People • Science • Regulation

PDA Letter

Volume LV • Issue 1 www.pda.org/pdaletter January 2019

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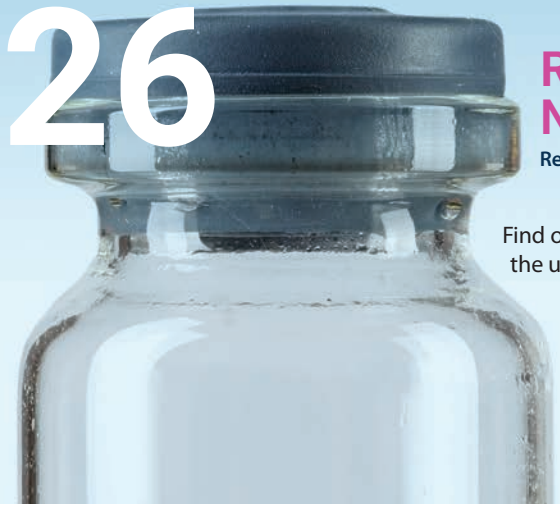
January 2019 PDA Letter

Parenteral Packaging conference

This year's *Parenteral Packaging conference* is scheduled for March 19–20 in Venice, Italy. Articles with this banner at the top of the page relate to this important meeting.

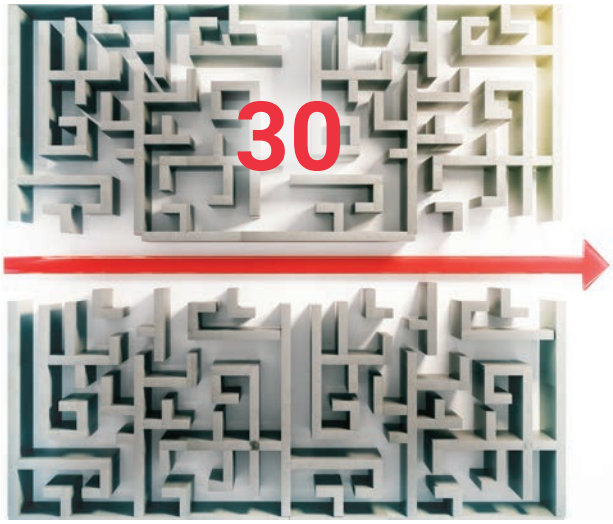


Regulatory Concerns Drive New Developments in Glass Packaging

Rebecca Stauffer, PDA

Find out what some of the speakers and program planning committee members behind the upcoming PDA *Parenteral Packaging* conference think is spurring development of new types of glass packaging.

Cover Art Illustrated by Katja Yount



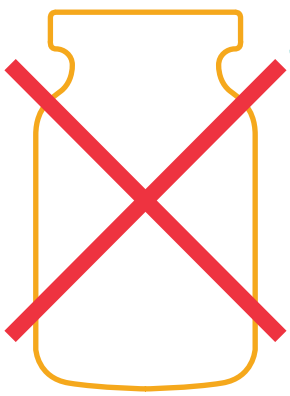
An Overview of Container Closure Integrity

Considerations for Achieving an Optimal Performance Window for Container Closure Systems

Qingyu Zeng, PhD, West Pharmaceutical Services, Inc.

A typical container closure system has three major components: a rubber stopper, vial and aluminum seal. In order to satisfy mandatory patient safety requirements, container closure integrity must be ensured through a holistic consideration of many critical aspects.

InfoGraphic



United States and Europe Align on Glass

Find out how the U.S. Pharmacopeia has aligned with the European Pharmacopoeia around glass packaging.

PDA Letter

Volume LV • Issue 1 www.pda.org/pdaletter

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Departments

Digital Exclusives

> **On the Issue** | Big Data
Roche's **Aaron Goerke** talks about what big data means for pharma manufacturing.

> **Holistic Verification Requires a New Mindset**
CSL Behring's **David Hubmayr** explains why holistic verification is key to manufacturing drug products in an increasingly patient-centric world.

> **Amsterdam Move Reflects Larger Trend**
EMA is not the only thing moving to Amsterdam!

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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 150
Bethesda, MD 20814 USA
Tel: +1 (301) 656-5900
Fax: +1 (240) 482-1659
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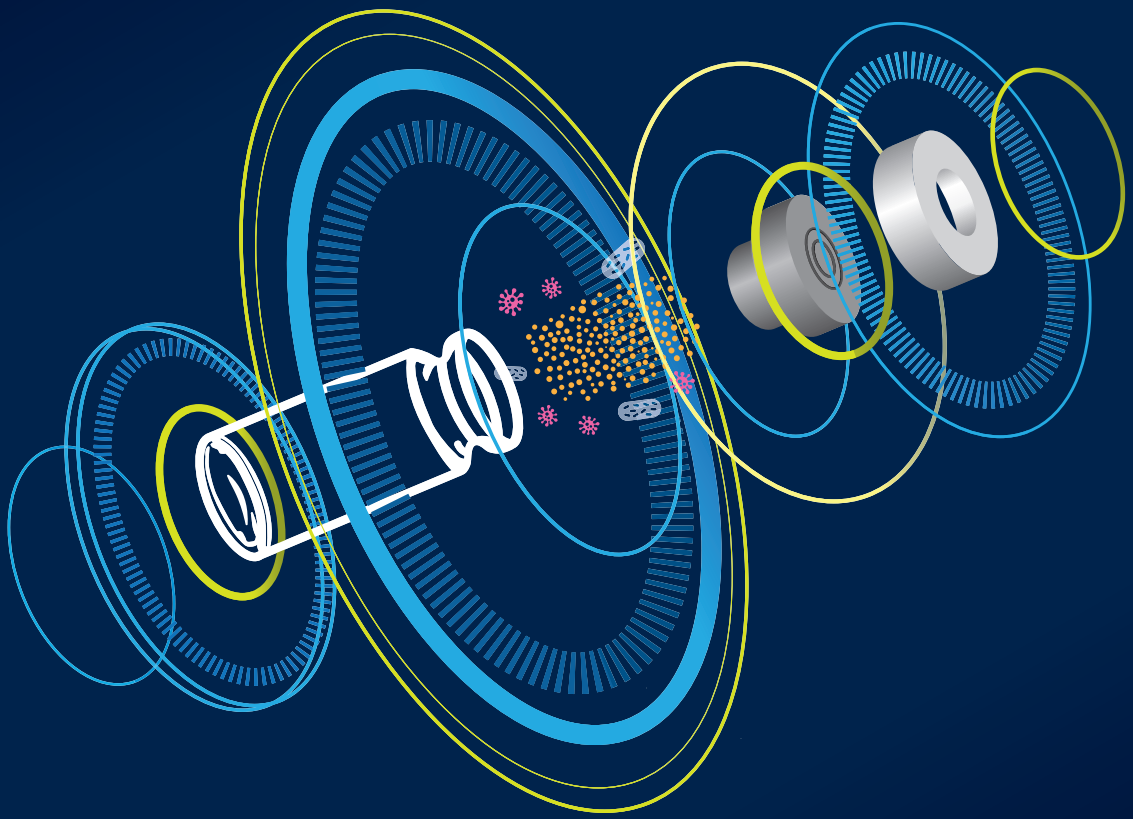
2019 PDA EUROPE

Parenteral Packaging

Interaction of Product, Package, and Process



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EDUCATION & TRAINING: 21-22 MARCH
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Editorial Committee Keeps PDA Letter Strong

Rebecca Stauffer

As we enter 2019, I would like to express my gratitude to the volunteer members of the *PDA Letter* Editorial Committee (PLEC). Their hard work throughout the year ensures that the Letter remains relevant to the needs of PDA members.

PDA formed the all-volunteer PLEC a dozen years ago to allow PDA members input into the content of the *PDA Letter*. PLEC has grown from the six-members of the inaugural committee to 16 members today. Our goal is to include a variety of backgrounds on the PLEC with representatives from suppliers, large pharma, small pharma, consultants, manufacturing, quality, QC testing, sterile processing and contract manufacturing organizations. This way the Letter can hit all points of interest within our diverse industry. To ensure the Letter's content aligns with PDA's strategic science and regulatory output, one member of each PDA Advisory Board—Science, Biopharmaceutical, and Regulatory and Quality—also liaises with the Editorial Committee; this was an important addition to the *PDA Letter* process.

What does the PLEC do, you ask? For starters, PLEC members primarily participate in the article-review process. While not a formal peer review, we ask them to rate articles based on how interesting the topic is to the community at large and to judge if anything written runs counter to industry best practice and regulations. These 16 subject-matter experts also read through the articles and, if warranted, point out areas that require additional clarification and/or information.

The PLEC also has two subcommittees to help with specific aspects of the Letter. One subcommittee reviews our cover art and infographics for accuracy and relevancy. The last thing we want is to depict someone gowned incorrectly! The other subcommittee identifies relevant topics and experts to interview for our popular "On the Issue" videos.

PLEC also helps the Letter staff set the future direction of the publication, including editorial themes. Each quarter, the committee discusses ideas for Letter content and coverage via teleconference. We also meet face-to-face at the *PDA Annual Meeting*. PLEC helps keep the Letter fresh and innovative. In fact, their input has been invaluable. When we revamped the *PDA Letter* website in 2015, I think they were more excited than I was to use the test site!

So, I want to thank the following Committee members who are now ending their terms: **Sharon Ayd, Claire Fritz Briglia, Christine Bui, Andrew Dick, Valeria Frigerio-Regazzoni, Christopher Hanff, Maik Jornitz, Stephan Krause** and **Mina Mitry.** Your contributions to the *PDA Letter* have helped keep it a strong membership benefit.

And I welcome the following new Committee members to the team: **Marcia Baroni, Brian Hawkins, Zena Kaufman, Gwendolyn Lohr, Aaron Mertens, Frank Matos, Ajay Pazhayattil, Cecilia Turoff** and **Kelly Waldron.** I look forward to working with all of you in the coming year.

If this all sounds like fun to you, I encourage you to think about applying to join the *PDA Letter* Editorial Committee. It may be early but, if you think you might be interested in joining in 2020, please let me know.

2019 PDA Board of Directors

PDA is pleased to announce the results of the 2019 Board of Directors election. Congratulations to the following Directors elected by PDA's membership to the Board:

Michael Blackton, Vice President, Quality, CMC, Adaptimmune

Bettine Boltres, PhD, Technical Account Manager, Technical Customer Support Europe, West (*Appointed to serve out term of Director who resigned*)

Stephan Krause, PhD, Director, QA Technology, AstraZeneca Biologics

Anil Sawant, PhD, Senior Vice President, Global Quality Compliance, Merck

Melissa Seymour, Vice President, Global Quality Control, Biogen

PDA thanks outgoing Directors **Susan Schniepp** and **Stephan Rönninger** for their many years of service to PDA.

Comment on PIC/S DI Guidance via PDA

A revised draft *PIC/S Guidance on Good Practices for Data Management and Integrity in Regulated GMP/GDP Environments* has been prepared by the PIC/S Working Group on Data Integrity, co-led by the Australian Therapeutic Goods Administration and UK MHRA.

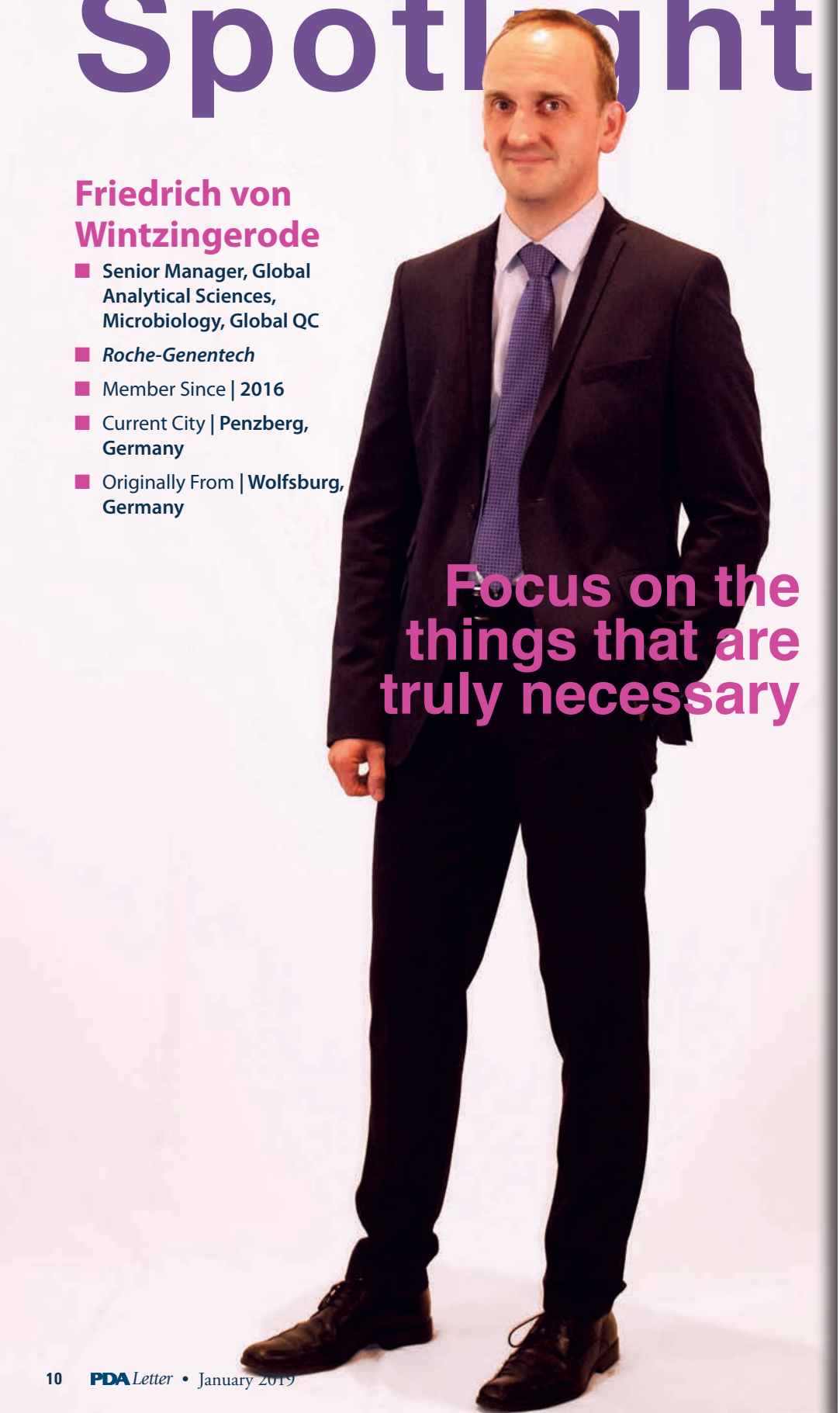
Providing inspectorates guidance in interpreting GDP/GMP requirements on data management and data integrity, including reporting, is one goal of this document. The guidance will also serve as a tool to facilitate a harmonized approach to inspections and ensure their quality, particularly regarding data integrity expectations.

PIC/S published a first draft of this guidance in August 2016. Following feedback received from PIC/S Participating Authorities during its six-month implementation trial period, the Working Group updated and expanded that draft.

To help develop a focused stakeholder consultation on this document, PDA seeks substantive comments on specific questions relating to the proportionality, clarity and implementation of the guidance requirements.

The consultation period will be open from Nov. 30, 2018, to Feb. 28, 2019. Comments can be sent to PDA's Vice President of Scientific and Regulatory Affairs **Tina Morris** (tmorris@pda.org) using the template found on the PDA website: tinyurl.com/y7swvul6.

PDA Volunteer Spotlight



Friedrich von Wintzingerode

- **Senior Manager, Global Analytical Sciences, Microbiology, Global QC**
- ***Roche-Genentech***
- Member Since | **2016**
- Current City | **Penzberg, Germany**
- Originally From | **Wolfsburg, Germany**

Focus on the things that are truly necessary

What has been your most recent volunteer role?

I recently served as co-chair of the *2018 PDA Endotoxins Workshop*. Throughout the process of organizing the workshop, all committee members were highly engaged, resulting in an excellent speaker panel. I also enjoyed working with the PDA staff; they are all professional, friendly people.

During the workshop itself, the presentations were all high-quality and we had fruitful discussions after every talk. All in all, I would rate this meeting as very successful.

What led you to volunteer with PDA?

I wanted to work closely with global regulators to improve processes and create solutions for the industry.

PDA provides the unique chance to work with global regulators on improved processes for the industry.

How has PDA contributed to your career?

My work co-leading the task force on low endotoxin recovery has allowed me to work closely with senior experts from academia, industry and global regulatory agencies. This greatly expanded my knowledge in pharmaceutical microbiology.

What significant changes have you seen in your area of expertise?

Growing knowledge about immunology and patient safety means we must look at pharmaceutical microbiology in a different light. We are no longer limited to classical microbiology dealing with intact/living cells, we also must look at subcellular structures. New analytical concepts are needed to address the risk of microbial impurities like toxins and pathogen-associated-molecular patterns on patient safety.

Who are your favorite musicians?

I am a big fan of **Johnny Cash** and **Nick Cave**. I would love to tell them in person how much I love their music!

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India Chapter Gets Hands-On with CCI Tech

Biny Joseph, Vienni Training and Consulting

PDA's India Chapter offered sterile drug manufacturers from various regions of the country a rare opportunity—to view the manufacture of vials and ampoules in action. Some 59 quality team leaders, research and development managers and technologists took advantage of the occasion at a workshop the chapter hosted August 28–29 in Vadodara, titled *Advancing Science in Drug, Device & Primary Packaging: A Primer to Containers, Closures & Integrity.*

The two-day workshop began with a tour of the nearby Schott-Kaisha manufacturing facility. Here, attendees witnessed firsthand how the site manufactures tubular vials and ampoules and learned the science behind heating, annealing, testing and checking the vessels, as well as developing defect mitigation strategies.

(l-r) Brandon Zurawlow, Arunava Ghosh, Vishal Sharma, Rajender Singh and Rahul Dev

Following the tour, participants were treated to an exhaustive program with a wide array of speakers. First, **Rajender Singh** discussed "Regulatory Considerations for Packaging Lifecycle," followed by **Arunava Ghosh,** who covered "As-

Attendees pose with workshop speakers for a group photo at the conclusion of the workshop

suring Packaging Quality Across Product lifecycle."

The next session dealt with defects in class vials—a particularly pertinent topic. This featured talks from **Eric Lheureux** and **Sanjay Jain,** both of whom provided needed clarity on how to address this critical challenge.

Next, attendees proved keen to hear **Brandon Zurawlow** present on "Container Closure Integrity & Testing and Challenges." **Koen Pagnaer** then spoke on container closure during development, scale-up and full-scale manufacturing.

Two additional talks explored drug delivery issues. Ghosh examined the role of quality evaluation and design for drug delivery and device packaging, and **Vishal Sharma** offered a case study detailing the challenges involved in the design and optimization of prefilled syringes.

…attendees pointed to blowback technique, leachable studies and advancements in vial manufacturing as topics that drew interest

All of the presentations drew praise from attendees, who indicated that these sessions would help them with routine operations and future planning. In particular, attendees pointed to blowback technique, leachable studies and advancements in vial manufacturing as topics that drew great interest.

Chapter leaders appreciated the feedback and felt encouraged by the dialogue, which brought together people, science and regulation—a primary PDA goal.

The chapter wished to thank the following sponsors for contributing to the success of the workshop: Schott Kaisha, Zeon Corporation, Grover International and Datwyler.

PDA Who's Who

Rahul Dev, Vice President Operations India, Datwyler

Arunava Ghosh, Deputy General Manager, Zydus Cadila

Sanjay Jain, Vice President, Amneal Pharmaceuticals

Eric Lheureux, Operations Director, Schott-Kaisha

Koen Pagnaer, Account Manager, Datwyler

Vishal Sharma, Director, Vienni Training and Consulting

Rajender Singh, Senior Vice President, Regulatory Affairs, Mankind Pharma

Brandon Zurawlow, Principal Consultant, Containsure

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2018 PDA/FDA Joint Regulatory Conference

Sept. 24–26 | Washington, D.C.

Welcome/Opening Remarks

(top) PDA President Richard Johnson

(bottom) PDA Chair and Conference Co-chair Rebecca Devine, Biopharmaceutical Consultant

Plenary 1
Taking Stock of the Drug Supply Chain

(l-r) Conference Co-chair Rick Friedman, CDER, U.S. FDA; Anna Abram, U.S. FDA; Esteban Santos, Amgen

Plenary 2
The Evolving Regulatory Landscape

(l-r) Rebecca Devine; Alonza Cruse, FDA; John Lynch, Irish Health Products Regulatory Authority

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Exhibit Hall/Networking

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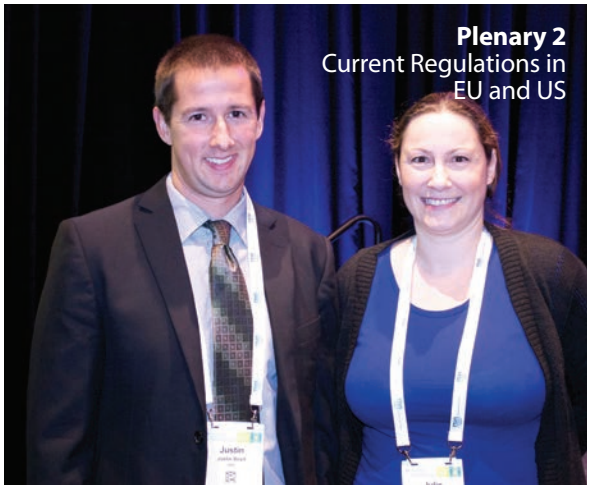
13th Annual PDA Global Conference on Pharmaceutical Microbiology

Oct. 15–17 | Bethesda, Md.

(l-r) Kerstin Wilken, PhD, PDA; Kimberly Schultz, CBER, U.S. FDA; Yoko Momonoi, Celgene; Kim Sobien, PETNET Solutions



(l-r) Justin Boyd, U.S. FDA; Julie Barlasov-Brown, Merck

(l-r) Ed Tidswell, PhD, Merck; Stephen Langille, PhD, CDER, U.S. FDA; David Keen, Ecolab; Hal Baseman, ValSource

(l-r) Cheryl Essex, Sanofi; Amy McDaniel, PhD, U.S. FDA; Austin Kuo, Eli Lilly

(l-r) Yeissa Chabrier-Rosello, PhD, CDER, U.S. FDA; Mitchell Garber, GlaxoSmithKline; Jessica Chiaruttini, PhD, CDER, U.S. FDA; Dennis Guilfoyle, PhD, J&J

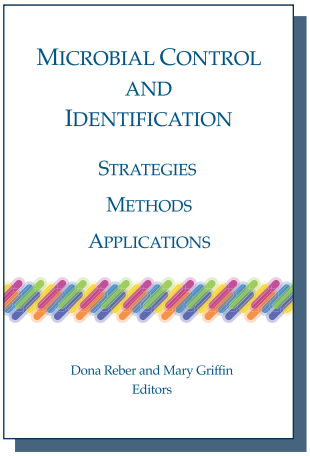
SNAPShot

Co-Authors Team Up for Book Signing at PDA Micro

Dona Reber, Pfizer, and Mary Griffin, MG Quality MIcrobiology Consulting, LLC

The recent *13th Annual PDA Global Conference on Pharmaceutical Microbiology* served as a comprehensive scientific forum, providing many excellent presentations, posters, events and venues to learn the latest in microbiology and to network with microbiologists across a variety of specialties. With the recent publication of our second edited PDA/DHI book, *Microbial Control and Identification: Strategies, Methods, Applications,* the meeting provided an opportunity for us to not only celebrate our accomplishment face-to-face but to also talk to readers and offer a book signing.

The editors and some of the authors pose for a group photo at the conference. (Back l-r) Jeanne Mateffy, Amgen; Jim Polarine, STERIS; David Shields, STERIS; Ed Balkovic, PhD, Consultant; and Angel Salaman-Byron, PhD, Janssen Biotech (J&J) (Front l-r) Mary Griffin, MG Quality Microbiology Consulting; Vanessa Vasadi-Figueroa, QxP; and Dona Reber, Pfizer



This book looks at microbial identifications in a new light, viewing microbial identification as a cornerstone in the concept of microbial and contamination control programs. It comprises three sections: "Strategies" covers regulations and regulatory expectations, the role of microbial identification in microbial control and trending, risk assessments and risk management. "Methods" includes current best practices, traditional and emerging rapid methods for detection and identification of bacteria, viruses, mycoplasma and fungi and a chapter on the timely topic of data integrity. "Applications" features a microbiology laboratory training plan for bacteria identifications, the use of

Continued on page 23

Journal *TOC*

Latest Research on Extraction/Leaching, Split-Cakes and More in Jan/Feb PDA Journal

Three new research articles in the January/February *PDA Journal of Pharmaceutical Science and Technology* address extraction/leaching, split-cakes and calculating random effects model tolerance intervals (journal.pda.org).

Research

Denise Bohrer, et al., "Extraction/leaching of Metal Containing Additives from Polyvinyl Chloride, Ethyl Vinyl Acetate, and Polypropylene Bags and Infusion Sets into Infusion Solutions"

Philippe Lam and Thomas W. Patapoff, "Split-cakes, still delicious"

Richard O. Montes, Richard K. Burdick, and David J. LeBlond, "Simple Approach to Calculate Random Effects Model Tolerance Intervals to Set Release and Shelf-life Specification Limits of Pharmaceutical Products"

Technology/Application

Diego Zurbriggen, et al., "Assessment of Extractable Elements from Elastomers"

Liang Fang and Cathy Zhao, "Modeling the Permeation Rates of Organic Migrants Through a Fluoropolymer Film"

Case Study

Xia Cathy Zhao, et al., "A Case Study to Address a Gap in the Device-to-Vial Interface Stopper Push-in by Chemo Spikes - An Overlooked Oncology Safety Risk"

Commentary

Dennis Jenke, "How One Might Experimentally Determine if Container Closure Systems and their Components and Materials of Construction Contribute Elemental Impurities to Packaged Pharmaceutical Drug Products"

Current Perspectives on the Monocyte Activation Test

Is the Monocyte Activation Test a Viable Alternative to Traditional Tests?

Djikolngar Maouyo, Pyrodex

In recent months, the market for the monocyte activation test (MAT) has grown. Many factors have spurred this growth, notably the potential for greater restrictions on animal testing. Yet as the test is relatively new, compared to the traditional rabbit pyrogen test, concerns about its effectiveness remain.

These concerns were at the forefront of presentations delivered at the *13th Annual PDA Global Conference on Pharmaceutical Microbiology* and associated the *2018 PDA Endotoxins Workshop* in Bethesda, Md., in October. My analysis and interpretation of these talks follows, and, in my opinion, the talks support the MAT as a valid alternative to traditional tests.

Perspectives ranged from a call for caution from **Devon Kleindienst** (Research Scientist, Bristol-Myers Squibb) to **Ned Mozier's** (Senior Director, Analytical R&D, Pfizer) and **Qing J. Zhou's** (Associate Director, Allergan) back-to-back balanced defense of this alternative approach ***(1–3).*** In between, **Peter Bruegger** (Head, Bioassay and Microbiology, Lonza) reported on the European adoption of the MAT in 2010 and its selection as a compendial method in the European Pharmacopoeia (Ph. Eur.) ***(4).*** This contrasts with the decision of the American Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) not to recommend replacing the rabbit pyrogen test with the MAT. The U.S. FDA, however, has expressed openness to considering new methods, including MAT, based on the most recent available data.

The Ph. Eur. MAT monograph (chapter 2.6.30) offers the flexibility to use human whole blood—isolated peripheral blood mononuclear cells (PBMC)—either from single donors or pooled from four to eight donors, or the well-characterized cell line Mono Mac 6. As presenters noted, however, testing performance varies from one donor to another depending on cell category, even within categories. To select single-donor PBMC sources for MAT application, Mozier and his team at Pfizer established criteria for a level of PBMC response to endotoxins. He explained that not only endotoxins, but also active ingredients and buffers inherent in drug formulation, degradation products or impurities, can cause pyrogenicity. He views the MAT as a powerful and useful tool for diagnosing issues in drug development, but not as a replacement for LAL-based endotoxin detection.

In an extensive evaluation of cell-based assays for immunogenic effects of biologics in ocular treatment, Zhou showed that impurities triggered and modulated innate immune responses with significant release of cytokines, including the pro-inflammatory interleukins IL-1 β, IL-6 and tumor necrosis factor alpha (TNF-α). These biologics impurities are one type of nonendotoxin pyrogen not detected by LAL-based testing that can cause significant inflammation; thus, negative results based on LAL tests must be verified using the rabbit pyrogen test (RPT). MAT results correlate highly with those of the RPT (> 90%), and the MAT's four-day turnaround is significantly shorter than the three-week animal tolerability study. Consequently, using the MAT (rather than the LAL/RPT sequential approach) accelerates decision making and manufacturing readiness.

A recurring question also came up: Of the three monocyte cell categories (whole blood, cell line or isolated PBMC), which provides the most consistent, reliable and reproducible test results? Bruegger proposed single-donor PBMC at 10^6 cells/mL coupled with IL-6 as a biomarker as the best combination for MAT-based pyrogen detection; its limit of detection is 0.01 EU/mL. This compares to 0.25 EU/mL for whole blood and 0.05 EU/mL for monocyte cell lines, based on two commercially available MAT kits. For blood donors for PBMC isolation and cryopreservation to be valid for MAT, they should test negative for HBV, HCV, HIV and Treponema.

The MAT has been evaluated using the same framework as the LAL, including for product positive control and the low endotoxin recovery (LER) phenomenon. On the endotoxin recovery test, using the quantitative method known as MAT method A and with liposome-based material, Kleindienst found that whole blood-based MAT does not recover the spike endotoxin, an indication of test failure. Bruegger, however, had consistent recovery of spiked endotoxin at recovery rates ➤

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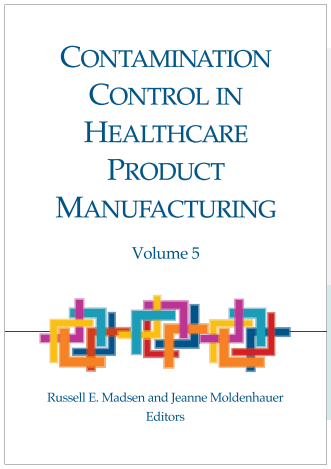
New Release

PDA's *Contamination Control in Healthcare Product Manufacturing, Volume 5* is here!



Contamination Control in Healthcare Product Manufacturing, Volume 5

Edited by: Russell E. Madsen and Jeanne Moldenhauer

PDA Member Price: $240 | PDA Non-member Price: $299

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ranging from 52.1% to 122.3%, based on single donor PBMC (from four different donors) activated by Pam3CSK4, USP reference standard endotoxin and flagellin. These three are ligands for TLR1/TLR2, TLR4 and TLR5, respectively. Whether the variation in these findings is due to the different cell categories used (whole blood versus isolated PBMC) has not been established.

The fact that current limits of detection using MAT methods are higher (LOD ≥ 0.01 EU/mL) than those of LAL-based kits and their derivatives supports the view that LAL-based methods are the best tests for endotoxin detection. Still, current MAT performance shortcomings present an opportunity for further development of this emerging pyrogen detection method. Possible growth areas include optimization of the MAT to reach or improve on 0.005 EU/mL (the current LOD of the chromogenic LAL method) and simplification of the process to reduce the time and expertise needed. Some conference attendees suggested promising results in these areas already.

Update on Low Endotoxin Recovery

At the *2018 PDA Endotoxins Workshop*, **Friedrich von Wintzingerode,** PhD (Senior Manager QC Microbiology, Global Analytical Science and Technology, Roche-Genentech) provided a brief report on PDA's Low Endotoxin Recovery Task Force, composed of experts from academia, FDA, the biopharmaceutical industry and suppliers ***(5).*** Since 2013, evidence increasingly has shown LER to be an inescapable drawback of using LAL-based kits or factor C-dependent tests to evaluate drug formulations containing surfactants, with or without citrate or phosphate salts, due to the inability of LAL or its derivative Factor C to detect the total amount of spiked endotoxin in therapeutic products over hold time. Studies indicate that LER is independent of endotoxin concentrations, and that citrate/Tween-20 buffer significantly inhibits endotoxin recovery within two hours ***(6,7).*** Because of the public health risk presented by the LER phenomenon, FDA recommends that manufacturers conduct endotoxin spike/hold-time recovery tests on therapeutic products to check for LER.

As the task force's technical report continues to evolve, the group encourages firms to generate more LER data and publish the results in peer-reviewed journals. In that vein, **Mark Kapeckas** (Biologics Corporate Quality Global Program Manager, Sanofi Biologics) presented a risk-based approach to LER for previously registered commercial products and investigational new drugs ***(8).*** **Anders Thorn (**Microbiologist, Novo Nordisk) reported on the work done by the hold-time section of the task force, particularly in regard to the burning question: Does the MAT address LER concerns? Mozier noted that the MAT does not always resolve the LER issue. Data from his group's study did not indicate that the reference standard endotoxin was recovered in their product, leading him to conclude that the MAT is most useful for products without LER.

Other studies, though, indicate that the "masked" endotoxin from the most inhibitory buffer (10 mM citrate/0.05% Tween 20) triggered biological activity ***(9,10).*** Using LAL-based and EndoZyme assays, they demonstrated that recombinant protein Tth, whether isolated from *E. coli* or its mutant ClearColi, and the endotoxin from *E. coli* O55:B5 (Sigma-Aldrich), when spiked in the masking buffer citrate/Tween 20, were detected even at significantly low levels. In transient transfection and NF-KB-luciferase reporter gene assays, masked endotoxin and Tth protein triggered a significant bioluminescence. The same masked Tth and LPS provoked a significant release of chemokine CXCL8 and pro-inflammatory cytokines IL-6, IL-8, IL-12 and TNF-α in isolated primary human monocytes. Their flow cytometry analysis was based on the cell surface expression of activation markers CD40, CD80, CD83 and CD86. Results showed that LPS at the concentration ≥ 1 EU/mL, masked or nonmasked, induced significant cell surface expression of activation markers on human monocytes. One group's investigation focusing on endotoxin masking by citrate and polysorbates Tween 20 and Tween 80 also supports another's conclusion that LPS, masked or nonmasked, is a potent inducer of immune response, with a significant release of pro-inflammatory cytokines ***(9,10).***

In the spirit of the PDA microbiology conference and endotoxin workshop and recent studies, I conclude that MAT could be the best method to address LER, and a promising development and risk-management tool for the safety of therapeutic products.

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About the Author

Djikolngar Maouyo, PhD, is Founder and President of PyroDex LLC, which provides MAT services to biopharmaceutical companies, CDMOs and CROs to improve the safety of therapeutic products, including injectable drugs and small implantable devices.

Are You (and Pharma) Ready for the Future?

Karen Walker, Seattle Genetics, and Tia Bush, Amgen

Welcome to the future! Are you ready? The pharmaceutical industry is being challenged, perhaps as never before, to remain relevant, current and capable to address the needs of patients.

Elements of this paradigm change including increasing globalization, better understanding of the science of disease and treatments/cures, patients with access to better information, digitization, automation, targeted treatments, the Internet of Things, manufacturing 4.0 … and so on. Elements of the past that get in the way of our industry being able to keep up with this evolution include an aging infrastructure, bureaucratic practices that impede adoption of enabling technology and a global regulatory framework frequently inflexible and difficult to navigate.

PDA has been at the forefront of continuous innovation in the pharmaceutical industry for decades. We welcome the opportunity to create diverse settings for the industry to come together to discuss and debate solutions to the real issues we are facing today and tomorrow. Through the flagship Annual Meeting, PDA sets the stage and provides venues for information exchange, discussion and exploration on topics related to the future of the pharmaceutical industry.

The *2019 PDA Annual Meeting*, through a combination of plenary sessions, information tracks, interest group meetings and poster presentations, will give attendees the opportunity to engage on topics such as accelerating innovation, meeting the needs of patients at the bedside, leveraging data to drive agility in process development and product delivery and managing the regulatory framework to support rapid innovation. In addition, Day 3 of the *2019 PDA Annual Meeting* will feature opportunities for young professionals to come together, be exposed to PDA's membership, and present their ideas for the future through a special networking session, poster presentations and a Young Professionals track.

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2019 PDA Annual Meeting

San Diego
March 11–15
www.pda.org/2019annual

Co-Authors Team Up for Book Signing at PDA Micro continued from page 18

environmental and control microorganisms, stock culture management, disinfectant effectiveness and best practices and, last but not least, a chapter on biosafety.

The book signing provided an opportunity for us to discuss the book with many interested attendees with a broad range of experience. From these discussions, we learned the book is a valued reference for both new and seasoned microbiologists. Comments included:

> *"My background is not microbiology, [but] this is the practical information I need."*

> *"Comprehensive coverage of topics, organism types and current issues"*

> *"This book is proving to be just what our industry needs now."*

The book can be purchased in the PDA Bookstore (www.pda.org/bookstore).

Editors Mary Griffin (left) and Dona Reber (right) sign copies of the book

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21 Container Closure Development
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26-28 Validation of Moist Heat Sterilization Processes – Option 1 ■
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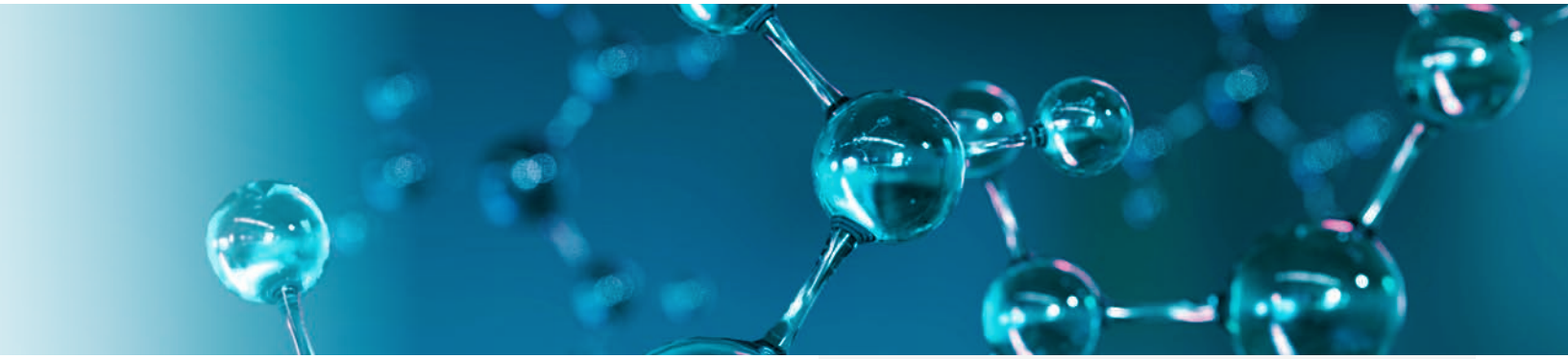

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23-24 **2019 PDA Visual Inspection Forum**
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29-2 **Fundamentals of Aseptic Processing – Option 3** ■
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GLASS
Regulatory Concerns Drive
New Developments in Glass
Rebecca Stauffer, PDA

Glass has a long history in parenteral packaging. In fact, for hundreds of years it was the only parenteral package option available. Yet almost ten years ago, the U.S. FDA expressed concerns about recalls due to glass defects, particularly delamination, in the industry advisory "Advisory to Drug Manufacturers: Formation of Glass Lamellae in Certain Injectable Drugs." Pharmacopeias followed suit, seeking to align their glass chapters.

To get a sense of the current regulatory and compendial climate, the PDA Letter *reached out to some of the speakers and planning committee members at the upcoming PDA* Parenteral Packaging *conference for their perspectives on the current state of glass packaging.*

PDA thanks ***Roger Asselta, Horst Koller,*** *and* ***Derek Duncan*** *for their contributions.*

PDA Letter: What is spurring the push for new packaging options, particularly with glass, for pharma?

Asselta: A lot of the glass companies have come up with new formulations, treatments or processing to enhance their glass offerings to better solve some of the issues around delamination and glass breakage. For example, Corning has developed their Valor® glass which is a chemically strengthened glass along with a special surface treatment to prevent surface damage. Schott came up with Next Gen, which also has enhancements, including some modifications to the formulation and to the surface, and Nipro has their VIALEX™ technology, which enhances the inner surface of the glass and is much more chemically resistant and less likely to be damaged. The industry has kind of responded to the needs of pharma firms for better glass options.

That is on the glass side. On the other side, there are new packaging challenges as well, including new applications. We are seeing a greater increase in biopharmaceuticals, particularly gene and cell therapies, which require unique packaging or have unique packaging circumstances such as deep cold storage that stress the typical package further than it was originally intended. Work has been done to make those packages more robust for those particular applications. Some of that is driven by the changes in USP <1207> Package Integrity Evaluation – Sterile Products and people now have a better understanding of container closure integrity and what the guidelines are going to be in the future. So, again, we are seeing advancements in that area as well.

Koller: The pharma industry has been heavily investigating delamination for quite some years now. Plus, glass breakage, dimensional tolerances, extractables and leachables continue to be hot topics. Based on these issues, the industry is looking for alternatives to these problems. Some of the improvements can only be done by the glassmakers, others by the glass-converting companies.

Duncan: One of the areas in which there is a push for new packaging options is cell and gene therapies. These products require deep cold storage ranging from -80 ˚C to cryogenic temperatures. Initial studies have shown that these low temperatures pose challenges to the traditional package for injectables—the rubber-stoppered glass vial. Specifically, the performance of the seal between the rubber stopper and the glass vial can become compromised due to the material behavior at these low temperatures. This can then introduce some risk to container closure integrity. Other types of product, such as viral vaccines, which are sometimes shipped frozen on dry ice can also suffer from this issue.

PDA Letter: Are companies actively looking into new types of packaging?

Koller: Yes, but it is well known that it takes some time before a new packaging option is finally accepted as an alternative to the existing portfolio. It is also clear that pharma will not "switch over" their drugs completely to these new developments. From what I see, new packaging options are used only if it helps to solve a problem that cannot be fixed with standardized packaging.

Asselta: I would say they are slowly adopting them. They are certainly evaluating them. Many firms are spending a lot of time and money evaluating these technologies. Some are further along than others. As far as the glasses go, I know nothing yet is [being used] for marketed product, but that is coming very soon. I expect to see some changes in this area very shortly.

Duncan: Yes, companies are starting to look into new types of packaging, but the options are fairly limited at the moment. ➤

About the Expert

Roger Asselta is Vice President of Technical Affairs at Genesis Packaging Technologies. He has over 25 years of experience in pharmaceutical packaging, working for firms producing glass containers, plastic containers and closures, elastomeric closures and seals, and sealing technology equipment. This year, he is co-chair of the PDA *Parenteral Packaging* conference.

Article at a Glance

- New types of biologics require new look at packaging options
- Regulators willing to learn about new glass packaging solutions
- Novel forms of glass take longer time for acceptance in Ph. Eur.

About the Expert

Horst Koller's consulting company focuses on technical, regulatory and quality management support around primary and secondary packaging systems. Prior to becoming a consultant, he worked for Abbott Diagnostic and SCHOTT Pharmaceutical Packaging and has more than 20 years of industry experience.

On the pharmaceutical company side, there is a desire to leverage existing manufacturing infrastructure. From a filling and container handling point-of-view, a lot of this infrastructure is designed to handle vials. This limits introduction of novel containers. On the packaging component supplier side, there is a hesitation to invest in developing new packaging options unless there is a clear business case.

PDA Letter: What are the main regulatory and compendial concerns around innovations in glass? Have these led to hurdles in adopting new types of glass packaging?

Koller: Well, for example, the European Pharmacopoeia (Ph. Eur.) describes different glass types and one of them is "neutral glass." Now, neutral glass is defined as borosilicate glass containing significant amounts of boric oxide, aluminum oxide, alkali metal oxide and/or alkaline earth oxide in the glass network. Due to its composition, neutral glass has a high hydrolytic resistance (Type I) and a high thermal shock resistance. So, if you solve one or a couple of the above-mentioned issues by having a different glass composition—and even if you can show that the glass is a Type I glass based on your composition—you still might not be able to make the case for falling under the Ph. Eur. requirements for glass containers for pharmaceutical use because your glass composition is not considered a borosilicate glass as described in these requirements. That can certainly be a hurdle.

Asselta: I personally have not seen that. In fact, I have seen almost the opposite, where regulatory agencies are very interested in what is out there. They want to understand it. They see the potential benefits and are willing to evaluate these new glasses in applications so long as the work has been done up front and sufficient data submitted. I do not think there is any concern on any agency's part as long as it is well documented.

> ***"we are at a stage where recognition of packaging issues is increasing"***

If firms evaluate the suitability of the new glass with the drug product, demonstrate it is going to be sufficient throughout the lifecycle of the product and work in ways it is intended, and have all that supporting data, they [the regulators] will easily accept that.

Duncan: The regulators have signaled a willingness to work with companies and suppliers to bring new cell and gene therapies to market. Much of the attention has been put on the development and manufacturing processes and not so much on the packaging. I think we are at a stage where recognition of packaging issues is increasing; hopefully, this will stimulate all parties to find appropriate solutions for packages that can withstand the challenges of extremely cold temperatures.

PDA Letter: Are there any major differences in the requirements for packaging in the USP versus the Ph. Eur.?

Koller: The glass monographs are harmonized but you still need to test according to USP or Ph. Eur. depending on your registration areas. Now the USP is not legally binding, whereas the Ph. Eur is legally binding but, of course, container closure systems need to be tested according to all required monographs/chapters per region-specific pharmacopeias.

Also, it is important to understand the working principles of the different pharmacopeias like for the Ph. Eur. For the Ph. Eur., a change in a monograph or a new monograph is based on actual existing data, e.g., new material is registered in different countries and therefore proven to be safe. It is not the intent of the EDQM to use the Ph. Eur. to promote new materials. That means that getting a new material into the Ph. Eur. or changing an existing monograph takes time.

PDA Letter: Does glass still have a future in the industry?

Asselta: Yes, I think it does. In fact, I think it has a very good future in the industry, but it is not the only thing. There are more choices out there. And choices are going to be made based on what is necessary to package and protect individual drugs. There are times when glass is the better choice and there are times when a plastic, like a cyclic olefin, would be the better choice or, in some cases, a combination of the two — like a plastic vial with a glass surface or a glass vial with a plastic surface — would be the preferred packaging type.

I do believe strongly that glass has a future but, again, it is not going to be the only thing out there. My guess? For a long time, it is going to remain the largest by far but there are going to be other things that have very specific applications and roles and do things for certain drugs that glass just cannot do.

Want to learn more about glass and other types of packaging? PDA will host its 9th *Parenteral Packaging* conference in Venice, Italy, March 19–20. To view the agenda and register, visit www.pda.org/eu/parpack2019.

About the Expert

Derek Duncan, PhD, is responsible for developing applications for pharmaceutical process monitoring and finished product inspection for Lighthouse Instruments. He is based in Amsterdam.

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An Overview of Container Closure Integrity

Considerations for Achieving an Optimal Performance Window for Container Closure Systems

Qingyu Zeng, PhD, West Pharmaceutical Services, Inc.

[Editor's Note: This is based on the author's presentation at the *2018 PDA Container Closure Performance and Integrity Conference*.**]**

A typical container closure system has three major components: a rubber stopper, a vial and an aluminum seal. In order to satisfy mandatory patient safety requirements, container closure integrity must be ensured through a holistic consideration of many critical aspects ***(1).***

The combination of compatible container closure system components, together with a proper capping process setup, is crucial to ensuring reliable container closure integrity performance—a fundamental requirement of every sterile drug package. Therefore, it is vital to have suitable container closure system components with reliable sealing properties to achieve long-lasting container closure integrity performance throughout the entire product lifespan. Here, lifespan refers to the time interval from the moment the vial assembly is capped until the drug is administered to the patient.

Fortunately, there is a way to achieve an optimal performance window by following the adage of "working smarter not harder."

In order to ensure acceptable container closure integrity performance, a container closure system must maintain adequate residual seal force (RSF), the force that a rubber stopper flange exerts against the vial flange surface in an assembled, capped container closure system ***(2).*** The RSF within a container closure system is time-dependent, decaying exponentially over time and eventually leveling off due to rubber stopper compression stress relaxation, as shown in **Figure 1** ***(3,4).***

Typically, rubber stoppers are made of rubber compounds primarily composed of polymers and fillers. Rubber polymer molecular structures may be linear, branched, cross-linked or networked, all of which affect the chemical, physical and mechanical properties of the rubber stopper ***(5,6),*** resulting in both elastic and viscous resistance to compression ***(7,8).*** In effect, rubber stoppers can retain the recoverable (elastic) strain energy partially, but also dissipate energy (viscous) partially if compression is maintained. Therefore, under constant compression, rubber stoppers undergo stress decay, known as compression stress relaxation ***(7,8).*** The Maxwell-Wiechert model simulates rubber stress relaxation under compression. ***(7,8).*** **Figure 1** is an example from a case study showing RSF decay testing data and modeling predictions based on the Maxwell-Wiechert theory.

Since the RSF relaxes over time due to the viscoelastic characteristic nature of the

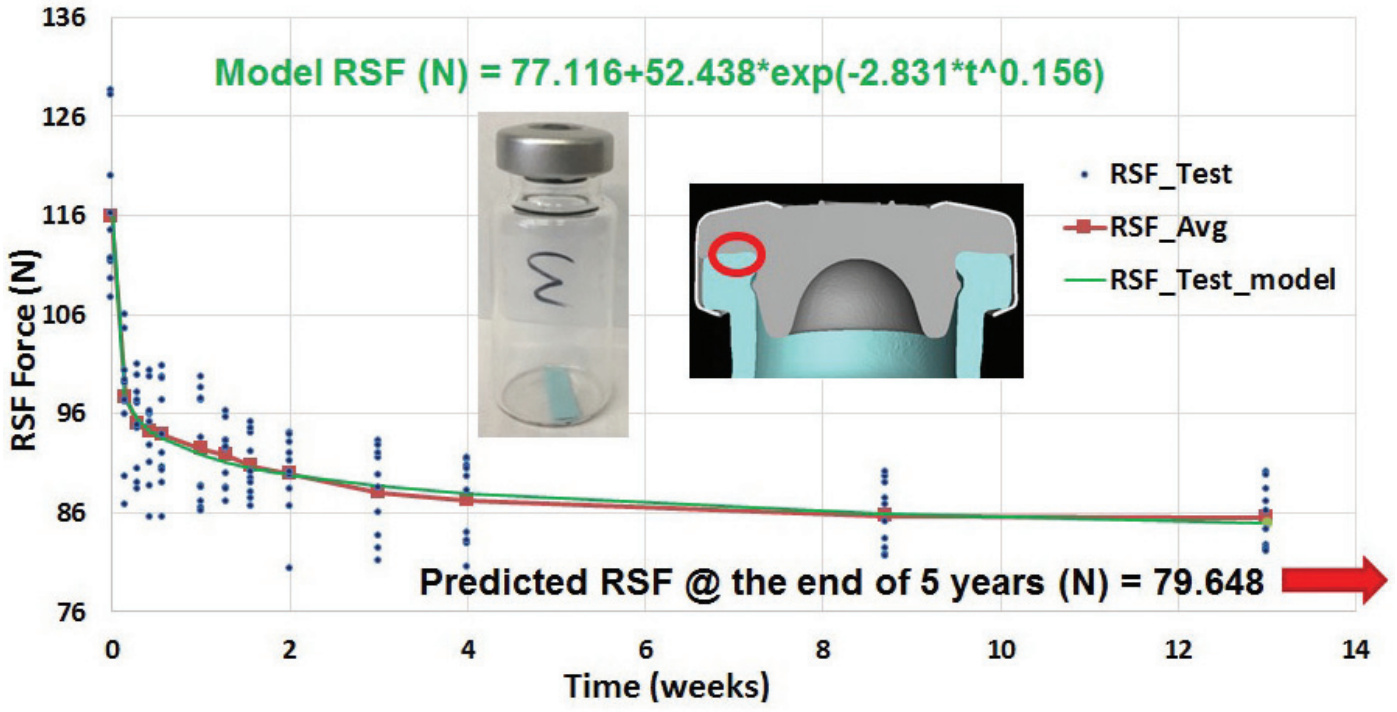

Figure 1 Time-Dependent RSF Testing Data and Modeling Prediction

rubber stopper materials, the magnitude and rate of RSF decay depend on rubber polymer molecular structure, rubber formulation, rubber properties, container closure system dimensions (stopper, vial, and aluminum seal) and capping process setup ***(4).*** In fact, RSF decay can be engineered, to a certain degree, through rubber molecule structure design and material property modification for optimal container closure integrity performance. The resultant stress relaxation has an impact on whether the container closure system can successfully maintain adequate container closure integrity throughout the entire sealed drug product lifespan. To ensure acceptable container closure integrity performance throughout the product lifespan, proper stopper compression must be imposed by the capping process for sufficient RSF beginning at time zero. Typically, a high compression percentage leads to high RSF. **Figure 2** represents an example taken from a time-dependent case study with testing data up to one year showing the relationship between RSF and helium leak container closure integrity results ***(9–11).***

> ***"working "smart" to ensure integrity of container closure systems requires focusing on compatible components"***

In general, high RSF leads to relatively low helium leak results with tight statistical spreads for good container closure integrity performance, while low RSF results are associated with poor container closure integrity performance, causing relatively high helium leak results and large statistical spreads, increasing the risk of failing the maximum allowable leakage limit (MALL).

In general, a capping process must be set up with sufficiently high stopper compression to ensure that the RSF is high enough at time zero and throughout the entire sealed drug product lifespan to ensure container closure performance. Excessive stopper compression may cause cosmetic defects, however, adversely affecting visual appearance of a vial assembly. **Figure 3** shows some photos of rejectable cosmetic defects due to excessive stopper compression during the capping process that resulted in visual inspection failure on a pharmaceutical manufacturing floor ***(9–11).*** These example defects include, but are not limited to, (a) seal skirt wrinkling under the vial flange, (b) stopper dimpling, (c) seal side buckling or (d) a combination of these defects—all because of excessive stopper compression during the capping process.

In light of all these conflicting challenges, it is imperative to strike a balance that satisfies ➤

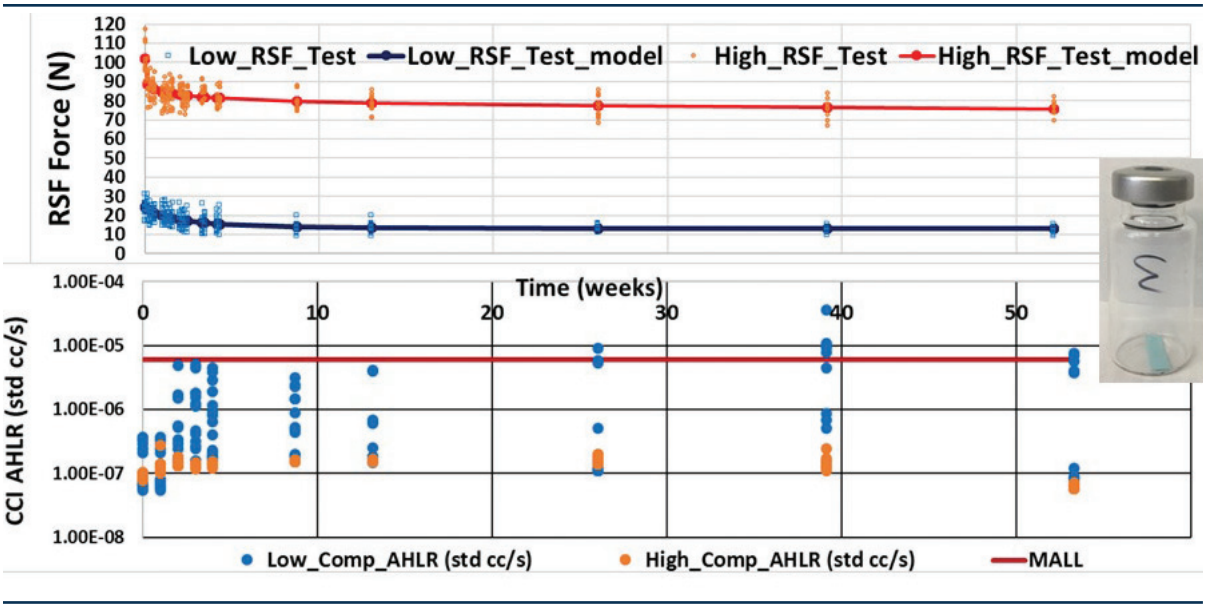

Figure 2 Relationship between RSF and Helium Leak Container Closure Integrity Results

all container closure system performance needs. In this situation, working "smart" means clearly defining and locating a balanced window to satisfy both RSF/container closure integrity performance with acceptable cosmetic visual appearance. As demonstrated in **Figure 3,** for mapping out a balanced container closure system performance window, the horizontal axis represents stopper flange compression percentage, and the vertical axis denotes seal skirt overhang length, defined as subtracting the summation of stopper flange thickness and vial flange thickness from the overall seal skirt length. Essentially, after completing the capping process at time zero, a vial assembly must have its container closure system stack-up dimension characteristics (located within the rectangular shadowed area in the chart on **Figure 3**) described as follows:

1. Actual seal skirt overhang length will depend on stopper compression percentage, and it must be larger than, minimum overhang limit (horizontal red line) to properly assemble container closure system components together

2. Actual seal skirt overhang length should be less than maximum overhang limit to avoid seal skirt wrinkling under the vial flange

3. Actual stopper flange compression percentage must surpass lower compression limit to ensure sufficient RSF throughout the entire sealed-drug lifespan for acceptable minimum container closure integrity performance

4. Stopper flange compression percentage should not be excessive and beyond the upper compression limit to avoid visual defects such as, but not limited to, seal skirt wrinkling under the vial flange, stopper dimpling, seal side buckling or any combination of these defects

In reality, stopper flange thickness, vial flange thickness and seal skirt length are statistical variables. As a result of container closure system stack-up, the seal skirt overhang length also becomes a statistic variable, in addition to its dependence on actual stopper flange compression percentage. The statistical distribution of overhang length is schematically represented as a green curve in the chart on **Figure 3**, and it moves along the track between the blue line and the yellow line depending on the actual compression percentage. The blue line represents maximum overhang length data points at discrete compression percentage points, and the yellow line corresponds to the minimum overhang length data points. The goal is to ensure the green distribution curve of overhang length is positioned within the rectangular shadowed area on the chart in **Figure 3**. This will lead to the satisfactory container closure system performance as described above.

In summary, working "smart" to ensure integrity ➤

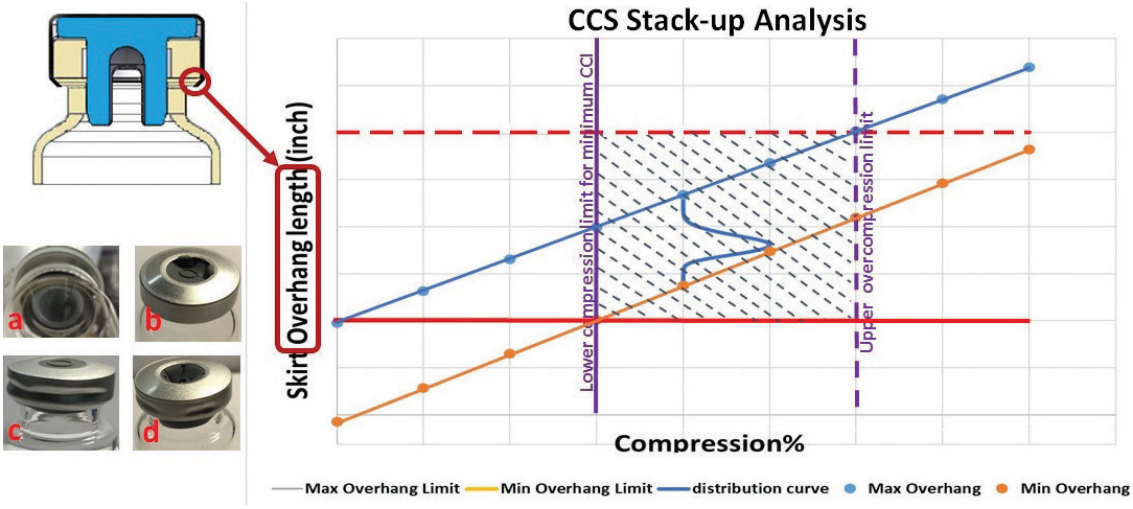

Figure 3 Mapping a Balanced Container Closure System Performance Window

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of container closure systems requires focusing on compatible components with good rubber material properties, together with appropriate container closure system stack-up through proper compression percentage process setup to ensure optimal container closure system performance (RSF, container closure integrity and visual appearance) throughout the entire sealed drug lifespan. In fact, this container closure system compatibility for optimal performance window can be calculated, simulated, predicted, tested and assessed through an integrated system approach for critical data-driven risk management, provided sufficient container closure system component data is available.

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[Editor's Note: The author's company is one of the sponsors of the PDA *Parenteral Packaging* conference**.]**

About the Author

Qingyu Zeng, PhD, is Fellow and Technical Director with West Pharmaceutical Services, Inc. He can be reached at qingyu.zeng@westpharma.com

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United States and Europe Align on Glass

Recently, the U.S. Pharmacopeia (USP) has sought to align its chapters on glass packaging with the European Pharmacopoeia (Ph. Eur.).

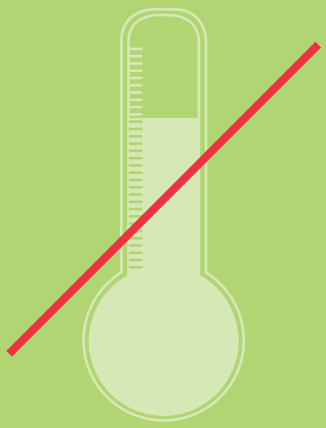
What spurred this alignment?

Between 2005 and 2010, there were more than 20 recalls associated with glass issues, resulting in more than 100 million units of drug product withdrawn from the market.

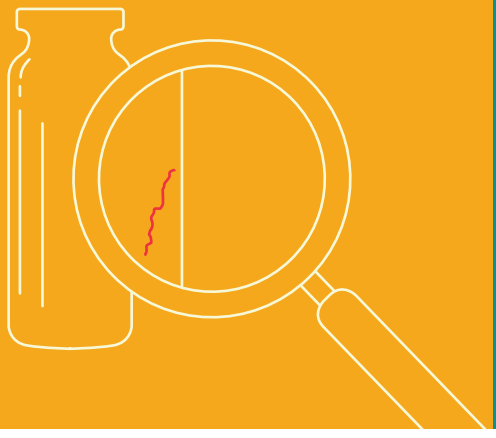
So, what are some of ways USP has aligned with Ph. Eur.?

Replacement of powdered glass test with glass grains test

Removing requirement for water attack test at 121 ˚C



Incorporation of surface glass test



Proposing a chapter on delamination

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Quality Metrics Still a Point of Discussion between Industry, U.S. FDA

Rebecca Stauffer, PDA

With only a few weeks of planning, PDA's Quality Systems Interest Group pulled off a successful session on quality metrics Sept. 24 at the *2018 PDA/FDA Joint Regulatory Conference.*

Despite having been listed on the conference agenda for a mere three weeks, the room was packed. Attendees came to listen to **Steven Mendivil,** Senior Advisor, International Quality External Affairs, and leader of PDA's quality metrics task force, share a dialogue on quality metrics with **Tara Gooen Bizjak,** Senior Science Policy Advisor, Pharmaceutical Quality, CDER, U.S. FDA.

Below is a sampling of the discussion:

Mendivil: This is the first time that I have seen a second, and possibly even, a third draft guidance. Can you speak to some of the challenges FDA has experienced in this journey?

Bizjak: This has been quite a big effort—almost unprecedented in my experience… everybody has their own opinion, right? Just like in FDA. And just like with stakeholders in either industry or academia as well. So, I think there have been challenges but there are also opportunities. This is a really large opportunity for the pharma industry to really take that next step forward encouraging more modern quality systems and more modern manufacturing as well as an opportunity for FDA to learn from some of that information and be able to really make a…change in our regulatory oversight.

Right First Time

Mendivil: I think when it came to the points about a "common definition," there was a sense that these might not be the most valuable metrics such as "right first time" metrics, which sounds conceptually great, but there is no common definition of what it is.

Bizjak: In fact, in the first *Federal Register,* notice we did not include right first time because of so many variable definitions for the concept of right first time and this internal evaluation process…we asked if right first time was a valuable metric to include and we did not receive a lot of feedback about that.

Recent Activity

Mendivil: Can you explain more about the two *Federal Register* notices that were published over the summer? One detailed how companies could arrange in-person meetings at FDA headquarters and the other covered how companies can request an FDA site visit.

Bizjak: There are two *Federal Register* notices. One is what we refer to as the feedback program and the other is the site visit program. The site visit program is fairly straightforward because everyone here is used to site visits—the concept of having FDA come out and visit the site, not issue a warning letter, not issue a 483, just to learn about the site. That is a more tangible process. It would be a one-time visit.

And, then, the second one is more of an in-depth opportunity to provide feedback and back-and-forth dialogue. We set this up using the meetings approach, like the Type C meetings and pre-IND meetings, as a mechanism to be able to have this dialogue. A company would provide information about metrics they feel are appropriate, definitions that work for them that they want to share with us and have that back-and-forth communication where a company could present, "This is what we do. This is how we run our quality metrics program, how we have adapted over time." That sort of thing… they [the meetings] can be done virtually, too. This just has an opportunity for follow-up and more discussion.

Audience Question: Are both of these open to anyone?

Bizjak: That is correct. All the mechanisms are open to anyone who is applicable… it is open to everyone [barring Agency prioritization needs for site visits].

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Innovative Tech Drives Drug Shortage Solutions

Robert Guidos, Corning

Drug shortages are receiving renewed attention by regulators. At a November 2018 public meeting sponsored by the U.S. FDA, oncologists, pharmacists and other healthcare professionals reported the tremendous burden shortages place on the healthcare system, often with dire consequences for patients. During the meeting, FDA reported that the impact of shortages on public health remains "high," revealing that the Agency is seeing increased numbers of shortages with longer durations and higher intensities. This uptick follows years of decline in drug shortages.

It comes as no surprise that sterile injectable products remain particularly vulnerable to short supply due to the additional safeguards needed to maintain sterility assurance. Economics is also a key factor. In a recent blog post, FDA Commissioner **Scott Gottlieb** and CDER Director **Janet Woodcock,** wrote that sterile injectable products "may sometimes be priced too low relative to the full cost of reliably producing a predictable and high-quality pharmaceutical product" ***(1).*** Moreover, in a seminal 2012 article, Woodcock and an FDA economist described how drug purchasers, including hospitals and clinics, force a race to the bottom in the sterile injectables market by valuing lower drug prices over quality:

> "A fundamental problem we identify is that the market does not sufficiently recognize or reward quality … The resulting lack of reward for quality may encourage manufacturers to keep costs down by, for example, minimizing quality investments … In the case of sterile injectables, there is very little margin for error…" ***(2)***

The resulting market failure has reignited Congress' interest as well. In June 2018, 148 Members from the U.S. Senate and House of Representatives wrote to Commissioner Gottlieb with their concerns. This outreach built upon work Congress undertook to address shortages as part of the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012. Although supportive, FDASIA's solutions have not fixed the problem. As a result, the drug shortages task force Congress created in 2012 is now exploring new policy recommendations, both within and outside FDA. Those recommendations will be submitted to Congress this year and likely would target drugs at risk of shortage as well as cover a list of medicines deemed "essential" based on criteria outlined by FDA and other experts. Government experts also seek to leverage U.S. national security efforts such as those that support the manufacture and stockpiling of medical countermeasures for national emergencies (e.g., pandemics, bioterrorism events). FDA outlined some of the solutions under consideration in a *Federal Register* notice with a commenting period that closed Jan. 11 ***(3).***

Quality Issues at Heart of Shortages

One proposed solution stakeholders have raised is financial incentives. These could come in the form of tax credits to encourage upgrades to aging manufacturing facilities or the adoption of beneficial, emerging technologies. Revised reimbursement policies are being considered to support health systems' purchasing of higher quality products from more reliable sources. The goal here is to overcome some of the inertia FDA leaders have observed in the pharmaceutical industry's willingness to invest in new tools that raise the bar on quality. Integral to many of the ideas floating around is the need to identify quality metrics for scoring the relative value of various technologies/manufacturing processes. Whether scoring algorithms are developed by FDA in partnership with industry or by a third party, providing manufacturers, payors and consumers with the information they need to make informed purchasing decisions based on price *and quality* could go a long way toward an enduring solution to sterile injectable shortages.

Stakeholders have stressed the importance of ensuring greater transparency of critical information held by FDA and drug companies. Availability of information linking manufacturing facilities to the production of specific drugs could allow pharmacists to prepare for shortages as FDA identifies quality issues within specific facilities. Moreover, posting detailed information on root causes of shortages, including separate FDA analyses describing the severity and frequency associated with such causes, would be ➤

helpful. Currently, FDA only posts vague information for each shortage, such as "manufacturing quality issues." With more detailed information, suppliers with expertise in critical areas—drug manufacturing equipment design, packaging, chemical synthesis, etc.—could design new technologies or consider new uses for existing technologies to overcome those deficiencies while also opening up new market opportunities.

Emerging Tech Plays Key Role

Of the emerging technologies that could be helpful, several obvious ones come to mind, notably 3-D printing and continuous manufacturing. These have received considerable media attention and tremendous support from FDA. But there are three additional technologies that warrant consideration.

1. Novel Glass Packaging

FDA leaders have highlighted "shards of glass" as one of the sources of contamination within multiple manufacturing facilities, resulting in a spate of sterile injectable shortages. Glass is the ideal packaging material for injectable drugs, however, borosilicate glass containers are inherently susceptible to delamination, particulate generation and damage that can lead to breaks and the spread of glass particulates on drug manufacturing filling lines ***(4).*** Such events require human intervention, furthering the potential to introduce contaminants into sterile space. Shortcomings such as these contribute to critical quality failures that often result in regulatory actions, recalls and drug shortages ***(5–7).***

Fortunately, new types of glass for primary packaging are becoming available that eliminate or significantly reduce the risk of certain key quality issues associated with borosilicate glass containers ***(8–10).*** Some of these new glass types promise to reduce the threat of shortages by permitting manufacturing lines to run at higher speeds with improved yields due to the stronger structure of the glass. Note that higher line outputs also offer manufacturers opportunities to consolidate manufacturing assets, decommission expensive obsolete equipment and defer costly capacity increases.

2. Meso Flow Reactors

Meso flow reactor technology can increase the efficiency, scalability, yields and quality of active pharmaceutical ingredient processing, while reducing performance variability, costs and the potential for safety issues ***(11).*** These reactors provide superior capabilities over batch-based production, by increasing reaction and yield rates, and enabling actions difficult to perform with batch processing. Moreover, continuous flow processing inherently offers fewer chances for quality issues. Additional advantages include: in-line quality testing, shortened production times, a smaller footprint that reduces operating costs and environmental impacts, improved efficiency that allows for greater volumes produced and more nimble testing and control that can help reduce the likelihood of manufacturing failures.

3. Isolator Technology

Although not an emerging technology, isolators for parenteral filling operations can help protect against contamination risks, and it is worth mentioning their role in assuring the sterility of inject-

able products, ensuring manufacturing reliability and reducing drug shortages. The value of isolator technologies has been highlighted by FDA leaders and by Civica Rx, a recently launched not-for-profit generic drug company focused on shortages.

Summary

Sterile injectable shortages continue to pose severe challenges to U.S. health systems and, most importantly, to patients. Without increased public and private sector investment in enhanced quality through upgrades in manufacturing infrastructure and adoption of supportive technologies, the industry will continue to witness an increase in the occurrence, duration and intensity of shortages.

[Editor's Note: The author's company is one of the sponsors of the upcoming *Parenteral Packaging* conference**.]**

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About the Author

Robert Guidos is Head of Pharmaceutical Regulatory Affairs and Policy with Corning Incorporated. He formerly served as the Associate Director for Legislative Affairs and Senior Advisor to the Director at CDER.

PDA Adapts to Changing Future

Richard Johnson

This new year marks the 73rd anniversary of PDA. Last year saw a surge of activity across our various focus areas and we will continue our focus on *Connecting People, Science and Regulation®*.

Much like the pharmaceutical community, our focus is on, first and foremost, people. While pharma companies and others throughout the supply chain focus on enhancing value to patients, PDA's role is to help them achieve this. Our members, and the larger community, benefit from our education, communication and scientific leadership. We completed our biannual customer survey of more than 1,600 individuals (member and nonmember) worldwide, and while the data showed that PDA is valued most highly in our credibility and value, we continue to strive for improvement.

We continued to grow, adding young professionals and regulators to our community. We offered 36 conferences and workshops in 2018, along with more than 110 training courses in locations around the world.

We also adapted our use of technology to better serve customers. Some examples of this include:

- Complying with data protection and privacy requirements enacted in several countries around the world
- Redesigning PDA's website to increase usability, expand mobile compatibility and allow users to navigate by topic
- Simulcasting key meetings to enhance the ability of attendees to hear from and interact with speakers across the globe
- Increasing the use of audience response systems to gather input from attendees
- Developing an e-learning platform anticipated to launch in early 2019 so we can begin to offer computer-based training
- Enhancing the PDA newsfeed, our *news uPDAte*SM, which employs artificial intelligence to fine-tune topics based on readers' preferences; we provide this at no cost to members and nonmembers
- Expanding our offering of online articles and videos to keep up with the continuing migration from print to electronic access
- Increasing our efforts to translate technical reports into other languages
- Improving PDA Connect℠ with a new platform and expanding it to all interest groups and chapters

We hope you have found these new technology features valuable, and we will continue to explore ways to use technology to enhance member and customer value.

All of this has been accomplished through the work of our dedicated staff and volunteers on committees and task forces, who collaborate with colleagues around the world to advance PDA's important mission. We look forward to your integral role in maintaining PDA's position as an industry leader.

We continue to value and appreciate your contributions! Remember, PDA is your association! We value your input. If you happen to be in Berlin or Bethesda and have the time, please feel free to stop by. We would love to meet you.

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Embracing the Future of Cell and Gene Therapies

Rebecca Devine, PhD, PDA Chair

If you have read the news lately, you probably are aware of some of the recent developments in cell and gene therapies. These innovative products offer potential life-saving treatments for cancer, genetic disorders, neurodegenerative diseases, etc. While a few have been approved in the United States and Europe, more remain in the pipeline. And as these therapies become mainstream, manufacturing will help bring them to light.

At the same time, cell and gene therapies present unique manufacturing and supply chain issues when compared to traditional large molecule drug products. PDA is excited to expand our involvement in this growing area. Last year saw PDA host its 10th *Advanced Therapy Medicinal Products* conference in Amsterdam in the spring. Later in 2018, PDA hosted a successful *Cell and Gene Therapy Conference* in the United States. In addition, our new Cell and Gene Therapy Interest Group held its first meetings.

We will continue to embrace cell and gene therapies even more in 2019. For the first time ever, PDA appointed a board member with a specific focus on cell and gene therapies. We welcome **Michael Blackton,** Vice President, Quality, CMC, Adaptimmune, to the board this year. He has been one of our leading volunteers in this area. He co-chaired the *2018 PDA Cell and Gene Therapy Conference* and is also the co-leader of the Cell and Gene Therapy Interest Group. I look forward to working with him on the board to advance PDA's efforts in this area.

This year you can expect a technical report on cell and gene therapy manufacturing. In April, the *Advanced Therapy Medicinal Products* conference will be held in Vilnius, Lithuania. During our *2019 PDA Biopharmaceuticals Week,* we will also hold the *2019 PDA Cell and Gene Therapy Conference,* May 6–7. In addition, we plan to expand our courses in this area. Cell and gene therapy manufacturing will continue to be a topic explored in *PDA Letter* articles and "On the Issue" videos as well as in the *PDA Journal of Pharmaceutical Science and Technology.*

This is an exciting area that is surely the future of pharma. We look forward to offering more to our members in this area. If this topic interests you, I encourage you to volunteer and get involved.

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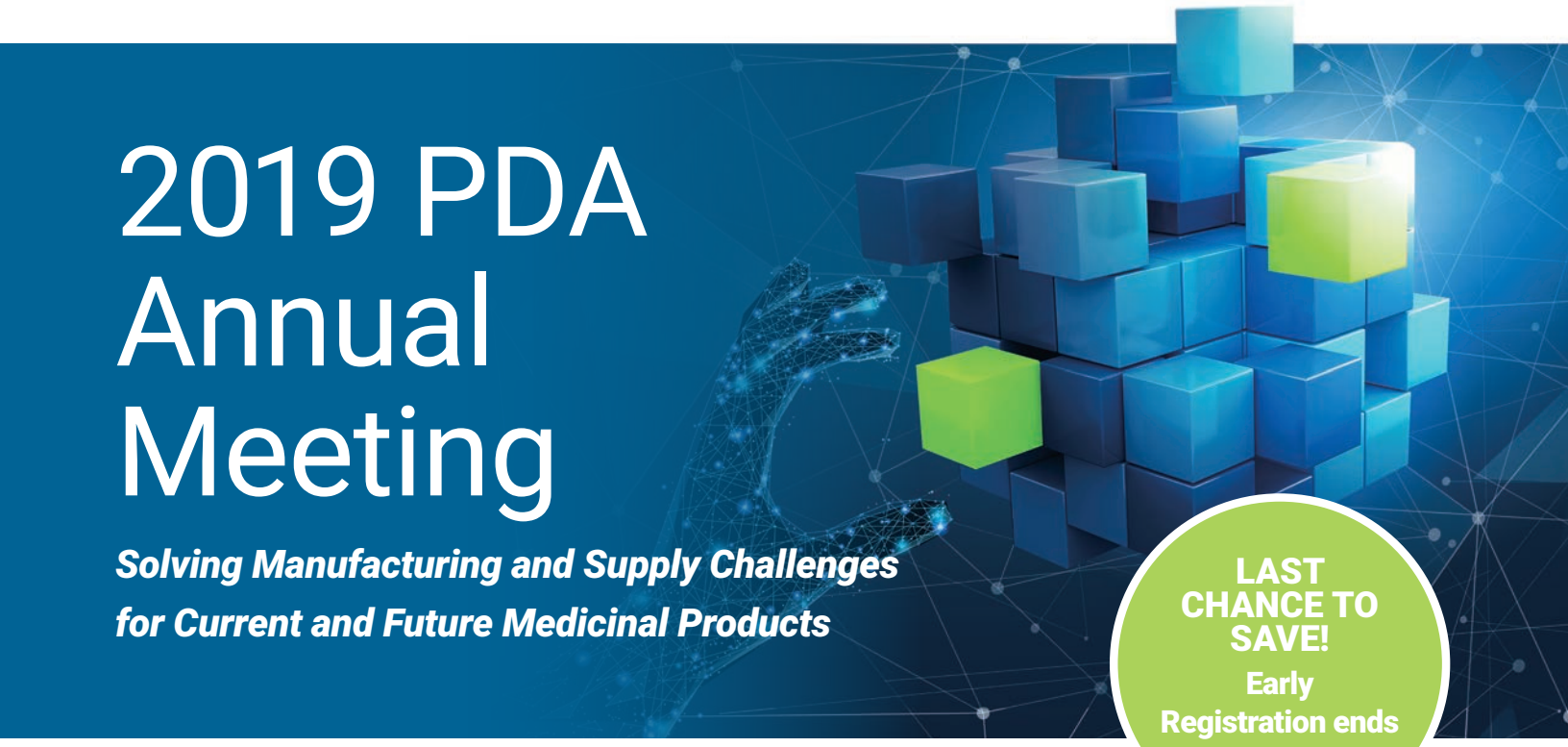

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