 4 Kill efficacy of *G. stearothermophilus* endospores spray-inoculated on Tyvek®

References

1. Semmler, E., et al. "Plasma Decontamination: A Case Study on Kill Efficacy on Geobacillus stearothermophilus Spores on Different Carrier Materials." *PDA Journal of Pharmaceutical Science and Technology* 70 (2016): 256–271.
2. "Sterile Drug Products Produced by Aseptic Processing - cGMP," 2004, Appendix 1, D.2.

About the Author

Egmont Semmler, PhD, is currently Director R&D with Groninger & Co. GmbH, where he focuses on new technologies and concepts in aseptic manufacturing.

Human Element Key to Digital Transformation

Rebecca Stauffer, PDA

The future of manufacturing for biotech products is looking increasingly digital. Automated factories that rely on networked robotics will lead to flexible operations and even real-time responses to potential issues. Biotech products will be monitored throughout their lifecycle, beginning with clinical development through manufacturing to patient consumption, in what is termed the "digital thread."

But how will the industry get there? And how can biotech manufacturers take advantage of the Internet of Things? It's easy to be wowed by the promise of new technology, but the challenge lies in implementing it successfully within a heavily regulated industry.

Ryan Smith, Vice President of Engineering and Product with SightMachine, a company that markets software platforms for a variety of manufacturing firms, believes that companies who achieve success in digital transformation do so through a strong investment in planning and relying on the right people for the role of the project.

He will go into more detail about the nature of digital transformation for the biotech industry in his talk, "Driving Digital Transformation: Best Practices for Realizing Value from New Technology Within your Organization," at the *2nd PDA Europe Annual Meeting* (9 a.m., June 14, Track A: "Connectivity, Smart Devices and Analytics").

"We've done enough engagement with big companies now that we have a sense of how things are going to work," Smith explained. In his experience, those companies that treat a new technology as if it were a smartphone, i.e., unwrap, install, and sit back, do not see as much success as those companies that strategically plan out the implementation and identify the right individuals for the project. And it's the latter approach that Smith believes is critical for a company to achieve digital transformation.

"There needs to be the right people in place at the site," he said, admitting that this can be a challenge if the technology is totally new. It may not be immediately clear who should be involved. This may require recruiting for individuals with specialized skills. Anyone leading a digital transformation project should ask "who are the experts that need to be involved in

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this project to make it a success, and how do we get them in order and in place prior to starting?

"Otherwise, you're a bit behind and you have to try and scramble and round up people," Smith added.

"Envision what the end goal of the project is and what success would look like if you looked back. So, who are the people to get that through...those are the types of backgrounds that are good to recruit for early in the process."

And a company's senior leadership must support and encourage the transformation in order for it to be realized.

"In order to actually initiate change, that has to come from within. And that's a culture shift for a lot of these companies. There has to be top level commitment by senior leadership, who say, 'we are going to move to adopt digital technology.' And that can be especially tricky in regulated industries. So, you really have to have that buyin in order to get that going," Smith said.

Once the right people are in place, the next step is figuring out the long-term goals of the project. Naturally, this will differ for each individual company, depending on the type of project.

"At the beginning of the project, you're adding infrastructure and foundation to what a digital landscape will look like for your organization in five years, but we also make sure we have the concrete nets or business gains we want to initiate with this first run."

Interestingly, while many biotech companies are concerned about how regulators will respond to their implementing new digital manufacturing technologies, in his experience, the regulators are generally accepting of new technologies provided companies ensure that product remains in compliance.

Smith believes that by 2027, almost all biotech companies will have been "digitally transformed."

"In ten years, I think it will seem very strange we did things like we do right now," he said.

About the Expert

Ryan Smith currently serves as Vice President of Engineering and Product at SightMachine, a start-up that leverages big data and internet technologies for manufacturing. He formerly worked at Amgen, developing novel robotic visual inspection systems.

2017 PDA Upcoming Events

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MAY

15-19
PDA #100 Aseptic Processing Option 3 Week 2: Jun. 12-16
Bethesda, MD
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22-25
Lyophilization Course Series
Bethesda, MD
pda.org/2017Lyo

23-24
Single Use Systems for the Manufacturing of Parenteral Products
Bethesda, MD
pda.org/2017SUS

29
The Principles of Viral Safety for Biologics and Vaccines
Dubrovnik, Croatia
pda.org/EU/Pre-WS-Viral2017

30-1
Virus & TSE Safety Forum
Dubrovnik, Croatia
pda.org/EU/Virus2017

31-2
Validation of Moist Heat Sterilization Processes
Bethesda, MD
pda.org/2017MayMH

JUNE

1-2
Virus Filtration
Dubrovnik, Croatia
pda.org/EU/Virus-Filtration2017

6-7
Isolator Technology
Bethesda, MD
pda.org/2017IT

12
Cleaning and Disinfection
Berlin, Germany
pda.org/EU/CD2017

12
Quality by Design for Biopharmaceuticals
Berlin, Germany
pda.org/EU/QBD2017

12
Supply Chain Strategies for API and Drug Products
Berlin, Germany
pda.org/EU/SupplyChain-API2017

13-14
2nd PDA Europe Annual Meeting
Berlin, Germany
pda.org/EU/Annual2017

15-16
Introduction to Aseptic Processing Principles
Berlin, Germany
pda.org/EU/TCAseptic2017

15-16
Practical Approach to Quality Culture
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pda.org/EU/Quality-Culture2017

19-20
2017 PDA Quality Risk Management for Manufacturing Systems Workshop
Chicago, IL
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19-22
Biotechnology Course Series
Bethesda, MD
pda.org/2017BCS

20-22
Environmental Monitoring Course Series
Bethesda, MD
pda.org/2017JunEMCS

26
Practical Application of Phase-Appropriate GMP & Quality to Clinical Development of ATMPs
Valencia, Spain
pda.org/EU/TCATMPs2017

26-27
2017 PDA Biosimilars Conference
Bethesda, MD
pda.org/2017Bio

26-30
Quality Course Series
Bethesda, MD
pda.org/2017QCS

27-28
Advanced Therapy Medicinal Products
Valencia, Spain
pda.org/EU/ATMPs2017

JULY

10-13
Fundamentals of Aseptic Processing
Bethesda, MD
pda.org/2017JulFundAP

24-28
PDA #100 Aseptic Processing Option 4 Week 2: Aug. 21-25
Bethesda, MD
pda.org/2017Aseptic4

31-1
Sterile Pharmaceutical Dosage Forms: Basic Principles
Bethesda, MD
pda.org/2017Sterile

AUGUST

2-3
Fundamentals of Cleaning and Disinfectant Programs for Aseptic Manufacturing Facilities
Bethesda, MD
pda.org/2017Clean

8-9
Mold Identification for Quality Control
Bethesda, MD
pda.org/2017QC

9-10
Assessing Packaging and Processing Extractables/Leachables
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Bethesda, MD
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SEPTEMBER

11-13
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Washington, DC
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13-14
2017 PDA PAC iAM Workshop
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14-15
2017 PDA Regulatory Course Series
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19-21
Validation of Biotechnology-Related Cleaning Processes
Bethesda, MD
pda.org/2017SeptBio

19-20
Pharmaceutical Freeze Drying Technology
Cologne, Germany
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21
Application of a Risk-Based Approach to Freeze Drying Processes
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21-22
Development of a Freeze Drying Process
Cologne, Germany
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21-22
Einfache und Prozessorientierte Qualifizierung
Cologne, Germany
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25-28
Filtration Processes in the Pharmaceutical and Biopharmaceutical Industry
Bethesda, MD
pda.org/2017Filtration

25-28
Sterilization Course Series
Bethesda, MD
pda.org/2017SterilizationCS

25
Particle Identification in Parenterals
Berlin, Germany
pda.org/EU/ParticleID2017

26
Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Validation and Ongoing Control
Bethesda, MD
pda.org/2017CDDVOC

26-27
PDA Exchange: Particles in Injectables Conference
Berlin, Germany
pda.org/EU/Particles2017

26-27
PDA Exchange: 10th Workshop on Monoclonal Antibodies
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27
Validation of Dry Heat Processes
Bethesda, MD
pda.org/2017DryHeat

28
Tailormade Strategies for High Level Expression of Biologicals
Berlin, Germany
pda.org/EU/Expression-of-Bio2017

28
Testmethoden für vorbefüllte Spritzen
Berlin, Germany
pda.org/EU/Test-Methoden-PFS2017

28-29
Extractables & Leachables Workshop
Berlin, Germany
pda.org/EU/E-and-L2017

28-29
An Introduction to Visual Inspection
Berlin, Germany
pda.org/EU/TC-Visual2017

28-29
Best Compliance Practices im GMP Prüflabor
Berlin, Germany
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28-29
CMC Regulatory Compliance for Biopharmaceuticals
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Lower the H_2O_2 Concentrations in Your Isolator with One Easy Upgrade

Stefan Kleinmann, PhD, METALL+PLASTIC, Matthias Scheu, METALL+PLASTIC, Roland Schuhwerk, Cilag AG, and Volker Baur, Cilag AG

In recent years, the number of protein-based biologic drug products has grown. Parallel to this, the use of filling line isolators in biopharmaceutical manufacturing plants has increased. Some of these products are extremely sensitive to oxidation. The majority of aseptic manufacturing isolators are decontaminated with H_2O_2, so potential oxidation of these sensitive products has become a concern ***(1).*** Although this concern has mainly been associated with isolators, there is also oxidation risk to drug products filled in traditional cleanrooms due to the use of oxidative liquid chemical agents for wipe downs and mopping. Residual vapors from sodium hypochlorite (bleach), a commonly used cleanroom sanitizing agent, have been found to cause oxidation in proteins more quickly when compared to hydrogen peroxide/peracetic acid mixtures ***(2).***

A study was conducted on a syringe filling line to benchmark the residual concentration of vapor phase hydrogen peroxide (VPHP) in an isolator after the existing aeration process was completed using a Picarro G1114 Cavity Ringdown Spectrophotometer (CRDS) with a VPHP measurement range of 100 ppm to 0.1 ppm. The programmed aeration phases totaled approximately four hours and 33 minutes, at which point all of the built-in electrochemical cell sensors were measuring ≤ 1.0 ppm H_2O_2. Measurements with the Picarro instrument were taken at three locations, representing areas where the drug product would be directly or indirectly exposed to oxidation. An area near the stopper bowl was selected because of the potential for stoppers to absorb H_2O_2, which results in an indirect exposure to the product. Areas in the filling location and in the N_2 gas overlay station were sampled because these are places where liquid drug products are still exposed to the aseptic environment. Air samples were taken using polytetrafluoroethylene (PTFE) tubing positioned at the three locations using the built-in sampling pump in the Picarro unit. The isolator was fully loaded with the supplies that would normally be required for a produc-

> **The catalytic converter upgrade reduced the residual H_2O_2 concentration by more than tenfold**

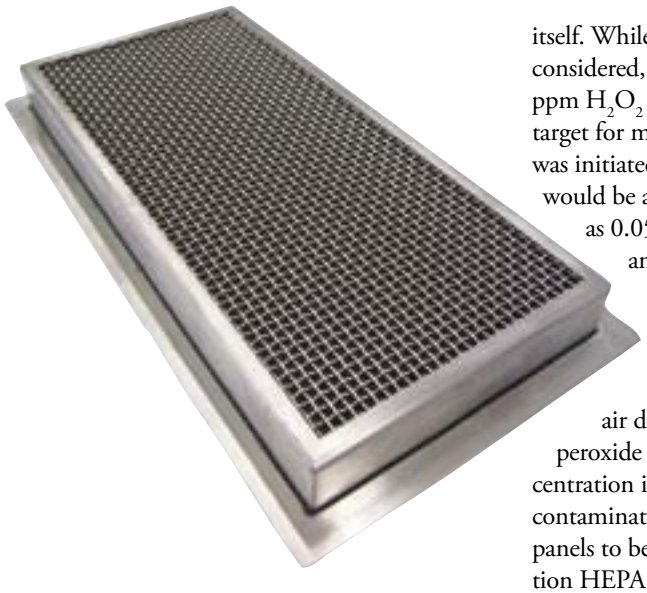

Figure 1 Catalytic Panel

tion run. Approximately six hours after aeration began, the Picarro measurements ranged from 0.328–0.494 ppm H_2O_2 in the three locations.

Catalytic Converter Upgrade

After six hours, the residual H_2O_2 concentration inside was considered to be too high for many oxidation-sensitive products. The acceptable limit for H_2O_2 concentration inside an isolator during a filling process depends on many factors, including line speed, vial, or syringe size, allowable line stoppage time before triggering a line clearance and, ultimately, the oxidation sensitivity of the drug product itself. While there are many factors to be considered, a concentration limit of 0.050 ppm H_2O_2 (50 ppb) has been used as a target for many recent projects. A project was initiated to upgrade the isolator so it would be able to reach low levels, such as 0.050 ppm H_2O_2, in a reasonable amount of time.

In most isolators, the fresh air supply rate is the main factor affecting aeration. The fresh air dilutes the outgassing hydrogen peroxide until the desired low-level concentration is reached. Using single-pass decontamination piping allowed for catalytic panels to be inserted above the recirculation HEPA filters without compromising the decontamination process. The catalytic material is a porous 316L stainless steel substrate coated with proprietary metallic oxides. Panels are constructed with a stainless steel frame and wire mesh to contain the catalytic substrate. A typical catalytic panel is shown in **Figure 1.** The panels are made in the same rectangular shapes as the recirculation HEPA filters in the isolator. This way they can be slipped above them and fastened with existing hardware. No other mechanical modifications to the isolator are required. A typical catalytic panel installation is shown in **Figure 2.**

The recirculation blowers are not turned on during the decontamination process. During the aeration process and normal operation, these blowers are turned on and recirculate a substantial amount of air through the working space of the isolator to provide the unidirectional air flow (UAF) required for an aseptic filling system. The catalytic panels in the recirculation loops destroy a significant amount of the VPHP residue while, at the same time, reducing the concentration via dilution from the fresh air exchange.

The syringe filling isolator has five recirculation blowers that provide the large amount of airflow required to provide the UAF in the working area. The isolator was upgraded by installing catalytic panels between the recirculation blowers and the terminal HEPA filters. The volume of air recirculating within the isolator is much higher than the fresh air supply. For example, the isolator in question has a total volume of 16.3 cubic meters (m^3) and a maximum fresh air supply of 3,100 m^3/hour, which yields an air exchange rate of 190 air exchanges per hour. The UAF volume can be calculated based on the 5.9 square meter footprint of the isolator's recirculation unit and the UAF set point of 0.45 m/sec used during aeration,

Article at a Glance

- Isolators can present oxidation risks to protein-based biologics
- Catalytic panels can reduce oxidation risk when inserted above HEPA filters
- Upgrade to catalytic panels also resulted in a reduction in hold time

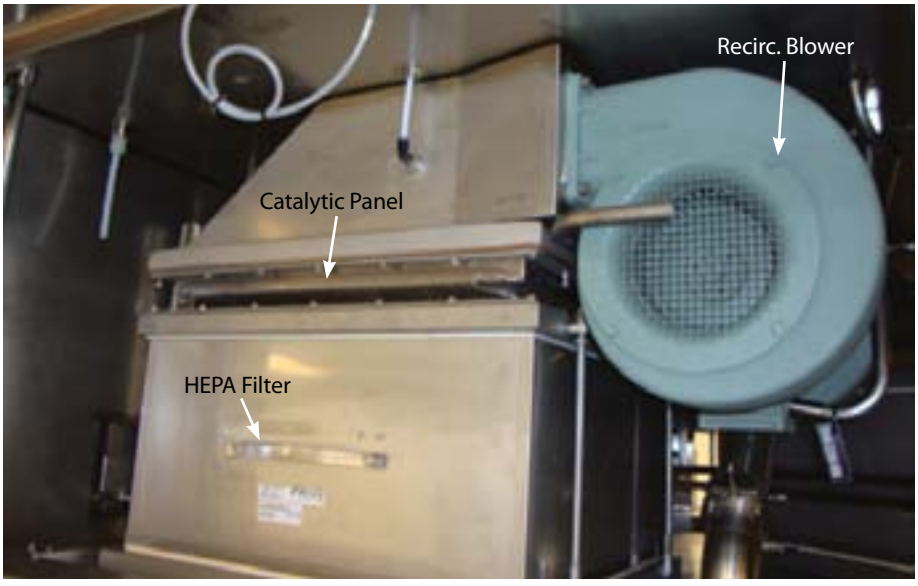

Figure 2 Catalytic Panel Installation

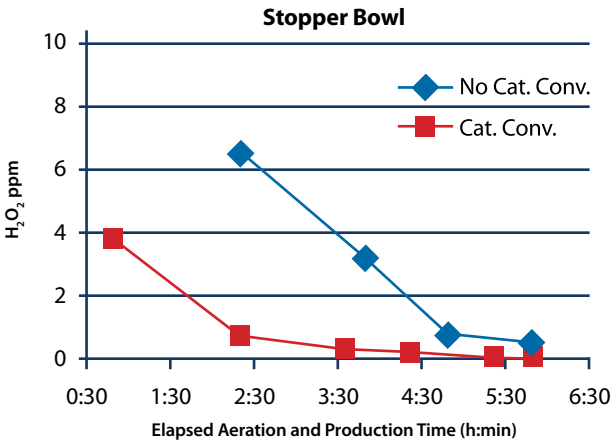

Figure 3 Residual H_2O_2 Concentration at Stopper Bowl

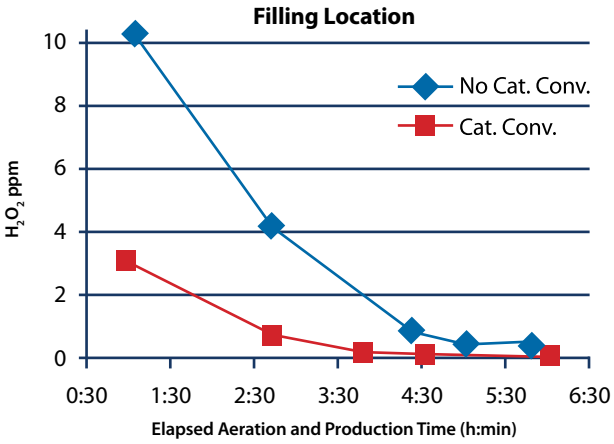

Figure 4 Residual H_2O_2 Concentration in Filling Location

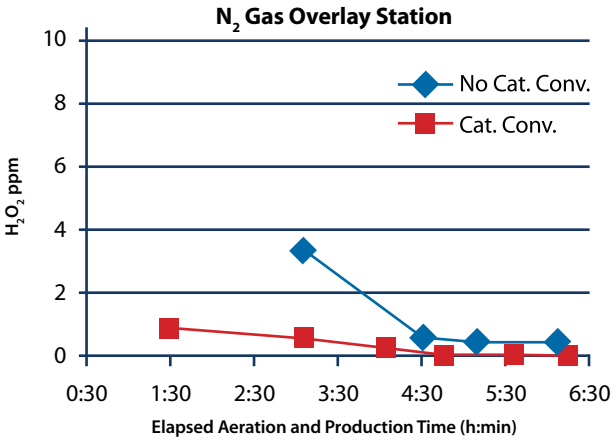

Figure 5 Residual H_2O_2 Concentration at Nitrogen Overlay Station

which yields an airflow rate of 9558 m^3/hour. Based on the total volume, the UAF airflow produces an exchange rate of 586 air exchanges per hour ***(3).*** The UAF air flow passes through the catalytic panels, so it decreases the concentration of the VPHP during aeration more quickly than the isolator could prior to the upgrade.

Residual Levels Before and After Upgrade

After the system was upgraded with catalytic converters, a study was conducted to measure the H_2O_2 residual concentration during and after aeration when the system was switched to production mode. Residual H_2O_2 concentration data from the three locations taken before and after the catalytic converter upgrade are shown in **Figures 3–5.** The H_2O_2 injection phases for these cycles lasted 2:15 (h:min). The isolator is heated during the first 3:33 (h:min) of aeration. By the end of the heated phase the air temperature within the isolator is approximately 40 °C. The warm temperature increases the outgassing rate of the H_2O_2 residue, which causes relatively high concentration measurements during this phase. During the next hour of aeration, the temperature set point changes to the production set point of 21°C. The cooler temperature slows the outgassing of the H_2O_2 residue causing the measurement to drop to ≤ 1.0 ppm before the catalytic converter upgrade, and to much lower levels after the upgrade by the time the 4:33 (h:min) Aeration phase is complete. Concentration measurements continued after Aeration was completed and the isolator was switched to production mode.

The concentration data shown in **Figures 3–5** clearly show that the catalytic converter upgrade improved the performance of the process during the initial stages of aeration. The catalytic converter upgrade reduced the residual H_2O_2 concentration by more than tenfold in the samples taken near the stopper bowl and nitrogen gas overlay station at the six-hour mark. The reduction in the filling location was also substantial: the H_2O_2 concentration measure dropped from 0.328 ppm to 0.058 ppm after the upgrade.

Conclusion

The catalytic converter upgrade of the isolator enabled the syringe filler to be used to fill oxidation-sensitive products without enduring extremely long hold times after the end of the decontamination process. Reducing the hold-time decreases costs and saves energy. The data from the three locations shows that residual H_2O_2 concentration varies within the isolator. It is important to consider various locations along the path of the filling line when making risk assessments regarding exposure of sensitive drug products to oxidizing agents.

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Pharma Has its Head in the Cloud

Big Data is Leading Pharma Manufacturing to Greater Maturity

Toni Manzano, bigfinite

Today, huge amounts of information are continuously being generated and stored in many different systems: external and internal hard drives, virtual disks, network storage systems, pen drives, e-drives, etc. In addition, social networks, multimedia platforms, and Internet of Things (IoT) technology contribute increasingly greater bytes of data. In fact, 2016 saw about 2.5 trillion (2.5×10^{18}) bytes of data created each month ***(1).*** This enormous amount of electronic information, commonly referred to as "big data," is directly related to two factors: (1) the ease in which data can be stored, and (2) the ability to connect to the internet.

Behind both factors lie cloud technologies. Cloud systems enable both cost-effective and quick deployment of storage and access to information. Tools in the cloud support what is commonly termed the three "Vs" of big data: "volume," "velocity," and "variety." But when it comes to big data in regulated pharma, two more Vs appear: "veracity" and "validity." These two Vs provide context to the knowledge pulled from massive amounts of information. Consider the following questions as applied to a manufacturing site:

- How difficult is it to manage information when data is saved through the different site activities in different formats, on different databases, and from multiple applications producing isolated siloes of information?
- Is there uncontrolled critical information locally used or accessed individually (e.g., dashboards built into spreadsheets, critical documents saved in local computers, deviations studies, or pieces of information related to the batch)?
- Are current devices ready to share information about the processes they control and with new equipment that will be acquired?
- Can knowledge be extracted from the primary data of production equipment and systems, or have they been processed through partial filters, and is there a technology solution that can aggregate that information?
- What is the maturity level of the company in terms of efficiency and effectiveness?

These entire questions boil down to one particular point: a site's deployed technologies must serve as a driver of knowledge innovation.

The majority of manufacturing sites are managed by computer applications and electronic devices with digital output. The amount of information generated by a medium-sized pharmaceutical site can easily reach a terabyte of data per year ***(2).*** If this is the case, then why is it so difficult to get valuable information from the IT systems across a company within our industry?

For one, pharmaceutical manufacturers rely on a variety of specialized software applications to ensure efficiency and quality within drug production. The diverse amount of information generated can lead to serious problems, however, when it comes to providing globally required knowledge. Over the years, companies have gradually acquired a number of software applications from different suppliers to address varying objectives; integrated access to knowledge across these systems was not a consideration when they were purchased. While each of these applications generally meets their particular niche, they prove difficult to integrate for generating interoperational data.

The amount of data produced by these multiple systems cannot be effectively managed using classical assets. Furthermore, when the data must be processed statistically, this demands an applied methodology that must be diverse, voluminous, and fast.

And finally, when tons of data must be processed, a legion of resources is needed to organize the information: dedicated servers and networks, specialized technicians, data and advanced analytics specialists, and specific software. Naturally, all this comes

with a high upfront investment. The costs and resources needed to design and enable a digital plant can be so high as to seem overwhelming. On top of that, it requires plant management to focus less of pharmaceutical activity and more on IT systems.

So, this begs the question, what is the solution?

Cloud technologies offer the machinery and logic to obtain "pull" information from vast amounts of data within a plant without significant investment in nonpharmaceutical activities. Some of the more common cloud technologies currently being deployed across the industry are:

- **Power computing:** These are servers and parallel calculation processes that can rise on demand without any limitations.
- **Artificial intelligence (AI) resources:** There are many components based on the mathematical algorithms that have been developed during the last decades to generate predictions using large data sets.
- **Advanced analytics:** Similar to AI components, there are different sets of preconfigured objects that allow implementation of the most complex analyses based on advanced statistics.
- **Infinite storage:** Nowadays, there are no limits for storage in the cloud.
- **Encryption:** A few providers are offering data encryption as a configurable attribute associated with its storage.
- **Indexing:** Some cloud components can index information so that users can easily conduct fast queries and transversal researches without maintaining any local infrastructure.
- **Other resources:** There are many functionalities for specific customization are available in the cloud—image recognition, natural language process, data queues, IoT, etc.

Used individually or combined, all these solutions offer manufacturers greater maturity in global information management. This

> **A site's deployed technologies must serve as a driver of knowledge innovation**

can be considered part of the digital supply chain. An advanced degree of knowledge about all the interrelated events occurring through a site results in a high maturity level. Think of a digital supply chain as a self-driving car. Like the driver, the facility has to be *conscious* about everything going on around it to make the right decision at every moment and under any circumstance. Yet the facility doesn't have to be "at the wheel."

What Are the Risks?

Innovation always presents risks during the early phases. At the same time, early adopters have an edge while remaining mindful of the risks. In fact, with cloud technology, its early adopters are already taking advantage of the results arriving from their initial efforts. Studies have shown that companies gain approximately **30%** in cost savings by applying predictive maintenance, a **25%** reduction in product lifecycle by verifying performance in real time, and an estimated market growth of **15%** for digital services, including automation ***(2).***

Yet from a regulatory perspective, there are some risks that deserve special consideration. These are: the security and privacy of the data, the commitment and quality behind service level agreements, data integrity, and disaster recovery processes. Nevertheless, each of these elements can be addressed by building on the strength of cloud technologies. Many common cloud platforms even feature their own cybersecurity, such as Amazon, Google, or Microsoft platforms. Now, consider a manufacturer that has installed sensors to feed data into an AI system to help improve process performance. How can that manufacturer address the risks?

If the manufacturer in question uses a "software as a service" (SaaS) application that delegates security to a platform such as Google or Amazon, and this platform provides standard security options like secure authorization and a public key certificate along with some security tools (e.g., multifactor authentication), then the risk is automatically mitigated. Throw in good practices, such as prohibiting repeated passwords and avoiding passwords saved in public places, and the risk is further minimized. Furthermore, some providers offer native encrypted data for read and write actions.

In other cases, the technology itself decreases or even eliminates the risk. The data acquisition process for big data storage uses standard technologies and procedures that replicate automatically each single byte of data in several locations. Some providers also guarantee the automatic reproduction in three different geographically separated data centers. Furthermore, users can configure extra automatic backups. This process is far more robust than the traditional backup system that relies on transporting manually labeled rotational tapes by truck.

Overall, big data and cloud-based technologies can provide benefits to the pharmaceutical and biopharmaceutical industries. And cloud services are expanding their good practices to meet many security and quality standard certifications. For example, Amazon Web Services recently published a GxP Compliance white paper defining their certifications and procedures ***(3).***

There are many considerations that can justify the mitigation of detected risks. Other sectors with strong regulatory requirements, such as the financial industry, have already adopted these technologies. (Look at NASDAQ, which currently makes six billion transactions per day using big data and cloud technologies.)

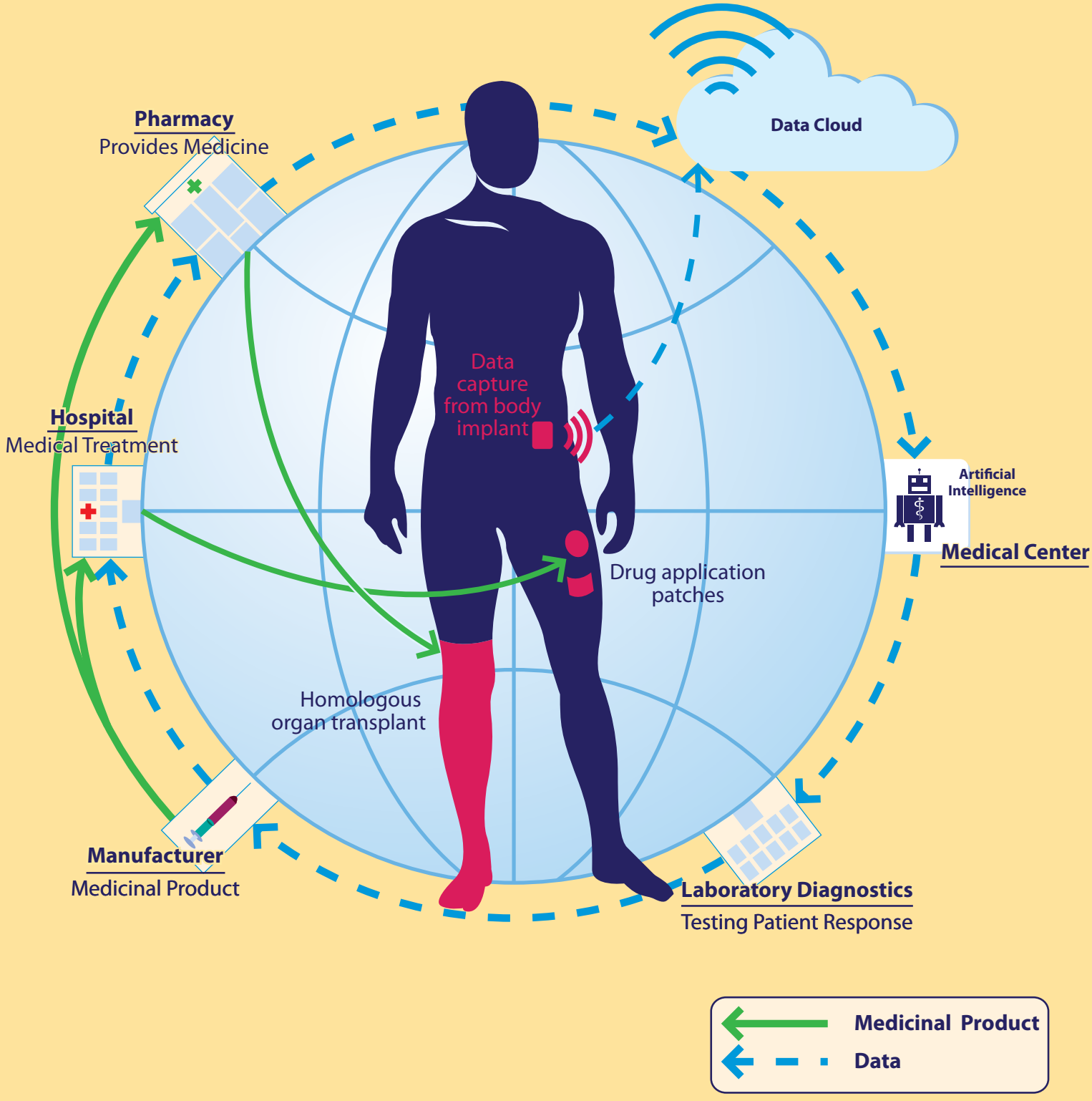
Inevitably, the evolution of technology provokes a disruption in society, and

Continued at bottom of page 43

The Future of Medicine

2nd PDA Europe Annual Meeting

Drug manufacturing is becoming increasingly patient-centric. Thanks to wearable devices and cloud technology, data from the drug/device provides more accurate information about the drug product. And manufacturers, hospitals, pharmacists, and laboratories must work together in an interconnected web. To learn more, attend the Closing Plenary "Technologies and Regulations of the Future" at the 2nd PDA Europe Annual Meeting.



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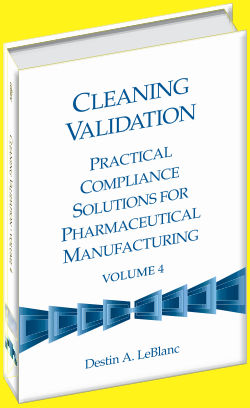

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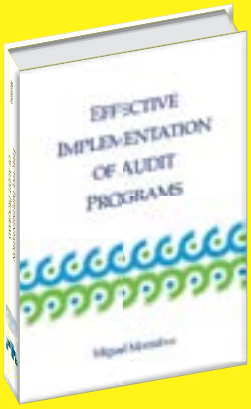

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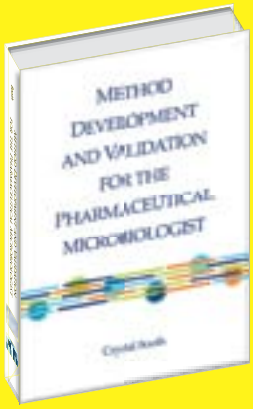

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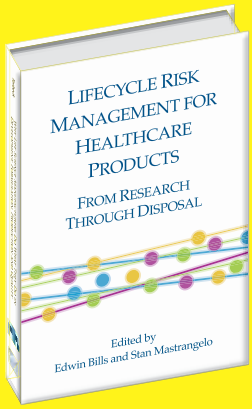

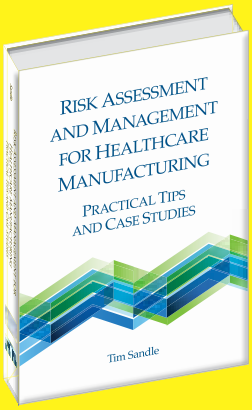

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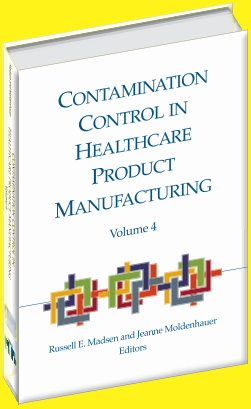

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Cost of Quality Still a Factor

Rebecca Stauffer, PDA

Tor Gråberg, *Head of External Advocacy, will be moderating the session, "Managing the Quality-Cost Dilemma" at the* 2nd PDA Europe Annual Meeting *in Berlin, Germany (June 13, 4:15 p.m.). The* PDA Letter *interviewed him for his thoughts on the Cost of Quality.*

The cost of quality has been a point of discussion for awhile. In your opinion, is the industry making headway on improving quality?

The focus of quality has been on the agenda for the pharmaceutical industry for decades and the correlation to cost is something that pops up now and then. One way to look at this is that lack of quality will immediately increase cost. As for all businesses, there needs to be cost awareness. Quality is not a stand-alone area and quality should be integrated at all levels in a company and owned by all employees. The pharmaceutical industry should learn from other industries to increase and improve our own quality standards and implement and maintain this knowledge within pharma.

There have been calls for quality to become more integrated with business operations and vice versa. Are you seeing more companies moving in this direction?

The main focus for the pharmaceutical industry should always be the patient in order to meet their medical need. Development, quality, manufacturing, and business operations are interlinked to meet requirements from patient and healthcare. Global harmonization of regulations is another important issue to facilitate this.

Can quality be quantifiable?

There are several Key Performance Indicators that could give an overview of lack of quality, e.g., numbers of complaints and recalls. Absence of quality understanding within the pharmaceutical industry will have a direct outcome regarding lack of trust from patient and health authorities. Quality aspects must therefore be considered vital to the pharmaceutical industry.

Where do you see the role of quality ten years from now?

The pharmaceutical industry needs to continuously improve its way of working to increase quality and right first time [thinking]. Focusing on patients and their medical needs will be the driving forces for the pharmaceutical industry, and quality aspects are paramount to achieving this. The use of lean philosophy, including how to simplify and standardize, will be an important tool to achieve this quality improvement. Another issue for the pharma industry is being more attentive to preventative maintenance with quality as a guiding star. In addition, new technologies and implementation of safety features will be beneficial for quality and safety for the patients. Harmonization initiatives and trust-building activities between the pharma industry and regulators are also very important elements to develop further.

About the Expert

Tor Gråberg works at AstraZeneca as Head of External Relations, Corporate Quality. Before joining AstraZeneca in September 2015, he was Chief Pharmaceutical Inspector and Head of Drug Inspectorate for the Medical Products Agency (MPA) in Sweden for 19 years.

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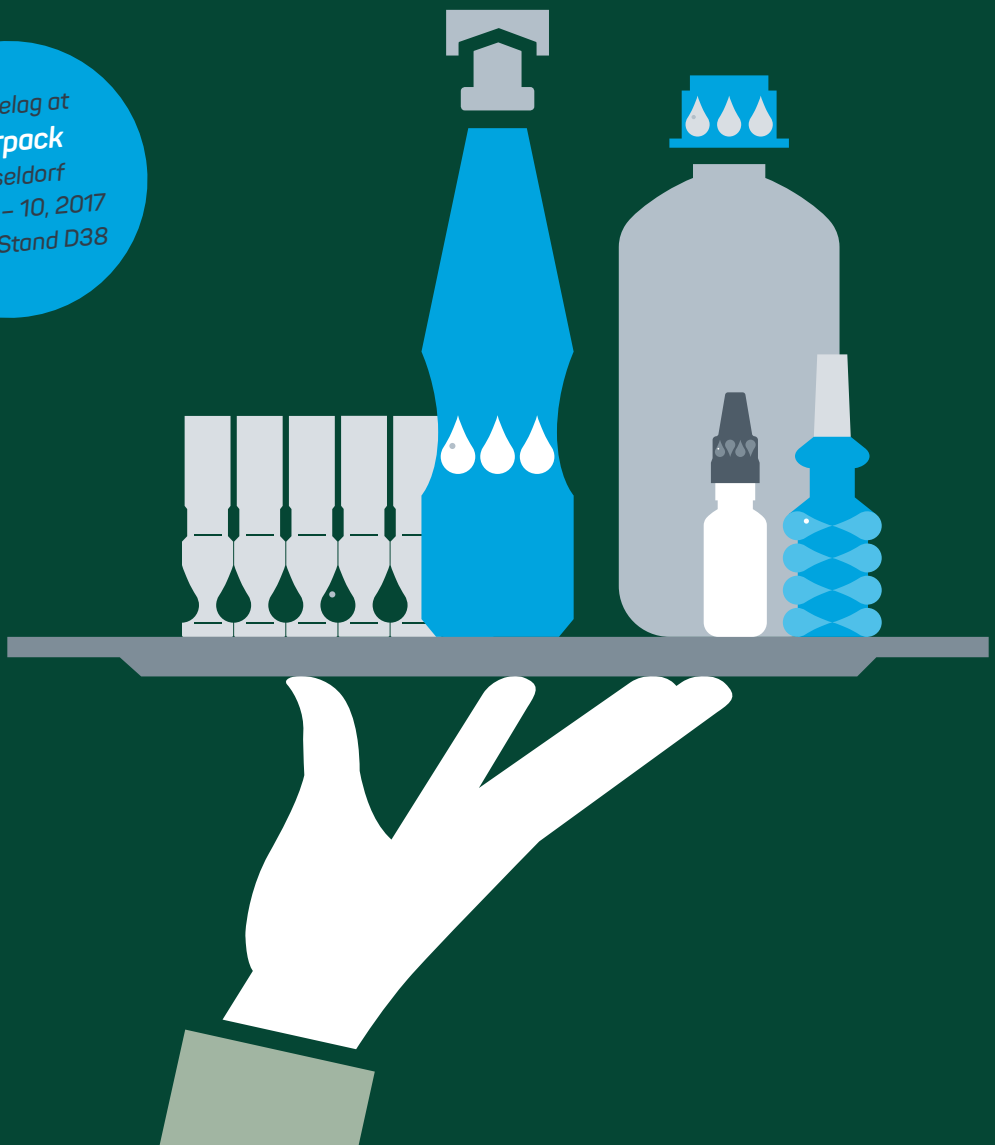

Regulators, USP Taking a Close Look at Visual Inspection

John Shabushnig, PhD, Insight Pharma Consulting, and Markus Lankers, PhD, rap.ID Particle Systems GmbH

The visual inspection process is a critical step in the reliable supply of high-quality injectable medicines. It is required by regulatory authorities and specified in various international pharmacopeias. This important step also provides information on process performance and informs where and how to improve the manufacturing process. Yet there continue to be challenges in this area as evidenced by persistent drug product recalls due to particulate matter. In addition, in the first few months of this year, the US FDA released two Warning Letters on visual inspection issues.

For many years, the requirements for visual inspection have been ambiguous, with little direct guidance on how to inspect and what acceptance criteria to apply to the inspection process. This has resulted in a wide range of inspection practices as evidenced by a PDA survey on visual inspection conducted in 2014. This situation has improved with the release of USP <790> *Visible Particulates in Injections* in August 2014 and USP <1790> *Visual Inspection of Injections* in March 2017 ***(1).*** PDA is also completing a technical report to provide guidance on difficult-to-inspect products, such as lyophilized powders, strongly colored solutions, and those packaged in amber containers.

Since 2000, PDA has held the *Visual Inspection Forum* each year to discuss new technical and regulatory developments in this field. It alternates between the United States and Europe; this year's meeting will be held in Bethesda, Md. The meeting provides a forum to present and discuss new developments in the field of visual inspection, including a basic understanding of the sampling and inspection process, special aspects of biotech products, the identification, risk assessment, and control of particles, and the contribution of packaging materials to these observed particles.

This is an excellent opportunity to learn more about visual inspection and to discuss inspection challenges with colleagues and experts. The Call for Papers is now open for this meeting; abstracts can be submitted at www.multisoftevents.com/Visual17.

Reference

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This year's *PDA/FDA Joint Regulatory Conference* offers answers to these questions within the theme, "Ensuring Product Quality in an Era of Innovative Therapies." Some of the plenary sessions have been transformed into panel discussions. Here, thought leaders from the US FDA and industry are poised to discuss future trends for the industry and the importance of innovative therapies as the industry moves forward. Other plenary sessions will feature company executives sharing their expertise about the challenges executive management faces and how their decisions impact quality. Concurrent sessions will fall under the following three tracks: "Product Quality," "Lifecycle," and "Innovation." "Product Quality" includes sessions focusing on data integrity and quality metrics. "Lifecycle" sessions will look at quality systems, change and risk management, lifecycle management, and global harmonization trends. And the "Innovation" track will tackle such subjects as the importance of expedited pathways and advanced therapies, and will include a discussion of the current regulatory findings taken directly from the most current Form 483 citations.

Last, but not least, a variety of breakfast sessions will entice even night owls to get up early. These sessions will cover SOPs, investigations, good documentation practices, practical guidance for conducting smoke studies and media fills, API quality requirements for sterile drug manufacturing, and laboratory controls.

As you can see, there will be a topic of interest for everyone, from recent graduates to seasoned experts. So be sure to mark your calendar and join us this September!

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The Parenteral Drug Association presents...

2017 PDA Quality Risk Management for Manufacturing Systems Workshop

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Effective and Practical Application of QRM to the Design, Qualification and Operation of Pharmaceutical Manufacturing Systems

Photo courtesy of Sartorius AG

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- System- and process-driven approaches to characterizing the system design
- Practical implementation of QRM for manufacturing system lifecycle
- An overview of the PIC/S Expert Circle on QRM
- A QRM approach to designing a more efficient and effective pharmaceutical quality system
- And more!

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A QUICK Guide to Selecting a CMO

Brittany Cloud, Eurofins Lancaster Laboratories, Inc.

In recent years, the pharmaceutical industry has increased efforts to outsource many previous in-house activities, such as manufacturing, testing, and packaging. Naturally, this means increased scrutiny on both sides of the outsourcing partnership to ensure proper compliance and robust business practices. Since release of the 2015 US FDA guidance, *Request for Quality Metrics*, many firms are using metrics as a tool for assessing a contractor's Quality Management System (QMS).

But numbers are only one factor when it comes to determining the amount of oversight needed to ensure cGMP compliance. Two questions remain: How should a firm evaluate whether a contract partner is the best fit for their intended needs? And, ultimately, how do they determine the correct level of involvement needed to guarantee a successful relationship? One way to make this determination is to use the QUICK method. It offers a thorough and systematic process to holistically gauge the attributes of a firm that are critical to creating an effective outsourcing relationship. What exactly is QUICK? It stands for:

Q — Quality Systems
U — Unparalleled Service and Performance
I — Innovative Technology and Facilities
C — Communication and Transparency
K — Knowledge and Reputation

Firms that analyze a contract partner using the QUICK indicators will be able to establish a mutually agreeable and successful relationship.

Quality Systems

The QMS of a firm is a key component on any auditor's checklist when performing an evaluation of a contract facility; however, procedures and policies only touch the surface of the underlying structure of the process. A thorough QMS evaluation must include a physical walkthrough of the contract facility to understand an organization's procedures as they occur in real time. While a desktop audit provides a high-level review of existing procedures, it does not show if those procedures are being followed. Onsite evaluations provide a wealth of information that may otherwise be missed using only a questionnaire. There is nothing more reassuring than walking onto a manufacturing floor or laboratory and observing the QMS in action. It also reveals one of the most important elements of QMS: the people. A solid foundation for any QMS lies within a company's quality culture. Interaction with the contract firm's personnel can demonstrate whether or not there is a strong commitment to quality.

Unparalleled Service and Performance

While quality remains a top priority, performance also plays an important role in determining the strength of a contract service provider. A manufacturer can have the most robust quality systems in place, but without a strong team of people to ensure that all regulatory and client requirements are met, critical projects risk falling short of expectations.

Before placing any work with a contract facility, a firm must ensure there is a strong performance management system in place as a guarantee that the contractor can provide unparalleled service. A contract facility does not merely manufacture a drug or provide laboratory results; it is a critical business partner, fully vested in the success of the client by maintaining an intimate business relationship. Routine business review meetings or steering committee meetings are key to keeping a pulse on a contractor's performance and service ratings. Without routine review of performance or service, critical problems in a relationship can escalate when preventative actions could have been taken to avert the larger issue.

Innovative Technology and Facilities

As mentioned previously, the onsite tour of a contract facility is a paramount activity in the contract partner relationship. Further, upon review of a facility, an auditor can immediately identify the state of the instruments, equipment, and buildings. Aging facilities, outdated instrumentation, or dilapidated equipment can point to potential cGMP problems. Investing in updated facilities and equipment displays that a contractor's senior management is committed to the success of the enterprise.

With release of the FDA data integrity guidance, industry has reacted strongly to comply, implementing more stringent controls of data. In particular, legacy systems in a contract facility pose a significant risk if not adequately controlled to produce quality data. For this reason, it is important that a potential client ascertain if the contractor has a continuous improvement plan to implement the guidance's data integrity recommendations across all systems.

Communication and Transparency

Too many firms focus on lengthy checklists and questionnaires to evaluate a potential contract partner. Yet two of the most vital fundamental measures of a relationship are communication and transparency. A healthy business affiliation cannot be managed without effective collaboration and open lines of communication. A contract facility is primarily—if not wholly—client driven, and therefore must provide a high level of cohesive correspondence. This goes beyond day-to-day status updates; instead, it should focus on building a partnership that can withstand any bumps in the road. A firm's worst nightmare is being left in the dark about a critical issue occurring at a contract location. The last thing they want is for a regulatory agency to uncover something that could have been addressed proactively. Preventive communications can avert disasters and build trust within a relationship.

Knowledge and Reputation

Contractor knowledge is pivotal in deciding the level of engagement a company's

product will receive. Merely manufacturing or testing a drug for many years does not necessarily equate to a strong knowledge base. A firm must ensure that contractors are continuously improving and building on their current body of knowledge. Ultimately, a company entrusts its most important asset—the product—with an outside vendor. Does the contractor have the competencies needed to provide the highest level of quality? Are they up-to-date with current regulatory and industry trends? Again, this is a great opportunity to seize the onsite audit and speak directly with the subject matter experts involved with the project. Another important question to pose is: What does the firm's regulatory history reveal? While this may not be an all-encompassing barometer of quality, it can demonstrate the frequency of inspections and results of regulators throughout the world. After all, would a company send a product for testing to a lab that has not been inspected by FDA in over five years.

The QUICK method can be used as a mechanism for identifying a core set of attributes that should be present within an outsourcing firm. As increased scrutiny is placed on contract vendors, firms must ensure they are using the most appropriate and comprehensive tools possible to demonstrate proper surveillance of all contract partners.

About the Author

As a Group Leader for Eurofins Lancaster Laboratories' Quality Compliance group, **Brittany Cloud** hosts client audits and agency inspections and provides quality oversight for the company.

Pharma Has its Head in the Cloud continued from page 33

activities like computer validation will adapt to the new context. Regulations should not be seen as an obstacle, rather, they should be seen as something that can be addressed by the disruption.

[Editor's Note: The author will be moderating the session, "Connectivity, Smart Devices, and Analytics" at the 2nd PDA Europe Annual Meeting, June 14 at 9 a.m.**]**

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About the Author

Toni Manzano is Chief Scientist Officer for bigfinite, a company that provides analysis and control solutions for biotech and pharma companies.

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Regulatory Briefs

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

North America

FDA Establishes Oncology CoE

The US FDA has established the Oncology Center of Excellence (OCE) and appointed **Richard Pazdur,** MD, as its director. The OCE is part of the FDA's larger effort to better address the needs of cancer patients through a coordinated clinical review of drugs, biologics, and devices across the Agency's three medical product centers.

Europe

Paper Addresses Non-distillation WFI

In March, EMA released a concept paper outlining plans to revise the Agency's guidance covering the quality of water used for pharmaceutical purposes. The revision takes into account the recent decision by the European Pharmacopoeia to accept non-distillation water technologies to produce water for injections (WFI).

Comments are due June 6.

Asia-Pacific

China Publishes 5-Year Drug Plan

In late February, the China FDA published its five-year plan (2016–2020) on food and drug safety. The Agency intends to use the plan to set stricter standards for medical equipment and drug quality by enhancing supervision. The plan finalizes the quality consistency evaluation for 289 generic drugs, revises 3050 national drug standards and 500 medical equipment standards, and requires a 100% rate of updates for periodic drug safety reports.

PIC/S

Concerns Shared About ATMP GMPs

PIC/S expressed concerns about the European Commission's proposed advanced therapy medicinal products (ATMP) GMP guidelines in a letter dated Feb. 24. In particular, PIC/S is concerned the proposed guidelines will lead to a nonharmonized approach to ATMP GMPs in addition to lowering standards for ATMP GMPs.

International Inspections

FDA, EMA Agree on Mutual Recognition of Inspections

In early March, both the US FDA and EMA announced that the European Union and United States have agreed to recognize each region's GMP inspections of pharmaceutical manufacturing facilities. This agreement follows three years of work between both agencies on the Mutual Reliance Initiative. Mutual recognition of inspections is expected avoid duplicate inspections, reduce inspection costs, and allow regulators to better allocate resources to regions that present greater risks.

The European Union is expected to have completed its assessment of FDA by Nov. 1; FDA has currently completed its own assessment of eight EU member states.

Key Regulatory Dates

Comments Due

June 6 — EMA Paper Addresses Nondistillation WFI

PDA Bylaw Revisions

Keeping Up with the Needs of a Diverse Membership and Industry

Hal Baseman, ValSource

As my colleague, **Deb Autor,** noted in last month's Voices of the Board, the Board of Directors has recommended revisions to our current bylaws. These revisions are designed to allow PDA to better meet the needs of its members in a modern operating environment. To that end, I would like to discuss one of the recommended bylaw changes that I feel particularly illustrates this point.

Over many years, PDA's membership has become more diverse, both geographically and technologically. This is, in part, the result of people in our industry recognizing there are increasing challenges to manufacturing quality healthcare products in a globally regulated industry, and realizing the benefits of PDA service and membership to meet these challenges. This diversity is evident in the addition of PDA chapters and members from around the globe, more representation from manufacturing, manufacturing science, and operations, and more involvement with the technologies needed to develop, produce, and support new therapies such as personalized medicines, alternative therapies, and cell therapies.

To address this paradigm shift, PDA has expanded the range and breadth of its services. But it is crucial that the leadership and members of the PDA Board of Directors reflect the diversity of its membership and the needs of the industry we serve.

As with any new endeavor, it is challenging to identify and elect representatives from new segments of our market. We have found that it sometimes takes longer for representatives from these new segments to work their way through the system and onto Board positions. And in a particularly dynamic industry, PDA must react to such changes in a manner consistent with the growth of both our membership and the industry.

With this in mind, the revision I wanted to highlight is the modification of the nomination process for the Board of Directors. This revision allows for the appointment of up to three Directors who are vetted and chosen by the Board at large. Each year, one Director will be appointed, and three will be elected. The Board will be responsible for maintaining the balance of the PDA leadership through the nominating process and selection of appointed members. While appointed Directors will make up a small portion of the 17-member Board, they will be able to bring important perspectives from new sectors of PDA's membership.

This gives the Board the opportunity to address specific needs and gaps in our leadership as well as keep up with the needs of a changing membership without adversely affecting association governance and oversight. The result will be more inclusive leadership that better represents PDA's diverse membership.

PDA Bylaws Update
ww.pda.org/bylaws

We feel this is one of the more significant, strategically focused revisions, and it will greatly enhance PDA's ability to maintain and expand its services and leadership in Connecting People, Science, and Regulation® in a dynamic industry. We ask you to support this, and other recommended changes, in the revised bylaws. If you have any questions or want to discuss these changes in more detail, please feel free to contact PDA's headquarters or me directly.

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