People • Science • Regulation

PDA Letter

Volume LIV • Issue 5 www.pda.org/pdaletter May 2018

3-D PRINTING AND BIOPHARMACEUTICAL MANUFACTURING 26

PDA
Parenteral Drug Association

On the Issue Videos by the *PDA Letter*

Interviews with leading industry experts on the issues important to you

Watch the following experts:

Bristol-Myers Squibb's Paula Peacos — Contamination Recovery Rates for Environmental Trending

Baxter's Kevin Cloonan — A Quality System Maturity Model

Amgen's Arleen Paulino — Next Generation Manufacturing

NNE's Alex Severin — Designing for Flexible Engineering

For more information on all PDA podcasts and other interviews, please visit:

www.pda.org/pdaletter

May 2018 PDA Letter

3rd PDA Europe Annual Meeting

Show Issue

Annex 1. Big data. Industry 4.0. ICH Q12. Data integrity. These are the current topics of interest across our industry. And these topics will be addressed in sessions at the *3rd PDA Europe Annual Meeting* in Berlin, June 26–27. For articles in support of this meeting, look for this banner at the top of the page.

Cover Art Illustrated by PhonlamaiPhoto

InfoGraphic

3-D Printing Leading Medical Advancements

3-D printing offers clear advantages for biopharmaceutical manufacturing. Yet it also has implications for other parts of healthcare.

PDA Letter

Volume LIV • Issue 5 www.pda.org/pdaletter

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

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

Subscriptions are not available.

Departments

Digital Exclusives

> **On the Issue** | Strategies for Reducing Human Error Nonconformances
PDA Education instructor **Elaine Lehecka Pratt** discusses the role of quality culture in preventing human error.

> New Drugs Need Agile Biomanufacturing
NNE's **Jeffery Odum** discusses the need to adjust manufacturing practices for new therapies.

pda.org/letter

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

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

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

Pizza, Pills and Packaging!

It seems that every few months, something new can be 3-D printed. Organs. Houses. Cars. Various components. Last year, a Silicon Valley startup launched Chef 3D, a machine that can 3-D print a pizza complete with dough, sauce and cheese ***(1).*** No word yet on if it can print anchovies.

NASA provided the company with a grant to produce the machine, the idea being it could help bring astronauts on a lengthy Mars mission a little taste of home. The creators of the machine plan to sell it to certain theme parks, malls and sporting arenas in the next few years, so you may soon get a chance to try it out yourself.

But I know what you are thinking. How does this relate to my day-to-day work in quality, sterile processing or the shop floor?

3-D printing is one technology that will impact pharmaceutical manufacturing in the next decade. GE Healthcare and GlaxoSmithKline are already exploring its applications to biopharmaceutical manufacturing (see cover story on p. 26). On the oral solid dosage side, a team of chemists have taken the first steps to develop a machine that may enable patients to produce their own pills at a pharmacy—or possibly even their own homes ***(2).***

More relevant to parenterals, packaging suppliers are now looking at 3-D printing for manufacturing packaging components. West is now focusing on 3-D printing at its innovation center in Washington, N.J. Ten years ago, the company purchased its first 3-D printers, now the company can 3-D print molded parts for preproduction instead of forcing customers to wait for them ***(3).*** Undoubtedly, other suppliers will soon follow suit.

3-D printing is just one of many innovations coming to biopharma manufacturing. If this topic interests you and you want to get it involved with where it can take the industry, I encourage you to contact us. Our Manufacturing Science and Operations Program (MSOP[SM]) continues to explore how PDA can help shape the future of manufacturing, and if you are directly involved with 3-D printing in the industry, I encourage you to reach out.

Rebecca Stauffer

References

1. Garfield, L. "This robot can 3D-print and bake a pizza in six minutes." *Business Insider.* (March 4, 2017). http://www.businessinsider.com/beehex-pizza-3d-printer-2017-3#beehexs-bot-called-the-chef-3d-can-produce-any-type-of-pizza-in-any-shape-french-says-like-most-3d-printers-it-hooks-up-to-a-computer-that-tells-it-which-dough-sauce-and-cheese-to-use-1

2. Service, R. "You could soon be manufacturing your own drugs—thanks to 3D printing." *Science* (Jan. 18, 2018) http://www.sciencemag.org/news/2018/01/you-could-soon-be-manufacturing-your-own-drugs-thanks-3d-printing

3. Skoda, E. "3D Printers Revolutionise Pharmaceutical Packaging and Delivery." Packaging Europe. (Feb. 16, 2018) https://packagingeurope.com/3d-printers-revolutionise-pharmaceutical-packaging-and-delivery/

Corrections

In the article, "PDA Task Force Meets Face-to-Face in Venice," on page 18 of the April issue, SPAMI was incorrectly listed as "APAMI" in the last paragraph.

Additionally, task force members **Alessandro Zannini** and **Gaetano Baccinelli** are affiliated with Optrel.

The Envelope, Please!

Each year, PDA recognizes members whose contributions have helped the Association fulfill its mission at the Awards Dinner, held during the Annual Meeting. PDA congratulates each winner for their service to the Association.

Honorary Membership

This is PDA's most prestigious award, conferring lifetime membership benefits to the recipient. The award has traditionally been given in recognition of long service significant in nature to PDA and requires unanimous approval from the Board of Directors.

Rich Levy, PhD

Gordon Personeus Award

Presented in memory of the late **Gordon Personeus,** past PDA President and longtime volunteer, this award is intended to honor a PDA member, other than a Board member, for long-term acts or contributions that are of noteworthy or special importance to PDA.

Michael De Felippis, PhD
Janeen Skutnik-Wilkinson

Frederick J. Carleton Award

This award is presented as a tribute to lifetime contributor, past President, past Executive Director, and Honorary Member **Frederick J. Carleton,** and is designated for past or present Board members.

Gabriele Gori
Christopher Smalley, PhD

Martin VanTrieste Pharmaceutical Science Award

Established in honor of long-time contributor and Chair **Martin VanTrieste,** this award is given annually for outstanding contributions to the advancement of pharmaceutical science.

Michael Miller, PhD

Michael S. Korczynski Award

An award established in recognition of contributions made toward the development of PDA's international activities by **Michael S. Korczynski,** PhD

Ursula Busse, PhD
Hirohito Katayama, PhD

Edward Smith Packaging Science Award

In honor of long-time volunteer **Edward Smith,** who led PDA's packaging science activities, this award is given in recognition of extraordinary contributions to PDA and the packaging science.

Mathias Romacker

Distinguished Service Appreciation Award

This award is given in recognition of special acts, contributions or services that have promoted the success and strength of PDA.

Patricia Hughes, PhD
Maria Jacobs, PhD
Stephan Krause, PhD
Hanns-Christian Mahler, PhD
Roman Mathaes, PhD
Tsuguo Sasaki, PhD

James P. Agalloco Award

The James P. Agalloco Award is presented annually to the PDA faculty member who exemplifies outstanding performance in education. The award is named for **James P. Agalloco,** in honor of his work in developing the PDA Education program.

Lee Leichter

Frederick D. Simon Award

The Frederick D. Simon Award is presented annually for the best paper published in the *PDA Journal of Pharmaceutical Science and Technology.* This award is named in honor of the late **Frederick D. Simon**, a former PDA Director of Scientific Affairs. This year's award went to three recipients for their article, "Particulate Generation Mechanisms during Bulk Filling and Mitigation via New Glass Vial," which was published in the September/October 2017 issue of the PDA Journal.

Christopher Timmons
Chi Yuen Liu
Stefan Merkle

Distinguished Editor/Author Award

This award recognizes the author or editor selected by PDA members for their contribution to PDA's technical books. This year's award went to the author of the book, *Method Development and Validation for the Pharmaceutical Microbiologist.*

Crystal Booth

PDA Europe Service Appreciation Award

This award is presented annually for special acts, contributions or services that have contributed to the success and strength of PDA's European activities.

Siegfried Schmitt, PhD

Service Appreciation Award

This award is presented annually for special acts, contributions or services.

Deborah Autor
Hal Baseman
Ursula Busse, PhD
Joyce Bloomfield
Stephan Rönninger, PhD
Maureen Hertog
Keith Koehler
Sanjit Singh Lamba
Jason Mattis
John Michael Morris
Kenneth Paddock
Leticia Quinones, PhD

President's Award

This award recognizes a PDA staff member, other than senior staff, whose exemplary performance has contributed to PDA's success during the previous year.

Emily Lyons
Katie Ruiz

PDA Welcomes Tina Morris

Richard Levy, PhD, Sr. VP of Scientific and Regulatory Affairs Stepping Down After 13 Years

PDA is pleased to welcome **Tina Morris,** PhD, as the Association's new Vice President of Scientific and Regulatory Affairs. Currently, she serves as Senior Vice President of Compendial Sciences at the U.S. Pharmacopeia, with whom she has worked for 15 years. She will join the PDA family effective June 4.

In her new role, Morris will oversee PDA's scientific and regulatory affairs activities, which include industry-leading technical reports, the newly launched standards-development program through the American National Standards Institute (ANSI), regulatory commenting, and overseeing PDA's four technical/regulatory advisory boards.

"Dr. Morris has strong leadership capabilities in a volunteer-based organization that we believe are essential to PDA's efforts to continue PDA's legacy of leadership in bio/pharmaceutical science," said **Richard Johnson,** President and CEO, PDA.

Morris began her career at USP as a Senior Scientific Liaison in 2003, and saw her responsibilities grow each year before becoming Senior Vice President in 2015. Prior to USP, she worked for Human Genome Sciences, Inc. and at Ciphergen Biosystems, Inc. She received her PhD in molecular virology from the Medical University of Luebeck, Germany and a Bachelor of Science and Master of Science in biology from the Carl von Ossietzky University in Oldenburg, Germany.

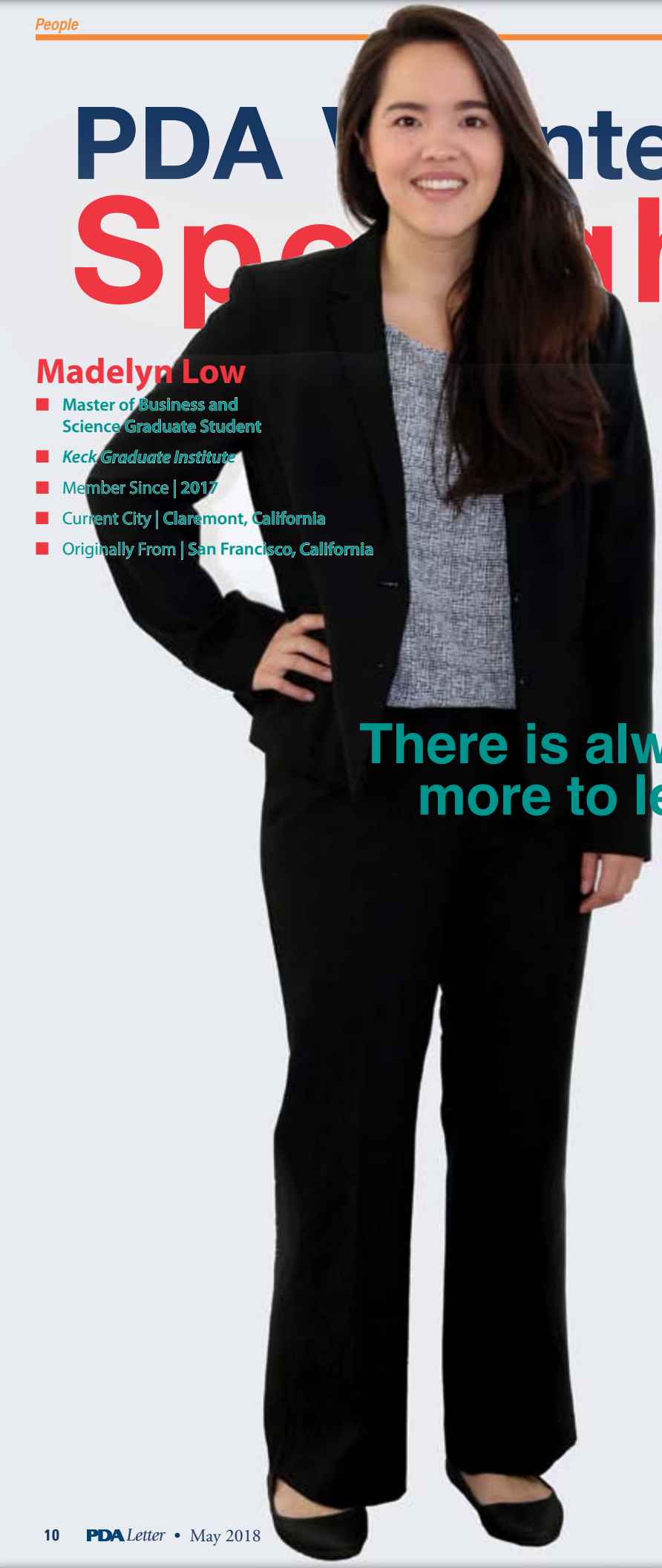
Richard Levy

Tina Morris

Richard Levy, PhD, PDA's outgoing Senior Vice President of Scientific and Regulatory Affairs, announced his retirement earlier this year after 13 years in the role. Among his many accomplishments in the role, Levy oversaw a marked increase in the number of technical documents published annually, the conversion of the *PDA Journal of Pharmaceutical Science and Technology* from a print to an online-only publication, and the growth in the number of staff in the Scientific and Regulatory Affairs department to better support the efforts of member volunteers. He will take on the role of Editor of the *PDA Journal of Pharmaceutical Science and Technology* on May 21.

"Dr. Levy's many contributions to PDA, both as a volunteer for many years and as part of the staff since 2005, are numerous," said Johnson. "He was most instrumental in ramping our technical activities to a level higher than any time in our history. We look forward to working with Dr. Levy as the editor of the Journal for many years to come."

PDA Volunteer Spotlight



Madelyn Low

- Master of Business and Science Graduate Student
- *Keck Graduate Institute*
- Member Since | 2017
- Current City | Claremont, California
- Originally From | San Francisco, California

There is always more to learn

What is your main volunteer role for PDA?
I am the President of the PDA Southern California Student Chapter at Keck Graduate Institute, where I am focusing my master's degree on clinical and regulatory affairs. PDA bridges the gap between my education and industry experience by connecting me to professionals with a wide array of experience. PDA helps supplement my education with industry-specific training, information and resources.

Leading the student chapter puts me in a unique position to create professional development opportunities for students and young professionals.

Which PDA activity have you enjoyed the most?
Through our organized facility tours at local biopharmaceutical companies, students have had the opportunity to directly experience the manufacturing process for therapies that are improving the lives of patients worldwide. Following the process from raw materials to finished product has given them their first taste of how these medicines are made.

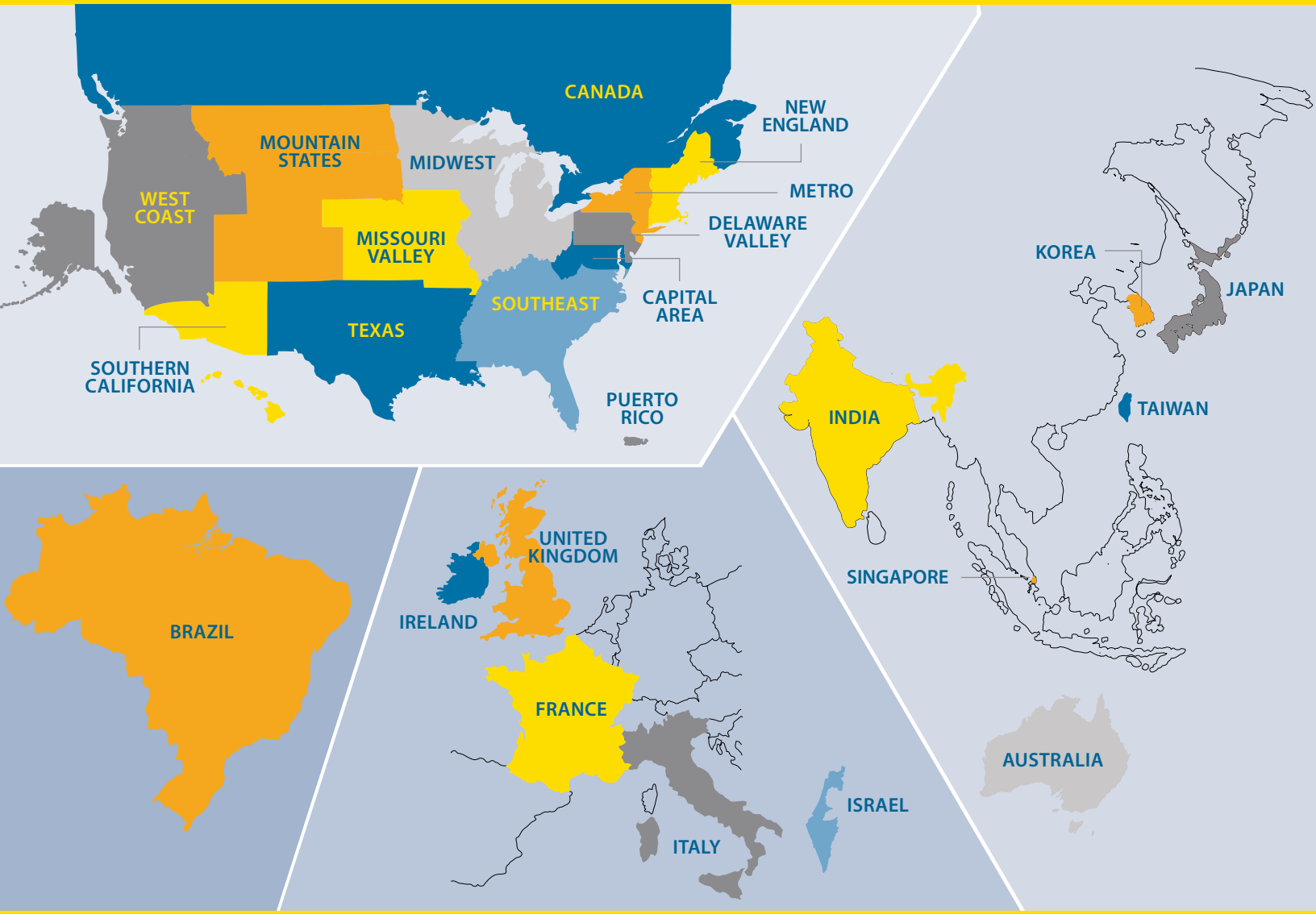
What lessons has your work life taught you?
Prior to attending graduate school, I worked at a small biotech company in Santa Cruz, Calif., which instilled in me the value of resourcefulness and networking. Excellent communication and collaboration can enhance your career. There is always more to learn; surrounding yourself with talented professionals is the best way to continue to improve your skills and technical expertise.

What do you do in your free time?
As a full-time graduate student and active volunteer with PDA, I am currently working toward having free time! Still, I enjoy maintaining close relationships with my family and friends, exploring new places and pursuing creative activities.

Tell us something surprising about you.
In the summer of 2015, I went on a ten-day trek on horseback in the foothills of the tallest mountains in Mongolia within the Altai Tavan Bogd National Park.

PDA Chapters

Your Local PDA Connection



Are you curious about the issues unique to your region?

Another layer of PDA leadership resides at the grassroots level in the Chapter organizations. Regional PDA Chapters provide local services to the membership, including translations of PDA publications, networking social events, student scholarship and annual regulatory and technical conferences. Each Chapter is managed by volunteer leaders.

Learn more about your local Chapter at www.pda.org/Chapters.

Amgen Team Brings Expertise to Taiwan Chapter

Yi-Yin Lu, Secretary General of PDA Taiwan Chapter

The importance of quality culture has been increasingly recognized across the industry as it has a strong influence on product quality. In fact, regulators have been paying more attention to it recently due to an uptick in data integrity issues observed within the industry. In addition to quality culture, knowledge management is crucial. ICH Q10: *Pharmaceutical Quality System* identifies knowledge management as one of the enablers to implementing an effective pharmaceutical quality system.

(l-r) Ivy Chen; Jung-Jung Hsia; Chi-Wen Hsieh; Mark DiMartino; Dan Weese; Cylia Chen-Ooi; Brian McBreen; John Lin

To provide more depth on quality culture and knowledge management, PDA's Taiwan Chapter invited a team of representatives from Amgen to give a one-day workshop on March 8 to 58 attendees. The Amgen speakers included **Cylia Chen-Ooi, Dan Weese, Brian McBreen** and **Mark DiMartino**. **Ivy Chen** served as the facilitator for the training sessions in the workshop. four addressed recent advances in quality culture and knowledge management, including techniques for storing knowledge, ways other companies are disseminating knowledge and some ideas for analyzing stored knowledge. The content of the workshop included lectures, surveys and interactive group exercises. Chen-Ooi also presented on behalf of PDA's quality culture team.

Participants split into small groups for an exercise

The following day, the four speakers delivered the same content to 51 inspectors from the Taiwan FDA. This was the first workshop focused on quality culture and knowledge management in Taiwan. Both groups of attendees developed a greater understanding of the importance of quality culture and knowledge management from this workshop, as well as gaining some useful tools. One individual from a Taiwanese pharma company commented, "When I signed up for the seminar, I thought I would not understand too much, but I left here with an overall understanding of knowledge management."

A Taiwan FDA inspector also said, "This seminar changed our mindset on quality culture. Our staff is already discussing how to use what they learned today in their daily jobs."

The chapter thanks the speakers for sharing their impressive expertise.

PDA Who's Who

Cylia Chen-Ooi, Senior Manager, External Affairs Quality, Amgen

Ivy Chen, Senior Manager, QA, International Quality, Taiwan

Mark DiMartino, Director, Quality Data Science, Amgen

Jung-Jung Hsia, Technical Specialist, Taiwan FDA

Chi-Wen Hsieh, Section Chief, Taiwan FDA

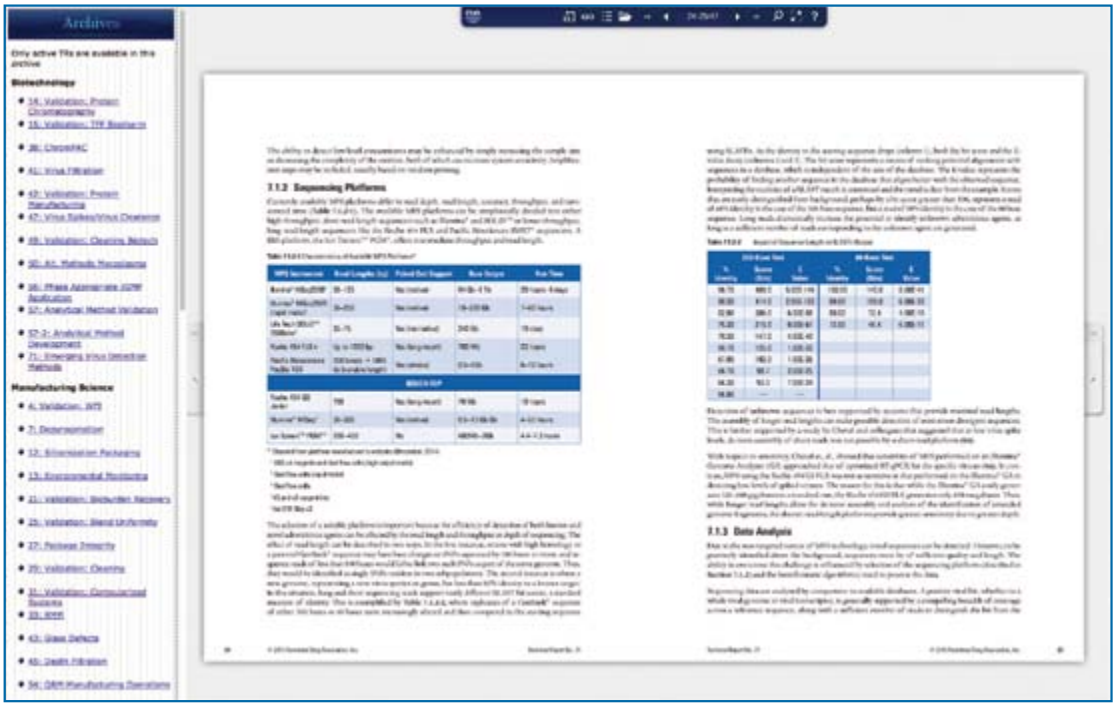
John Lin, GMP consultant, PDA Taiwan

Yi-Yin Lu, Secretary General, PDA Taiwan Chapter

Brian McBreen, Director of Knowledge Management, Amgen

Dan Weese, Executive Director, Quality Data Science, Amgen

PDA's Technical Report Portal



View the complete library of current PDA Technical Reports anywhere, anytime

For more information and to view PDA's Technical Report Portal please visit:

trarchive.pda.org/t/26426

Licensing options available; contact Janny Chua at chua@pda.org

Make New Buddies in Berlin

3rd PDA Europe Annual Meeting

In addition to the interesting sessions featuring global experts within the industry, there will be opportunities to network and make lasting connections at the *3rd PDA Europe Annual Meeting* in Berlin.

Networking Reception
June 26, 6 p.m.

Celebrate the end of the first day of the meeting by enjoying drinks and refreshments with your colleagues, both existing friends and new connections.

Farewell Coffee
June 27, 4:30 p.m.

Following the closing remarks, stick around to close out the meeting with a farewell coffee. After two days of invigorating sessions, you will probably want to discuss what you learned.

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

Post pictures and highlights from the *3rd PDA Europe Annual Meeting* on Twitter! #pdaeuannual

Are You a Young Professional?

Come see "Young Professionals in PDA," Wednesday, June 27 at 11:15 a.m. This session will feature a variety of presentations from industry professionals and entrepreneurs. PDA Chair-Elect **Jette Christensen,** Novo Nordisk, will moderate the session.

If you are interested in participating, contact programs-europe@pda.org.

Connect with Key Decision Makers in Container Closure Design and Testing

The *2018 PDA Container Closure Performance and Integrity Conference* offers many opportunities to engage with experts in the field of container closure design, performance, and testing. Gain valuable visibility and position your products and services in front of this ideal audience by exhibiting at or sponsoring this exciting Conference!

High-impact, cost effective sponsorship and exhibition packages are available for:

- Lanyards
- Tote Bags
- Notepads
- The Networking Reception
- Pens
- Refreshment Breaks
- Networking Luncheon
- and More!

Don't pass up this opportunity to increase your company's visibility, acquire new leads, and showcase your company's new products and services!

Ready to start customizing a package that best fits your business needs?

Contact **David Hall**, Vice President, Sales, *PDA*, at hall@pda.org or +1 (240) 688-4405.

PDA Parenteral Drug Association

June 13-14, 2018 | Bethesda, MD
Exhibition: June 13-14
#PDACCPI

CONNECTING PEOPLE SCIENCE AND REGULATION®

Course Addresses Test Methods for Prefilled Syringes

The prefilled syringe market has grown considerably over the past decade. A number of innovative prefilled syringe products are now available to patients. But, like any other parenteral container, these products must undergo compliance testing. **Horst Koller,** CEO, HK Packaging Consulting, and **Roman Mathaes,** PhD, Senior Group Leader, Lonza Drug Product Services, will present the course, "Test Methods for Pre-filled Syringe Systems," that follows the *3rd PDA Europe Annual Meeting*.

The *PDA Letter* reached out to Koller who provided an overview of the course.

What test methods will the course cover?

The course looks at the combination of a syringe cartridge with a delivery device. The system functionality needs to be proven over the complete shelf life of the combined system. We will also cover the safety systems around prefilled syringe systems.

What regulatory requirements will be addressed?

We will address the regulatory requirements for three types of products:

- empty prefilled syringes ready for filling
- final filled product
- combination products, such as autoinjectors

If I have some years of experience, what can I get out of the course?

It provides a good overview of the complete lifecycle of a prefilled syringe in general. From the basic idea of a syringe as a primary container to the functional, biological and regulatory performance of a prefilled syringe, including functions for delivery devices. This can be very complex. This is a chance for someone who works solely in manufacturing to understand the development of a prefilled syringe and vice versa.

What materials will the course cover?

It will cover glass and polymer containers.

How will the course be structured?

We will give an introduction and then go from there. Interaction between the attendees and instructors is very important for this course. In fact, we plan for it to be an interactive session for the complete two days. Students are welcome to ask questions as we work through the various topics.

About the Expert

Prior to becoming a consultant, **Horst Koller** worked for Abbott Diagnostic and SCHOTT Pharmaceutical Packaging with a total of more than 20 years of industry experience. His consulting company focuses on technical, regulatory and quality metrics support around primary and secondary packaging systems, including medical devices.

Horst Koller

Test Methods for Pre-filled Syringe Systems

Berlin
June 28–29
www.pda.org/EU/Annual2018

2018 PDA Container Closure Performance and Integrity Conference

Assuring Packaging Quality in Delivery Systems




At the *2018 PDA Container Closure Performance and Integrity Conference*, attendees will exchange ideas with industry peers and regulatory experts and learn how to meet the packaging demands of new medicines, novel delivery devices, and evolving regulations!

Explore the most current information and best practices related to containment, container closure integrity, and drug delivery system performance evaluations, including:

- Protecting the drug product across the product lifecycle
- Considering container design features to enhance functionality and usability
- Applying standard and novel container closure integrity testing technologies
- Investigating drug product intrinsic interactions with delivery and device systems
- Developing strategies for ensuring delivery and device systems performance and integrity
- Understanding novel drug product container filling/sealing processes

To learn more and register, please visit pda.org/2018CCPI

PDA® Parenteral Drug Association

June 13-14, 2018 | Bethesda, MD
Exhibition: June 13-14
#PDACCPI

CONNECTING PEOPLE SCIENCE AND REGULATION®

SNAPShot

3rd PDA Europe Annual Meeting

Freeze-Drying IG to Meet before Annual Meeting

Interested in learning about the latest developments in lyophilization? PDA's Freeze-Drying Interest Group will convene one day before the *3rd PDA Europe Annual Meeting,* June 25, in Berlin. This all-day interest group meeting will explore the technical evolution of cooling equipment and state-of-the-art validation for freeze-dried products. To register, visit: www.pda.org/EU/IGFreezeDrying2018.

You do not need to be a member of the interest group to attend this meeting.

Journal TOC

The Latest Sterile Filtration Research Available in the May/June PDA Journal

Interested in the latest research on filtration? The May/June issue of the *PDA Journal of Pharmaceutical Science and Technology* features three research articles on filtration-related topics. Read more at journal.pda.org.

Editorial

Govind Rao

Research

Thomas Loewe, et al., "Benchmarking of Sterilizing-Grade Filter Membranes with Liposome Filtration"

Eric Vozzola, et al., "Life Cycle Assessment of Reusable and Disposable Cleanroom Coveralls"

Steven Novick, Perceval Sondag, Tim Schofield and Kenneth Mille, "A Novel Method for Qualification of a Potency Assay through Partial Computer Simulation"

Alexander Helling, et al., "Retention of Acholeplasma laidlawii by Sterile Filtration Membranes: Effect of Cultivation Medium and Filtration Temperature"

Stefanie Funke, et al., "Methods To Determine the Silicone Oil Layer Thickness in Sprayed-On Siliconized Syringes"

Roberto Menzel, et al., "Comparative Extractables Study of Autoclavable Polyethersulfone Filter Cartridges for Sterile Filtration"

Technology/Application

Cleyton Lage Andrade, et al., "A Model of Risk Analysis in Analytical Methodology for Biopharmaceutical Quality Control"

PDA Paper

Deborah Autor, et al., "PDA Points to Consider: Best Practices for Document/Data Management and Control and Preparing for Data Integrity Inspections"

Emma Ramnarine, Kevin O'Donnell, "Demonstrating PQS Effectiveness and Driving Continual Improvement: How to Get There Through Evidence-Based Risk Reduction: Part 1 – Conceptual Thinking"

2017 Universe of Pre-filled Syringes and Injection Devices

Novel Manufacturing Tech Drives Novel Products

Rebecca Stauffer, PDA

"Consumer electronics and pharma move at different speeds," according to **Simon Wilson,** Device Development Lead, Pfizer, during opening plenary talks at the *2017 PDA Universe of Pre-filled Syringes and Injection Devices* in Vienna. He was referring to the perception that drug products and devices lag behind technological innovations, such as smartphones. One could argue that this observation also applies to the manufacturing processes and equipment used to produce today's prefilled injection products.

Anyone walking through the Exhibit Hall at this meeting could clearly see that innovative drug delivery devices have already been developed or are currently under development. Insulin pods. Needleless injections. Smart injection devices. But creating such novel products requires advancements in the industry's manufacturing processes and equipment.

Aptly, the breakout sessions in the Manufacturing and Technology Track signaled that manufacturers are aware of the need to upgrade and modernize current processes. In fact, these sessions suggested that the day when consumer electronics and pharma move at the same speed may not be too far off.

Day 1: Dreaming of Flexibility

Many of the new formulations entering the market are being produced in small batches. This necessitates flexible manufacturing lines. **J. Martin Bultmann,** Associate Director, Process Engineering Sciences NBE, AbbVie, looked at how, based on his firm's experience, robotics can assist with small-scale filling. **[Editor's Note:** For more on Bultmann's experience implementing robotic manufacturing, read the October 2017 cover story**.]**

In 2011, AbbVie had two lines: one for vials and one for syringes. Filling on the vial line occurred within an isolator, while filling on the syringe line took place in a restricted access barrier system (RABS). While both lines performed well, there were limitations. Lengthy times were needed for product changeover and the company was considering changing to a newer packaging material that neither of these machines could handle. In addition, specific nesting configurations for tubs and cleaning validation were required.

The two lines were acceptable for large batches but his company was moving to a different model that required a new form of manufacturing technology.

"The needs of the new machine were that we wanted to go more in the direction of low batch volumes and smaller batches," Bultmann said.

His team decided to build a prototype filling line that relied on robotics that could easily scale from clinical to production. It would be flexible for product changeovers and able to introduce new packaging materials as well as capable of both liquid fill and lyophilization.

"We said we wanted to have a flexible line," he explained. "'Flexible line' for us meant that we would like to have a variable workflow. But what is a flexible workflow in the end? For us, it was a fast changeover suitable for all the unknown packaging material, not [only] those we can already buy off the shelf."

At the same time, his company also knew what it did not want: off-the-shelf components, complicated format parts and new formats that necessitated hard coding, as these would lead to long lead times.

Ultimately, AbbVie chose an automated filling line using two robotic arms. The machine receives nested tubs from one end; then, the first arm draws one unit at a time, places it on the weighing and filling station, and moves it over to stoppering and capping. The second arm then places it back in the nested tub.

The line was installed in early 2017. Though currently not optimized for changeover, it is planned for the future.

In conclusion, Bultmann referred to a sign he saw at Walt Disney World: "If you can dream it, you can make it."

"We were dreaming of that machine, we made it," he said, "and we succeeded."

The filling line Bultmann discussed was designed for small batches, which the next speaker, **Susanne Lemaine,** President, Vetter Development Services USA, also addressed—specifically aseptic filling of prefilled syringes for clinical trials. She pointed to the trend toward prefilled syringes, both current and in the future. The advantages of prefilled syringes for clinical trials include product differentiation during the trial period due to ease of use, less waste of valuable API and patient/clinician safety. Many of Vetter's clients begin developing a product in a vial but switch to a prefilled syringe for Phase II and Phase III; although, a handful are using prefilled syringes even in the preclinical stages.

Lemaine presented a case study involving a Vetter client. This company started the clinical trial process using a vial but then switched to a prefilled syringe. The trial required Vetter to establish a compounding and aseptic filling process for global supply. Some of the challenges in aseptic processing include shear stress during mixing and pumping, filling accuracy, breakloose and glide forces, and compatibility with primary packaging and process materials. The milestones for this case study were primary packaging material selection, lab studies, a tech run, formal stability, clinical fills and process validation. By following these steps, Vetter's client was able to launch in a prefilled syringe.

Day 2: Manufacturing "Smartly"

Markus Bauss, Managing Director, SHL ConnectMeSmart, and *Egmont Semmler,* PhD, Director, R&D Pharmaceutical Fill and Finish, Groninger, offered a joint presentation exploring how smart objects and intelligent machinery could change current manufacturing best practices. Bauss provided some background on the concept of Industry 4.0, also known as the industrial Internet of Things, which he described as embedded system production technologies connected to smart production processes.

"Now we are at the stage where we talk about the fourth industrial revolution, which is about cyber-physical systems. So, really, making use of the Internet...for connected technology, of products that really [interface] with machines and doing the entire lifecycle," Bauss explained. Data plays a very important role in making Industry 4.0 happen.

Semmler showed how so-called "smart machinery" will drive Industry 4.0 in pharma. Many recalls involve drug delivery devices; thus, defining critical parameters for functionality during the product lifecycle is very important. This is where gathering data from the very beginning helps, starting with information from the packaging and component supplier(s). Data is collected throughout the manufacturing process, as well, from fill/finish to distribution and even to administration to the patient.

He also discussed "object awareness" in the next generation of production equipment. As the machinery collects data throughout the lifecycle, machines can adjust based on the type of products inserted and even make adjustments for products entering different markets with specific regulatory requirements. These improvements reduce human interventions and enhance safety. And because the data is collected throughout, root cause analysis becomes easier.

The closing plenary offered another take on the future of syringe and device manufacturing. **Jerry Cacia,** Head of Biologics Drug Product Manufacturing, Roche Pharma, spoke from the perspective of a biologics manufacturer. More and more biologics are being manufactured in combination products. This lengthens production time and the supply chain, adding to the expense of an already costly product. Reducing time to launch is critical.

The solutions include close collaboration between design and manufacturing as well as leveraging platform technologies and strategic partners.

Like many other presenters, Cacia pointed to smaller batch sizes as another force driving flexible manufacturing. This has already resulted in changes within manufacturing, including modular filling lines, which he characterized as a "real phenomenon within the industry."

But whatever the manufacturing technology, quality will remain key.

"Developing medicines is a time-consuming and expensive endeavor..." Cacia concluded, "so, for that reason, optimizing the quality of our work is really important,"

*Published online first
letter.pda.org

Glass Versus Cyclic Olefin Polymers

Container Closure Integrity in Cryogenic Storage Environments

James McCaw, West Pharmaceutical Services, Inc.

Many biologic drugs require low-temperature storage under certain conditions, all the way down to the cryogenic range (-180 °C). Such low temperatures can be problematic for glass vials. If the glass vial for a biologic drug experiences breakage, or does not maintain container closure integrity, a cyclic olefin polymer (COP) system may be the solution. COP has several features that make it suitable for drug packaging. It is transparent and fracture-resistant, offers resistance to oxygen and water and has the ability to maintain container closure integrity at low temperature.

Glass has been used to store and deliver drugs for years; however, it presents several issues:

- *Glass is intrinsically brittle.* At low temperatures, it is even more brittle and agitation from shipping/handling increases the likelihood of fracture.

- *Glass is not inert.* It can negatively interact with a biologic drug product. Leachables from glass pose the same risk. Delamination—the presence of glass flakes in a drug product, causing detachment from the glass surface—is another issue ***(1).*** Since 2010, delamination has caused many product recalls and FDA has issued an advisory on its website ***(2).***

- *Glass poses a risk of loss of container closure integrity.* At cryogenic temperatures, glass and rubber are fundamentally incompatible, resulting in the high likelihood of a container closure integrity failure of a vial/stopper system ***(3).*** The substantially different coefficients of thermal expansion—rubber shrinks much more than glass—results in gap formation. In contrast, rubber and COP shrink at comparable rates, substantially reducing the risk of gap formation that results in loss of container closure integrity.

So, how do COP vials compare with traditional glass cryogenic temperatures? A recent study looked at how glass and COP vials respond to cryogenic temperatures. Two different vial/stopper systems (one consisting of 2 mL glass and another comprised of COP with 13 mm rubber serum) were filled with air and placed in a liquid nitrogen chamber (approx. -165 °C) for eight days. With frequency-modulated spectroscopy, the O_2 concentration in the vials was measured. **Table 1** shows the results of this study.

The COP vial showed only a very slight change in O_2 concentration. In contrast, the glass system showed a substantial change consistent with a leak resulting from the rubber stopper pulling away from the glass vial.

In summary, a system comprising a COP vial and a rubber stopper can be a choice for storing biologic drugs. In addition to the many benefits of COP, the system enables optimal container closure integrity at cryogenic temperatures, whereas a system using a glass vial may not.

Image of Daikyo Crystal Zenith® vial courtesy of West Pharmaceutical Services, Inc.

References

1. "The Causes and Implications of Glass Delamination." *Pharmaceutical Technology* 6 (2011) supplement. tinyurl.com/y755znlk (Accessed April 24, 2018)

2. "Advisory to Drug Manufacturers: Formation of Glass Lamellae in Certain Injectable Drugs." *U.S. FDA.* March 25, 2011 tinyurl.com/y9w-fon7l (Accessed April 24, 2018)

3. Coefficients of Linear Thermal Expansion. *Engineering ToolBox* (2003) tinyurl.com/ycsz9esm (Accessed April 24, 2018)

About the Author

James McCaw is the supervisor of the Container Closure Integrity group, West Analytical Services.

Table 1 Comparison of COP and Glass Vials at Cryogenic Temperatures

Vial Type	O_2 Concentration (%)	
	T = 0 days	T = 8 days
COP	20.1	19.4
Glass	20.4	8.0

RMAT Program Raises a Few Questions

Austin Caudle, IQVIA

Gene and cell therapies hold the potential to transform medicine and create a seismic shift in our ability to treat, and possibly cure, many diseases once considered untreatable. Exciting improvements have been observed in recent years. But this requires updating the regulatory structure as existing rules have not been designed for these kinds of therapies. To expedite the development and review of these innovative products, the 21st Century Cures Act includes the regenerative medicine advanced therapy (RMAT) designation. Prior to adding RMAT, only four possible designations existed: Fast Track, Breakthrough Therapy, Priority Review and Accelerated Approval ***(1).***

In November 2017, the U.S. FDA issued a draft guidance document to describe the expedited programs available to sponsors of regenerative medicine therapies for serious conditions, including products designated as RMATs. According to the guidance, "regenerative medicine therapies to treat, modify, reverse, or cure serious conditions are eligible for FDA's expedited programs, including Fast Track designation, Breakthrough Therapy designation, RMAT designation, Priority Review designation, and Accelerated Approval, if they meet the criteria for such programs" ***(2).*** To qualify for this designation, a product must be **1)** defined as a cell therapy, therapeutic tissue engineering product, human cell and tissue product, or a combination product using such therapies or products; **2)** intended to treat, modify, reverse or cure a serious or life-threatening disease or condition; and **3)** preliminary clinical evidence must indicate the product has the potential to address unmet medical needs for such a disease or condition.

RMAT designation as a mechanism to expedite regenerative therapies to market is a key advantage, since this new designation requires less evidence than other expedited programs to indicate whether a therapy shows significant improvement over existing therapies. RMAT is significant as it signals to industry and patients that there will be a defined pathway for a new product where one previously did not exist. The designation also enables a company to meet with FDA early in the clinical trial process, and facilitates use of Real World Evidence (RWE) such as Electronic Health Records (EHRs). RWE can be a valuable tool at times when recruitment for a large clinical trial is nearly impossible but evidence shows that a particular molecule might have an impact on a rare disease.

Despite the criteria for a therapy to qualify for RMAT, questions have since been raised regarding the requisite level of evidence needed to obtain RMAT versus other designations ***(3).*** For example, how does FDA distinguish between the level of evidence required to determine if a therapy can be designated as a RMAT?

Regulations impacting the development and commercialization of

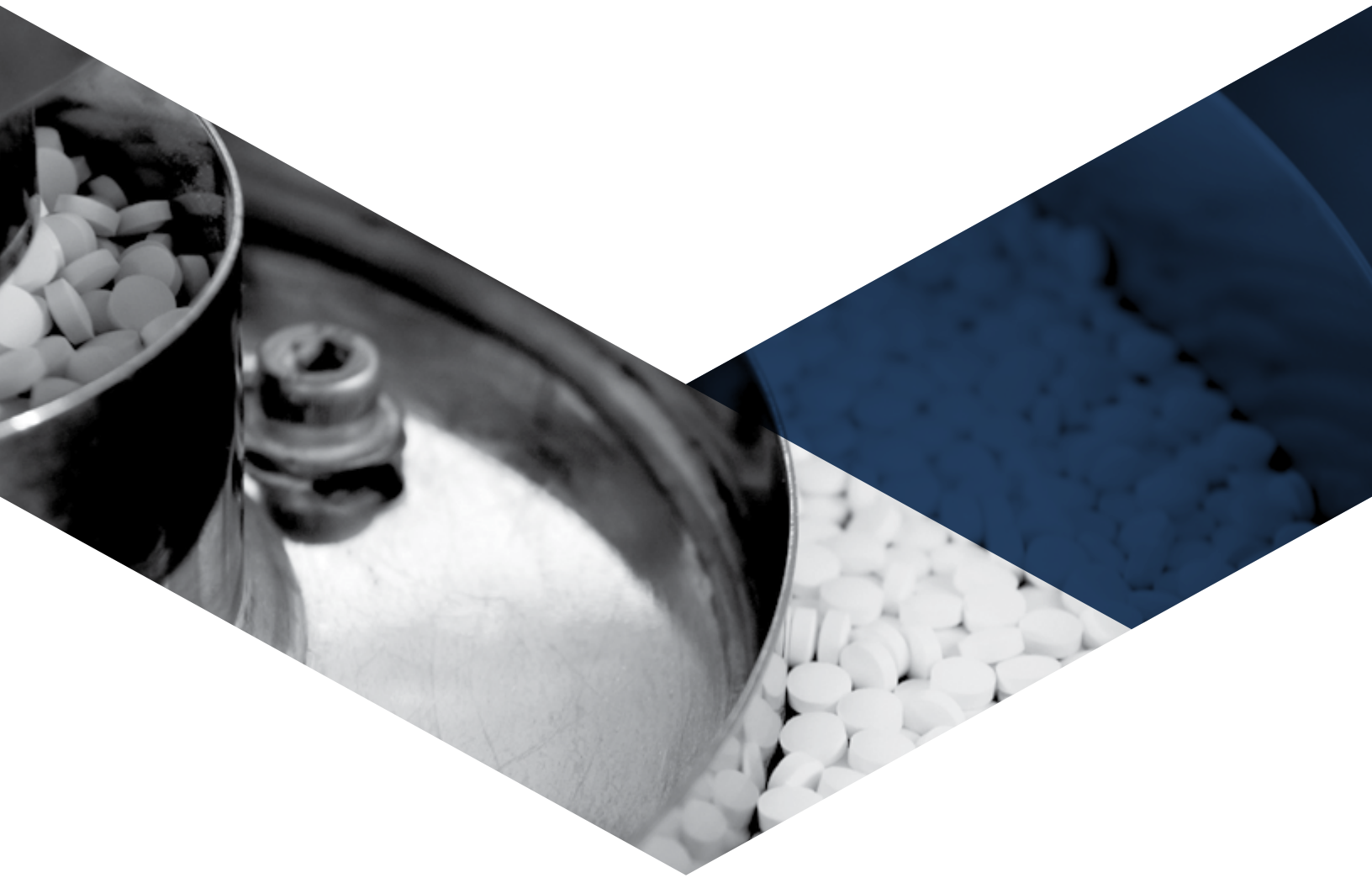
Continued at bottom of page 30

PDA Parenteral Drug Association

PDA Publishing presents

Contamination Prevention For Nonsterile Pharmaceutical Manufacturing

Andrew Dick, Johnson & Johnson



For more information on all PDA publications please visit:

store.pda.org

2018 PDA Upcoming Events

SAVE THE DATE for PDA's 2018 Events

MAY

17
Annex 1 Workshop
Dublin, Ireland
pda.org/EU/Annex2018

21-24
SOLD OUT
■ **Fundamentals of Aseptic Processing – Option 2**
Bethesda, MD
pda.org/2018MayFundAP

21-25
PDA Lyophilization Course Series
Bethesda, MD
pda.org/2018Lyo

29-30
Pharmacopoeia Conference
Vienna, Austria
pda.org/EU/pharma2018

JUNE

5-6
Advanced Therapy Medicinal Products Conference
Amsterdam, The Netherlands
pda.org/EU/ATMPS2018

7
Practical Application of Phase-Appropriate GMP & Quality to Clinical Development of ATMPs
Amsterdam, The Netherlands
pda.org/EU/TCATMPS2018

7-8
NEW COURSE
PDA Quality Culture Transformation
Bethesda, MD
pda.org/2018JunTransform

12-14
NEW COURSE
Quality Risk Management Facilitator Training
Bethesda, MD
pda.org/2018Facilitator

13-14
2018 PDA Container Closure Performance and Integrity Conference
Bethesda, MD
pda.org/2018CCPI

18-21
■ **Fundamentals of Aseptic Processing – Option 3**
Bethesda, MD
pda.org/2018JunFundAP

25
Interest Group Meeting: Freeze Drying
Berlin, Germany
pda.org/EU/IGFreezeDrying2018

25
Interest Group Meeting: Quality Systems
Berlin, Germany
pda.org/EU/IGQualitySystems2018

25-27
PDA Quality Course Series
Bethesda, MD
pda.org/2018QCS

26-27
3rd PDA Europe Annual Meeting
Berlin, Germany
pda.org/EU/Annual2018

26-27
■ **Isolator Technology**
Bethesda, MD
pda.org/2018JunIT

28-29
Practical Approach to Quality Culture
Berlin, Germany
pda.org/EU/quality-culture2018

28-29
Best Compliance Practices at the GMP Testing Laboratory
Berlin, Germany
pda.org/EU/Compliance2018

28-29
Test Methods for Pre-Filled Syringe Systems
Berlin, Germany
pda.org/EU/TestPFS

29
Passive Thermal Protection Systems for Global Distribution: Qualification and Operational Guidance
Bethesda, MD
pda.org/2018Thermal

JULY

3-4
Temperature Controlled Distribution: An Interactive Walk Through
Voorhout, The Netherlands
pda.org/eu/TCD2018

9-12
Quality Risk Management Certificate Program
Bethesda, MD
pda.org/2018QRM

■ 23-27
PDA Aseptic Processing – Option 4
Week 2: Aug. 13-17
Bethesda, MD
pda.org/2018Aseptic4

30-1
■ **PDA Environmental Monitoring Course Series**
Bethesda, MD
pda.org/2018JulEMCS

31-1
■ **2018 Mold Identification for Quality Control**
Bethesda, MD
pda.org/2018Mold

Denotes laboratory courses taught in Europe. | ■ This course is taught in PDA's U.S. manufacturing training facility.

PDA Parenteral Drug Association

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

AUGUST

2

NEW COURSE

Addressing Biofilm and Other Non-Routine Microbial Events
Bethesda, MD
pda.org/2018Biofilm

20-23
PDA Biotechnology Course Series
Bethesda, MD
pda.org/2018Biotech

20-24
■ **PDA Cleaning Course Series**
Bethesda, MD
pda.org/2018CCS

SEPTEMBER

4-5
Mastering Environmental Monitoring
Wattwill, Switzerland
pda.org/EU/EM2018

10-14
■ **PDA Visual Inspection Course Series – Option 2**
Bethesda, MD
pda.org/2018SeptVI

12-13
Best Practices for Glass Primary Containers
Mainz, Germany
pda.org/EU/GPC2018

17-21
■ **PDA Aseptic Processing – Option 5 Week 2: Oct. 15-19**
Bethesda, MD
pda.org/2018Aseptic5

18-19
All About Virus Filtration – A Practical Approach
Cologne, Germany
pda.org/EU/VirusFiltration2018

24-26
2018 PDA/FDA Joint Regulatory Conference
Washington, DC
pda.org/2018pdafda

26-27
2018 PDA Biosimilars Workshop
Washington, DC
pda.org/2018Biosimilars

26-28
■ **Recommended Practices for Manual Aseptic Processes**
Bethesda, MD
pda.org/2018RPAP

27-28
PDA Regulatory Conference Course Series
Washington, DC
pda.org/2018RegCourses

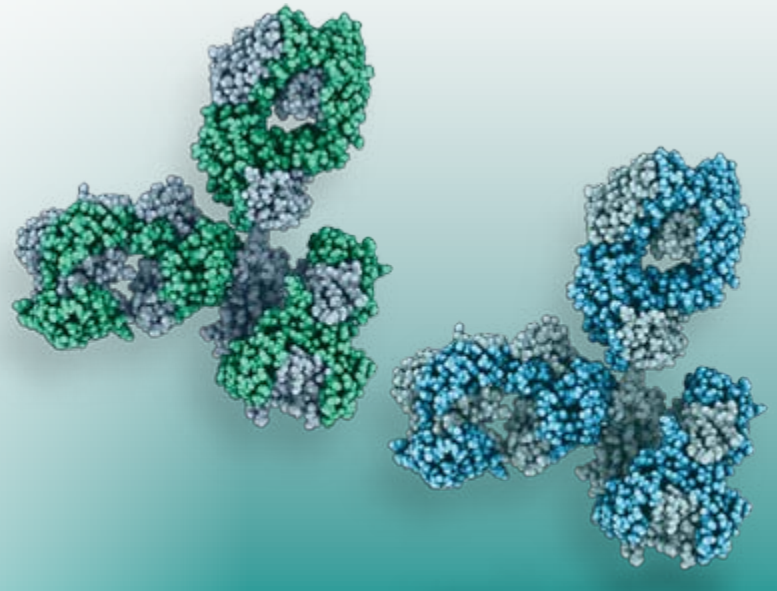
27-28
PDA Quality Culture Transformation Program
Washington, DC
pda.org/2018SeptTransform

Stay engaged, informed and ahead of the complex challenges of the bio/pharmaceutical manufacturing world by following PDA on:

Twitter at **@PDAOnline**

LinkedIn at
LinkedIn.com/company/PDA

PDA Connect℠
community.pda.org
PDA's members-only online discussion forum



3-D Printing and Biopharmaceutical Manufacturing

Lina Genovesi

> **Since each part is built separately, 3-D printing allows more flexibility than standard manufacturing**

Additive manufacturing (AM), which includes the 3-D printing process, may prove to be a game changer for biopharma as 3-D printing becomes widespread.

The AM process covers a range of categories defined by the American Society for Testing and Materials (ASTM) such as VAT photo-polymerization, binder jetting, material jetting, material extrusion, powder bed fusion, sheet lamination and directed energy deposition ***(1).***

3-D printing refers to the various processes used in the manufacture of products by printing layers of material on top of each other following a digital 3-D model. This process is less wasteful than traditional subtractive manufacturing in which material is machined off from a material blank to make the final product.

AM technologies present new opportunities to pharmaceutical companies. Several printing technologies can be used in applications such as laser sintering and stereo lithography for devices, binder jetting for excipients and drugs and laser transfer for biologics. In addition, AM processes are applicable to medical devices such as implants, guides, imaging, controlled-release drugs along with biologics such as the cell and tissue structures, combination products and research and regulatory tools.

"3-D printing technology has a lot of potential and we will continue to explore new manufacturing strategies and opportunities where additive manufacturing can bring technical improvements to our supply chain and products," says **Susan Burke,** Senior Manager, Applications, Bioprocess R&D Life Sciences at GE Healthcare.

Still, it remains to be seen whether pharmaceutical companies will take advantage of these new opportunities to the point where AM technologies are fully incorporated into mainstream biopharmaceutical manufacturing processes.

Applications of 3-D Printing

Several companies are involved in research and development around 3-D printing to speed up the launch of new innovative products for the healthcare industry.

"AM is a very important area for GE Healthcare," explains Burke. "We work closely with two centers—the GE Healthcare Additive Manufacturing and Engineering Center in Waukesha, Wisconsin, and the Innovative Design and Advanced Manufacturing Technology Center for Europe in Uppsala, Sweden, which we opened last fall. The teams at the Uppsala center collaborate with the teams at the Waukesha center, sharing knowledge and working on new design ideas to look at opportunities where additive manufacturing can bring supply chain and technical improvements."

Per Burke, one key aspect of 3-D printing is that it can be used for fast prototyping and product customization. A prototype can be designed, printed and tested on the system in a short time. The process is iterative and several parts of the system can be prototyped and tested.

"When looking at the 3-D printing of a device, we consider all aspects, such as device design, software workflow, device build, device post-processing and device final testing," says Burke. "We also have to go through design verification, performance testing, material characterization, and validation, in order to make sure that the device meets the quality requirements.

"One of the advantages of prototype preprinting is that complicated parts can be manufactured with little additional cost," says Burke. "Some pieces that used to be molded separately and then assembled can now be produced as one piece in a single run, even for some precision components. In addition, since each part is built separately, 3-D printing allows more flexibility than standard manufacturing, and modifications or improvements can be made in few steps."

She adds, "Workflow and processes are streamlined and the use of prototypes allows companies to quickly test multiple configurations to determine customer preferences. This reduces the iterative process, which accelerates the product development cycle and results in savings in cost and time."

Article at a Glance

- Additive manufacturing processes, including 3-D printing, offer potential for biopharma
- GE Healthcare runs two additive manufacturing centers
- U.S. FDA is following 3-D printing

What is SPRITAM®?

SPRITAM® is a 3-D-printed orodispersible high dosage form of levetiracetam ((S)-2-(2-oxopyrrolidin-1-yl)butanamide; (-)-(S)-.alpha.-ethyl-2-oxo-1-pyrrolidine acetamide). Layers of the drug are 3-D printed by binding the layers of powder together while excess powder is blown away. This means the pill dissolves faster than other pills in about 15 seconds or less when taken orally.

SPRITAM®, which is available in 250 mg, 500 mg, 750 mg and 1000 mg tablets, is used to treat partial-onset seizures in patients four years of age and older weighing more than 20 kg with epilepsy, myoclonic seizures in patients 12 years of age and older with juvenile myoclonic epilepsy and primary generalized tonic-clonic seizures in patients six years of age and older with idiopathic generalized epilepsy.

Currently, GE Healthcare is manufacturing parts for use in the biopharmaceutical process. Currently, GE Healthcare is working with Amgen to test the performance of a chromatography column used to develop biopharmaceuticals. "The 3-D printed column has been custom-designed," says Burke. "It is now being tested to see if it can be used in Amgen's research to help develop improved processes for the purification stage of biopharmaceutical production."

Several elements are considered when manufacturing parts for 3-D printing for biopharmaceutical applications. "If a part manufactured with 3-D printing comes within product contact during a biopharmaceutical process, we need to take into account its biocompatibility with cells and proteins," says Burke. "Under different process conditions or steps, the printed part may behave differently. Overall, we need to ensure that the process used does not adversely affect biocompatibility.

"3-D printing technology has a lot of potential and we will continue to explore new manufacturing strategies and opportunities where additive manufacturing can bring technical improvements to our supply chain and products," concludes Burke.

""AM is another area for GlaxoSmithKline to watch closely across several application areas," says **Martin Wallace,** Director of Technology Seeking at GlaxoSmithKline. "We have been investigating the advantages of 3-D printing to the development and manufacture of pharmaceuticals to decide on which areas we should be focusing.

"We have collaborated with leading universities to explore the potential of AM as an alternative platform either to simplify development and/or optimize manufacturing."

According to Wallace, AM is not intended to replace current pharmaceutical production methods. For example, 3-D printing may initially focus on clinical settings where ability to produce many relatively low volume batches quickly can speed up the development of a new product.

This approach leverages the inherent flexibility and agility of 3-D printing while circumnavigating the throughput limitations present in currently available 3DP techniques for pharmaceuticals. One key consideration is that when a tablet is printed, the quality needs to be assessed each time and it must consistently meet cGMP.

"Although 3-D printing does not amount to a volume proposition where you can match current technology in throughput, there is a potential for the technology when one needs to print a formulation and the old technology does not work," says Wallace. "In the case of SPRITAM®, a seizure drug manufactured by Aprecia Pharmaceuticals, 3-D printing was a more suitable technology to use than conventional technology to achieve an almost instantaneous dispersion of the drug, with a very high drug loading.

"3-D printing has its own advantages when it comes to tailoring medicine to patients. In this case, it can provide an on-demand solution which would address very specific patient needs where we can print patient-specific dosage forms. Its benefit could be huge if it is used to develop very personalized medicine and combination therapies. With aging populations and increasing awareness of patient-specific treatment needs, the ability to tailor patient care opens an exciting opportunity to deliver medicine in a better, more convenient way. AM has the potential to indirectly impact the way medicines are produced. For example, additively manufactured custom reactors can improve efficiency, speed, quality and cost of the chemical synthesis step of the process, leading to near term benefits for the pharmaceutical industry."

What Do the Regulators Think?

The U.S. FDA has shown an interest in 3-D printing technology. To promote AM, FDA has engaged in several public and private partnerships. One such public partnership is the National Additive Manufacturing Innovation Institute (NAMII), composed of members from industry, academia and the federal government. NAMII provides infrastructure support for new products created with AM.

3-D printing is a powerful tool

Through its Center for Device and Radiological Health, FDA is involved in 3-D printing research with the goal to understand the printing processes and quality assurance parameters, then evaluate finished products. Specifically, research activities are focused on understanding the material parameters controlling printability, bioburden and biocompatibility of 3-D printed samples, the performance of patient-matching guides, the process parameters for making biodegradable tissue scaffolds and the effect of scaffold geometry on cell differentiation.

Another area FDA has focused on is 3-D printed tissue-simulating phantoms as regulatory tools. This applies to mammographic imaging quality control and tissue-simulating phantom biophotonics.

From a regulatory standpoint, FDA has evaluated and cleared several 3-D printed devices, including patient matched implants, medical devices with orthopedic implants, patient-matched surgical guides and dental implants. And in August 2015, FDA gave its stamp of approval to the first 3-D printed drug, SPRITAM®.

Acknowledging the need to establish a more comprehensive regulatory pathway that can keep pace with technological advances, FDA issued a guidance on the on Dec. 5, 2017, organized into two sections: Design and Manufacturing Process Considerations, which provides technical considerations that should be addressed when fulfilling quality system requirements, and Device Testing Considerations, which describes the information that should be provided in premarketing applications. The guidance provides recommendations for the testing and characterization of devices that include at least one AM component or additively fabricated step.

Of note, not all considerations in the guidance apply to every AM technology, material or device. Furthermore, the guidance does not address regulatory policy for point-of-care/hospital printing, device-specific regulations and direct printing of cells and issues.

Conclusion

3-D printing is a powerful tool and holds ➤

the potential to disrupt the ways in which a product is designed, developed and manufactured. The coming years are expected to bring new opportunities and challenges that will change the pharmaceutical landscape. Pharmaceutical companies with the necessary talent and organizational capabilities will be well positioned to face these challenges and take advantage of these new opportunities.

Reference

1. ISO/ASTM52900-15 Standard Terminology for Additive Manufacturing – General Principles – Terminology.

About the Author

Lina Genovesi writes about pharmaceutical, regulatory, science and business topics. She has many years of experience in clinical research and FDA regulatory approvals, a JD from Temple University and a PhD in Chemical and Biochemical Engineering from Rutgers University.

RMAT Program Raises a Few Questions continued from page 22

cell and gene therapies will be examined and discussed during the *2018 PDA Cell and Gene Therapy Conference*. Mark your calendar and register to share your experiences as industry experts come together for this highly-anticipated event!

References

1. Barlas, S. "The 21st Century Cures Act: FDA Implementation One Year Later, Some Action, Some Results, Some Questions." *Pharmacy and Therapeutics* 43 (2018): 149-151, 179.
2. U.S. Food and Drug Administration. "Draft Guidance for Industry: Evaluation of Devices Used with Regenerative Medicine Advanced Therapies," November 2017. www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM585417.pdf
3. Brennan, Z. "RMAT vs. Breakthrough vs. Fast Track: Companies Seek Clarity on FDA Draft Guidance." *Regulatory Focus* (February 19, 2018).

2018 PDA Cell and Gene Therapies Conference

Bethesda, Md.
Oct. 23–24
www.pda.org/2018cgt

PDA Bookstore New Release

PDA Technical Series: Pharmaceutical Glass

PDA MEMBER PRICE: $150

PDA NON-MEMBER PRICE: $250

DIGITAL: ITEM NO. 48003

The *PDA Technical Series: Pharmaceutical Glass* is a collection of articles previously published in the *PDA Journal of Pharmaceutical Science and Technology*. This compilation organizes 19 articles on glass published between 2007 and 2017 into four categories: Overview, Material Composition, Delamination, and Quality Methods.

A decade ago, the focus on the quality of pharmaceutical glass was sharpened with a series of product recalls due to findings of glass particulates in finished products. The *PDA Technical Series: Pharmaceutical Glass* shows that much work has been done to help understand this issue and other quality issues pertaining to glass.

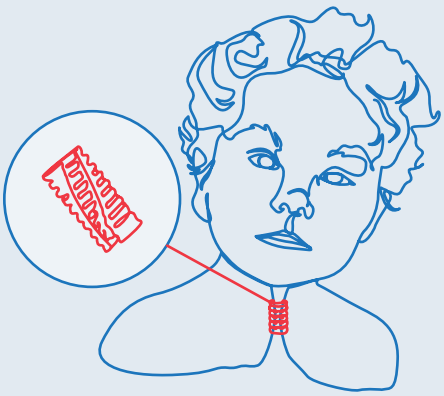
The publication of this book supports a major initiative launched by PDA in 2017 to connect pharmaceutical manufacturers and glass suppliers to prepare for complex products and manufacturing processes of the future.

go.pda.org/Glass

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

3-D Printing Leading Medical Advancements

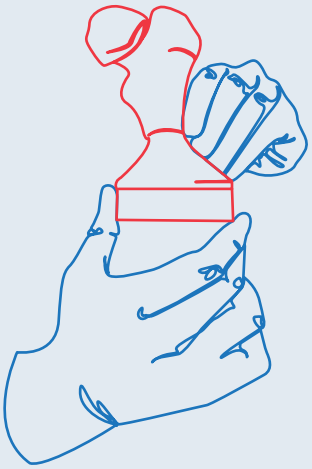
3-D printing offers clear advantages for biopharmaceutical manufacturing. Yet it also has implications for other sectors of healthcare. Below are some of the latest medical advancements involving 3-D printing.



Tracheal Cartilages

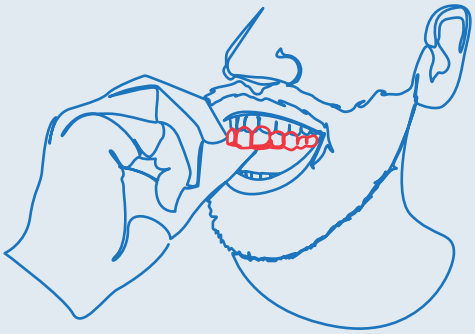
Researchers have used 3-D printing technology to create tracheal cartilage. Already, scientists have 3-D printed splints to support weakened tracheas in infants.

This opens the door to eventual 3-D printing of a trachea, eliminating the need to operate on a vital, complex organ.



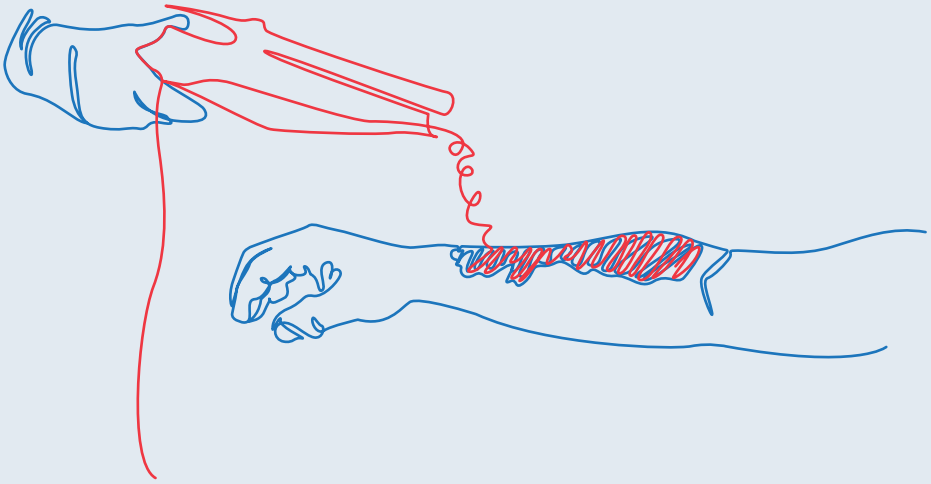
Medical Modeling

3-D printed models allow surgeons to more strategically plan out complicated surgeries. Over time, surgeries will become more efficient.



Bye Bye, Clunky Braces!

A college student 3-D printed his own set of clear braces at the New Jersey Institute of Technology. Orthodontics of the future will be more personalized, ready-to-use and cheaper.



Synthetic Skin

Prototype bioprinters for creating functional skin suggest new possibilities for burn victims. Burn treatments will be less painful with reduced risk of rejection and scarring.

Customized Prosthetics

Want an arm like your favorite superhero? A seven-year-old boy received a 3-D printed, custom "Iron Man" arm, complete with red and gold coloring (minus the superpowers!). On the serious side, 3-D printed prosthetics will be cheaper and more adaptable for growing children.

Make PDA Your Bio/Pharmaceutical Manufacturing Resource

PDA®
Parenteral Drug Association

For more than 70 years, PDA has been providing high-quality, expert manufacturing resources to the industry.

To better serve patients, we must improve manufacturing processes and efficiencies and build quality *into* our products, not by inspecting after.

PDA is committed to helping to advance technological enhancements by identifying achievable improvement and facilitating dialogue with regulators to encourage adoption.

To learn more about how PDA is promoting progress in bio/pharmaceutical manufacturing, visit us at www.pda.org

PDA – *Connecting People, Science and Regulation®*

Strategies for Reducing Data Integrity Challenges

Rebecca Stauffer, PDA

Data integrity. These two words continue to draw considerable interest from regulators around the globe. Considering the nature of data integrity, it can be easy to say, "It sounds so simple. Why is it a problem?"

Fortunately, the concern around data integrity has resulted in discussions that are leading to proposed solutions to this challenge. For an in-depth look, on June 27, **Aidan Harrington,** PhD, Principal Consultant, DPS, will moderate a breakout session on data integrity at the *3rd PDA Europe Annual Meeting* in Berlin, at 11:15 a.m. In this session, **Matthew Paquette,** Product Specialist, Charles River, will look at how to eliminate data integrity failures in manufacturing and laboratory environments, **Christian Scheidl,** Global Head AS&T, QC, OpEx, Solids and Special Technologies, Novartis, will look at how audit trail reviews can be valuable in resolving data integrity issues, and **Danilo Neri,** PhD, Vice President, Operations and Partner, PQE group, will look at how metrics can reduce data integrity risks.

All three speakers believe that data integrity is an obligation of all individuals working within an organization.

"Data integrity is the responsibility of everyone," Scheidl said. "To some degree, the increase in data integrity findings is expected—if we focus on a topic, we will find evidence of the topic."

"The one fundamental barrier to creating and sustaining a successful data integrity program in today's landscape is how an organization investigates the root cause of their data integrity problems and how they manage the process of decision-making and change after the root cause is determined," Paquette said.

"Top management is failing to enforce data integrity requirements within day-to-day routine operations, where data management is in most cases over-complicated through the use of uncontrolled records, like forms and spreadsheets not meeting ALCOA+ requirements," Neri said.

Data Integrity in the Micro Lab

When it comes to common data integrity issues that occur in the microbiology lab, Paquette believes that solving them requires upgrading existing processes, a difficult challenge when dealing with entrenched procedures.

"As an industry, taking a step back and looking critically at our current processes and methods, it is clear that many of these methods are considered antiquated in the face of how our quality management systems and manufacturing processes have evolved over time," he said. "It is imperative that we start to look at ways that we can modernize the laboratory with process improvements to solidify our data integrity compliance.

"The modern microbiology laboratory is a complex system of inputs and outputs that culminate in a decision being made about the quality or suitability of a product based on the data collected. This is just one reason that it's so important for modern laboratories to adopt behaviors and policies that encourage a strong stance on data integrity, as data is the backbone of all the decisions we make as microbiologists."

The key to solving these issues may lie in building an organizational culture that supports data integrity.

"I think a culture surrounding data integrity and product quality should be reinforced throughout all departments, job functions and personnel within an organization because it's the right thing to do for the safety and health of the patients we serve," Paquette said. "Training programs are important in terms of data integrity but we, as an industry, need to ensure that our trainings are effective, and that there is a culture of continuous improvement established where investigating, driving to root cause and using data to justify decision-making is a key priority of the quality organization."

So how can this be achieved? Paquette thinks organizations should extend an invitation to patients to visit manufacturing sites and microbiology labs.

"In my experience, the importance of patient safety is also emphasized by firms with patient visits to the sites that manufacture their medication," he explained. "This experience provides a learning opportunity for the patient and drives home the message for all personnel that data integrity compliance is actually about keeping the medicines we manufacture for our patients safe and effective."

➤

Follow That Audit Trail!

Audit trail reviews are another method for ensuring data integrity.

"The audit trail captures the relevant information on system logins as well as system changes and method changes and performed measurements, including potential changes/adjustments made," said Scheidl.

He used the example of a sample measured for water content titration. If the calculated result is out-of-specification (OOS), someone could theoretically hide the result by measuring another sample that already passed the test earlier under the batch number of the OOS sample. Without records, like logbook entries, it is unlikely this would ever come to light, especially if printouts are destroyed. But an audit trail review would bring to light the fact there had been two measurements for the same batch with only one result.

So how should a company conduct an audit trail review? According to Scheidl, the first step is preparing a risk assessment of the system and determining the critical data to review.

"Most of the audit trails in current software solutions are very comprehensive and it is sometimes quite difficult to find the entries in the audit trails that are really relevant to ensure the integrity of our data." he said. "By looking into every single line of the audit trail, you can spend more time in reviewing the audit trail than in testing of the product. Fortunately, the best practices endorsed by health authorities do not mandate a review of every line item contained in an application or system audit trail."

Scheidl also explained that the audit trail review must be part of the electronic data review for all the information and actions taken for routine measurements. The audit trail is considered metadata. Reviewing this information is another layer of review for results generated in the lab or on the manufacturing floor.

Metrics are another tool for proactively addressing data integrity, according to general principles set forth by the recent U.S. FDA guidance on the reporting of quality metrics and importance of quality culture. Neri believes that data integrity-specific metrics should consist of the following: preventive, corrective and monitoring. Preventive metrics are oriented around rules that forestall data integrity failures while corrective metrics cover completion and outcomes of records compliance. Monitoring metrics encompass supervision of data integrity failures and subsequent follow-up.

The final UK MHRA guidance on GxP, issued in March, provides further clarification, "since this guidance now applies to GxP data relied upon within the entire lifecycle of the pharmaceutical product life, whereas the previous guidance was limited to the GMDP environment."

Further, the guidance specifies that companies are expected "to provide documented evidence of the GxP processes executed through the system and to ensure that the necessary controls for electronic data are in place and that the probability of the occurrence of errors in the data is minimized," he explained.

Continued at bottom of page 41

2018 PDA Europe Conference, Exhibition, Education

3rd PDA Europe Annual Meeting

Global Healthcare of the Present & the Future

25 June	Interest Group Meeting **Freeze Drying**
25 June	Interest Group Meeting **Quality Systems**
28 June	Training Course **Best Compliance Practices at the GMP Testing Laboratory**
28 June	Training Course **Test Methods for Pre-filled Syringe Systems**
28-29 June	Training Course **Practical Approach to Quality Culture**

pda.org/EU/Annual2018

PDA®
Parenteral Drug Association

26-27 June 2018

Marriott Hotel
Berlin | Germany

"This is the best PDA course I have ever taken!"
-Stephan Krause, PDA Member

Be Transformed!!

What are the most important positive quality culture behaviors that impact product quality?

Can you identify which mature quality attributes have the biggest impact on quality culture behavior?

Would you like to quantify the strengths and weaknesses of quality culture maturity at your plant site?

Take the first step on a journey to transform your Quality Culture with resources developed by PDA volunteers specifically for pharmaceutical manufacturing sites.

Quality Culture Transformation Program

Following a successful pilot conducted over the last 18 months, PDA is pleased to launch the Quality Culture Transformation Program to the industry.

When you enroll in this new program, PDA will train your assessors, teach you how to use the Maturity Model, offer an anonymous survey to your site staff and give you access to PDA's composite benchmarking results so you know where you stand with your peers.

Your site leadership will be able to gauge employees' views of quality culture and have a better understanding of where to take action, how to track progress, and which decisions to take to improve the site culture.

PDA Quality Culture Transformation Resources

Your registration fee includes:

1. **COURSE**: Hands-on active learning in a two-day course on "Quality Culture Transformation"
2. **TOOL:** Quantitative assessment of current quality culture
3. **SURVEY:** Blinded, direct employee feedback on aspects of your Quality Culture
4. **BENCHMARK:** Compare your results against more than 40 sites from 24 companies in North America, Europe, and Asia that have already completed Quality Culture Assessments

Who Should Participate

This program will benefit pharmaceutical and biopharmaceutical manufacturing leaders who want to measure quality culture maturity at their plant sites and identify areas for improvement. It will also prepare assessors to conduct site evaluations in a consistent and verifiable manner using the PDA Model and Tools.

The University of St. Gallen and the Parenteral Drug Association (PDA) are providing tools, resources, and training to help you assess and benchmark your manufacturing site's current **quality culture and operational excellence**. Learn more about St. Gallen's tools, resources, and training at tectem.ch/institute/opex

Learn more about PDA's training and register today!

Option 1: Jun. 7-8 | pda.org/2018JunTransform
Option 2: Sept. 27-28 | pda.org/2018SeptTransform

PDA Parenteral Drug Association

SNAPShot

3rd PDA Europe Annual Meeting

Quality Systems IG to Meet before Annual Meeting

Quality remains a popular topic for PDA members. PDA's Quality Systems Interest Group will convene one day before the *3rd PDA Europe Annual Meeting,* June 25, in Berlin. This all-day interest group meeting will explore current issues impacting quality systems. To register, visit: www.pda.org/EU/IGQualitySystems2018.

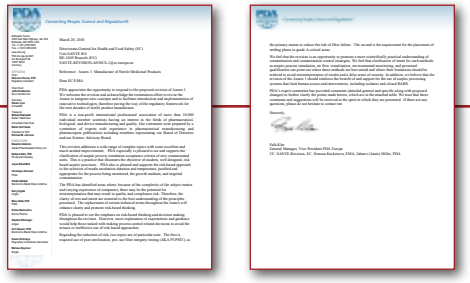
You do not need to be a member of the interest group to attend this meeting.

Update on Annex 1 at PDA Europe Annual Meeting

Since the release of the EU Annex 1 revision at the end of 2017, the pharma industry has been abuzz about its implications for the global pharma community.

On June 26 at 11:30 a.m., Session 1 of the *3rd PDA Europe Annual Meeting* will include three talks addressing topics related to Annex 1. An EMA speaker has been invited to discuss the revision and a representative from the PDA Commenting Team will provide an overview of the team's comments on the revision. The third speaker will review activities around pre-use/post-sterilization integrity testing (PUPSIT)—a key part of the Annex 1 revision.

PDA Responds to Annex 1 Revision



March 20, 2018

Directorate-General for Health and Food Safety (EC)
Unit SANTE B/4
BE-1049 Brussels (EU)
SANTE-REVISION-ANNEX-1@ec.europa.eu

Reference: Annex 1: Manufacture of Sterile Medicinal Products

Dear EC/EMA:

PDA appreciates the opportunity to respond to the proposed revision of Annex 1. We welcome the revision and acknowledge the tremendous effort to revise the Annex to integrate new concepts and to facilitate introduction and implementation of innovative technologies, therefore paving the way of the regulatory framework for the next decades of sterile product manufacture.

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by a committee of experts with experience in pharmaceutical manufacturing and pharmacopeia publications including members representing our Board of Directors and our Science Advisory Board.

This revision addresses a wide range of complex topics with some excellent and much needed improvements. PDA especially is pleased to see and supports the clarification of aseptic process simulation acceptance criteria of zero contaminated units. This is a practice that illustrates the objective of modern, well designed, risk based aseptic processes. PDA also is pleased and supports the risk-based approach to the selection of media incubation duration and temperature, justified and appropriate for the process being monitored, the growth medium, and targeted contamination.

The PDA has identified areas where, because of the complexity of the subject matter and varying experience of companies, there may be the potential for misinterpretation that may result in quality and compliance risk. Therefore, the clarity of text and intent are essential to the best understanding of the principles presented. The replacement of certain technical terms throughout the Annex will enhance clarity and promote risk-based thinking.

PDA is pleased to see the emphasis on risk-based thinking and decision making throughout the revision. However, more explanation of expectations and guidance would help those tasked with making process control related decisions to avoid the misuse or ineffective use of risk-based approaches.

Regarding the reduction of risk, two topics are of particular note. The first is required use of post sterilization, pre- use filter integrity testing (AKA PUPSIT), as the primary means to reduce the risk of filter failure. The second is the requirement for the placement of settling plates in grade A critical areas.

We feel that the revision is an opportunity to promote a more scientifically practical understanding of contamination and contamination control strategies. We feel that clarification of intent for such methods as aseptic process simulation, air flow visualization, environmental monitoring, and personnel qualification can point out where these methods are best suited and where their limitations should be realized to avoid misinterpretation of results and a false sense of security. In addition, we believe that the revision of the Annex 1 should reinforce the benefit of and support for the use of aseptic processing systems that limit human access and interventions, including isolators and closed RABS. ➤

PDA Commenting Team

Hal Baseman , ValSource (chair)
Gabriele Gori , GSK Vaccines (co-chair)
Masahiro Akimoto , Otsuka
Jette Christensen , Novo Nodisk
Veronique Davoust , Pfizer
Phil DeSantis , DeSantis Consulting Associates
Guenther Gapp , Independent Consultant
Salim Mamujee , Kite Pharma
William Miele , Pfizer
Vincent O'Shaughnessy, Amgen
Darius Pillsbury, Adaptimmune LLC
Michael Sadowski, Baxter
Edward Tidswell, Merck
Geert Vandenbossche, Novartis
Richard Johnson, PDA
Jahanvi (Janie) Miller, PDA

PDA's expert committee has provided comments (detailed general and specific along with proposed changes) to further clarify the points made herein, which are in the attached table. We trust that these comments and suggestions will be received in the spirit in which they are presented. If there are any questions, please do not hesitate to contact me.

Sincerely,
Falk Klar
General Manager, Vice President PDA Europe
CC: SANTE-Revision, EC, Simona Keckesova, EMA, Jahanvi (Janie) Miller, PDA

Strategies for Reducing Data Integrity Challenges continued from page 35

This could prove challenging as companies are collecting massive amounts of data, colloquially referred to as "big data."

"Big data shall be assessed to identify risky records, taking into account that the decisions that data influences may differ in importance, and the impact of the data on a decision may also vary," he said. "The control measures required to ensure data integrity should be commensurate with the criticality of the information provided by the record against patient safety and product quality," Neri said.

Data integrity remains a focus of regulators. Recent FDA 483s and warning letters have been issued to manufacturers regarding data integrity issues. MHRA and EMA have also become heavily involved in this area. Ensuring data integrity requires top-down support across all levels of an organization. Reviewing audit trails and developing metrics around data integrity are two ways companies can address the growing concern around this important topic.

About the Experts

Matthew Paquette provides technical expertise that for Charles River customers implementing rapid microbial solutions for endotoxin testing, identification and detection.

In over 20 years of experience, **Danilo Neri** has managed the validation process for most of the common computerized systems used in the life science environment.

Christian Scheidl is responsible for 36 solids and special technology sites.

Awareness Key for Container Closure Components: Part III

A Summary of the 2017 PDA Container Closure, Devices and Delivery Systems Workshop

[Editor's Note: Parts I and II of "Awareness Key for Container Closure Components" were published in the March and April issues. Session moderators for the *2017 PDA Container Closure, Devices and Delivery Systems Workshop* summarized their respective sessions. The article can be read in its entirety, complete with figures, on the Letter website**.]**

Plenary 5: Particle Challenges Associated with Delivery Systems and Devices

Moderator: Isabel Tejero del Rio, MD, PhD, Lead Consumer Safety Officer, CDRH, FDA

Paolo Golfetto, Director, Business Development, OMPI, spoke about industry initiatives around visible particulate specifications. Triggered by a recent increase of regulatory findings related to particles in injectable drug product containers, the Pharmaceutical Manufacturers Forum collaborated with PDA to create a task force to address the issue. They aim to create alignment across the industry, driven by "end-to-end" parenteral process mapping, with the goal of defining a practical guidance to assure delivery of injectables that are also in compliance with a new set of proposed particulate requirements.

The work of the task force is ongoing, currently focused on three specific areas: **1)** sterile injectable primary container closure systems; **2)** API manufacturing (including related nonprimary container closures); and **3)** process equipment (including single-use processing components).

Fran L. DeGrazio, Vice President, Scientific Affairs and Technical Services, West, then spoke about the impact of pharmaceutical packaging on particulates. Particles from packaging components have a complexity that must be understood in order to minimize their impact. The source of particles and the fact that some particle types may be inherent to the elastomeric formulation is important to understand. And understanding the level of quality from purchased components is critical. Are the elastomer components purchased in a bulk format? Or do they receive a pharmaceutical wash and other post-treatments by the closure manufacturer or contract manufacturer?

In addition to understanding these specifics, consistent testing procedures are needed to assure appropriate comparisons can be made among components. Variability in sample preparation and testing methods can mislead a drug applicant working to find the root cause of an issue or comparing products from multiple sources or environments.

Plenary 6: Compatibility of Delivery Systems with Biologics

Moderator: Nazia F. Rahman, Biomedical Engineer, CDRH, FDA

Understanding particulates from biologic products and the container closure system depends on choosing the right techniques to properly assess particle profiles as explained by **Amber Fradkin**, PhD, Director of Particle Characterization, KBI Biopharma. Raw materials, manufacturing processes, packaging systems, storage and shipping are among the factors that influence particle profiles. Regulators scrutinize visible as well as subvisible particulates in therapeutic proteins. The presence of visible particulate matter is one of the top ten reasons for the recall of parenteral products. USP specifies that injectable drug products be "essentially free" of visible particulates. In therapeutic proteins, USP has limits for subvisible particles not to exceed 6000 per container equal to or greater than 10 µm and should not exceed 600 per container equal to or greater than 25 µm. Light obscuration and membrane microscopy are the techniques used in compendial assessments; however, particle detection methods are becoming more sensitive and can provide significantly more information on products. Fradkin explained that orthogonal measurements allow for better understanding of particle profiles.

Susan Kirshner, PhD Review Chief, Division of Biotechnology Review and Research, CBER, FDA, then described how to qualify delivery system platforms for biologics. The evidence of suitability for container and delivery systems with a biologic should be contained within a BLA. She specifically focused on purified, naturally derived biologics, excluding blood products or cell/gene therapy products. Information on the development of the delivery system should include data that proves protection, compatibility, safety, performance, stability and quality control.

There are different regulatory considerations for container closure and delivery systems that follow current good manufacturing practices (CGMP) versus delivery devices that fall under the quality systems (QMS) regulations. Biologics classified as combination products may need to comply with both GMP and QMS regulations. Leachables, Kirshner said, can have a major effect on biologic quality as well as safety. Biocompatibility tests on extractables can be leveraged for safety, but biologics must be assessed for leachables and the impact on product quality.

She cited several case examples related to delivery system/protein issues: metal leaching from stoppers resulting in protein degradation; aggregation of protein due to interaction with tungsten oxide originating from the pin used to insert the needle into the glass barrel; protein oxidation due to solvents leaching from glue used in stake needle syringes; and occurrence of visible particles in a prefilled syringe at three-month stability due to supplier process change. These examples highlighted the need for qualifying container closure/delivery systems during development, throughout the product shelf life and throughout the product lifecycle.

Lei Li, PhD, Engineering Advisor, Eli Lilly and Company, then presented on container closure integrity for combination products. He emphasized that container closure integrity is not only a container attribute but also a product system attribute. The increasing complexity of delivery systems with intrinsic interactions and interdependencies must be thoroughly evaluated throughout product development phases with consideration for patients and end users. Design requirements should encompass a systems approach in order to identify and mitigate risks during manufacture and throughout the life of the product. Risk to container closure integrity can be related to chemical interactions or physical incompatibilities as well as to processes used for filling, sealing, storage, shipping and end use.

Li's examples included optimization of a system design through modeling, selection of appropriate container closure integrity test methods and overcoming interferences when testing assembled devices. He explained that container closure integrity testing is a journey with a database of fully integrated information that must meet a diverse set of requirements. Interactions are complex and influenced by time, temperature and pressure. To build a meaningful control strategy, a robust integrity profile should be developed to prevent material interactions and process variations to establish the maximum allowable leakage of the system. A key takeaway from Li's talk is how critical it is to connect the drug product with component materials and manufacturing processes to achieve inherent package integrity. Li also provided a sample design and process risk assessment for attendees to consider.

Plenary 7: Quality Considerations for Combination Products and Devices

Moderator: Richard Levy, PhD, Senior Vice President, Scientific and Regulatory Affairs, PDA

Specialty applications for drug delivery systems and devices continue to evolve but providing fit-for-use criteria remains a challenge for suppliers. Compliance with national and international standards is a starting point but cannot encompass all uses. A set of baseline requirements and documented risk factors can support suitability studies and provide insight on quality expectations.

The final plenary session examined these areas. **Kesley Gallagher,** Senior Regulatory Affairs Manager, Amgen, began by offering a device perspsective on change control for marketed combination products. Gallagher's presentation covered device change control and subsequent filing considerations of combination products where the drug is the primary mode of action.

She discussed change control and assessment based on the measure of risk to the drug from changes. When assigning risk, she suggested asking some questions. Are clinical data needed? What level of design verification and validation testing will be needed? Are there any new biocompatibility concerns due to the proposed changes? Is there a new sterilization method being introduced? Does the change necessitate a change in the way the device will be used?

Continued at bottom of page 44

Container Closure Integrity Requires Adaptation

Dominick DeGrazio, PhD, Janssen R&D, LLC

The development of biopharmaceutical products is shifting from a traditional platform approach to one comprised of complex modalities like chimeric antigen receptor T-cell therapies, oligonucleotides and oncolytic immunotherapy viruses. This means traditional reliance on a platform comprised of monoclonal antibody (mAb) products may not be adequate for newer, unconventional therapies. Instead, an end-to-end holistic strategy that integrates formulation and package development with manufacturing and administration is necessary to ensure that drug product quality, safety and efficacy are not compromised throughout the shelf life of a product.

Industry will have to adapt to the challenges presented by the emergence of these novel therapeutics. The complexities involved include drug product/packaging material incompatibility, robustness of integrated delivery systems and development of container closure integrity methods suitable throughout product lifecycle. Concurrently, regulatory bodies are revising outdated guidances in an effort to compel companies toward critical thinking and decision-making driven by high-quality science. An example of this can be seen with the recent implementation of updated USP <1207> Sterile Product Packaging—Integrity Evaluation, and the impending EU Annex 1 revision. With these changes, industry is being pushed to reevaluate its strategy for assessing container closure integrity and use deterministic-based methodologies. As novel drugs may be more sensitive than traditional mAbs, the preservation of sterility and product integrity is of utmost importance.

At the *2018 PDA Container Closure Performance and Integrity Conference,* **Charlotte Masy** from GlaxoSmithKline and **Carole Langlois** from Sartorius Stedim will discuss the maintenance of container closure integrity throughout the manufacturing process. Additional talks will focus on the interface between container closures and functionality, while others examine unforeseen obstacles encountered during the development of integrated delivery systems. Representatives from the U.S. FDA will also review technical considerations for complex delivery devices and lifecycle management for combination products. In total, the depth of topics to be presented should provide relevant information that companies can use to tackle challenges they face when developing these new therapies while successfully adjusting to evolving regulatory expectations.

2018 PDA Container Closure Performance and Integrity Conference

Bethesda, Md.
June 13–14
www.pda.org/2018ccpi

Awareness Key for Container Closure Components: Part III continued from page 43

Will there be a substantial impact on the drug product because of the change?

Gallagher also made several points about change control: a change control process should be documented in an SOP and reassessed often; drug constituent parts and device constituent parts should be distinguished from each other; and types of changes should be defined for the device and a process flowchart created as a decision tree. She concluded that it is all about defining the levels of risk and reporting in an organized manner that is easy to follow.

Lee Nagao, PhD, Science Advisor, Drinker Biddle, then discussed partnering across the supply chain to develop and communicate risk-based requirements for material quality. Orally inhaled and nasal drug products (OINDPs) are drug/device combination products falling under CDER as the primary review division in the FDA. Nagao's presentation focused on recommendations summarized in the updated *Baseline Requirements for Materials used in Orally Inhaled and Nasal Drug Products* document published by the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS). Originally released in 2011, IPAC-RS revised the document in 2017 due to the evolving regulatory landscape. The new document seeks to integrate and bring structure and hierarchy to the many global quality requirements expected for inhalation and nasal product devices and container closure system materials and components. The guidance specifically covers the rationale, development and baseline requirements for the quality of materials, as well as discussing how best to engage with suppliers and consider differences that might be encountered.

Nazia F. Rahman, Biomedical Engineer, CDRH, FDA, and **M. Isabel Tejero del Rio,** MD, PhD, Lead Consumer Safety Officer, CDRH, FDA, both offered regulatory insight on supplier controls for the quality of delivery systems. They first reviewed selected definitions from 21 CFR, such as "combination product," "constituent" and "modes of action." Those definitions formed the foundation for a review of combination product regulation history and CGMP regulatory requirements for supplier control. Next, they discussed how the requirements may be applied, defining what is considered a manufacturer, a specification developer and a contract manufacturer, since the complexity of these delivery systems can cause some confusion.

All of the presentations at the *2017 PDA Container Closure, Devices and Delivery Systems: Compatibility and Material Safety Workshop* illustrated the complexity surrounding container closure systems and offered a look at how industry and regulatory agencies can work together to identify relevant issues and develop solutions. Anyone interested in further discussion about this topic is encouraged to attend the *2018 PDA Container Closure Performance and Integrity Conference* in June.

Running the Numbers for Analytical Similarity

Beverly Ingram, Pfizer

Systems for regulating biosimilar applications have been successfully operating for 13 years, first in Europe, and more recently, in the United States. Yet challenges still exist in gaining approvals, often as a result of registration information outside the analytical similarity demonstration itself. In particular, the extent of product development data generated to support commercial activities and the readiness of manufacturing sites to produce and control the intended commercial biosimilar product remain obstacles. In addition to the established expectations for biosimilar product development, one of the newer areas that represents an emerging area of regulatory science is the application of statistical tools in analytical comparisons.

The U.S. FDA has provided further thoughts on the assessment of biosimilar product development and has recommended the use of a statistical approach to evaluate quality attributes consistent with the risk assessment principles set forth in ICH Quality Guidelines Q8–Q11. In this concept, the analytical similarity assessment is based on a tiered system in which varying statistical rigor is applied. A draft EMA reflection paper coverings statistical methodologies for comparing assessments of quality attributes has broadened the consideration for statistical analysis, including the ICH Q5E comparability evaluation scenario as well as generic product development.

Use of statistical data for analytical similarity will be among the topics subject to in-depth discussion at the *2018 PDA Biosimilars Workshop* as it represents a topic of particular interest to biosimilar product developers; the workshop will include a session on how to use statistical tools to demonstrate analytical similarity. This session is intended to foster dialogue on the practical challenges of applying statistical tools to support the demonstration of similarity.

This workshop will focus on the most common challenges identified in biosimilar applications as experienced by the FDA and other regulatory authorities such as EMA and Health Canada.

2018 PDA Biosimilars Workshop

Washington, D.C.
Sept. 26–27
www.pda.org/2018biosimilars

Find Your Particular Interest in a PDA Interest Group

Susan Schniepp, Regulatory Compliance Associates

PDA's Board of Directors is responsible for setting the strategic direction of the organization. Input for this comes from a variety of sources, including PDA's interest groups. There are 28 PDA interest groups that report into one of three PDA Advisory Boards, depending on their particular focus. Interest groups with a focus on biotechnology report into the Biopharmaceutical Advisory Board (BioAB) while interest groups concentrating on regulatory and quality issues report into the Regulatory and Quality Advisory Board (RAQAB). Interest groups concentrating on science and technology issues report into the Science Advisory Board (SAB). Interest group membership is free and open to all PDA members. PDA members can join as many interest groups as they want.

Participation in an interest group offers a unique opportunity to connect with your colleagues across the globe. Through PDA Connect[SM], you can correspond with other interest group members and discuss issues you may be facing around a certain topic. For instance, maybe you are having trouble getting a quality agreement from one of your suppliers. In this case, you might want to consult with members of the Management on Outsourced Operations Interest Group. Or, perhaps you want to understand more about current regulatory trends others have noticed. In this situation, you would want to connect with the Regulatory Affairs Interest Group. If you need help with an issue that arose from a recent inspection, you might want to seek advice from your colleagues who are members of the Inspection Trends Interest Group. Whatever your need, chances are PDA has an interest group with members who can help you with your issue or question. Interest groups are also a chance for you to share information with your colleagues. You may have a unique perspective that you think would be of benefit to others in the industry. Interest groups are a great way to share that information.

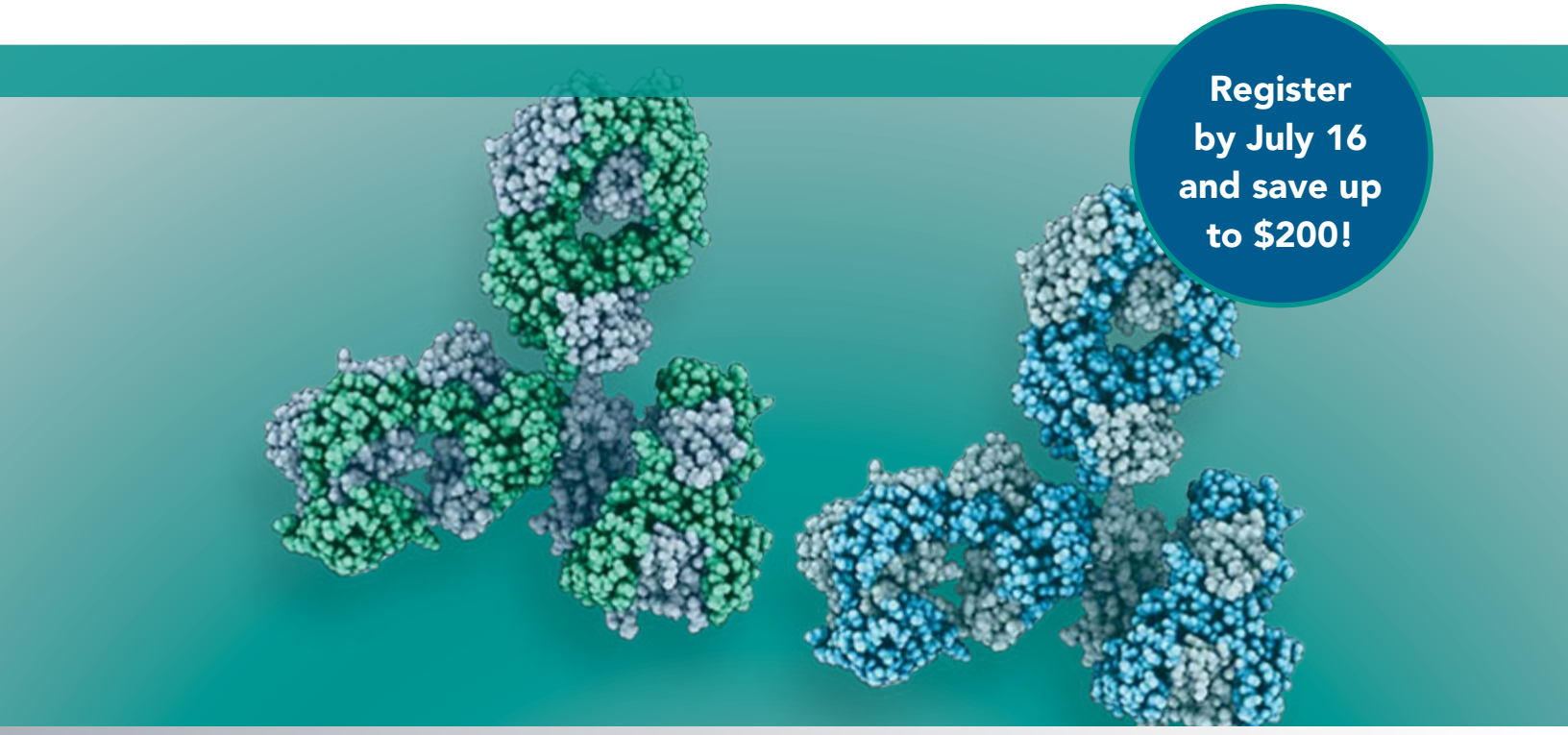
In fact, PDA has two new biopharmaceutical-focused interest groups: The Cell and Gene Therapy Interest Group and the Biosimilars Interest Group.

Interest groups conduct meetings in a variety of ways. Some hold online meetings while others meet face-to-face at related PDA conferences. Others do most of their communication through PDA Connect[SM]. As an interest group member, you can participate as often as you wish, depending on your individual circumstances.

So why are interest groups important to PDA? Issues and ideas stemming from interest group discussions usually reflect current trends facing the industry. When these trends are discussed in one of the interest group forums, interest group leaders can communicate them to the overseeing advisory board, which in turn can communicate the issue to the Board of Directors. If an issue is global in nature and deemed critical to the industry, the Board of Directors can help set a strategy to address this new concern.

Interest groups are important contributors in making PDA an industry leader because they are often the first to identify current industry problems and bring them to the attention of PDA's membership. To get the most out of your membership and to stay current in your industry knowledge and understanding, it is well worth the cost of membership to choose and participate in one or more of PDA's interest groups. For more information on the interest groups and their specific charters go to www.pda.org/scientific-and-regulatory-affairs/interest-groups.

2018 PDA Biosimilars Workshop



Register by July 16 and save up to $200!

The *2018 PDA Biosimilars Workshop* will focus on the most common challenges identified in biosimilar applications by the U.S. FDA and other regulatory authorities, including EMA and Health Canada, both in established requirements and in more progressive areas.

Attend this Workshop to gain practical approaches to avoid the pitfalls frequently encountered during biosimilar candidate development, including:

- Expectations for manufacturing development and control strategies
- Compliance standards for analytical similarity data
- The application of statistical tools, including practical challenges, potential solutions, and considerations for the analytical similarity study design

To learn more and register, please visit pda.org/2018Biosimilars

PDA® Parenteral Drug Association

September 26-27, 2018 | Washington, DC
Exhibition: September 26-27
#PDABIOSIMILARS

CONNECTING PEOPLE SCIENCE AND REGULATION®

Chris enjoys playing just like his friends – thanks to FIOLAX® borosilicate glass

Chris does not yet understand that he can play just like his friends, because of the high dosage accuracy of his diabetes medication. This dosage accuracy results from a container closure system which is manufactured from FIOLAX® borosilicate glass tubing with unparalleled inside diameter quality.
In fact Chris doesn't need to care – because we do – since 1911.

What's your next milestone?

www.schott.com/fiolax

FIOLAX® glass tubing
Made with perfeXion™

www.schott.com/tubing/english/products/fiolax.html
SCHOTT AG, Tubing, info.tubing@schott.com

SCHOTT
glass made of ideas