People • Science • Regulation

PDA Letter

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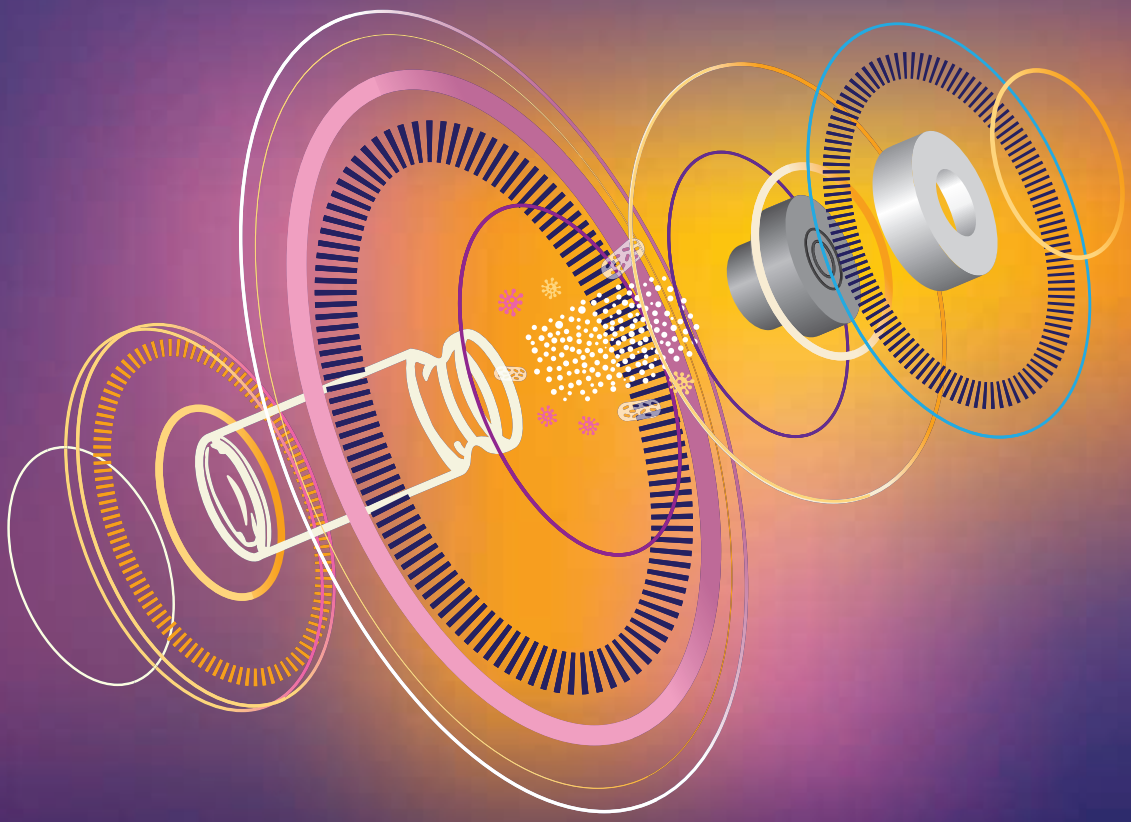

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January/February 2020 PDA Letter

2020 PDA Annual Meeting

Discover the latest advancements in parenteral manufacturing at the *2020 PDA Annual Meeting* by reading through our special Annual Meeting supplement!

Cover Art Illustrated by Katja Yount

A Glimpse at FDA's Micro Regulations

Rebecca Stauffer, PDA

Throughout the conference, attendees could submit questions on cards to be read during the session. This is a popular session of the microbiology conference, and, if you missed it, consider attending the *15th Annual Global Conference on Pharmaceutical Microbiology,* Oct. 19–21, in Washington, D.C.

FDA Panel Addresses EtO Sterilization

Rebecca Stauffer, PDA

In order to prevent potential shortages of critical medical devices, manufacturers and state regulators must resolve environmental concerns about ethylene oxide (EtO) sterilization. This was the consensus of the U.S. FDA CDRH General Hospital and Personal Use Devices Advisory Committee panel following one-and-a-half days of discussion at a public meeting Nov. 6–7 in Gaithersburg, Md.

5 Challenges of Closed System Transfer Devices

New USP Chapter Specifies Use of Closed System Transfer Devices for Hazardous Drugs Spurring Industry Response

Cathy Zhao, PhD, and Allison Radwick, PhD, West Pharmaceutical Sciences

USP <800> Hazardous Drugs—Handling in Healthcare Settings, effective Dec. 1, 2019, provides standards for limiting occupational exposure to hazardous drugs for healthcare personnel. The chapter clearly applies to any healthcare site handling hazardous drugs including pharmacies, hospitals, clinics, doctor offices and treatment centers. So why should pharmaceutical manufacturers and their associated suppliers care about the new chapter?

The PQL Team Part I: Building the PQL Role

Stephan Krause, PhD; Mariam Khan; Callum Chapman; Rob Gaglione; Andy Spasoff; Anthony Mire-Sluis, AstraZeneca

In addition to greater quality assurance, the PQL role also serves as a development path to build up the leadership skills of emerging quality leaders within the company who have also provided fresh ideas for the role as well.

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The Parenteral Drug Association (PDA), the leading provider of bio/pharmaceutical industry education and training, is pleased to introduce the all-new

Compounding Training Course Series

Gain expert solutions to common compounding pharmacy challenges that pose risks to patients.

PDA has introduced a new Compounding Training Course Series – designed specifically for compounding pharmacy professionals. The three training courses in this series will help compounding pharmacy staff understand the practices and techniques that ensure safe pharmaceutical preparations meet the personalized needs of patients. Participants will also discover important background information along with practical skills and solutions to the problems that compounding pharmacies are facing.

Compounding Pharmacy – Improving Aseptic Operations

This training course provides an in-depth understanding of microbial control and prevention of cross-contamination for better quality compounded preparations. Gain important skills in aseptic technique through hands-on learning activities, including environmental monitoring, smoke studies, gowning, and aseptic filling of media.

In addition, you will learn how to:

- Achieve and maintain environmental control
- Achieve sterilization and be able to differentiate between sterilization and sanitation

Cleaning Compounding Environments – Understanding Contaminants and How to Remove Them

Inconsistent cleaning and disinfection practices can lead to contaminated drugs. This training course will examine the theory behind cleaning and disinfecting surfaces and provide practical information for the successful selection and use of tools to clean and apply disinfectants. Get hands-on experience in effective and proper use of cleaning tools in typical compounding environments.

Gain a foundational understanding of:

- The microbial risks to sterile compounding
- Contaminant sources and the behavior necessary for effective control
- Best practices for cleaning and disinfection based on the newly published version of USP <797> and other regulatory guidelines
- The relationship between the environmental control systems, cleaning tools and protocols, and compounded pharmaceutical product quality

Compounding Pharmacy – Key Concepts in Microbiological Quality Control

This training course will help close the knowledge gap about how compounders should be performing their microbiological quality control testing and will address control measures that should be implemented to contribute toward sterility assurance of products.

Find out:

- Why a robust quality control program is critical to ensuring microbiological integrity of products
- What testing is needed
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- How to properly perform testing
- How to develop and interpret results

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PDA Parenteral Drug Association

Medical and technological advances are revolutionizing patient treatment options, creating new challenges and opportunities for the parenteral packaging market.

PDA is a recognized leader with longstanding expertise and focus in packaging science. In light of new developments and the dramatic impact of primary packaging on the safety and efficacy of drug product, PDA is intensifying its efforts to provide the most up-to-date tools and resources to the industry.

A snapshot of PDA's extensive offerings includes:

- **Global Conferences and Workshops** on topics such as glass quality, parenteral packaging, container closure integrity testing, and pre-filled syringes
- A broad array of **Topic-specific Training Courses**
- **Technical Reports and Resources,** both already published and under development
- **Interest Groups** dedicated to addressing pharmaceutical packaging issues
- **The Ed Smith Packaging Science Award,** granted annually to recognize outstanding contributions to PDA and Pharmaceutical Packaging Science

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To find out more about how PDA is leading the way to improved patient safety through better pharmaceutical packaging processes and practices, please visit pda.org.

New Decade, New Focus for *PDA Letter*

Rebecca Stauffer

@RebeccaStauPDA
www.linkedin.com/in/rebecca-stauffer-782b2310

The *PDA Letter* began the new decade with a focused on publishing all content to the website first.

You have probably seen more content on the site lately. As indicated in my previous message, we are publishing more content each week on the site. From articles to videos to even our long-awaited and anticipated PDA podcast, we are delivering more to our readers who are hungry for the latest information to help them in their jobs within the pharmaceutical manufacturing community.

Print issues will now collect popular articles already published on the Letter website. The January/February issue includes content covering critical topics of interest such as a new USP chapter and its impact on closed system transfer devices, building up a product quality leader team and a potential U.S. EPA regulatory change that could affect medical device sterilization.

In addition, we are preparing for the first regional edition of the *PDA Letter* that will feature content of interest for our European readers. An Asia-Pacific-focused one will then follow.

But I could not have done these changes alone. In addition to the hard work of the other PDA publishing staff—**Katja Yount, Walter Morris** and **Marilyn Foster**—the members of the *PDA Letter* Editorial Committee have been of great assistance in reviewing articles. With this in mind, I would like to welcome the following new members to the Editorial Committee this year, some of whom are also assisting with the regional editions: **Claire Briglia, Subrata Chakraborty, Robert Guidos, David Hubmayr, Jason Kerr, Ivy Louis, Siegfried Schmitt** and **Raji Vathyam.**

I would also like to thank those Committee members coming off their terms as of the end of 2019: **Joanne Beck, Stephanie Gaulding** and **Richard Hameister.**

As the Letter offers more weekly content, I would encourage you, if you have not already, to consider writing an article. I would be more than happy to help and share our Author Guidelines. Email me or send me a message via my Twitter or LinkedIn account.

2020 Board of Directors

PDA is pleased to announce the results of the 2020 Board of Directors and Officers election.

Executive Committee

Chair:
Jette Christensen,
Novo Nordisk

Chair-Elect:
Susan Schniepp, RCA

Treasurer:
Glenn Wright,
Exelead Biopharma

Secretary:
Melissa Seymour,
Biogen, Inc.

Immediate Past-Chair:
Rebecca Devine,
Consultant

PDA thanks outgoing executive committee members **Martin VanTrieste,** Civica Rx**, Mike Sadowski,** Baxter Healthcare, and **Steven Lynn,** Lynn Consulting.

Directors

Masahiro Akimoto, Otsuka Pharmaceutical Factory, Inc.

Barbara Allen, Eli Lilly and Company

Michael Blackton, Adaptimmune

Bettine Boltres, West Pharmaceutical Services

Tia Bush, Amgen

Ghada Haddad, Merck & Co.

Joyce Hansen, Johnson & Johnson

Stephan Krause, AstraZeneca Biologics

Mary Oates, Pfizer

Emma Ramnarine, Genentech/Roche

Mathias Romacker, Pfizer (ret.)

Anil Sawant, Merck & Co.

PDA also thanks outgoing directors **Joyce Bloomfield** and **Veronique Davoust,** PharmD, Pfizer.

Board of Directors Nominations Needed

The PDA Nominating Committee is seeking recommendations from members for candidates to fill Board of Director positions for terms beginning in 2021. Nominees must be current PDA members in good standing. Recommendations will be considered and evaluated by the PDA Nominating Committee and approved by the Board of Directors. This year's committee is chaired by Immediate Past Board of Director's Chair **Rebecca Devine** and includes current Board of Director's Chair **Jette Christensen** and Board of Director's Chair-Elect **Susan Schniepp**.

If you are interested in being considered or want to recommend a colleague, send the recommendation via email (nominate@pda.org) or mail to PDA Global Headquarters, Bethesda Towers, Suite 600, 4350 East West Highway, Bethesda, MD 20814, USA, attention: President. In addition to your recommendation, please include any other supporting information that may make it easier for the Nominating Committee to evaluate your recommendation.

Nominations are due May 1.

If you have any questions or feedback about the nominating process, please feel free to contact PDA President **Richard Johnson** (johnson@pda.org).

Panel Inspires Next Generation of Female Biotech Leaders

Tony Yang, Communications Board Chair, Pacific Northwest Chapter

Women entering the biotech space need to turn obstacles into opportunities while staying true to their personal development.

This "Women Leaders in Bio" panel was hosted jointly by PDA's Pacific Northwest Chapter and WIB-Seattle, an organization of biotechnology professionals promoting opportunities for women in the life sciences, Sept. 12, in Seattle. The event drew over 70 attendees along with seven exhibitors.

The five panelists consisted of: **Anna Gilbert, Amber Randall, Heather Brammer, Kaye D. Reiter** and **Lisa Smith**. Their backgrounds, career paths, and experiences were uniquely different; however, all delivered similar, inspiring messages.

The panelists took turns offering advice for women interested in becoming leaders in the field. Gilbert shared how she overcame significant barriers by relying on her "can-do" attitude. Kaye Reiter, in an equally compelling discussion, encouraged young women to step out of their comfort zones and embrace the unknown as opportunities.

Panelists also communicated the importance of striking a balance between work and family, meeting career objectives, and simply getting enough sleep. Many of their stories elicited chuckles and nods in agreement. In addition to speaking about their careers, the panelists also dived into their lives outside of work, stressing the importance of personal and family time.

The panel of female biotech leaders shared similar perspectives

Each panelist shared their motivations for pivoting or pursuing their current careers, discussed key figures, such as role models, who supported them through their journeys, and spoke of unique events that were impacting.

Through the individual experiences shared by the panelists, the same advice resonated for young women heading into the biotech industry: Be yourself, find people who support and help you grow, and take time for yourself.

The Pacific Northwest Chapter would like to extend a special thanks and recognition to the sponsors, exhibitors of the event and WIB-Seattle to bring this event to fruition. Furthermore, the chapter would like to thank the attendees who joined us for an exciting night.

PDA Who's Who

Heather Brammer, Associate Consultant, Spannerwerks

Anna Gilbert, Director, BioProcess Technology Consultant, BDO USA

Amber Randall, Director, Data Analytics, Fred Hutchinson Cancer Center

Kaye D. Reiter, PhD, JD, Co-Founder & General Counsel, Pluristyx

Lisa Smith, Quality Management Risk Champion, Process Improvement Consultant, Partner Therapeutics

Tony Yang, Student, University of Washington

PDA NE Chapter Enjoys a Day at the Lake

Laurie Masiello, President and CEO, Masy Bioservices, and President, PDA New England Chapter

What happens when you mix PDA families, a sunny day at the lake and great company? Well, lots of fun, for one, and stronger bonds between members!

On Aug. 17, 65 members of the New England Chapter, including spouses and children, attended the first ever Family Fun event at the home of Chapter President **Laurie Masiello,** situated next to a small lake. The day started overcast and became warm and sunny as the fun began. Thunder, lightning and rain waited until late at night when all the partygoers were safely home asleep in their own beds.

Attendees came throughout the day enjoying the cookout and the camaraderie of friends and business associates.

In addition to the traditional spread of picnic food, fishing served as a highlight for many of the young PDA members of the future. Four-year-old **Evelyn C.,** ten-ear-old **Amin Hussain** and 12—year-old **Mohammed Hussain** caught multiple sunfish. **Meredith Naskiewicz** caught the only catfish of the day while **Kevin Naskiewicz** only caught lily pads. **Tom Zaczkiewicz** and **Tracey Tamas** were patient but not lucky with a fishing pole. Good-natured **Phil Kendall** and **John Masiello** managed the hook removals.

Attendees of all ages enjoyed pontoon boat rides around the lake. Kayaks, canoes, paddle boats and swimming tubes provided even more fun.

Thank you to our sponsors who supported this event: Boston Analytical, ICQ, Masy BioServices, NSF, Particle Measuring Systems and Prudential Cleanrooms. Our generous sponsors contributed funds for hamburgers and hotdogs, drinks and desserts, salads, fruit and ice cream, ensuring no one went home hungry!

The chapter also extends a special thank you to **Emilee Mauro** and **Peter Fredricks** who not only cooked the delicious spread but also provided lifeguard duties.

Ultimately, the chapter's first-ever family fun event fulfilled its purpose—our PDA family had fun!

PDA Who's Who

Peter Fredericks

Phil Kendall, Senior Sales and Product Manager, Masy BioServices

John Masiello, Executive Vice President, Masy BioServices

Emilee Mauro

Female Biotech Leaders Discuss Their Careers

Women Working in Biotech Face Unique Challenges as They Seek to Develop Their Careers

Katja Yount, PDA

Last year, the PDA West Coast Chapter hosted a forum featuring female leaders in the biotech field to a packed room. In fact, chapter leaders declared the *4th Annual Women in Life-Science Event* on Aug. 22 was the chapter's largest event to date with 225 registered attendees.

There was a lot of energy and excitement among the attendees, all of whom eagerly wanted to ask questions of the panelists. Women in biotech find themselves uniquely looking for development opportunities in the field, so many of the attendees, which included students, gathered to hear advice to keep in mind as they advance their careers.

Leslie Konher moderated the panel and had all of the panelists talk about how they began their journeys in the biotech field. Some, like **Sangita Ghosh,** began by saying that no one ever starts out wanting to go into the biotech field. She herself wanted to dance professionally until realizing that there was little pay in it, so she threw herself into chemistry. Likewise, **Jodi Andrews** changed her mind about veterinary medicine.

Among the panelists there was a lot of emphasis on teamwork within the field. When asked about how important one's technical experience is when looking for a job, **Ruby Gulati** assured students, "It is not just what you bring to the table as a chemist but what you bring of yourself. Empathy, personality."

For the most part there was great general advice on employment and networking. But, as women in the industry, they did have to admit that there were some unique challenges within it. For instance, Konher emphasized that there is still a divide within the industry.

"There are more men in manufacturing and more women in quality. Is it that just more men are applying to manufacturing? We have to look at those reasons."

I-r: Leslie Konher, Jodi Andrews, Sangita Ghosh, Susanne Rommel, Ruby Gulati and Marisa Hewitt

Some attendees questioned if it was the physical demands of the jobs within manufacturing positions. Others pointed out that women are still expected to provide more childcare than their spouses, which affects shift selection and availability, contributing to the traditional view that women may not be reliable.

Ghosh followed this discussion with words of encouragement: "If you do want to do it, then do not let yourself be stopped because you are a woman."

Konher emphasized that there should be the open dialogue with men within the industry about expectations that they put their bodies on the line.

"We should open them up to talk about it."

Overall, there was advice to seek harmony and balance within the workplace as a woman, especially concerning the chance of conflict. **Suzanne Rommel** called for more compassion.

"Everyone makes mistakes, but you must make sure that conflict is resolved quickly. You can't carry them with you."

Marisa Hewitt pointedly observed, "There is the saying, 'pick your battles.' Well, no, you cannot, but you can pick when you have your battles."

Panelists and attendees, both seasoned industry veterans and students, expressed the importance of finding yourself within this industry, seeking mentorship and support from those that came before, growing with others and building up teams. Do not be shy. Make sure to network and make yourself seen. Show tenacity in the field. All messages that seemed to resonate with attendees.

PDA Who's Who

Jodi Andrews, Co-CEO, ProTrials

Dr. **Sangita Ghosh,** VP, Pharmaceutical Development and Manufacturing, Spruce BioSciences

Ruby Gulati, Quality Management, Genentech

Marisa Hewitt, Associate Director of Business Operations, BioMarin Pharmaceutical

Leslie Konher, Senior Scientist, Boehringer Ingelheim

Susanne Rommel, Executive Director, Quality, Gilead

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2020 Annual Meeting Training Course Series

Bring PDA Technical Reports to life with best-in-class training from PDA Education.

Following the *2020 PDA Annual Meeting*, these training courses will provide you with an in-depth understanding of the practical lessons and expert guidance found within each of these valuable industry resources:

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Technical Report No. 13: Fundamentals of an Environmental Monitoring Program

Technical Report No. 22: Process Simulation Testing for Aseptically Filled Products

Technical Report No. 54: Foundations of Quality Risk Management

Technical Report No. 62: Recommended Practices for Manual Aseptic Processes

Technical Report No. 65: Technology Transfer

Technical Report No. 70: Fundamentals of Cleaning and Disinfection Programs for Aseptic Manufacturing Facilities

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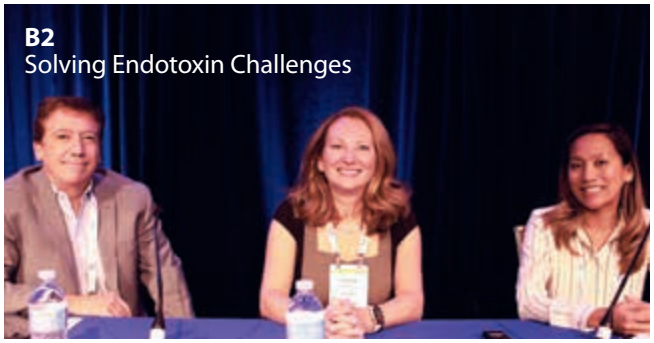
(l-r) Steffanie Strathdee, PhD, UC San Diego, and Amy McDaniel, PhD, Bristol-Myers Squibb



(l-r) Ed Tidswell, PhD, Merck; Crystal Booth, PSC Biotech; Hien Nguyen, Biogen

(l-r) Sarah L. Wallace, PhD, NASA Johnson Space Center, and MaryEllen E. Usarzewicz, Bristol-Myers Squibb

(l-r) Stacey Ramsey, Charles River; Rebecca Jordan, Celgene; MaryEllen E. Usarzewicz, Bristol-Myers Squibb

(l-r) Virginia Carroll, PhD, U.S. FDA; Karine Lebel, Health Canada; Geneviève Dufour, Health Canada; Christine Sherman, Takeda

(l-r) John Metcalfe, PhD, FDA; Kim Sobien, PETNET Solutions; Fatima Hasanain; Nordion; William Barry, BioFireDefense; Kenneth Tai, PhD, Genentech

(back) Irving Ford, Celgene
(front l-r) Timothy Kedzior, Novartis; Lily Koo, PhD, FDA; Ebony Arrington, Pfizer

(l-r) Leslie Furr, U.S. Pharmacopeia; Will Waterfield, PhD, Independent Consultant; Andrew Dick, J&J; J. Kevin Rice, PhD, FDA

(l-r) Janet Perez-Brown, Bristol-Myers Squibb; Reyes Candau-Chacon, PhD, FDA; Lauren Levac, PPD; Bo Chi, PhD, FDA

(l-r) Christine Sherman, Takeda; Friedrich von Wintzingerode, PhD, Genentech; Dona Reber, Pflzer; Andrew Dick, J&J; Michael Miller, PhD, Microbiology Conultants; Kim Sobien, Pfizer; James Polarine, STERIS

FDA Panel Addresses EtO Sterilization

Rebecca Stauffer, PDA

In order to prevent potential shortages of critical medical devices, manufacturers and state regulators must resolve environmental concerns about ethylene oxide (EtO) sterilization. This was the consensus of the U.S. FDA CDRH General Hospital and Personal Use Devices Advisory Committee panel following one-and-a-half days of discussion at a public meeting Nov. 6–7 in Gaithersburg, Md.

The panel urged FDA to take steps to mitigate the risk of shortages, including the possibility of overriding state legislation that has resulted in closures of facilities sterilizing devices using EtO. This would require high-level discussion with the leadership of the U.S. Department of Health and Human Services, the agency that oversees FDA.

The meeting follows two closures of Sterigenics facilities in Illinois and Georgia and the potential closure of a Becton Dickinson site in Georgia ***(1,2).*** The issue began in February when the Illinois Environmental Protection Agency issued a state order closing the Sterigenics plant in Willowbrook, Ill. due to concerns about the plant was releasing unsafe levels of EtO into the air ***(1).*** A recent bill in the

> **Few of the products currently sterilized with EtO can be sterilized using other methods**

Illinois House seeks to phase out EtO use by medical device manufacturers in the state due to concerns about cancer risks to communities near these facilities ***(3).***

Compounding the issue, the closure of any further EtO sterilization facility is likely to exacerbate existing capacity concerns regarding devices.

What is Ethylene Oxide (EtO) Sterilization?

Ethylene oxide (EtO) is a colorless, flammable gas used to sterilize medical devices made from specific materials or have multiple layers of packaging, such as catheters. EtO is often the only method for sterilizing these products without damaging the device during sterilization. According to the FDA website, 50% of all medical devices in the United States are sterilized with EtO.

EtO is also a carcinogen and falls under U.S. Environmental Protection Agency (EPA) regulations. The major concern is around emissions of EtO from plants into the surrounding environment.

Mark Leahy, representing the Medical Device Manufacturers Association (MDMA), offered some sobering statistics. MDMA represents 300 small- to midsize device manufacturers. Ten days prior to the meeting, MDMA surveyed its membership about the impact of further closures. 300 device manufacturers in the ten days prior the meeting.

"94% of respondents said that if their primarily sterilization went offline, they would have to eventually close," he said. "This is not anything theoretical…for a number of our small companies, the Willowbrook facility was the only place they sterilized their products."

He pointed out that even if a facility were to switch to an alternative or reduce EtO, even going offline for a short amount of time would cause a negative impact on supply, emphasizing that "the capacity right now in the EtO market is nonexistent."

This has the potential for disastrous outcomes, according to **Kara Mascitti,** MD, ➤

EPA Hearing on EtO Draws Debate

Rebecca Stauffer, PDA

The U.S. Environmental Protection Agency held a public hearing in Washington, D.C., Jan. 16, to allow stakeholders to speak directly to the Agency about proposed changes to the regulation of ethylene oxide (EtO).

Specifically, EPA is proposing amendments to the National Emission Standards for Hazardous Air Pollutants (NESHAP) for the Miscellaneous Organic Chemical Manufacturing category, often called MON. These amendments would require risk reviews to address EtO emissions from storage tanks, process vents and equipment leaks. In addition, EPA would require additional start/stop monitoring by manufacturers of EtO.

A number of stakeholders representing EtO manufacturers and environmental organizations addressed a panel of EPA representatives.

Epidemiologist **Kenneth Mundt,** MD, suggested EPA's data showing increased rates of breast cancer among workers exposed to EtO "grossly inflated the risk," citing a research paper his team published in December ***(1).*** **Bill Gulledge,** Senior Director of the Chemical Products and Technology Division with the American Chemistry Council and head of ACC's EtO Committee expressed concern that these proposed MON amendments could result in shortages in a number of industries, including healthcare.

Other stakeholders represented environmental concerns regarding EtO manufacturing plants and the impact on nearby communities. **Genna Reed** of the Union of Concerned Scientists, **Kathleen Riley** of Earthjustice, **Stephanie Herron** of the Environmental Justice Health Alliance for Chemical Policy Reform, and **Jennifer Sass** of the Natural Resources Defense Council, all urged EPA to implement the proposed amendments. Another speaker, representing citizens living near EtO manufacturing facilities, **Jennifer Burton,** urged those industries that rely on EtO to consider using these more stringent regulations as "an opportunity to innovate" and look to new technologies to replace or reduce EtO.

References

1. Vincent, M., et al. "Ethylene Oxide: Cancer Evidence Integration and Dose–Response Implications." *Dose Response* 17 (2019) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6906442/

an emergency room physician with St. Luke's University Health Network.

"As an infectious disease physician, I know firsthand the importance that physicians have access to sterilized products for patient care," she said. "Every single patient that is admitted to one of our hospitals or visits one of our emergency rooms requires at least one sterile product as part of their medical care."

Phil Cogdill, Senior Director of Quality, Sterilization Microbiology, Medtronic, expanded on the necessity of EtO and opportunities for device manufacturers to reduce use of it.

"Sterilization is a complex process that starts and ends with the patient," he emphasized, further explaining that sterilization for devices involves more than just eradicating microorganisms; it also requires ensuring that device functionality or performance is not impaired.

Even more challenging, few of the products currently sterilized with EtO can be sterilized using other methods. At this time, 50% of all devices worldwide are sterilized using EtO. While there are other sterilization methods (moist/dry heat, radiation, hydrogen peroxide, chlorine dioxide, etc.) in addition to ways to reduce EtO emissions (product packaging modifications, optimized processes, reduced exposure times, reduced gas concentrations and more optimized cycles), any changes to sterilization methods or approaches will require time and investment, again, resulting in potential shortages.

To emphasize the complexity of EtO sterilization, Cogdill showcased an oxygenator to show the complexity and the number of materials and components comprising a device. Due to this complexity it would be hard to switch to a different sterilization process, particularly when taking into account the time to develop and validate a new process.

Is This a Job for EPA?

Following the meeting, Cogdill answered some questions for the *PDA Letter.* While he spoke at an FDA meeting, he thinks this is more of a matter for EPA.

"We definitely want to see the EPA take a leadership role," he said. "We do understand the ISA regulations [Integrated Science Assessment for ethylene oxide] are currently under review. I believe the medical device industry is looking forward to working with the EPA and reducing the emissions to whatever requirements are provided by the EPA."

He hopes that any changes to the EPA's regulations on EtO helps reduce the public "anxiety around this chemical and its use for sterilizing medical devices."

In fact, he thinks EPA needs to address the state regulations, not FDA.

"I do not think the FDA is the appropriate government agency for that but with these new regulations it is certainly going to help the states to be consistent with the federal position and hopefully that ➤

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15th Annual PDA Global Conference on Pharmaceutical Microbiology

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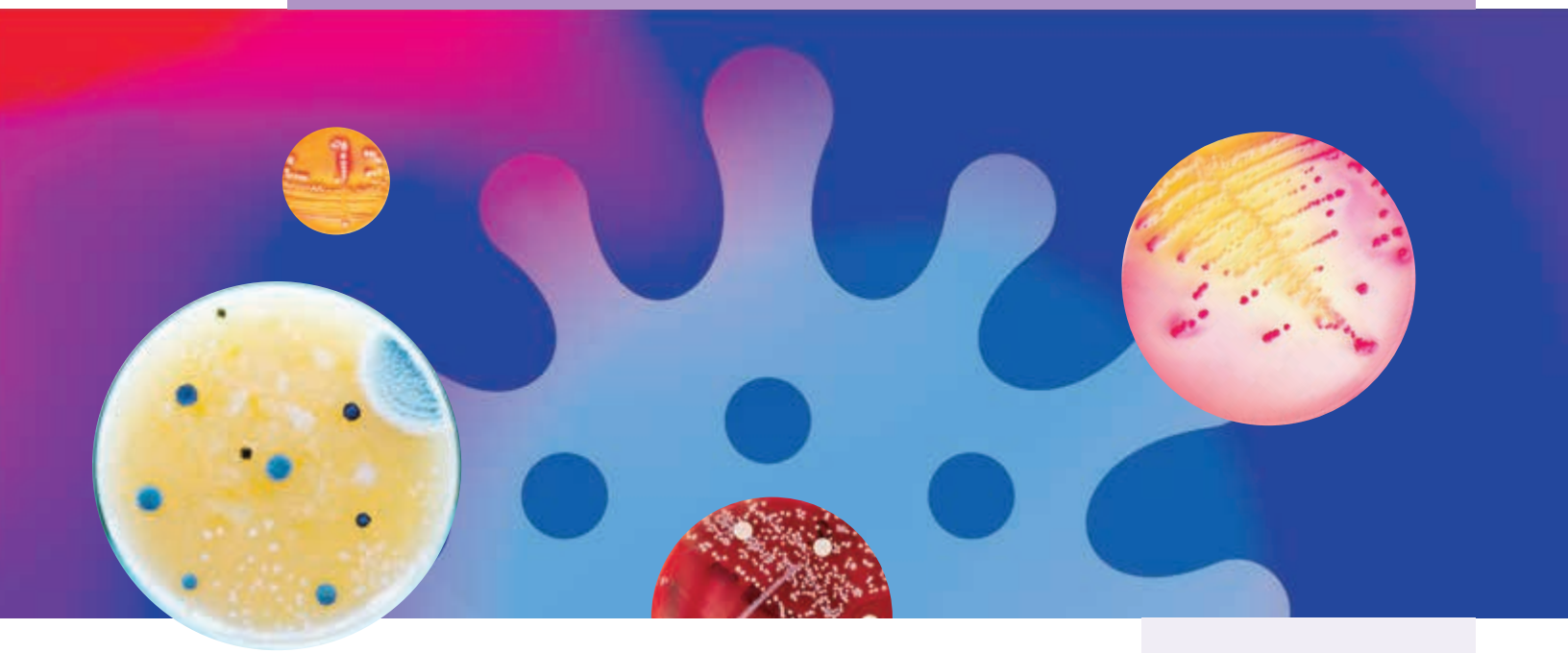

Register now for the *15th Annual PDA Global Conference on Pharmaceutical Microbiology*!

Continue the tradition of exploration into the most relevant topics in pharmaceutical microbiology at this best-in-class Conference.

Stay tuned for more information, including abstract submission details, agenda updates, and keynote speaker announcements.

To learn more and register, visit *pda.org/2020Micro*

PLEASE NOTE THAT WE'RE MAKING A MOVE!

This year's Conference will be held at the Grand Hyatt in Washington, DC!

OCTOBER 19-21 | WASHINGTON, DC

EXHIBITION: OCT. 19-20
2020 PDA RAPID MICROBIOLOGICAL METHODS WORKSHOP: OCT. 21-22
TRAINING COURSES: OCT. 22
#PDAMicro

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EPA tentatively expects to come out with proposed rules on EtO sterilization in May 2020

will stop some of the rash bill passing that has been going on other states."

Gary Socola, President, HIGHPOWER Validation Testing & Lab Services Inc., also took some time to answer a few questions for the *PDA Letter.* He explained that the crux of the current issues with EtO sterilization lies in changes the EPA made in 2014 to its calculation formula which determines the safe breathing level of EtO. 2014 was the last year EPA performed its National Air Toxics Assessment (NATA), and this data was released earlier this year.

"[FDA] does not have the ability to regulate EtO emissions. That is directly a function of the EPA," he said.

"A lot of the issues that have occurred have been because of the change that the EPA made with the methodology of how they calculate a safe level of EtO for breathing, and that changed from 2011 to 2014, and I believe a lot of the confusion was because of this change."

Socola thinks this change alarmed the public, particularly those living near EtO sterilization plants. "Emotions can certainly overrun scientific data and factual information if not reviewed thoroughly," he said.

When it comes to FDA's role, Socola would like FDA to prevent device shortages by looking at how the Agency currently responds to drug shortages. He pointed out that FDA has taken on a number of initiatives addressing drug shortages, including a team of staff within CDER responsible for preventing and mitigating drug shortages. Yet the Agency has little information available in the way of medical device shortages—something easily highlighted by a Web search.

"If you typed in 'FDA's jurisdiction for drug shortages,' and then typed in 'FDA's jurisdiction for medical device shortages,' you would notice that there is a significant difference in the amount of information that is available for drug shortages and what the FDA can do during them, as compared to what they can do for medical device shortages," Socola explained.

Reverberations for Drug Manufacturing

The EtO debate has been primarily a medical device issue but should sterile drug manufacturers be concerned?

"Whenever you are dealing with aseptic manufacturing and sterile drugs, a lot of the ancillary personal protective gear and a number of the equipment that is used with it can be EtO sterilized to help that process, so I would say that there is probably some impact if those sterilizers were to be shutdown," Cogdill told the *PDA Letter.*

Socola pointed to drug device combination products as another area that could be impacted.

"There are the delivery devices doing the injections of some of these pharmaceutical drugs," he said. "Diabetes in itself has a number of different types of medical devices that inject insulin and other types of pharmaceutical solutions. How are those types of devices going to be affected?

FDA, EPA Look Ahead

In addition to researching potential emergency measures to override state legislation, the Advisory Committee came to consensus regarding the following:

- While it is possible to change EtO sterilization cycles or loads to reduce EtO use and also maintain effective sterilization, no single method addresses all issues
- Alternatives to the overkill validation method should be considered by FDA
- Consistent with current standards, FDA should consider moving to a risk-based assessment of sterility assurance levels for some sterilized medical devices
- FDA should encourage manufacturers to look into the possibility of using existing large-scale industrial sterilization modalities to take over a portion of EtO sterilization
- Manufacturers should review which sterilization modalities are potentially compatible with their devices, and, where possible, validate alternate methods
- FDA must continue to collaborate with industrial stakeholders on alternatives to EtO sterilization and adoption of optimized EtO processes that use less EtO and emit less EtO into the environment in the near term

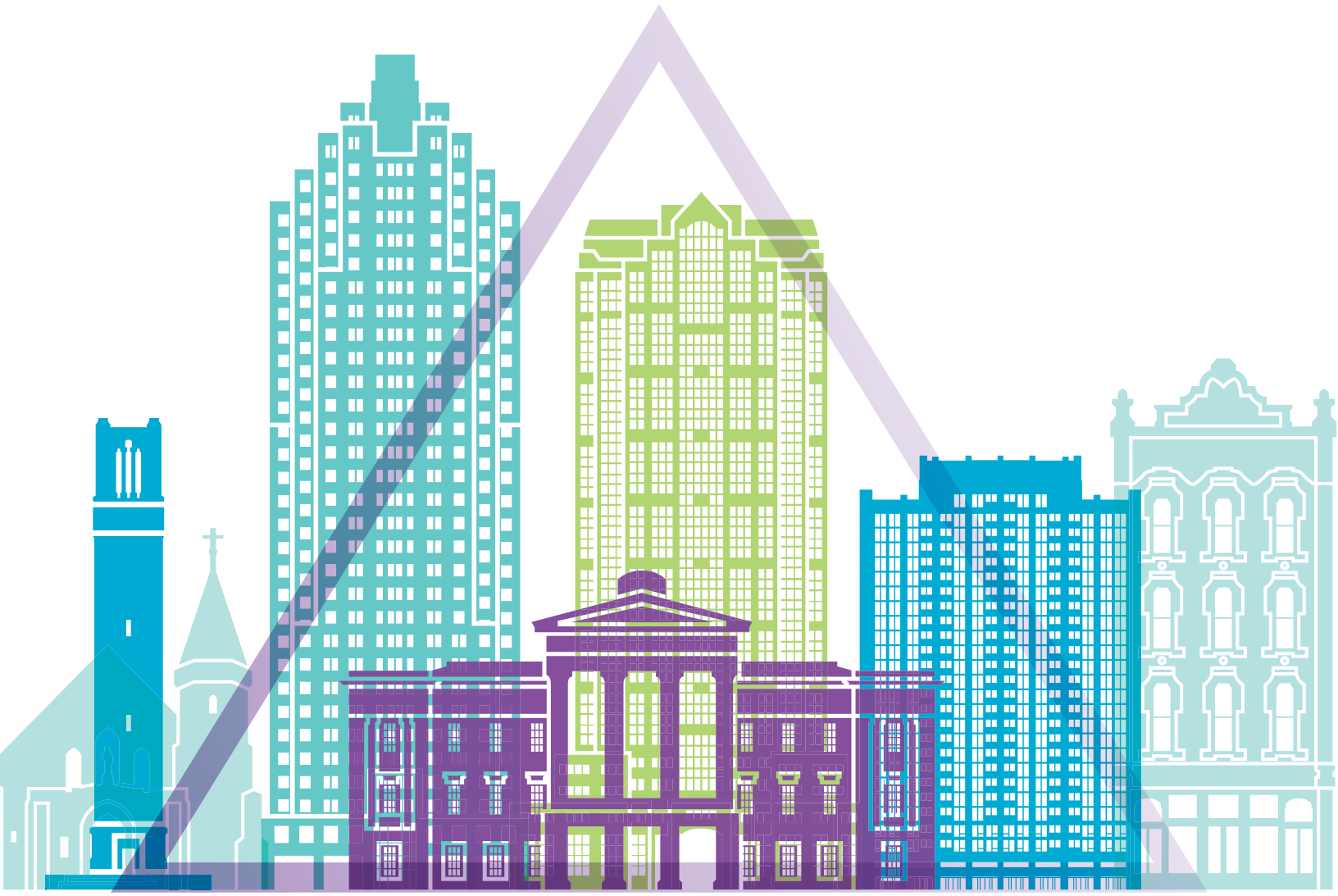
FDA will continue to review the situation around EtO and continues to seek input about alternatives ***(4).*** In addition, EPA tentatively expects to come out with proposed rules on EtO sterilization in May 2020 following public hearings this month ***(4).*** From the discussion at the Advisory Committee meeting, collaboration between the two agencies is likely, and both Agencies will continue to seek industry input.

References

1. Sookne, K. "FDA Comments on Potential Device Shortages in the Face of ETO Facility Interruptions/Closures." *Healthcare Packaging* (Oct. 25, 2019) "BD Statement on Georgia Facilities." (July 25, 2019)
2. Hawthorne, M. "Illinois House approves phaseout of cancer-causing ethylene oxide, but Medline Industries and business groups are working to quash bill in Senate." *Chicago Tribune* (Oct. 30, 2019).
3. Crotti, N. "Federal agencies will control the fate of medtech's most-used sterilization method." *Medical Design and Outsourcing* (Nov. 15, 2019)

Originally published online
Dec. 2, 2019

2020 PDA Annual Meeting



A Supplement to the PDA *Letter*

S2 Are You Ready for Pharma's Next Decade?

S3 A Q&A About Innovation in Pharma Manufacturing

S5 Schedule of Interest Group Meetings and Networking Events

Are You Ready for Pharma's Next Decade?

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

The theme of the *2020 PDA Annual Meeting* is "*Enhancing the Future with Innovative Medicines and Manufacturing.*" In selecting this theme, the planning committee's goal is to design a comprehensive event that encompasses the wide-ranging interests of all PDA members. Whether you are focused on improving existing processes or delving into entirely new technologies, we will cover relevant information important to small molecule, and biopharmaceutical, cell and gene therapy and other modalities.

Plenary sessions will inspire all of us to engage as we focus on the importance of what we do every day to improve the quality of life for millions of people. It is a daunting and empowering task we are faced with and these sessions will focus on key aspects of our work including getting personal with patients, understanding regulations, leveraging breakthrough designations, modernizing facilities, strategies for developing next generation medicines, and protecting integrated systems from external threats. Concurrent session tracks will cover new modalities, real-time and parametric release, data solutions and innovations in drug products and manufacturing.

Rounding out the program are interest group sessions, which offer participants a chance to hear from experts as well as engage in interactive discussions on a variety of important topics and specific disciplines.

The exhibition hall provides opportunities for one-on-one interactions with service providers and vendors who will showcase the latest services and technologies. Authors of numerous poster presentations will also be present to discuss their latest research and data. Social events and breaks are scheduled throughout the meeting to allow time for further networking and peer-to-peer discussions.

This meeting is a must attend knowledge-sharing event for everyone, from corporate executives to those who have recently joined the industry, it is an ideal opportunity to accelerate your impact and position in your company as well as in the pharmaceutical industry.

2020 PDA Annual Meeting

Raleigh, N.C.
March 20–April 1
www.pda.org/2020annual

4 Questions and 4 Answers About Innovation in Pharma Manufacturing

Rebecca Stauffer, PDA

The *PDA Letter* had an opportunity to ask **Melissa Seymour,** Vice President, Global Quality Control Operations, Biogen and Co-chair of the *2020 PDA Annual Meeting,* four questions about innovation in pharmaceutical manufacturing—a major topic at the meeting. Below are her responses.

1) PDA Letter: As we enter the 2020s, what innovations are on the horizon for pharma?

Seymour: We are living in an era of perpetual change and innovation, which is enormously exciting, but also a bit scary. How do we keep up? In pharma, personalized medicine is changing physician/patient interactions focusing on individual response to drugs and treatment regimens. Cell and gene therapy is becoming a reality with many new products in the pipeline. The science linked directly to manufacturing is also moving forward at a rapid pace with advancements in machine learning and artificial intelligence driving huge set of data. Informatics and data science will be critical to future approaches to manufacturing, supply chain and distribution. All of this coupled with increasing global complexity can sometimes leave us feeling overwhelmed!

2) PDA Letter: I'm not a C-Suite leader. How can I encourage innovation within my plant?

Seymour: Innovation is important at all levels of the organization and has an impact at all levels of the organization. Continuous improvement and providing efficiency gains as part of day to day activities is additive and results in overall improvement to processes. Whether you are updating an analytical method, defining process controls, or managing data flow, ideas that are implemented at the floor level are critical to overall operations. Bringing forward new ideas is important across the business from manufacturing to supply chain, to regulatory affairs and quality. Optimization happens at all levels of the business and is impactful and important.

3) PDA Letter: How can regulators, industry, and academia work together to ensure adoption of these innovations, particularly due to the globalized nature of the industry?

Seymour: As much as we are overwhelmed, it is increasingly important that regulators, industry and academia work together to provide harmonization, education, and solutions to today's challenges. The *2020 PDA Annual Meeting* is a great opportunity to do just that. This signature event is an outstanding opportunity for pharmaceutical professionals of all levels to network, learn and innovate. The theme of this year's meeting is "Enhancing the Future with Innovative Medicines and Manufacturing," focusing on the future and how innovative approaches can provide opportunities to improve patient access to important medications. There is also ample time for peer-to-peer networking where industry, regulators and academia can converse and share learnings. As employees in the pharma industry, we are privileged to have impactful roles and it is incumbent for each of us to take this seriously and work towards innovative and important solutions for patients.

4) PDA Letter: How will the *2020 PDA Annual Meeting* address innovation? Are there particular plenary talks, breakout sessions and interest group meetings I should consider attending?

Seymour: As I mentioned earlier, the theme of this year's meeting is "Enhancing the Future with Innovative Medicines and Manufacturing." Our goal is to provide learning and interaction through a comprehensive and informative program aligned with this theme. There will be opportunities to learn and engage on several key topics associated with data management, robotics, human factors, and modular manufacturing. We will have exciting talks around data integrity and managing our digital footprint to ensure data security. As always, we will hear compelling talks from patients, regulators and industry professionals as well as multiple networking opportunities to learn from and engage with peers. Of particular interest this year, we will have some focused activities for young professionals including speakers and networking events. We are really excited to bring forward a program that we feel will benefit all levels of the organization across multiple functions.

Originally published online
January 30, 2020

PDA Parenteral Drug Association

pda.org/2020ATMPs

2020 PDA Advanced Therapy Medicinal Products Conference

Cell and Gene Therapy – From Promise to Cure

ANNOUNCING
Peter Marks, MD, PhD, Director, CBER, *U.S. FDA*, to present on Global Regulatory Convergence for ATMPs!

Join us for another two-day Conference offering an in-depth examination into the latest advances in the rapidly evolving field of cell and gene therapy. This year, we are drawing on the expertise of industry insiders, regulatory authorities, and a diverse group of bio/pharmaceutical professionals to provide insight into this innovative area of medicine.

Sessions will examine topics, including:

- The quality of raw materials
- Technology transfer
- Testing
- Registration of ATMPS
- Clinical development
- Bringing product to market

Get a global perspective! Select sessions will be simulcast with the *PDA Europe Conference on Advanced Therapy Medicinal Products*. We invite you to participate in one of the industry's most recognized meetings on this topic!

To learn more and register, visit *pda.org/2020ATMPs*

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JUNE 24-25 | WASHINGTON, DC

EXHIBITION: JUNE 24-25
#PDAatmps

Build Your Network and Reconnect with Longtime PDA Friends!

The 2020 PDA Annual Meeting will feature the following networking opportunities:

Monday, March 30

5–6:30 p.m.

Grand Opening Celebration in Exhibit Hall

Young Professional and Early Career Professional Networking Reception

Tuesday, March 31

6–9 p.m.

A Taste of Raleigh Reception

11:30 a.m. to 2 p.m.

In addition, there will be two extended networking luncheons in the Exhibit Hall Tuesday and Wednesday

Interest Group and Southeast Chapter Meeting Schedule

Tuesday, March 31

10–11:30 a.m.

Filtration Interest Group

Microbiology Interest Group

2–3:30 p.m.

Quality Risk Management Interest Group

Vaccines Interest Group

4–5:30 p.m.

Biopharmaceutical Manufacturing Interest Group

PDA Southeast Chapter: Meeting of the Minds

Wednesday, April 1

10–11:30 a.m.

Technology Transfer Interest Group

pda.org/2020UPS

2020 PDA Universe of Pre-Filled Syringes and Injection Devices

REGISTER BY JULY 27 AND SAVE UP TO $600!

PDA is taking Pre-Filled to Las Vegas!

We're bringing together industry heavyweights, experts from academia, and regulatory representatives for this must-attend event. We will focus on the emerging issues related to development, materials, manufacturing processes, injection methods and safety devices, and regulatory requirements.

Get the latest information including abstract submission details, agenda updates, and keynote speaker announcements when you sign up for the event newsletter.

To learn more and register, visit *pda.org/2020UPS*

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OCTOBER 5-6 | LAS VEGAS, NV

EXHIBITION: OCT. 5-6
2020 PDA COMBINATION PRODUCTS WORKSHOP: OCT. 7
TRAINING COURSES: OCT. 7
#PDAups

2020 PDA Upcoming Events

FEBRUARY

24-28 Aseptic Processing ■
Week 1: Jan. 27-31
Week 2: Feb. 24-28
Bethesda, MD | *pda.org/2020aseptic1*

25-26 PDA Europe Parenteral Packaging
Basel, Switzerland | *pda.org/EU/ParPack2020*

- 24 Pre-Filled Syringes Interest Group Meeting
- 27 Packaging Science Interest Group Meeting
- 27 Container Closure Development
- 27-28 Container Closure Integrity Testing – Basic Course
- 27-28 Extractables and Leachables – Spring Edition

27-28 Container Closure Integrity for the Advanced User
Wohlen, Switzerland | *pda.org/EU/CCIT2020-advanced*

MARCH

9-13 Freeze Drying in Practice
Osterode am Harz, Germany | *pda.org/EU/fdp2020*

17-18 All About Virus Filtration – A Practical Approach
Cologne, Germany | *pda.org/EU/VirusFiltration2020*

23-27 Aseptic Processing ■
Week 1: March 23-27
Week 2: April 20-24
Bethesda, MD | *pda.org/2020aseptic2*

30-April 1 2020 PDA Annual Meeting
Raleigh, NC | *pda.org/2020annual*

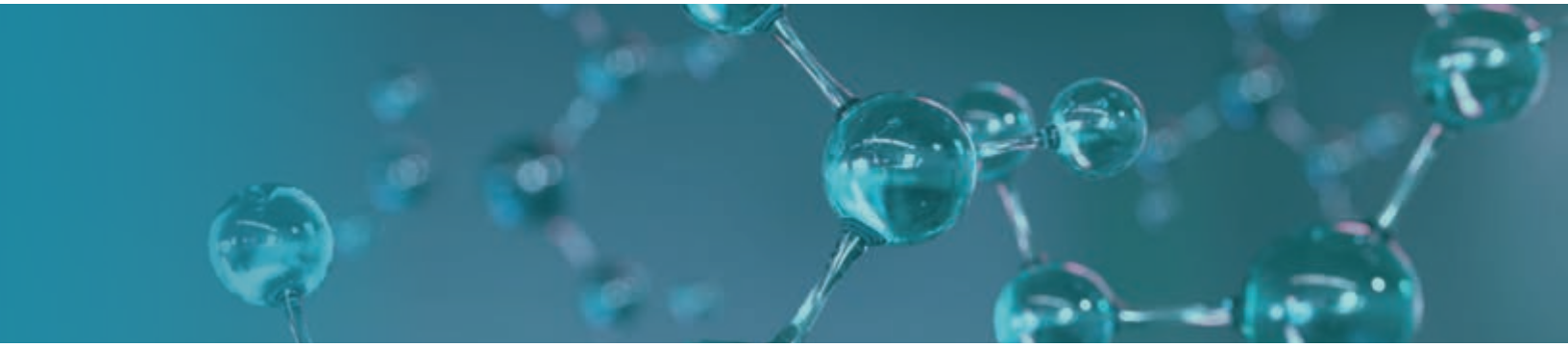
APRIL

2 2020 PDA Pharmaceutical Manufacturing Data Science Workshop
Raleigh, NC | *pda.org/2020datascience*

2-3 Annual Meeting Training Course Series
Raleigh, NC | *pda.org/2020annualcourses*

- 2 Technical Report No. 1: Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Validation, and Ongoing Control
- 2 Technical Report No. 13: Fundamentals of an Environmental Monitoring Program
- 2 Technical Report No. 22: Process Simulation Testing for Aseptically Filled Products
- 2 Technical Report No. 54: Foundations of Quality Risk Management
- 2 Technical Report No. 62: Recommended Practices for Manual Aseptic Processing
- 2 Technical Report No. 65: Technology Transfer
- 2 Technical Report No. 70: Fundamentals of Cleaning and Disinfection Programs for Aseptic Manufacturing Facilities
- 2-3 Quality Culture Assessment Tool and Training

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



6-10 **Environmental Monitoring Training Course Series**
Bethesda, MD | *pda.org/2020EMTCS*

- **6-7** Technical Report No. 13: Fundamentals of an Environmental Monitoring Program ■
- **8** Environmental Monitoring Methods and Investigations – Looking for the Needle in the Haystack ■
- **8-9** Analysis of Environmental Monitoring Data with Respect to cGMP and Data Integrity Guidelines
- **10** Developing a Microbial Monitoring Plan and Leveraging New Technologies for Effective Sterility Assurance in Aseptic Processes

13-16 **Fundamentals of Aseptic Processing**
Tonganoxie, KS | *pda.org/2020FundAP3*

20-24 **Aseptic Processing** ■
Week 1: March 23-27
Week 2: April 20-24
Bethesda, MD | *pda.org/2020aseptic2*

21-22 **PDA Europe Visual Inspection Forum**
Berlin, Germany | *pda.org/EU/VIForum2020*

- **23-24** Mastering Automated Visual Inspection
- **23-24** An Introduction to Visual Inspection: A hands-on course

28-30 **INTERPHEX**
New York, NY | *www.interphex.com*

SPOTLIGHT ON:

2020 PDA Annual Meeting

MARCH 30-APRIL 1 | Raleigh, NC
pda.org/2020annual

- **2** 2020 PDA Pharmaceutical Manufacturing Data Science Workshop
- **2-3** Annual Meeting Training Course Series

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

A Glimpse at FDA's Micro Regulations

Rebecca Stauffer, PDA

The 2019 PDA *Global Conference on Pharmaceutical Microbiology* closed with an engaging "Ask the Regulators" panel. **Yeissa Chabrier-Rosello,** PhD, Microbiologist, CDER, U.S. FDA, and **John W. Metcalfe,** PhD, Master Microbiology Reviewer, CDER, FDA, moderated the panel of FDA experts, which featured **John T. Arigo,** PhD, **Branch Chief,** CDER, **Reyes Candau-Chacon,** PhD, Quality Assessment Lead, CDER, **Rick L. Friedman,** Deputy Director, OMQ, CDER, **Anthony F. Lorenzo,** Lead Consumer Safety Officer, CBER, and **J. Kevin Rice,** PhD, Review Chemist, CVM.

Throughout the conference, attendees could submit questions on cards to be read during the session. This is a popular session of the microbiology conference, and, if you missed it, consider attending the *15th Annual Global Conference on Pharmaceutical Microbiology,* Oct. 19–21, in Washington, D.C.

The following is a lightly edited transcript of the session with the identities of the questioners hidden. The panelists were given an opportunity to review their answers.

***[Editor's Note:** This is an abridged summary of FDA responses during a panel dialogue at a conference. The responses below are an informal synopsis of the panel's opinions and should not be construed to represent FDA's views or policies.]*

Question: Are there any expectations for freeze-dried products to be terminally sterilized after lyophilization?

John Arigo: The answer to that is, no. There is no expectation to be terminally sterilized after lyophilization.

Question: Has FDA received any successful methods for validating low endotoxin recovery (LER)?

Reyes Candau-Chacon: Yes. We received one application where the drug product could not be detected using the standard LAL-BET method. The applicant committed to developing a method capable of detecting endotoxin from the drug product. It took them two years to develop and validate the new method. There are currently commercial endotoxin kits to help solve LER. The applicant used one of those kits as a starting point, eventually developing their own.

> **The rabbit pyrogen test is very insensitive. It should be used only as the last resort.**

Our current expectation is to verify whether you can recover endotoxin spiked in the undiluted drug product. If the drug product has LER, we ask the applicant to develop a new method capable of detecting endotoxin from the drug product. We also ask applicants to inject endotoxin-spiked drug product into rabbits (a one-time study) to make sure the endotoxin that cannot be detected with the standard method does not result in a fever in the rabbits.

If the rabbit develops a fever, we ask the applicant to implement, as an interim test, the rabbit pyrogen test until the new method is developed, because a pyrogen test is a regulatory requirement. We also ask them to implement stronger microbial control of the process as an additional risk mitigation strategy.

Rick Friedman: We actually had a recall in the last two years that relates to what Reyes [Candau-Chacon] was speaking of. The endotoxin test passed for all the lots, but pyrogenic reactions occurred in patients. In response to these adverse events, the firm investigated by testing products using the rabbit pyrogen test and the product failed the pyrogen test. The company is still working on the issues, but they have found that there were steps upstream in which pyrogen load and removal needed to addressed. It appears the fermentation process caused the high load. I believe this was a gram-positive fermentation-based (Streptomyces) product. Purification steps were insufficient, and some redesign was necessary to improve pyrogen removal efficacy.

Candau-Chacon: I have one thing to add to that. Even if we ask the applicant to conduct the rabbit pyrogen test, we make sure that it is an interim test. The rabbit pyrogen test is very insensitive. It should be used only as the last resort.

Question: What kind of personnel monitoring do you expect to see in a "low-bioburden facility" in a Grade B room?

Friedman: That is hard to answer. What this omits is the actual intended use of the product. Does this "low-bioburden facility" produce a sterile drug or an in-process intermediate that precedes sterilization? Or is this a nonsterile product with low microbial limits for bioburden? And what is going on in the room? The nature of the facility, including the operation of the room, as well as the dosage form and intended use of the product are critical considerations. All these things are at the core of making a risk assessment and determining what kind of personnel monitoring and guidelines may apply to that room.

This is very hypothetical, but in principle, it is normally a cascading processing situation that culminates in a Grade B (ISO 7 operational) room. The gowning would be appropriate to the ISO level. What needs to be proven, of course, is that this really is a low-bioburden facility by showing it is well designed and controlled. If those two things are not true, we all know the low-bioburden status can change overnight.

So, the concept of a low bioburden facility with appropriately stringent personnel controls is a good one. The reason you want to do environmental monitoring in the first place is to have a baseline on an ongoing to basis to show that you are in a state of environmental control.

Because we often discuss personnel and overall environmental control in the abstract, I think one example of lost environmental control at a sterile facility is useful to mention. We have all heard about the NECC [New England Compounding Center] findings. The data at that firm clearly showed that they had lost environmental control. They began to have signals early on that they should have acted on, and they ultimately lost control of it in a big way. Part of the problem was they performed personnel and environmental monitoring too infrequently. Earlier that year, products began to be made with drifting state of control. By about May, however, they were clearly making drugs that had clear links to clusters of infection reports showing the products were killing people.

In nearly all cases, infections due to contaminated medicines are typically detected by the healthcare system only after substantial time elapses, if at all. In the case of NECC, by that point, numerous patients were tragically harmed. This obviously illustrates why systems to ensure an ongoing state of environmental control are so important to prevent the potential for product contamination in the first place.

Question: If implementing a rapid method for product sterility, what is the best way to submit a post-approval change? Would you recommend a comparability protocol first or a Type C?

Anthony Lorenzo: From a CBER perspective, I am not really clear what product this is because that would make a pretty dramatic change when implementing a rapid micro method. So, I would recommend at least requesting a Type C first to alert the Agency about what the change is and to get the right personnel together for this possible change. Again, we deal with a lot of different types of products, and this could be a very good method in some cases. A comparability protocol would be a good start, if applying this method to several products. Because we would require data to be submitted, I do not think we would accept a CBE-0. Only a CBE-30 would be accepted so that we can review the impact to product before release for commercial use.

Question: For facilities that manufacture both human and animal drug products, what process is used to review 483 observations from an inspection? ➤

PDA
Parenteral Drug Association

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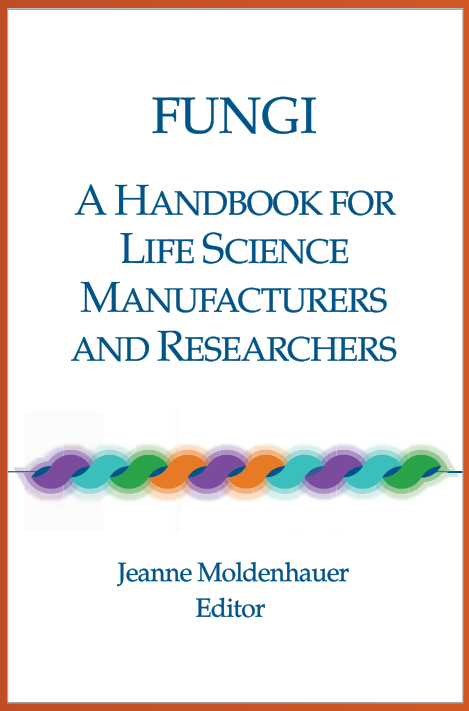

Understand the Value of Fungi with a New Technical Publication from PDA

Explore the amazing biology of fungi with the latest technical resource from PDA –

Fungi: A Handbook for Life Science Manufacturers and Researchers
Edited by Jeanne Moldenhauer

Use this text to identify and ameliorate fungal and mold problems and refer to its wealth of specialized information as a guide and handbook.

Topics discussed include:

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- Strategies for a Rapid and Accurate Fungal Identification
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J. Kevin Rice: The answer to that is, what type of inspection was carried out?'

Question: For joint CDER/CVM inspections, what are the responses for 483s?

Rice: Again, it depends on the type of inspection. For PAI surveillance inspections, whichever Center requested the PAI, will almost certainly review the firm's responses. If it were a general surveillance inspection, as our process currently stands, that would go to CDER for the review. Now, that does not mean that there cannot be collaboration between the Centers. If there are responses or observations specific to animal drugs being manufactured in that facility, we would certainly work with CDER and the investigators to make sure that those responses are sufficient.

Question: If changing from one USP <85> approved method to a second USP <85> approved method, is it necessary to use a CBE for post-approval changes, or is noting it in an annual report enough, if it is a low-risk change?

Arigo: For a change like that, I would check the post-approval changes guidance but, to me, that is a CBE change that we would want to review.

Question: Why is there a trend to force applicants to reduce the release specification information for compendial endotoxin tests?

Candau-Chacon: Sometimes the endotoxin specification is in EU/mg for liquid products and, when we convert it to EU/mL, we find that the specification is unacceptably high. I remember one recent application with a proposed endotoxin specification of 600 EU/mL. I do not think that a drug product with 600 EU/mL of endotoxin is under microbial control. In that case, we asked the applicant to lower that to levels consistent with good microbial control. We also want the applicant to include the endotoxin contribution from the infusion solution in the specifications.

Arigo: As long as the math works out where you are in the range of five, it is going to be fine.

Question: When it comes to environmental monitoring of personnel, should sampling be at random periodic intervals during the process, and should it include sampling of cleaning personnel?

Lorenzo: First of all, I am not sure at what stage this is referencing. In more critical areas, such as fill/finish, monitoring is fairly critical for personnel. The thing to consider in personnel monitoring is, what kind of information are you going to gather from it? Are you going to evaluate impact if there is a positive, or if there is product contamination from your personnel? That is critical information you need to know.

With random periodic intervals, I am not sure if that is beneficial. It is better to understand when sampling is performed, such as after personnel enter the critical zone, and you can determine if the impact from an intervention is captured. Regarding sampling of cleaning personnel, in manual cleaning, there is a similar expectation to randomly evaluate the cleaning effectiveness as it is being performed. ➤

Front l-r: J. Kevin Rice, PhD, CVM, U.S. FDA, Anthony F. Lorenzo, CBER, Rick Friedman, CDER, Reyes Candau-Chacon, PhD, CDER, and John T. Arigo, PhD, CDER
Back l-r: Yeissa Chabrier-Rosello, PhD, CDER, and John W. Metcalfe, PhD, CDER

Friedman: I have just one additional comment on random personnel sampling. There is the possibility of gaming the system. In fact, we included a statement in the aseptic guidance about sampling bias because it has been cited in inspections many times. More specifically, there were 483 observations where we would see in practice—even in front of an FDA inspector—that a company would sample aseptic processing operator gloves only after they fully sanitized them with isopropyl alcohol (IPA).That defeats the purpose of the sample, unless you are doing a study of how effective IPA is.

So, I think it is good practice to add some periodic random checks when aseptic personnel are exiting. This would augment the baseline program and provide further confidence in microbial control. QA or QC departments often add some sort of random check every month just to make sure there is no sampling bias in routine monitoring. The findings may indicate the need for even more frequent random sampling by, quality assurance as well as increased oversight of routine personnel/environmental monitoring activities.

Question: For a generic animal drug packaged in a multidose container, does the in-use statement for the higher-level drug apply to the generic drug if the vial is the same size?

Rice: We certainly look at in-use statements on animal drugs a bit different from human drugs. We have multiple patient sizes and body weights compared to humans. We also have drug products that can be packaged anywhere from single-use vials or ampoules to 1L vials for production animal drugs. We actually have a draft guidance for industry out now that talks about how to design and carry out in-use stability studies for new animal drugs. It is CVM specific. To this question, in particular, "Does the in-use statement have to match the reference listed drug," the answer is emphatically, "no." CVM considers the in-use statements totally data-driven for a drug product. The way we have in-use stability studies designed and laid out in the draft guidance speaks to the ability of container closure systems to maintain a safe and effective drug over than in-use period. That in-use statement is completely data-driven. The in-use statements for the generic will be based on the in-use study that is carried out for that drug product and container/closure system.

Question: When reviewing an NDA for a new small-molecule post-approval stability program, is FDA still accepting sterility testing at annual intervals?

Arigo: Yes, you can do a sterility test at regular intervals. There is no requirement for container closure integrity testing over stability.

Question: Is it okay to do container closure integrity instead of sterility during stability?

Candau-Chacon: Yes, it is. If you include the container closure integrity testing in your stability program, you do not have to test for sterility during stability, however, you still need to test for sterility at release.

Question: What are the expectations for endotoxin testing in INDs?

Candau-Chacon: For INDs, we ask for sterility and endotoxin at release because they are linked to safety. We do not require LER studies at the IND stage.

Question: What is FDA's current thinking for storage times and growth promotion studies in the final drug product? Should this be included in an IND? It is required in a BLA.

Candau-Chacon: Sometimes lyophilized products are stored before use. If those drug product solutions are growth-promoting, microorganisms may enter during product manipulations and grow out of control. In BLAs, we ask the ➤

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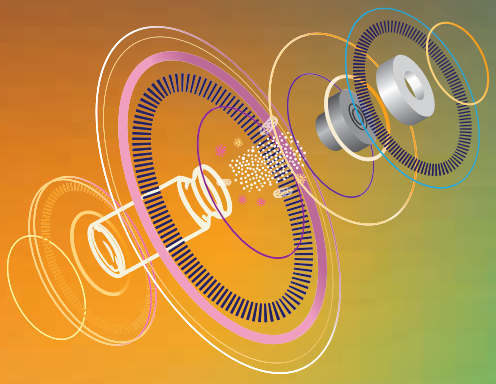

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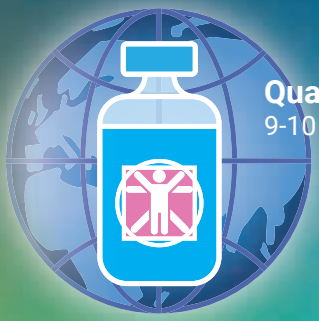

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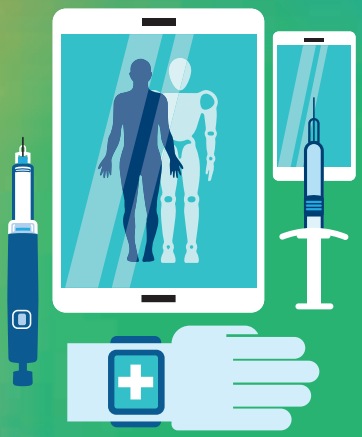

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24-25 September	Pharmaceutical Freeze Drying Technology	Dublin, Ireland
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applicant to conduct growth promotion studies if they intend to store the solution longer than four hours. We do not ask for hold studies in INDs, unless the sponsor has information that suggests that the drug product solution is growth-promoting.

Question: What would be a good environmental control strategy for continuous manufacturing processes?

Friedman: I would want to know more about your product. Continuous manufacturing comes in all shapes and sizes. It covers different products, from injectables to tablets, from the highest theoretical risk to the lowest. Again, I would need more information. An environmental control strategy for continuous manufacturing likely means that you are going to want real-time data, and there is some good equipment out there that could augment your process knowledge in real-time to give you rapid data on environmental or in-process bioburden. I have seen such methods coupled with routine sampling using traditional methods to ensure microbial identification. A balanced overall program would support batch release evaluation by establishing the appropriate combination of controls to be performed.

> **There are many opportunities to better leverage technology to improve detectability**

When it comes to biotech, or any kind of process where you are worried about microbiological risk—which is many of them—it is really important to build quality into the process. Early identification of adverse process signals can be an integral part of the overall design. There are many opportunities to better leverage technology to improve detectability. Detectability of contamination using final product testing alone is limited, although it does still reveal many sterility failures each year. The sterility test is really crucial as the last in a series of controls to determine whether the product is suitable for the market. But some sterility problems could be missed, and advanced environmental monitoring technology, if used properly, could help provide data that can help prevent exposure of patients to a product that lacks sterility assurance.

For nonsterile products, there are a lot of other things to consider. There is a really good bioburden chapter in USP. It includes about 20 variables that should be looked at in terms of designing for quality and ongoing assurance of in-process bioburden control. ➤

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My last point is about liquid and semisolid products. This is a big topic on our guidance committee for nonsterile dosage forms. There have been real problems, particularly on the sanitary systems side, due to lack of circulation, ambient temperatures, choices of materials of construction, etc. I recommend that everybody with liquid and semisolid products ensure they have a good team of engineers and microbiologists with manufacturing knowledge who can contribute a really good understanding of sanitary design.

Question: Regarding cell and gene products, what are the most commonly seen issues?

Lorenzo: Cell and gene products are relatively new to the Agency in terms of the technology and processes and understanding the manufacturing process. There is a lot of exchange going on between the Agency and the sponsors through the formal meetings and through the IND process. I think the most important thing for the Agency to learn is probably the unique aspects of these products in order to formulate reasonable regulatory policies. In terms of the facility and the manufacturing process, some of the issues we see coming up are contamination control issues with the facilities. A lot of cell and gene therapies are rapidly moving from a clinical stage that features very manual operations. We see this has a lot of impact on the commercial operations when they do the scale-out.

One of the things we look at when you are claiming production scale is, can you demonstrate it? It is very difficult for us to license a single-patient dose scale-out to a hundred patient doses. We often see the sponsors do not have a lot of the expertise to do the scale-out, and they do not have the time to practice for the scale-out. There is a lot of impact. For example, it is not just sampling one batch in bigger volumes than we saw in scale-up operations. The challenge for the QC department in a scale out is harder since they to get to perform hundreds of batches in a product that has one batch for one patient.

[I recommend sponsors] come into the Agency and discuss their plans. There is a big push to get to market and being able to produce in the quantities you need.

Question: Biologics for animals are regulated by the U.S. Department of Agriculture. Do you see this moving to CBER in the future?

Rice: I think it is important to make a distinction here. Certainly, animal vaccines are regulated by the USDA, but cell-based products, stem cell products, for example, are not regulated by USDA, they are regulated by CVM. I think that is important to note. I do not know of any plans to transfer these cell-based products to CBER.

Question: For container closure integrity testing, what is the FDA's position on studies that do not use vacuum pressure but, instead, only subject test files to one or the other?

Arigo: I think, in general, we want to see both pressure and vacuum for the container closure integrity test.

Question: Are you seeing facilities using nondistinct water purification, such as by osmosis at upstream stages?

Candau-Chacon: Yes, we have seen firms using highly purified water by reverse osmosis along with firms that use purified water for the upstream part of the manufacturing process. Firms not using WFI need to demonstrate that the water generation system is able to reduce endotoxins and bioburden. Water sanitization and storage at high temperature will help maintain microbial control.

Question: USP <60> Microbiological Examination of Non-Sterile Products Tests for *Burkholderia Cepacia* Complex will become effective Dec. 1. What about products already on the market?

Friedman: Just because a USP general chapter is coming out in December does not mean no attention has been paid to the *B. cepacia* issue before this. Led by Office of Pharmaceutical Quality experts in micro, we wrote a statement on the FDA website a few years ago. We also published a paper on *B. cepacia*. We have been talking about this stuff for a long time.

We are stressing risk assessments on objectionable organisms including, but not limited to, *B. cepacia*. This is especially important for products that may be used in susceptible patient populations—neonates and babies, pregnant women, immunosuppressed transplant patients, and so on. *B. cepacia* is not going away.

Also, sometimes preventing objectionable contamination is not enough. Our medical officers addressed medical risks when there were contaminated antiseptic topical swab recalls several years ago. They recommended that hospital administrators buy sterile wipes if the wipes are used presurgically, or in other, similarly vulnerable, clinical settings.

John Metcalfe: From my perspective, I am very happy to see the USP chapter going in. For applicants that are submitting applications for nonsterile aqueous products, you can expect that, when the application comes in, if you do not have *B. cepacia* testing in your release specification, our reviewers will be sending you a note to put that in. I have not heard anything or spoken to anyone at CDER who has said we are going to have you go back and put that information into older approved applications. We would hope, as Rick [Friedman] pointed out, that this is something you are already doing under basic GMPs but, as far as I know, at this point, there will be no regulatory requirement to update your application for existing approved products.

Friedman: GMPs provide the basic standard that products must be tested for microbiological contamination that is objectionable in view of their intended use. As our posted communications have noted, *B. cepecia* testing would be required as a batch-release test depending on the product and its intended use. And any water system, of course, has to be routinely tested for total counts and appropriately monitored for objectionable microbes and in many cases, that monitoring program should include *B. cepacia*. Another thing we are looking at is: Are you doing the right test for *B. cepacia?* USP <60> should help firms establish the right testing approach.

Metcalfe: I am going to mention one other thing—and I am not going to ➤

belabor this point—but there were people who approached me at this meeting and asked about a tablet product that was recalled from the market due to contamination with *Pseudomonas* and *Burkholderia*. The question that was asked of me was, "When this USP <60> goes in, will there be an FDA expectation that *B. cepacia* testing is performed on the water system for nonsterile drugs?" The comment was made to that, there is a line in the chapter that says the tests could be applied to testing water systems. I am not sure if that was from an older version but I went back last night and looked in the latest draft of the chapter that is going to be coming out, and I did not see anything in reference to water systems. Certainly, FDA's position would be that we hope you are testing your water systems for the organism. But the publication of USP <60> alone does not create a requirement to test pharmaceutical water. FDA's GMP requirements and the intended uses of your products determine that.

Question: What considerations do you recommend for a filling machine used for a variety of products?

Lorenzo: There are expectations for aseptic filling addressed in various guidance documents. When you start dealing with multiple varieties of products, it depends. On the CBER side, we see multiple types of virus vaccines being filled. This poses cross-contamination issues if you do not have proper line clearance and robust cleaning procedures. There is also a need to evaluate other products when you do not own the filling line. New product on a line needs to be reported to all the sponsors because of its potential to affect other products. Specifically, if you are a contract manufacturer, you are going to have to let your clients know what is going to be exposed in that facility. A sponsor would have to evaluate that impact and report it to the Agency.

The most critical thing to consider is the impact to the sterility of products. It is not unusual for filling lines to fill a variety of products and vial types. You should do a media fill simulation of the vials and vial types but you do not have to do all of them. If you can provide the rationale and the justification, it will probably be easier to apply a bracketing approach. There are also considerations for cleaning, making sure that materials that are touching multiple products are not going to pass residue from other products.

> **You have to follow good science and monitor the signals in your operations**

Question: The 2004 FDA guidance only requires 0.5 or greater micron particles for monitoring cleanroom classification. For GMP, Annex 1 also requires 5.0 micron. My question is, Does FDA have any plans to start requiring the 5.0 micron particle as a metric?

Friedman: In the early part of the 21st century, we met with our European colleagues who were working on an earlier version of Annex 1. Our goal, as we wrote the aseptic guidance at that time, was to endeavor to make the guidances *equivalent*. We accomplished that. But the FDA guidance and Annex 1 do not have to be *identical,* and our guidance is silent on a few topics, including 5.0 micron. From our point of view, it was difficult to determine an exact magic number that is objectionable, but that does not mean you should ignore a significant issue with 5.0 micron particles as a matter of control. So, what we can say is that it is important to look at 5.0 microns in certain cases. If the results are abnormal in an ISO 5 area, you should look into why it is occurring.

If you use regulatory guidance as the finite cookbook to tell you what to do, this feeds a misconception that rote or checkbox compliance is all you need to do to make sure each batch of products are manufactured to be safe and effective. There is no comprehensive checklist that this is "all the things FDA told me to do, and I now can sleep soundly at night because I checked those boxes." You have to follow good science and monitor the signals in your operations, and do all the things that you have to do.

Question: Can I use a rapid microbial test method for my water system and water for injection in parallel with traditional plate count tests, even if the rapid test has not been validated?

Friedman: With PAT [process analytical technology], the industry was worried about being innovative with more sensitive methods and thought the results of potentially more sensitive tests would trigger a disproportionate response during inspections. That is one of the reasons why CDER and ORA staff were trained in this area, and we also have processes within ORA and CDER involving preapprovals and compliance evaluations.

The bottom line is, we did address it in the PAT guidance toward the end of the document. There is close to a quasi-safe harbor for you to do side-by-side testing during the research phase. The exception, of course, is in the highly unlikely event that a legitimately serious hazard was revealed by the testing; it would then be incumbent on any responsible firm to take action and investigate, if appropriate. The PAT approach was intended to encourage interest in a technology that may be beneficial. We encourage innovative methods, including rapid methods, that are suitable for their intended use.

Lorenzo: I want to say from a CBER perspective, particularly around cell and gene therapy products, we encourage it because it reduces the risk to the patient, who is receiving the product almost immediately, and there is no way for traditional testing evaluate it. The patient cannot wait that long.

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5 Challenges of Closed System Transfer Devices

New USP Chapter Specifies Use of Closed System Transfer Devices for Hazardous Drugs Spurring Industry Response

Cathy Zhao, PhD, and Allison Radwick, PhD, West Pharmaceutical Sciences

Photo courtesy of West Pharmaceutical Services, Inc.

USP <800> Hazardous Drugs—Handling in Healthcare Settings, effective Dec. 1, 2019, provides standards for limiting occupational exposure to hazardous drugs for healthcare personnel ***(1).*** The chapter clearly applies to any healthcare site handling hazardous drugs including pharmacies, hospitals, clinics, doctor offices and treatment centers. So why should pharmaceutical manufacturers and their associated suppliers care about the new chapter?

USP <800> stipulates the use of closed system transfer devices during compounding and administration of hazardous drugs. Yet vial transfer devices, including closed system transfer devices, present challenges not only to end users but also to pharmaceutical manufacturers, distributors and even packaging suppliers. Below are five areas of concern along with efforts to address them.

1. Lack of Standards, Guidances or Requirements for Functionalities

The principal challenge for all vial transfer devices is the lack of standards, guidances or requirements. While vial transfer devices are like infusion transfer devices in some ways, they differ substantially in how they connect to the primary packaging of drugs due to their much smaller size compared to large infusion vials. Although there are many ISO standards for infusion transfer devices, these do not necessarily apply to vial transfer devices. Therefore, when healthcare sites complain about issues with vial transfer devices, no recommendations or standards exist to support issue resolution. Vial transfer device manufacturers want to design products that achieve user and patient safety but lack quantitative specifications to test their devices in real-world conditions.

A recently assembled PQRI working group (sponsored by PDA) consisting of pharmaceutical and medical device manufacturers is exploring the development of standards and guidance for the interconnectability between vial container closure systems and vial transfer devices ***(2).*** Led by Eli Lilly, most major pharmaceutical companies such as Amgen, Genentech, Pfizer, Shire and AstraZeneca are participating. Many device manufacturers, namely B. Braun, BD, ICU Medical, Yukon and Baxter, and the stopper

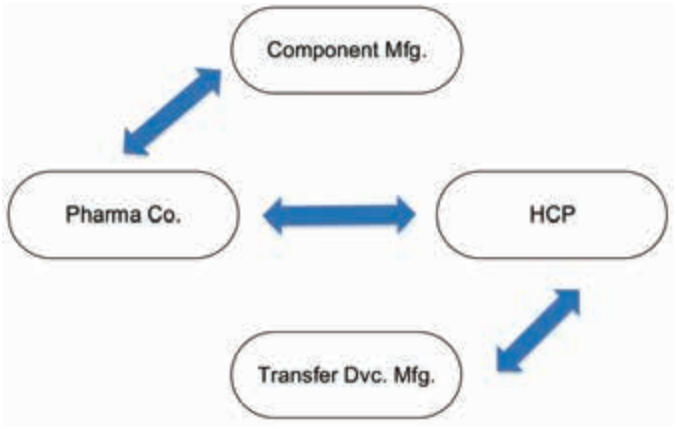

Figure 1 Current Flow of Communication and Information

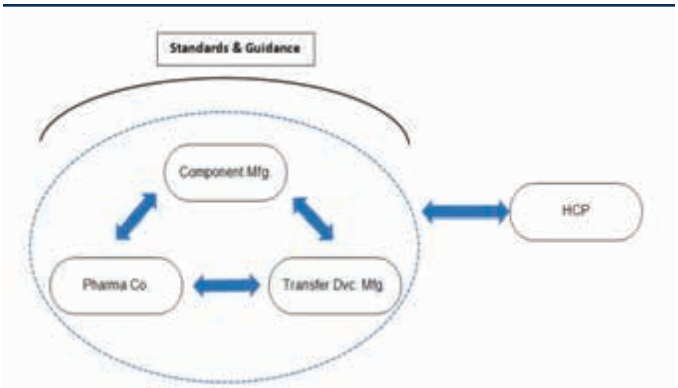

Figure 2 Desired Flow of Communication and Information

manufacturer West Pharmaceutical Services, are also participating in the consortium. This team aims to establish dialogues among all stakeholders and to improve the communication chains **(Figures 1** and **2)** with the following objectives ***(2):***

- Communicate with key stakeholders and build consensus
- Develop and promote best practices to mitigate the risks to patients and caregivers/healthcare professionals
- Develop proposed quality and performance requirements for vial transfer systems

2. Closed System Design Magnifying Problems of Current Vial Transfer Devices

Some closed system designs magnify the problems presented by current vial transfer devices. High attachment force has been one of the major complaints, for example. Vial transfer devices without guiding wings (left in **Figure 3)** provide lower attachment forces than those with guiding wings (right in **Figure 3).** The attachment force of a spike without wings equals its maximum penetration force into a stopper, while the attachment force of a vial adapter with wing(s) is the maximum combination value of the spike penetration force and wing attachment force onto the side of the vial seal. Some closed system transfer devices have very rigid wings, which increases the high-force issue. Healthcare sites have reported user fatigue and hand injuries caused by the extremely high force required to attach closed system transfer devices ***(3).*** High forces may also lead to vial breakage. As healthcare sites are faced with using closed system transfer devices with hazardous drugs in vials as small as 2 ml, the high forces required to insert the closed system transfer devices create the risk of vial breakage, resulting in complete failure of the system designed to protect healthcare workers.

Figure 3 Vial Transfer System without Wing (left); Vial Transfer System with Wings (right)

Figure 4 shows the comparison of attachment forces of various vial transfer devices and stoppers. Nine vial transfer devices are represented by nine color codes. The closed system transfer device (green) displayed extremely high attachment force from its very rigid wings, which are designed to prevent needle sticking. Attachment force varies considerably with different designs of vial transfer devices and stoppers; therefore, evaluating their performance before selecting vial transfer devices or stoppers is recommended.

An additional issue created by closed system transfer devices is the residual volume of drug in a vial. The U.S. FDA limits vial overfill volume to 10%. A needle can be manipulated to extract a full dose of a drug; however, closed system transfer devices with plastic spikes usually have very rigid designs that do not allow any manipulation. This can result in failure to extract a full dose of a drug from the vial. Thus, delivering a full (100%) dose is an issue, along with drug waste.

Yet USP <800> has some limitations

3. New Challenges in Vial Transfer Devices Applications

Although some ISO standards for infusion transfer devices can be adapted to fit vial transfer devices, there are issues unique to closed system transfer devices. New standards are needed. For example, a noticeable number of complaints have been registered regarding the intrusion of stoppers into vials during the insertion of closed system transfer devices. Since stopper intrusion rarely occurs during infusion, there is no ISO standard addressing it. A study to understand the issue was recently conducted ***(4,5),*** and a comprehensive process to assess the probability of stopper intrusion has been developed **(Figure 5).**

Another problem is vial breakage, primarily caused by the excessive force required during attachment of the closed system transfer device.

4. Performance Differences as the Result of Design Differences

The differences in vial transfer device and stopper designs result in significant variations in performance. Coring and fragmentation have been a challenge for needle-puncturing; however, the designs of the piercing device for various vial transfer devices may increase the likelihood of coring and fragmentation compared to needles. **Figure 6** illustrates the fragmentation performance of various transfer devices with different stoppers. West recommends evaluating the performance of the combined container system (vial, stopper and seal) with the transfer system before making a decision or recommendation.

5. No Measurement Method of Closed System Transfer Devices Efficacies Covering All Closed System Transfer Devices Types

The intent of USP <800> is to protect healthcare providers from exposure to hazardous drugs. Closed system transfer devices are required to contain the drugs and prevent spills, sprays and vapors ***(7).*** Yet USP <800> has some limitations: it neither instructs on acceptable test methods, nor provides criteria for pass/fail.

A summary of independent tests showed key differences in protective efficacy of closed system transfer devices ***(8–10).*** Six brands of closed system transfer devices were investigated: PhaSeal™, Equashield®, ChemoClave®, ChemoLock™, SmartSite® and OnGuard®/Tevadaptr®. The first test followed the two-task procedure described in the NIOSH protocol ***(9,10).*** This test uses 70% IPA as a surrogate drug solution and is performed in a closed desiccator. The vapor of IPA is a measure of leakage. The PhaSeal and Equashield devices passed with no detectable IPA leak. This protocol method cannot be applied to a ➤

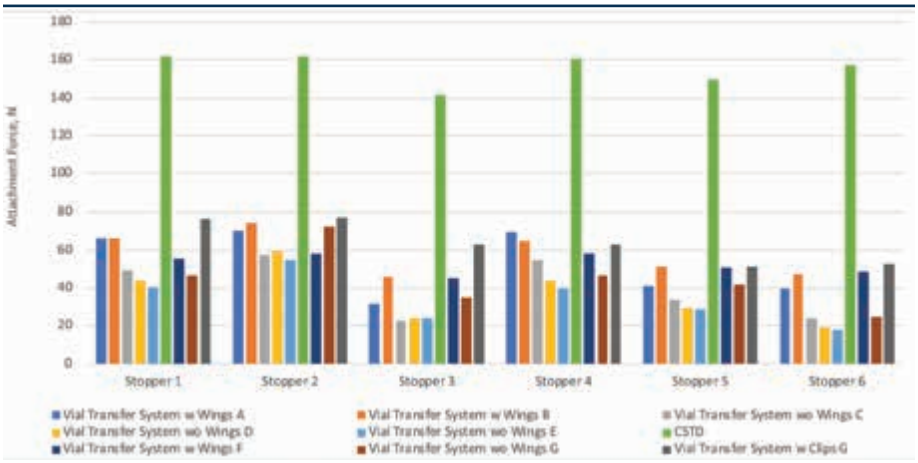

Figure 4 Comparison of Attachment Force with Different Vial Transfer Systems and Stoppers

Figure 5 3-Step Process to Assess Stopper Intrusion Probability

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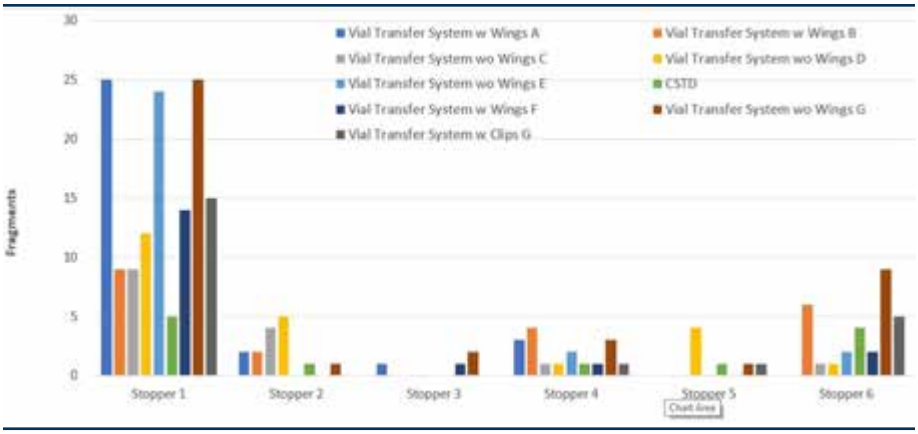

Figure 6 Fragmentation Impacted by Vial Transfer System and Stopper Designs

CSTD with an air-cleaning technology like the OnGuard/Tevadaptor system, however. The second test used the basic chemotherapeutic drug 5-fluorouracil (5-FU) ***(9,11).*** The color change of the litmus paper is indicative of leakage. Only the Equashield device passed this test. The third test was performed on CSTDs with air-cleaning technology ***(9).*** This test showed that the results varied with the level of manipulation.

Conclusion

Closed system transfer devices have been developed to prevent occupational exposure to hazardous drugs and to protect patients, healthcare personnel and the environment from their effects. Yet, USP <800> neither provides limits of pass/fail nor instructs on acceptable test methods. Multiple challenges in the implementation USP <800> need to be addressed as there are numerous variabilities on the functionality of vial transfer devices and the efficacy of closed system transfer devices depending on their designs. Standards and testing methods must be developed and validated with pass/fail limits to assess the performance of vial transfer devices, including closed system transfer devices and a screening process must be recommended for healthcare sites to select transfer devices. Addressing these issues now will help ensure successful implementation of USP <800>.

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About the Author

Cathy Xia Zhao, PhD, has over 15 years of experience in the medical/pharmaceutical industry. She is currently the Director of Scientific Insights Lab in West Pharmaceutical Services, Inc, and has held various positions in West prior, such as Global PPS Research Director. Before joining West, Zhao worked for BD as a Principal Materials Scientist.

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The PQL Team Part I: Building the PQL Role

Stephan Krause, PhD; Mariam Khan; Callum Chapman; Rob Gaglione; Andy Spasoff; Anthony Mire-Sluis, AstraZeneca

Since launching the Product Quality Leader (PQL) role in 2018, AstraZeneca has seen success by leveraging the role to ensure greater quality assurance of the company's biologics operations in only a year.

In addition to greater quality assurance, the PQL role also serves as a development path to build up the leadership skills of emerging quality leaders within the company who have also provided fresh ideas for the role as well.

What is the Product Quality Leadership Role?

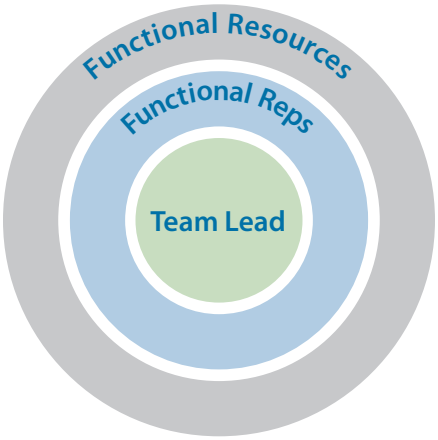
The Product Quality Leader (PQL) is an independent representative who provides effective and efficient feedback and oversight regarding quality issues between the CMC team and functional quality groups. The position requires a technically competent quality professional who has experience in leadership, management, decision-making, strategic planning and organizational effectiveness and comfortable in working within a matrix organization. This function is intended to build quality into the product and provide global ownership of the manufacturing behind specific products.

The PQL provides functional expertise and guidance to their assigned team, communicating project needs to quality functional areas (e.g., external quality, quality assurance, lot release) and developing the overall product quality strategy for the CMC team. **Figure 1** illustrates the basic relationship of CMC team representatives within their functions and within the CMC team.

Some of the responsibilities of the PQL include:

- Representing the quality function at clinical CMC team
- Engaging with all quality stakeholders impacted by product team strategies
- Approving product specifications and justification reports
- Approving comparability protocols and reports
- Owning combination product specifications
- Approving process performance qualification control strategy document
- Reviewing regulatory submissions to ensure a consistent "story"
- Managing CMC change log
- Advise on product impact for nonconformance events and product complaints
- Engage in external and influential activities, as available

Figure 1 Basic CMC Team Structure



The First Steps

As a newly established function, the team overseeing the role promoted it internally as a career-growth opportunity, encouraging newer and somewhat less-experienced staff to apply. This resulted in a flood of applications. Applicants with scientific knowledge, openness to working within a team, good communication skills and strong organizational effectiveness skills who were also identified as being "developable" were recognized as those most likely to thrive in the PQL role.

At the same time, AstraZeneca actively promoted the PQL program to the entire company, strongly encouraging that some existing roles and responsibilities within the overall quality department transition to the PQL role. To ensure the success of the PQL program, the team overseeing it provided regular updates on its development and any resulting changes to quality operations. Communications also focused on the new "footprint" for stakeholder/partner-agreed review and approval tasks.

For instance, review tasks for the new PQL function were mapped out for each

major product development stage. A simplified example, illustrated by **Figure 2,** shows some of the major CMC tasks during late-stage development that are reviewed/approved by the PQL. The tasks (blue boxes) are associated with each accountable functional group along with the types of documents identified that the PQL function reviews and approves.

> **Ultimately, it provided an established foundation for improved future operational effectiveness**

To standardize the PQL review process and achieve consistent outcomes, detailed process maps were developed. Additionally, job aids from the shared review/approval experience covering all relevant lessons learned were included with the process maps. This helpful information was made readily available to all PQLs via a shared-access database; each of the CMC teams have access to this information as well. By ensuring this information is directly visible to all CMC team members, organizational effectiveness improved.

The success of the project also required collaboration among various quality groups to establish the required changes. Some PQL members drafted a roles-and-responsibilities matrix and provided initial suggestions to other quality staff. Multiple meetings with individual functions were required to resolve differences; the final draft matrix was then reviewed by all quality functions before being published in a shared-access database.

Figure 3 illustrates a simplified matrix table. For example, while the product expiry date assignment (EDA) is the approval responsibility of the PQL, an out-of-specification (OOS) investigation is conducted and approved by site Quality Assurance (QA), with the PQL functions in a consulting role, analyzing for any potential effects to product quality. A sufficient level of clarity and granularity was needed for new or changed review/approval roles so responsibilities could be properly assigned. This was deemed crucial to making the transition process as transparent and painless as possible. Ultimately, it provided an established foundation for improved future operational effectiveness—one of the many benefits of the PQL function.

One year after starting this program, the PQL role has proven to be a successful way to ensure quality within the biologics function at AstraZeneca. The involvement of emerging quality leaders have also enhanced the role by continually refining it.

[Editor's Note: Part II of this article will look at a team building exercise based on lean principles that involved a team consisting of all the PQLs**.]**

Figure 2 Examples of Major PQL Reviews During Late-Stage Product Development

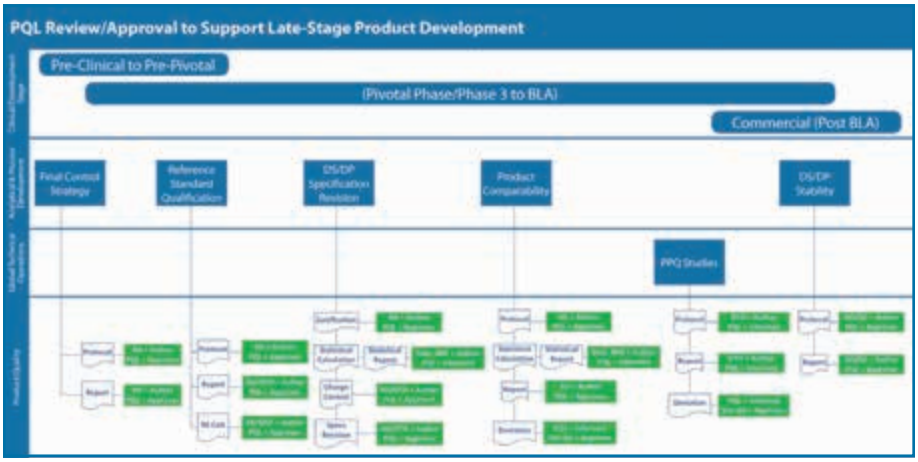


Figure 3 Examples for Finalized Roles/Responsibilities Among Different Quality Functions

Quality Review Task Description (A=Approver, C=Consulted, I=Informed, CoPI=Consulted for Product Impact)	External Quality	Product Quality	Quality Assurance	Device Quality
Communication with External CMOs and Partners	A			
External Quality Record Management	A	CoPI		
Drug Substance and Product Master Specifications	I	A		
Combination Product Lot Release Specifications		A		
Design History Files (DHF) Documents				A
Stability Protocols for Drug Substance and Drug Product		A		
GMP Stability Protocols for Combination Product (CP)		A		C
Combination Product (CP) Control Strategy		A		C
External Device CMO Audits	A	C		C

About the Authors

Stephan Krause, PhD, is the head of AstraZeneca Product Quality Leader Group. He is a frequent PDA volunteer and current member of PDA's Board of Directors.

Continued at bottom of page 53

Joint PDA, IPEC TR Addresses Excipients

Eva M. Urban, CSL Behring and M. Schousboe, Novo Nordisk

PDA's latest technical report, *Technical Report 54-6: Formalized Risk Assessment for Excipients,* is a joint initiative between PDA and the IPEC Federation. This technical report provides guidance on quality risk management (QRM) principles that can be used to assess the risks to the quality, safety and function of an excipient in a drug product. The Technical Report provides practical guidance to be used in conjunction with existing regulatory and industry standards.

Technical Report No. 54-6 includes:

- Evaluations that can be used to provide an overall view of the risk question, "Is the excipient fit for use?"
- A generic risk assessment model and a holistic strategy applicable to excipient use for all dosage forms
- Discussion of end-to-end supply chain risks and information gathering
- Control strategy: benefits and challenges

Technical Report No. 54-6 is a response to 2015 European Commission guidelines on risk assessments for excipients. In 2018, PIC/S incorporated these same provisions for formalized risk assessment into a publication of the same name, extending the provisions to have global applicability. The technical report is grounded in the general principles outlined in ICH Q9: *Quality Risk Management.* Technical Report Series 54 is part of PDA's collection of QRM-centered technical reports.

Technical Report 54-6: Formalized Risk Assessment for Excipients is available in the PDA Bookstore.

ICH Q9: Quality Risk Management Revisions on Horizon

Rebecca Stauffer, PDA

International Council for Harmonisation of Technical Requirement for Pharmaceuticals for Human Use (ICH) is considering revising portions of Quality Guideline No. 9: *Quality Risk Management* (Q9), though the guideline as a whole will not be rewritten, according to **Stephan Rönninger,** PhD, Director Quality External Affairs, Amgen. He spoke on "15 Years of ICH Q9: Practical Implementation & Pitfalls" at the *2019 PDA Risk Management in the Regulatory Landscape Conference* in Washington, D.C., Dec. 10.

The future revision was discussed during the "questions and answers" following his presentation. Two years ago, he explained, ICH formed an informal quality discussion group to look at all existing guidelines to determine which ones need to go to a maintenance procedure or should be fully revised. Many of the regulatory members of the group expressed an interest in revising ICH Q9.

"It was discussed in the last ICH meeting in Singapore that ICH [Q9] should undergo a revision by a 'development of integrated addendum,'" Roenninger said.

A development integrated addendum according to ICH parlance means only specific sections of the guideline will be targeted for revision, Rönninger explained, but a complete revision is off the table. He said the sections to be revised have yet to be identified and no timeline is available.

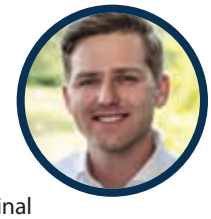
During the lunch directly following the Q&A, conference attendees developed a list of recommended revisions to ICH Q9. This list will be published on the Letter website soon. Within PDA, a team will also review the suggestions to potentially respond to ICH.

Stephan Rönninger

Originally published online Dec. 11, 2019

The PQL Team Part I: Building the PQL Role continued from page 51

Mariam Khan has over ten years of biotech/pharmaceutical industry experience in analytical sciences and quality working on biologics in clinical development. She is currently the PQL on cell therapies and various other monoclonal antibodies.



Callum Chapman is the PQL for multiple molecules across AstraZeneca's pipeline, working mostly with inhaled biologics and advanced therapy medicinal products. He is a UK-registered Pharmacist and is interested in the area where CMC meets clinical development.

Rob Gaglione serves as a lean practitioner for AstraZeneca's Biologics Development Quality Department. Prior to joining AstraZeneca, he worked as a supplier quality professional in the medical device industry.

Andy Spasoff has worked in the biotechnology industry for over 18 years at multiple large companies. He has spent time in Process Development, Global Operations and Quality focused on the commercialization and commercial support of biologic products.

Anthony Mire-Sluis, PhD, is currently Head of Global Quality at AstraZeneca. Prior to working at AstraZeneca, he held the role of Vice President of Quality at Amgen. He was also Principal Advisor, Regulatory Science and Review, Office of Biotechnology Products, CDER and Head of Analytical Sciences and Standards, Office of the Director, CBER, U.S. FDA.

Originally published online Jan. 15, 2020

Plunging into Six Sigma

Stephenie Overman

Artificial intelligence and automation may sound sexy, but when it comes to maintaining quality in pharmaceutical manufacturing, nothing really tops taking an organized, risk-based approach to eliminating human error.

Matthew Paquette, operational excellence manager for Charles River Laboratories International, Inc., is heading up a team to do just that at the company's microbial solutions business facility in Charleston, S.C.

Specifically, the team is introducing Lean Six Sigma principals, according to Paquette, who has a master's degree in Six Sigma/Quality Management.

In an industry where one misstep can have devastating consequences, "it is critical to avoid errors through at all stages of sterile pharmaceutical manufacturing," he said, and in biological manufacturing "the opportunity for improvement is great."

The plan is to start with the Charleston facility, then move to other Charles River sites. The Wilmington, Mass.-based company has more than 14,700 employees working at 80 facilities in 20 countries.

Six Sigma is a method that provides organizations with tools to improve the capability of their business processes, according to the American Society for Quality (ASQ). According to the ASQ website: "This increase in performance and decrease in process variation helps lead to defect reduction and improvement in profits, employee morale, and quality of products or services."

In an article in the *International Journal of Pharmaceutics,* **Lawrence X. Yu** and **Michael Kopcha** proclaimed Six Sigma "the future of pharmaceutical quality." ***(1).***

Further, they note that "consumers and patients deserve six sigma quality pharmaceuticals with minimal risks of shortages or recalls...the fundamental destination of pharmaceutical quality has been long envisioned: a maximally efficient, agile, flexible

pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight" ***(1).***

The path to get there, according to Yu and Kopcha, includes economic drivers, performance-based regulation, quality-by-design, advanced manufacturing technologies, and continuous improvement and operational excellence.

With Six Sigma, teams are assigned well-defined projects that have a direct impact on the organization's bottom line, per ASQ. Employees at all levels receive training in statistical thinking and key people receive extensive training in advanced statistics and project management. In the long-run, operations using Six Sigma ideally should have no more than 3.4 defects per million opportunities.

More Than Cost-Cutting

Lean Six Sigma combines lean manufacturing/lean enterprise and Six Sigma, which helps eliminate waste, but Paquette warns that companies sometime focus too much on the "lean" aspect.

"Companies often think of it as cut costing. There is a component of cost saving but improving and confirming quality is more important," he said. "Six Sigma does not succeed unless you show you that you've got better in some way. Often companies go with cost savings because that's easy to measure. Product quality is hard to measure."

Six Sigma is based on the DMAIC approach, (define, measure, analyze, improve, control) an improvement system for existing processes falling below specification and looking for incremental improvement.

Six Sigma breaks down each component in the manufacturing process to solve problems and "to prove you solved the problem," Paquette said. "In pharma, regulators expect you work to find ways to reduce variability."

Don Maida, senior consultant for TBR Associations, stresses that, done right, Six Sigma "decrease costs, improves quality and improves profitability."

But too many companies that try to practice Six Sigma don't really follow DMAIC, according to Maida. "They often skip measure and analyze. Then they have the same problem again. You need to find the root cause of the problem, those things that get in the way of doing things perfectly each time."

What often gets in the way of doing thing perfectly is employee-introduced variability, said Maida, who consults with manufacturing companies on Six Sigma programs. "Employees are all doing things their own way, so it's hard to get consistent

results. To eliminate human error, eliminate decisions. Mistake-proof the process."

As an example, he noted that automobiles have tabs attached to their gas caps so drivers don't accidently leave the caps behind. "With the tab on your gas cap, you can't help but do the right thing."

Too often, manufacturers tend to rely on end-process testing – "they produce the product and then see where it falls in the Six Sigma range," he said. The real goal is "to solve problems when they happen, not wait until you get to the end of the process. If you don't solve problems upstream, it creates a lot of waste. You have to throw the batch out the window."

In the end, Lean Six Sigma "is a journey, not a destination," Maida said. "It takes discipline, you need to build in the tools to sustain it. With Six Sigma every time there's a next step, that is an opportunity."

Six Sigma experts emphasize that for the process to succeed, management must be fully committed, but Paquette and Maida believe it's also important to have a culture where rank-and-file workers feel their contributions are valued.

"If they think something's wrong, employees need to feel free to raise their hand and say something," Paquette said.

Maida worked with one client who was very top-down oriented, explaining, "I said, 'why do you not let them make up the rules? Let them contribute. Employees have to have a vested interest.' We did this in two departments and they had it locked down. If you are going to do all the thinking, you are going to have to do it for the rest of your life."

Getting Started

A company will find many benefits from implementing Six Sigma, but "it takes time and resources. It takes years to get an operational excellence program up and running," Paquette said. "You want to make sure you're moving the needle in the right direction."

Companies that want to implement Six Sigma should make the investment in specialized training, he adds. "You can hire outside consultants; once you hire a consultant, you want them to train others in house in Six Sigma."

It does take time to fully implement Six Sigma, but it is worth it, according to Maida. "When we do a project, it takes about 28 months from start to finish.

"When you get started, in the first six months, you are not going to see much because it is getting people engaged," he said. "But once that kicks in, hold on, it is a fantastic ride."

Reference

1. Yu, L.X., and Kopcha, M. "The future of pharmaceutical quality and the path to get there." *International Journal of Pharmaceutics* 528 (2017): 354–359.

About the Author

Stephenie Overman specializes in writing about health and workplace issue. She is author of *Next-Generation Wellness at Work*.

Originally published online Nov. 11, 2019

Crystal Booth

Regional Manager | ***PSC Biotech*** | Member Since **2015** | Currently living **Raleigh-Durham, North Carolina** | Originally from **Collinsville, Virginia**

What significant changes have you seen take place in your profession/area of expertise through the years?

I have seen a push for microbiology to be faster, better and more accurate. This covers the spectrum of preventing contamination to rapid microbiology and data integrity. I have also seen updates to microbial identification methods, endotoxin testing methods, bioburden testing, sterility methods, microbial enumeration methods, environmental monitoring, and updates for the use of isolator technology, to name a few changes.

When I started out, microbiology assays were manually intensive. There is still manual labor present today, but the idea of automation in modern laboratories is gaining momentum and popularity.

What has been your most memorable PDA experience to date?

My most memorable experience with PDA to date is winning the PDA/DHI Distinguished Editor/Author Award for writing *Method Development and Validation for the Pharmaceutical Microbiologist*. It was such an honor to be recognized.

What was it like writing the book, *Method Development and Validation for the Pharmaceutical Microbiologist?*

I had the concept of writing the book planned out in my mind for many years. I just did not know how to go about getting published, nor did I have the spare time that was required to focus and write a book.

One year, I was invited to speak at a conference and Jeanne Moldenhauer was a speaker as well. We spoke briefly after her presentation, and she asked me to write a chapter in one of her books. Of course, I said yes. It was this process and the introductions that Jeanne gave me to DHI Books that I needed in order to begin writing my book for PDA/DHI. I am forever thankful to Jeanne and Amy Davis.

I feel blessed to have numerous mentors and role models in my career. It is now my turn to pay it forward. I am still actively writing articles and speaking at conferences as much as possible.

What are some other volunteer activities you have done for PDA?

I am currently the president-elect of the Southeast chapter, and I am on the membership advisory committee. I also spoke at the *14th Annual PDA Global Conference on Pharmaceutical Microbiology* in October.

What do you like to do in your spare time?

I learned to scuba dive in college as part of my curriculum. I do not get to go often, but I love diving when I get to go. Being underwater is a wonderful, relaxing experience.

I was also born with an artsy side and an ability to carry a tune. Occasionally, I will take craft classes at Michaels. I have taken cake decorating courses and knitting courses. My church choir and band helped me become better singer.

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PDA Enters 2020 on Strong Note

As the new chair of the PDA board of directors, I hope you are ready for the new year and are excited to see what PDA will provide to help you in your daily work throughout 2020.

To effectively deliver value to you, we will focus on agility, simplification and innovation—the keywords for our activities in 2020.

With this said, we will, as always, be science-based in all our products and quality risk management (QRM) will be included wherever possible.

PDA plans for an ambitious start to the new decade with a slate of activities and offerings. Below are some that I think may be of interest to our members.

- We plan to host several conferences in Asia throughout 2020 following the successful launch of our new Asia-Pacific office in Singapore last year
- We will continue to focus on encouraging young professionals to be engaged with PDA, including involvement in our task forces
- You will still receive quality publications, including Points to Consider papers, technical reports and ANSI standards
- E-learning courses will now be offered in addition to our recognized face-to-face courses held at the PDA Training and Research Institute in Bethesda, Md.
- We will continue to conduct applied research to help support industry initiatives
- We will work with our global regulatory partners to encourage support for efficient technologies and innovation
- We will continue to advocate for global harmonization, simplification, efficiency and practical implementation based on science, technology and risk; and we will continue to comment on relevant regulatory draft requirements with science and risk-based argumentation to help achieve the best science and risk-based requirements to the benefit of the patient

Keep an eye on the PDA website for more information about all of these exciting projects and initiatives.

2020 will be a busy year, and therefore, we encourage you to help us achieve our goals by actively volunteering with us, because both hands are needed; PDA leadership and staff are one hand and our volunteers are the other.

Get involved by joining one of our chapters or interest groups. You can also write an article for the *PDA Letter* or *PDA JPST,* serve on a task force for a Points to Consider paper or technical report, or support one of our conferences by sitting on a planning committee.

By being active in our community, you will help build up the PDA family that will support agility, simplification and innovation within our industry.

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