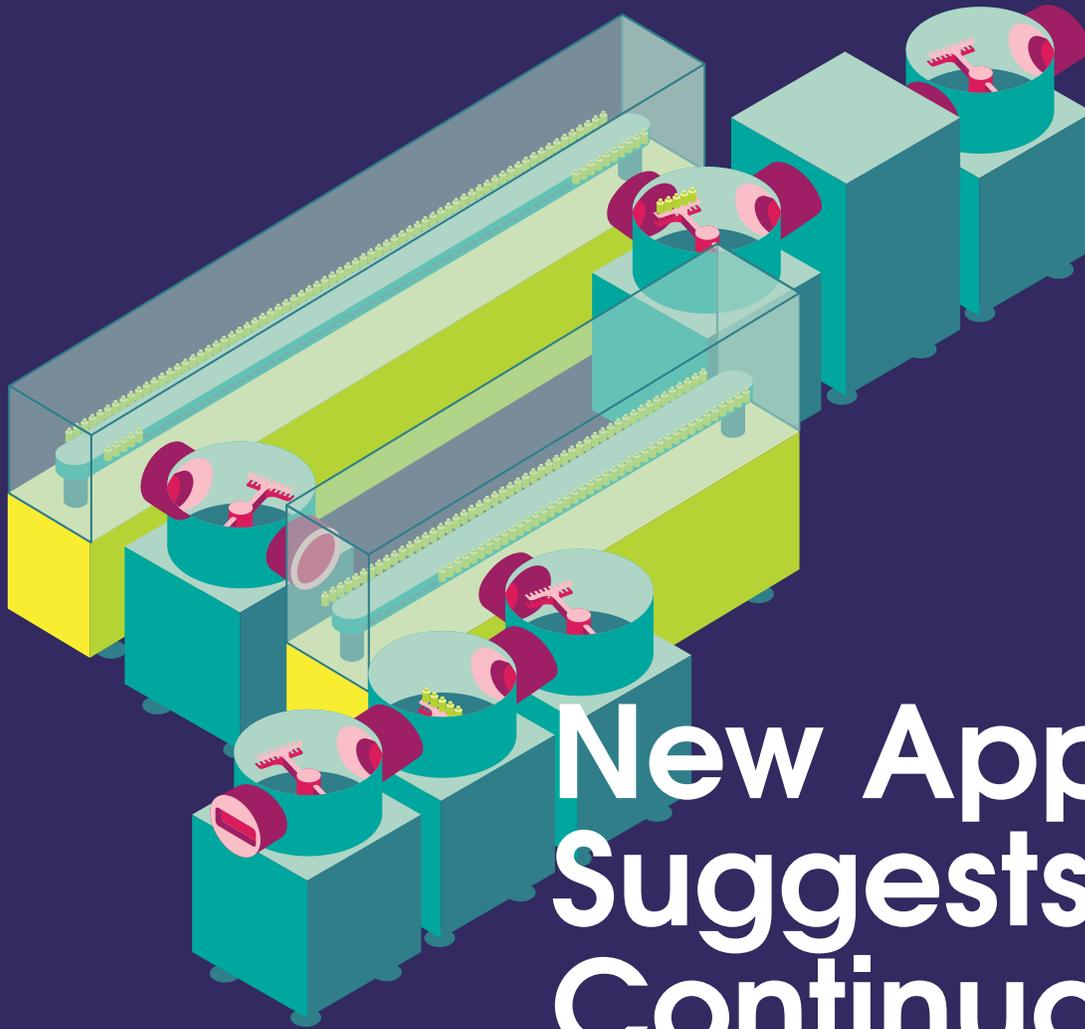


# PDA Letter

Volume LIV • Issue 3

[www.pda.org/pdaletter](http://www.pda.org/pdaletter)

March 2018



## New Approach Suggests Continuous Lyophilization is Possible 26

20 Microbial Counts  
and EM

35 Airflow Visualization  
Helps Aseptic Control

40 Summary of Container  
Closure Workshop

# SAVE THE DATE!

**Registration is now open for the following 2018 PDA events:**

**MARCH**  
19-21

**2018 PDA Annual Meeting** | Orlando, FL

Explore current and future trends in patient centricity, disruptive technologies, process development and manufacturing, and next-generation facilities. Learn more and register at: [pda.org/2018Annual](http://pda.org/2018Annual)

**MARCH**  
21-22

**2018 PDA Manufacturing Intelligence Workshop** | Orlando, FL

This Workshop will focus on digital quality management, designing data strategies, and examining the risks and challenges surrounding the use of modern data. Learn more and register at: [pda.org/2018MI](http://pda.org/2018MI)

**APRIL**  
17-18

**2018 PDA Biopharmaceuticals Conference** | Seoul, Korea

Industry and regulatory experts will discuss biopharmaceutical industry trends and their regulatory and technical impact. The challenges of commercialization of biosimilars in a competitive global environment will also be addressed. Learn more and register at: [pda.org/2018Biopharma](http://pda.org/2018Biopharma)

**APRIL**  
24

**2018 PDA Packaging Science Interest Group Workshop** | Bethesda, MD

For the first time in the United States, PDA is hosting a one-day Packaging Science Interest Group Workshop. This workshop will be a venue for the exchange of knowledge and ideas about pharmaceutical packaging. Learn more and register at: [pda.org/2018PackagingIG](http://pda.org/2018PackagingIG)

**APRIL**  
25

**2018 PDA Visual Inspection Interest Group Workshop** | Bethesda, MD

This one-day standalone meeting will facilitate in-depth discussion the issues of greatest interest and concern to the field of visual inspection. Learn more and register at: [pda.org/2018VisualIG](http://pda.org/2018VisualIG)

**MAY**  
14-15

**2018 PDA Sterile Medicinal Products Manufacturing Conference** | Bethesda, MD

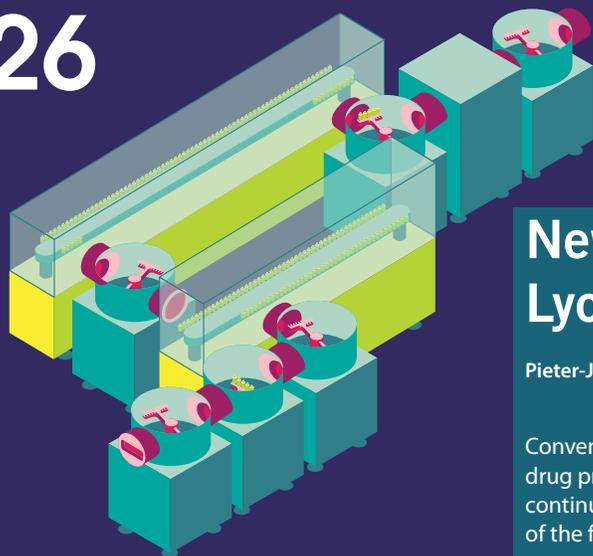
This Conference will cover modern approaches to aseptic product manufacturing and will focus on the following sterile product manufacturing essentials, with special reference to the draft revision of the EU GMP Annex 1. Learn more and register at: [pda.org/2018Sterile](http://pda.org/2018Sterile)

**JUNE**  
13-14

**2018 PDA Container Closure Performance and Integrity Conference** | Bethesda, MD

Broaden your understanding of holistic requirements related to performance and protection by learning how to identify potential failure modes throughout the life of a product and de-risking container closure design during development. Learn more and register at: [pda.org/2018CCPI](http://pda.org/2018CCPI)

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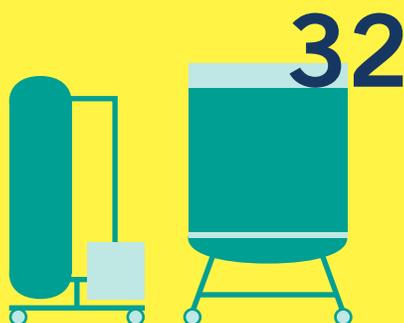
## New Approach Suggests Continuous Lyophilization is Possible

Pieter-Jan Van Bockstal, Ghent University, Jos Corver, RheaVita, Thomas De Beer, Ghent University

Conventional batch freeze-drying has long been the mainstay for stabilizing biologic drug products in storage and distribution, but it presents many challenges. An innovative continuous process for freeze-drying has been developed, however, that may offer a view of the future of freeze-drying for biologics.

Cover Art Illustrated by Katja Yount

### InfoGraphic



## A Model for Downstream Continuous Biomanufacturing

Many biologics manufacturers wonder if continuous manufacturing is achievable for downstream processing. A model approach indicates it is.

35

## Smoke Signals One Plant's Secret for Assuring Aseptic Control

Tony Pavell, Fresenius Kabi

Airflow visualization testing, conducted as part of a routine review program, can help assure that aseptic filling areas remain under a state of proper control.



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

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### Digital Exclusive

- > **Adapt Your Nest-and-Tub System as the Industry Evolves**  
How can ready-to-use components such as nests and tubs support flexible manufacturing?
- > **New Tech Disrupts Traditional Aseptic Processing**  
Two speakers from the 2018 PDA Annual Meeting discuss recent advancements in isolator technology.

[pda.org/letter](http://pda.org/letter)

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# Volunteer Opportunities at PDA

## Leadership

- ◉ PDA Executive Officers

- ◉ Director

- ◉ Scientific Advisory Board
- ◉ Biotechnology Advisory Board

- ◉ Regulatory Affairs and Quality Advisory Board

- ◉ PDA Committee Chair/Co-Chair
- ◉ Task Force Co-Chair

- ◉ Author/Contributor to the *PDA Letter*
- ◉ Author/Contributor to the *PDA Journal*
- ◉ Poster Presenter
- ◉ Attend Chapter Committee/Planning Meetings
- ◉ Technical Report Peer Reviewer

- ◉ Speaker
- ◉ Chapter Leader
- ◉ Task Force Member
- ◉ TRI Instructor
- ◉ Interest Group Leader

### PDA Committees:

- ◉ Program Planning Committee
- ◉ PDA Letter Committee
- ◉ Membership Committee
- ◉ Education Committee
- ◉ Audit Committee

- ◉ PDA Membership
- ◉ Attend Global PDA Meetings

- ◉ Attend Chapter Events
- ◉ Survey Reviewer

- ◉ Interest Group Member
- ◉ Attend TRI Courses

## Getting Involved

1,000

Over 1,000 volunteers worldwide actively carry out PDA's Mission

[volunteer@pda.org](mailto:volunteer@pda.org)



# 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](http://www.pda.org/pdaletter)**

# Continuously Continuous Pharma

The United States and Europe have seen a massive flu outbreak. Not surprisingly, this has led to concerns about the supply of available vaccines, not just flu vaccines. In February, the U.S. FDA Commissioner requested additional funding for Agency initiatives in support of continuous manufacturing, citing the need for a stable supply of vaccines (1). This follows the Agency's 2015 approval of a cystic fibrosis drug manufactured using a continuous processing line (2). In that instance, the manufacturer—Vertex Pharmaceuticals—worked directly with the FDA's Emerging Technology Team.

Many large pharma companies are currently investing in continuous manufacturing. Pfizer, Eli Lilly, GlaxoSmithKline, and Novartis are some of the big names moving into continuous manufacturing. Novartis has even partnered with the Massachusetts Institute of Technology on a continuous manufacturing collaboration project (2). While many of the current continuous manufacturing projects are designed around oral solid doses, as the technology for continuous manufacturing advances, it is inevitable that continuous manufacturing of biologics will follow.

In fact, PDA has quite a few volunteer teams involved in support of continuous manufacturing. The Manufacturing Science and Operations Program (MSOP<sup>SM</sup>) has members involved in this area. The topic has been addressed at a PDA workshop in 2015 as well as in sessions at many of our major meetings, including the Annual Meeting and *PDA/FDA Joint Regulatory Conference*. It also a topic of articles found in the *PDA Letter* and *PDA Journal of Pharmaceutical Science and Technology*.

Continuous manufacturing is also seeping into other areas. A team of researchers at Ghent University in Belgium are working on a solution for continuous lyophilization (see p. 26). This could potentially impact biologics, including special, personalized batches.

The future of pharmaceutical and biopharmaceutical manufacturing looks to be primarily continuous. And PDA's volunteers and members will be there to lead it.

## References

1. "FDA's Gottlieb on Funding to Promote Innovation Including Advanced Manufacturing Technologies." U.S. FDA, February 13, 2018. <http://www.pda.myindustrytracker.com/en/article/89828/fda-s-gottlieb-on-funding-to-promote-innovation>
2. Neil, S. "Pharma Catches on to Continuous Manufacturing." *AutomationWorld*. (Dec. 6, 2017) <https://www.automationworld.com/article/technologies/dcs/pharma-catches-continuous-manufacturing>



Rebecca Stauffer

# Nominate a Candidate for the PDA Board of Directors

PDA's Nominating Committee seeks member recommendations for nominees of candidates to fulfill Board of Director positions for the 2019–2021 term. Nominees must be current PDA members in good standing. This year's committee is chaired by **Martin VanTrieste**, Immediate Past Chair of the Board of Directors.

If you are interested in being considered or want to recommend someone, send a recommendation (including full name, contact information and rationale for nomination) by email to [nominate@pda.org](mailto:nominate@pda.org) or by regular mail to PDA Global Headquarters, Bethesda Towers, Suite 600, 4350 East West Highway, Bethesda, MD, 20814, USA, Attention: Nominating Committee. Please include any supporting information, which may make it easier for the Nominating Committee to evaluate your recommendation. Nominations are due May 15.

If you have any questions, feel free to contact PDA President **Richard Johnson** at [johnson@pda.org](mailto:johnson@pda.org) or Martin VanTrieste at [mvantrieste@gmail.com](mailto:mvantrieste@gmail.com). 🍷



**PDA**  
Parenteral Drug Association

The Parenteral Drug Association presents:

# Freeze Drying in Practice

PDA Europe Training Course

**23–27 April 2018**

Martin Christ Gefriertrocknungsanlagen GmbH  
**Osterode (Harz) | Germany**

MARK YOUR CALENDAR

[www.pda.org/eu/fdp2018](http://www.pda.org/eu/fdp2018)

# INTERPHEX Roundtables Address PUPSIT, Big Data

PDA is once again the Premier Association Sponsor for the *INTERPHEX* show scheduled for April 17–19 in New York City.

In this role, PDA will be hosting three informational roundtables as part of the INTERPHEX Technical Conference. Here, experts will share the latest thinking on key topics, including:

- State of the Industry Practice for Pre-Use, Post-Sterilization Integrity Testing (PUPSIT), **Tuesday, April 17, 10:30 a.m. – 11:30 a.m.**
- Technology and Process for Cell and Gene Therapy Manufacturing, **Wednesday, April 18, 2 p.m. – 3 p.m.**
- Use of Big Data for Predictive Process Control, **Thursday, April 19, 10:30 a.m. – 11:30 a.m.**

To view an agenda for the show and to register, please visit [www.interphex.com](http://www.interphex.com). 



[pda.org/2018Sterile](http://pda.org/2018Sterile)

## 2018 PDA Sterile Medicinal Products Manufacturing Conference

The *2018 PDA Sterile Medicinal Products Manufacturing Conference* will bring sterile product experts together with the sterile products community to highlight contemporary approaches to aseptic processing using **case studies and personal experiences**.



May 14-15, 2018  
Bethesda, MD  
Exhibition: May 14-15  
#PDASTERILE

With tightening regulatory expectations for sterile product quality and safety-based on patient risk, this conference is a “must-attend” for anyone involved in sterile manufacturing!

With special reference to the recently released draft revision of the EU GMP Annex 1, this Conference will explore sterile manufacturing essentials, including:

- Risk- and science-based assessment and approaches in sterile product facility design and manufacturing processes
- How to better use existing sterile product technologies
- PDA and industry responses to the proposed revision to Annex 1 and other regulatory trends and expectations
- New thinking on sterile product manufacturing validation and process simulation

**Register now** to join the dialogue between manufacturers, suppliers, and regulators working together to solve issues and improve sterile manufacturing processes!

**To learn more and register, please visit [pda.org/2018Sterile](http://pda.org/2018Sterile)**

CONNECTING  
PEOPLE  
SCIENCE+  
REGULATION®

# PDA Volunteer Spotlight

## Christopher Smalley, PhD

■ Pharmaceutical and Compounding  
Pharmacy Consultant

■ ValSource

■ Member Since | 1982

■ Current City | West Chester, Pennsylvania

■ Originally From | New Brunswick, Canada

The world is changing very rapidly, and PDA is a key tool in my toolkit

**You used to be on the PDA Board of Directors. Now you are the Secretary for the Delaware Valley Chapter. How is your experience on the Board helping you?**

Having served on the Board of Directors, I better understand the important role of chapters in engaging with members on a frequent basis, being more responsive to hot topics, and involving people who might not have an opportunity to otherwise participate due to time or budget.

It also has highlighted for me the importance of pushing up local/regional topics to the global level by PDA, such as engaging with the U.S. FDA and other regulators, and setting standards using PDA's technical reports.

**Which PDA event/training course is your favorite?**

Do I have to choose only one? I enjoy so many of the training courses because they are taught by professionals who do the job daily—they are current on the issues and techniques. But I enjoy the *PDA/FDA Joint Regulatory Conference* because the U.S. FDA is truly an active partner in the program, not only contributing speakers and expressing the current thinking at the Agency, but also sharing where they see the industry going in the future.

I would also say the Annual Meeting is another favorite. This conference offers so much to choose from that I struggle with which session to attend during breakouts!

**How are you giving back to the community?**

With an undergraduate and graduate degree in pharmacy, I remain committed to the profession. My work since retiring from Merck (MSD) has been with ValSource, providing part-time consulting services to compounding pharmacies, and I volunteer time at Veterans Administration (VA) hospitals and clinics in the pharmacies. The VA dispenses 149 million outpatient prescriptions a year and is struggling with the ongoing drug shortages, as are many pharmacies across the country.

**What do you like to do in your spare time?**

What spare time?! I remain actively involved in PDA. But I do take time out to spend with my grandchildren, with another grandson due in June.

My wife and I have also recently adopted a female miniature dachshund who is very sweet. Several of our daughters want to take her when they visit.

**TUESDAY, APRIL 17, 2018**

INTERPHEX INNOVATION STAGE	MEETING ROOM 1 Optimizing Facilities through Innovation and Technology	MEETING ROOM 2 PDA, CRB Tech Tank and Continuous Manufacturing	MEETING ROOM 3 Manufacturing Efficiencies and Improvements	MEETING ROOM 4 Quality Metrics and Systems/Risk Management	MEETING ROOM 5 (Vendor Presentations)	FORMULATIONX	CMO/CDMO	INTERPHEX LIVE Crystal Palace	
9:45am - 10:00am Exhibit Hall Grand Opening & Exhibitor Awards									
10:00am - 5:00pm Show Floor Open & IPX/BPI Poster Hall									
10:30am - 11:15am	Pharmaceutical Technology Keynote Series <b>Oral Solid Dosage Manufacturing</b> 10:30am - 10:55am Employing the Internet of Things and PAT for Solid Dosage Forms Manufacturing 11:00am-11:25am PCMM (Portable, Continuous, Miniature and Modular) OSD Manufacturing Facility Platform 11:30am - 12:30pm Continuous Manufacturing Roundtable: Best Practices for Implementation	Integrating a Programmable Robotic Bioreactor System with a Biochemical Analyzer for Real-time Analysis	10:30am - 11:30am <b>PDA Roundtable</b> State of the Industry Practices for Pre-Use Post-Sterilization Integrity Testing	Accelerating Freeze-Drying: From Model to Production of a Semi-Continuous Aseptic Spray Freeze-Dryer	Bioprocess Simulations the Means to Decision Making From Feasibility Through Detailed Design	MasterControl Inc.	<b>ELSEVIER:</b> Driving Digital Transformation in Chemistry & Advanced Materials Industry through Decision Support Information Solutions	A Molecules Journey is Breaking Down Roadblocks to Commercial Success - Navigating Through the Important Considerations Necessary to Successfully Bring a Biologic Molecule to Market	10:15am - 11:00am Formulation and Delivery of Biologics and Complex Small Molecule Compounds
11:30am - 12:15pm	11:30am - 12:30pm Continuous Manufacturing Roundtable: Best Practices for Implementation	Data Integrity and Management in the Pharmaceutical Industry. Understanding and Complying with GMP & FDA Requirements	Building the Foundation for Continued Process Verification with Industry 4.0 Manufacturing Analytics	Impact of Tank Cone Bottom Interior Angle on Agitator Design: Lowest Mixable Volume, and Process Results	Cleaning Validation Different Approaches to Limit Setting for Detergents	MilliporeSigma	Coming Soon	Coming Soon	11:15am - 12:00pm Advantages of Continuous Manufacturing for Solid Dosage
1:30pm - 2:15pm	Pharmaceutical Technology Keynote Series <b>Aseptic, Sterile, and Biologics Drug Manufacturing</b> 1:30pm - 2:10pm Analytics and Instrumentation: Best Practices for Lyophilization 2:15pm - 3:00pm Continuous Manufacturing for Biopharm. Visions of an End-to-End Approach	Start-ups: Moving out of the Incubator into a New Pilot/Manufacturing Facility	<b>CRB TECH TANK</b> Flexible Manufacturing - Adapt or Die!	Tablet Press and Encapsulating Machine Transactions	Remediation Challenges of Aging Facilities	1:00pm Rockwell Automation	Coming Soon	Coming Soon	1:30pm - 2:15pm Pharma Intelligence: 2018 Industry Outlook
2:30pm - 3:15pm	1:30pm - 2:10pm Analytics and Instrumentation: Best Practices for Lyophilization 2:15pm - 3:00pm Continuous Manufacturing for Biopharm. Visions of an End-to-End Approach	Optimized Manufacturing of mAb-based Products: Flexibility, Speed, and Efficiency can Co-exist	<b>CRB TECH TANK</b> Keep'em separated! Integrating segregation for gene vector production	Single Use Vial Air Monitoring in Critical Environments of a Specialty Multi-Purpose Contract Manufacturing Organization	On-dose Identification for Tablets and Capsules Dosage Design and Equipment Innovation to Mitigate Risks in Patient Safety and Brand Protection	2:00pm LB Bohle LLC	Coming Soon	Coming Soon	2:15pm - 3:00pm Biosimilars 4.0
3:30pm - 4:15pm	Case Studies: Steam Sterilization Regulatory Requirements and End User Impact Analysis and Common Mistakes	<b>Case Study: Capacity</b> Expansion and Conversion to Single-Use BioProcessing at an Existing cGMP CDMO Facility	<b>CRB TECH TANK</b> Solving the riddle of flexible facilities - biotech & fill/finish	A Case Study for an Improved Approach to Cleanroom Disinfection, Minimizing the Impact and Reducing Downtime	Risk Analysis: Present State and Industry's Demand	3:00pm Sika Corp.	Coming Soon	Coming Soon	3:00pm - 3:45pm Automated Visual Particle Inspection for Hard to Inspect Containers
4:15pm - 5:00pm	Coming Soon	Process Economics: The Driving Force Behind the Criteria for Cell Therapies Facility Design	Continuous OSD: Designing a Controls Model (Continuous Manufacturing track)	A Novel, Real Time Adaptive Process Control System for Optimizing Feeding in Bioreactors	Settling the Frontier of Fill-Finish Operations - High Tech Filling in a Proper Abode (Optimizing Facilities track)	4:00pm SP Scientific/PennTech	Coming Soon	Coming Soon	3:45pm - 4:30pm The Impact of Critical Utilities 4:30pm - 4:45pm Show Wrap Up Day 1

**WEDNESDAY, APRIL 18, 2018**

INTERPHEX INNOVATION STAGE	MEETING ROOM 1 Optimizing Facilities through Innovation and Technology	MEETING ROOM 2 PDA, CRB Tech Tank and Continuous Manufacturing	MEETING ROOM 3 Manufacturing Efficiencies and Improvements	MEETING ROOM 4 Quality Metrics and Systems/Risk Management	MEETING ROOM 5 (Vendor Presentations)	FORMULATIONX	CMO/CDMO	INTERPHEX LIVE Crystal Palace		
10:00am - 12:00pm IPS TECHNOLOGY TOUR (Tour Registration Required)										
10:00am - 11:00am	10:00am - 11:00am <b>FDA Presentation with PDA:</b> The Future of Pharmaceutical Quality and the Path to Get There	10:30am - 11:00am Ensuring Reliable, Consistent Production in Pharmaceutical Water Systems	10:30am - 11:00am Integrating IoT into your Life Sciences Packaging and Supply Chain Strategy - Best Practices to Take this Valuable Leap	The use of Extractables Data from Single Use Components for Risk Assessment	Verifiable Containment Performance of Isolator Technologies	ADENTS	Coming Soon	Coming Soon	10:15am - 11:00am New Regulations, Real Case Studies: ASME BPE Cabinet Washer Standards (S0-5.3.1)	
11:00am - 12:15pm	Pharmaceutical Technology Keynote Series <b>Information Technology Trends and Best Practices</b> 11:00am - 11:30am Regulatory Requirements for Data Integrity: Applying ALCOA+ 11:30am - 12:30pm Best Practices in Data Integrity and Process Security with Automated Systems	10:30am - 11:30am <b>FACILITY FOCUS 1:</b> Flexibility by Design: GMP Manufacturing for the Diverse Product Portfolio	Integrating IoT into your Life Sciences Packaging and Supply Chain Strategy - Best Practices to Take this Valuable Leap	The use of Extractables Data from Single Use Components for Risk Assessment	Verifiable Containment Performance of Isolator Technologies	ADENTS	Coming Soon	Coming Soon	11:15am - 12:00pm Automation Trends Facing the Industry	
1:00pm - 3:00pm IPS TECHNOLOGY TOUR (Tour Registration Required)										
1:15pm - 2:00pm	Pharmaceutical Technology Keynote Series 1:30pm - 2:10pm The Industrial Internet of Things, Blockchain, and Smart Contracts 2:15pm - 3:00pm Serialization: Moving Beyond Compliance to Value	1:00pm - 2:00pm <b>FACILITY FOCUS 2:</b> Restrictive Access Barriers: Best Industry Practices for Retrofitting a Legacy Filling Lines with a RABS Barrier 2:15pm - 3:15pm <b>FACILITY FOCUS 3:</b> Central Utilities for GMP Manufacturing: A Practical Dialog on Cost and Reliability	Global Pharmaceutical Packaging Trends, Beyond Serialization (Optimizing Facilities track)	2:00pm - 3:00pm <b>PDA Roundtable</b> Technology and Process for Cell and Gene Therapy Manufacturing	Making 'Spray and Pray' Obsolete with New Technologies	Data Driven Control Strategy for Critical Drug Container Closure Systems (CCS) Performance at Digital Age	1:00pm Eschbach GmbH	Coming Soon	Coming Soon	1:30pm - 2:15pm Utilizing AR/VR in Pharma Development and Manufacturing
2:15pm - 3:00pm	2:15pm - 3:00pm Serialization: Moving Beyond Compliance to Value	Current Trends & Considerations for Drug Delivery Device Assembly of Self-Administered Products	Single Use Applications in Continuous Biopharmaceutical Processing	Total Organic Carbon for Enhanced Verification of Bioprocess System Cleaning CQ	A Comprehensive Approach to Cleanroom Certification for Reduced Risk of Environmental Contamination and Improved Regulatory Compliance	3:00pm MilliporeSigma	Coming Soon	Coming Soon	2:15pm - 3:00pm Emerging and Transformational Technologies in Personalized Medicine - A Paradigm Shift	
3:15pm - 4:00pm	Coming Soon	Lessons Learned from Microbial Contamination in Pharmaceutical Manufacturing: Benefit of End User and Supplier Collaboration	Facility Prefabrication - Coupling Flexibility, Mobility and Rapid Deployment into Turnkey Solutions (Optimizing Facilities track)	Real-Time Analytics with Timeline View for Improved Analytics	Bridging the Gap Between Rinse Water Analysis and Surface Cleanliness	Vendor Presentation	Coming Soon	Coming Soon	3:45pm - 4:30pm FDA Inspection Preparations: What's New, What's Different 4:45pm - 5:00pm Show Wrap Up Day 2	

**THURSDAY, APRIL 19, 2018**

INTERPHEX INNOVATION STAGE	MEETING ROOM 1 Optimizing Facilities through Innovation and Technology	MEETING ROOM 2 PDA, CRB Tech Tank and Continuous Manufacturing	MEETING ROOM 3 Manufacturing Efficiencies and Improvements	MEETING ROOM 4 Quality Metrics and Systems/Risk Management	MEETING ROOM 5 (Vendor Presentations)	FORMULATIONX	CMO/CDMO	INTERPHEX LIVE Crystal Palace	
10:00am - 3:00pm Show Floor Open & IPX/BPI Poster Hall									
10:30am - 11:15am	Life Cycle Cost for Multiple-Effect Water Still	The Theory Behind Automatic Inspection Technologies for Subvisible-to-Visible Particle Detection and Container Closure Integrity	10:30am - 11:30am <b>PDA Roundtable</b> Use of Big Data for Predictive Process Control	Work Smart: Risk based Approach for Cleaning Validation	Endotoxin Remediation Strategies	10:30am Rockwell Automation	Coming Soon	Coming Soon	10:15am - 11:00am Regulatory Requirements Relating to Water
11:30am - 12:15pm	Prescriptive Maintenance Leveraging IIoT Technology Can Become Your Competitive Advantage	How Understanding Loss in Weight Feeder Principles and Optimization of Feeder Refill and Overall Design can actually improve the Continuous Pharmaceutical Process	Achieving Manufacturing Efficiencies with Advanced Batch Management Technology			Vendor Presentation	Coming Soon	Coming Soon	11:15am - 12:00pm Process Control Interpretation within a Manufacturing Line 12:15pm - 12:30pm Show Wrap-in Day 3

\*As of February 15, 2018. Schedule subject to change.

## Korea Chapter Inaugurates New KPDA Hall

PDA's Korea Chapter celebrated its 20th anniversary on Dec. 12 in Seoul, featuring a ribbon cutting for the new KPDA Hall at the College of Pharmacy at Seoul National University.

The anniversary ceremony opened with a commemorative speech from Chapter President **Woo-Hyun Paik**, who also read a congratulatory message on behalf of PDA President **Richard Johnson**,

who could not attend the event. Other industry and PDA leaders also delivered remarks, including **Hee-Mok Won**, **Bong Jin Lee** and **Kunio Kawamura**.

The opening ceremony also featured the installation of a special plaque for the KPDA Hall delivered from PDA's headquarters in Bethesda, Md.

For 20 years, the Korea Chapter has offered a variety of seminars and publications for the Korean parenteral manufacturing community. Photos from chapter events and samples of chapter publications were on display throughout the celebration. Additionally, Chapter President Paik received further recognition for his work compiling the *Dictionary of GMP and Pharmaceutical Technology by Terminology*.

The day before the anniversary celebra-



Members of the chapter as well as leaders within the South Korean pharmaceutical community pose in the 20th anniversary ceremonial hall

[pda.org/2018Biopharma](http://pda.org/2018Biopharma)

## 2018 PDA Biopharmaceuticals Conference

At the 2018 PDA Biopharmaceuticals Conference, industry and regulatory experts will discuss trends in the biopharmaceutical field, and the regulatory and technical impact of these trends will be detailed. The challenges of commercialization of biosimilars in a competitive global environment will also be addressed.

Global industry and regulatory experts will focus on topics, including:

- Regulatory Updates
- Trends in Biopharmaceuticals
- Single-Use Systems and their Role in Manufacturing
- Aseptic Processing and Fill Finish Operations
- IPC and Final Product Testing
- Devices

The Conference will also feature an exhibition showcasing the latest in equipment and services and ample time for in-depth discussion and networking with colleagues!

To learn more and register, please visit [pda.org/2018Biopharma](http://pda.org/2018Biopharma)



April 17-18, 2018 | Seoul, Korea  
Exhibition: April 17-18  
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tion, the chapter hosted a seminar on data integrity, which featured an unprecedented number of attendees.

The Korea Chapter thanks PDA for their support over the past 20 years. 🍷



(l-r) Bong-Jin Lee, Kum-Ki Lee, Woo-Hyun Paik, Kunio Kawamura and Alain Kupferman



Leaders from the chapter and the South Korean pharmaceutical community open the new KPDA Hall

**PDA Who's Who**

**Richard Johnson**, PDA President

**Kunio Kawamura**, Advisor of Otsuka Pharmaceutical Co. in Japan

**Bong Jin Lee**, Dean of College of Pharmacy, Seoul National University

**Woo-Hyun Paik**, President of Korea Pharm. Tech. Education Center (KPTEC) and President of KPDA

**Hee-Mok Won**, Chairman of Korea Pharmaceutical and Bio-Pharma Manufacturers Association



2018 PDA Europe Conference, Exhibition

# 3<sup>rd</sup> PDA Europe Annual Meeting

**26-27 June 2018**

Marriott Hotel  
**Berlin | Germany**

Register by  
29 April 2018  
and SAVE!

[pda.org/EU/Annual2018](http://pda.org/EU/Annual2018)

# Honoring PDA's Female Volunteer Leaders

**Martin VanTrieste**

As the Immediate Past Chair of PDA and a longtime volunteer, I have had the exciting opportunity to work closely with many volunteer leaders within the Association. These leaders have come from a variety of backgrounds, industry segments and countries. And many of these leaders have been women.

Take a look at the PDA Board of Directors, here we have a special focus on diversity. The current Board consists of five officers and 12 directors for a total of 17 members, and the majority of those serving are women. Nine of our board members are women and six of these members represent areas outside the United States.

For the next two years, **Rebecca Devine** from the United States will be the PDA Chair and **Jette Christensen** from Denmark will be the Chair-Elect.

Women also hold leadership roles in various volunteer capacities for the organization, including task force members, officer positions for PDA local chapters, and interest group leaders, among others. Women play a key role as members of program planning committees and they serve as moderators and speakers at PDA conferences. The West Coast Chapter also hosts a very popular "Women in Biotech" event.

The women of PDA continue to play a vital role in delivering results to serve patients and fulfill the PDA mission. I want to personally invite anyone interested in volunteering to support women in pharma to contact PDA's Volunteer Coordinator at [volunteer@pda.org](mailto:volunteer@pda.org).

**In recognition of Women's History Month, here are some female leaders from PDA's past.**



In 1998, Joyce Aydlett was PDA's first female Chair



Jennie Allewell (right) and Nikki Mehringer (left) were two female leaders who also served on the PDA Board; Mehringer served as Chair 2004–2005



Nina L. DeMuth of DeMuth Development Corporation was the first woman to deliver a paper at a PDA conference and to serve as a program chair for an annual meeting



The PDA West Coast Chapter will host its third "Women in Biotech" panel Aug. 23. Check the chapter website <https://www.pda.org/chapters/north-america/west-coast> for updates.

2018 PDA Glass Quality Conference  
January 23-24 | Washington, D.C.



**P6:**  
**Evaluating Key Issues  
with Glass Containers**

(l-r) Jim Varner, Alfred University; James McFarland, Gerresheimer; Daniel Haines, PhD, SCHOTT



**Opening Plenary  
Regulatory Perspectives and Updates**

(l-r) Roger Asselta, Genesis Packaging Technologies; David Jaworski, U.S. FDA; Carol Rea Flynn, Corning; Daniele Zuccato, Nuova Ompi



**P7:  
PDA Updates**

(l-r) Richard Johnson, PDA; Carol Rea Flynn, Corning; James McFarland, Gerresheimer



# PDA Staff Try a Hand at Aseptic Processing

Marilyn Foster, PDA

“What is the difference between aseptic and sterile?”

**David Talmage**, PDA Senior Director of Education, posed that question to some PDA staff in a special, half-day “Fundamentals of Aseptic Processing” class Jan. 9 as part of PDA’s staff development program. (The answer? *Aseptic* means free from contamination caused by harmful bacterial, viruses or other microorganisms, while *sterile* means free from living microorganisms.)

In this training (held in the PDA Training and Research Institute located at the Bethesda, Md. headquarters), Talmage provided an overview of the equipment, facilities and typical filling operations involved in aseptic processing, stressing the importance of airflow and proper cleanroom behavior in maintaining the ISO 5 environment. Learning the basic procedures of traditional cleanroom practices, he said, ensures that technicians will consistently use the correct techniques, even when working in a restricted access barrier system (RABS) or isolator environment.

**Kimberly McIntire**, PDA Manager of Education, presented a short course in microbiology following Talmage’s portion. She displayed the types of microorganisms that pose the most common threat to aseptic manufacturing (bacteria and mold), where they are found (everywhere) and how to identify them (morphology, Gram staining and biochemical tests).

“Recognizing what they are is the first step in knowing how to control, eliminate or reduce them,” she said. It also makes it possible to monitor the environment, ensuring that the controls put in place are working as designed.

Hands-on training followed the classroom session, giving PDA staff an even greater appreciation of what is involved in aseptic processing. The cleanroom gowning alone proved a protracted lesson in riotous frustration. Had it been a game show, the buzzer would have sounded incessantly. This exercise in gowning, however, instilled a better understanding of how easily contaminants could be introduced into operations if proper aseptic technique is not followed. While half of the team entered the TRI fill room, the other half observed their actions and logged any violation of proper cleanroom behaviors and intervention in the processes.

During this activity, Talmage demonstrated how the equipment moved bottles down the line to be filled, stoppered, capped and collected, as well as the careful use of tools so as not to interrupt airflow. Attempts by staff to perform those tasks resulted in a number of aseptic violations, helping them recognize the intricacies of aseptic manufacture.

PDA provides opportunities like this class to broaden the staff’s understanding of the world of aseptic processing, enabling them to better assist PDA members in meeting the challenges of the industry. The staff involved truly appreciated this opportunity to get a sense of the nature of aseptic processing. 🍷



PDA staff keep their arms above waistline level as part of proper aseptic technique



## SNAPShot

# New Survey Follows Up on 2013 Glass Survey Data

Rebecca Stauffer, PDA

At the *2018 PDA Glass Quality Conference*, PDA President **Richard Johnson** offered a glimpse into PDA's latest glass survey, currently scheduled for release sometime in Q1.

Previously, PDA published surveys in 2011, 2012 and 2013 on the topic of glass. For these surveys, manufacturers spanning most segments of the pharma industry were queried about their experiences with glass products, including handling, breakage and relationships with suppliers. The latest survey uses the same questions from the 2013 survey, offering a look at any changes in the five years since the last survey.

"PDA has conducted this survey a number of times and we did it again in preparation for this meeting," Johnson said. "What we are trying to do is show you a comparison with the responses to the same questions back in 2013."

The 2018 survey will be available for purchase in the PDA Bookstore ([www.pda.org/bookstore](http://www.pda.org/bookstore)). The bookstore also offers a comparison of the 2012 and 2013 surveys in addition to proceedings of the *2013 PDA/FDA Glass Packaging Conference*.

Johnson also pointed to other PDA resources that cover glass packaging. These include a number of conferences such as the *Parenteral Packaging* meeting and the *Universe of Pre-filled Syringes and Injection Devices*; interest groups (Packaging Science, Prefilled Syringes and Visual Inspection); PDA Education courses and active task forces involved with glass handling and control of visual particulates. Information about many of these activities can be found on the PDA website ([www.pda.org](http://www.pda.org)). 

## Journal Preview

### Latest Issue of PDA Journal Looks at Particle Formation, Packaging and Vaccine Research Topics

Subvisible particle formation, rubber stopper seal performance, and antigen adsorption are some of the latest research topics in the March/April issue of the *PDA Journal of Pharmaceutical Science and Technology*. Check out the latest pharmaceutical research at [journal.pda.org](http://journal.pda.org).

#### Review

Anil K. Rattan, "Data Integrity: History, Issues, and Remediation of Issues"

#### Research

Yuh-Fun Maa, et al., "Mechanistic Investigation on Grinding-Induced Subvisible Particle Formation during Mixing and Filling of Monoclonal Antibody Formulations"

Patrick L. Ahl, et al., "Quantitative Analysis of Vaccine Antigen Adsorption to Aluminum Adjuvant Using an Automated High-Throughput Method"

Qingyu Zeng, Xia Zhao, "Time-Dependent Testing Evaluation and Modeling for Rubber Stopper Seal Performance"

Ganapathy Gopalrathnam, et al., "Impact of Stainless Steel Exposure on the Oxidation of Polysorbate 80 in Histidine Placebo and Active Monoclonal Antibody Formulation"

#### Case Studies

Laurent Siret, et al., "Development of a Premium Quality Plasma-derived IVIg (IQYMUNE®) Utilizing the Principles of Quality by Design—A Worked through Case Study"

#### Technology/Application

Daniel Coleman, et al., "A Risk Index and Data Display for Process Performance in the Pharmaceutical Industry"

Tony Cundell, David Jones, "Method Verification Requirements for an Advanced Imaging System for Microbial Plate Count Enumeration"

#### Commentary

Derek Willison-Parry, et al., "Microbiological Control for Affinity Capture Chromatography Processing: An Industry Perspective" 

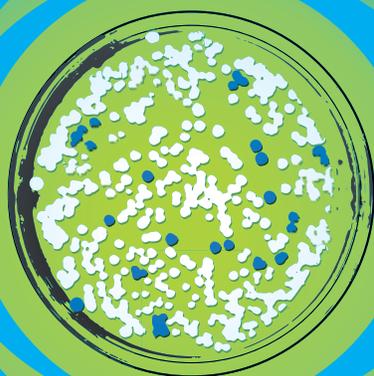


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Marriott Hotel  
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**15-17 October 2018**

Bethesda North Marriott Hotel  
**Bethesda | USA**

## H<sub>2</sub>O Requirements for Superheated Sterilization

*The following blinded, unedited remarks are taken from PDA Connect<sup>SM</sup>, an online forum that allows PDA members to share some of the most challenging issues confronting the pharmaceutical industry. The discussions on PDA Connect<sup>SM</sup> do not represent the official views of PDA, PDA's Board of Directors or PDA members.*

*The following is taken from the Sterile Processing Interest Group forum.*

*Go to [community.pda.org](http://community.pda.org) to continue the conversation!*

### Questioner

Looking for guidance documents on this topic [chemical and microbiological requirements for water used for superheated water sterilization]. Same question for condensate of steam used for liquid load sterilization of sealed containers.

I could not find guidance on this topic, that's why I brought this up.

If there are no guidance documents on this topic, I would be interested to know what is practiced: if/how water or steam condensate used for superheated water and steam used to sterilize sealed liquid loads are monitored (chemical and microbiological).

### Respondent 1

WHO has a guidance about water for pharmaceutical use:

[http://www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/GMPWatePharmaceuticalUseTRS970Annex2.pdf](http://www.who.int/medicines/areas/quality_safety/quality_assurance/GMPWatePharmaceuticalUseTRS970Annex2.pdf)

Section 4 may help you.

### Questioner

Thank you, I was looking for that kind of information.

### Respondent 2

There are requirements for clean steam

### Questioner

I know the requirements for clean steam but could not easily find requirements for water and steam subject to this discussion.

### Respondent 3

In the PDA TR #1 "moist heat sterilisation in autoclaves", there were specific requirements for terminal sterilisation in which the process cooling water, in direct product contact, even with container closures, was to be WFI or PW. (section on utilities) The later had to comply with WFI in terms of microbial and endotoxin levels. 🙄

# Seeing the Hidden

## How Contamination Recovery Rates Offered a Better Look at the True State of Microbial Control

Rebecca Stauffer, PDA

Using contamination recovery rates to evaluate an environmental monitoring trending program changed the way **Paula Peacos**, Associate Director, Global Microbiological Compliance, Bristol-Myers Squibb, viewed the movement of microbial contamination within a facility, according to her presentation, “Using Contamination Rates for Environmental Monitoring Trending,” Oct. 16, at the *12th Annual PDA Global Conference on Pharmaceutical Microbiology*.

Her experience in using contamination recovery rates in this manner resulted from an actual environmental monitoring program she implemented about eight years ago for a previous employer. Peacos believes it still offers valuable insights into how facilities can look more holistically at environmental monitoring. She presented a fabricated model to demonstrate how such a program operates and its benefits.

### Limits to Traditional EM

There were many reasons for adding contamination recovery rates to the existing trending program. The facility was a low bioburden facility which used an almost entirely manual process to manufac-

ture a biologic product with a 72-hour turnaround. Therefore, the process was highly dependent on exceptional process control (i.e., the facility had to be clean at all times and operators had to maintain constant vigilance). The existing environmental monitoring trending program was largely based on the excursion rates.

Although this program was robust, it did have limitations. Since any actions taken were generally based on excursions (including actions involving adverse trends), the program was reactive as opposed to proactive. An excursion would usually not be detected until two to three days after sample collection. More importantly, however, trending by excursion rate focused only on individual plate counts. It did not account for any of the microbial recoveries obtained on the other samples collected at the same sampling interval.

Peacos envisioned a program that would detect and mitigate issues before limits were exceeded, proactively identify adverse trends and offer more effective data analysis. She looked to USP <1116> Microbiological Control and Monitoring of Aseptic Processing Environments, which recom-

mends using contamination recovery rates in place of traditional alert and action levels in aseptic areas (*I*). In aseptic areas, there are inherently low bioburden levels present and the available environmental monitoring methods are limited in terms of their ability to recover microorganisms. She applied this rationale to other areas of the facility, including ISO 5, ISO 7, ISO 8 and Controlled Not Classified (CNC) areas.

To determine the contamination recovery rates, Peacos used the following equation:

$$\text{Contamination rate} = (\text{total number of samples greater than } 0 \text{ cfu} / \text{total number of samples collected}) * 100$$

This equation takes into account the total number of recoveries across all samples collected for a given area and better reflects the actual state of the environment with the end result that “you know how much microbial contamination you have and where it is,” she explained.

The study compared excursion rates versus contamination rates within four different types of locations (ISO 5, ISO 7, ISO 8 rooms and CNCs). For each location,

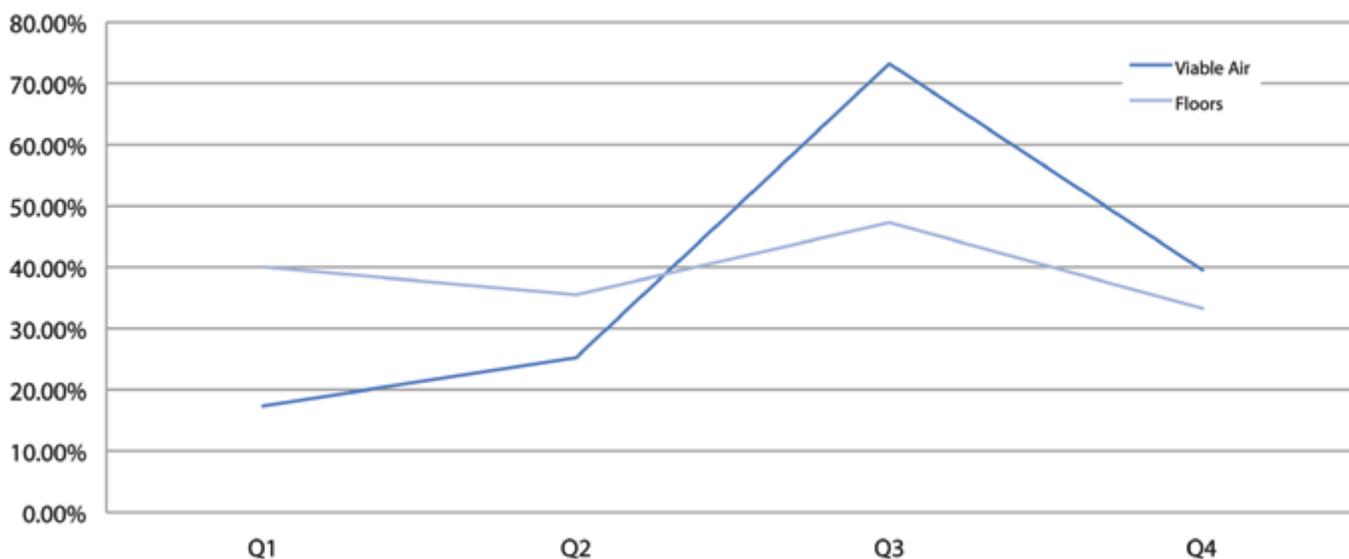


Figure 1 Contamination Rates: Seasonal Variation in ISO 8 Rooms

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excursion and contamination rates were compared for active air viables and surface viables.

### CRR Show Surprising Trends

The impact of adding the contamination recovery rates to the existing trending program surprised Peacos. For example, she had expected the floor to be the prime location for contaminants, but the contamination recovery rates showed that the prime location was actually the air.

“I used to worry about operators picking organisms up from the floor and tracking them in,” she said. “I still worried about that, but I paid more attention now to things like rapid movements in the clean areas, operators holding doors open too long and changes in differential pressure, because the contamination rates in the air were actually higher.”

By reviewing all of the samples holistically using the contamination recovery rate, she could better see drift in the overall state of control. Areas of greater risk became visible, as did effects of unplanned events. She was also able to more effectively track the performance of individual operators.

Peacos found that the contamination recovery rate was a better indicator of an operator’s aseptic technique than of the excursion rate. The data showed that while some operators had excursion rates of 0%, these same operators had contamination recovery rates much higher than other operators. This meant that these particular operators were more likely to introduce microbial contamination into the process because it was present more often on their gowning materials. Yet none of this data was apparent when looking at the number of exceeded alert and action limits alone.

Interestingly, seasonal variations became visible. An example is presented in **Figure 1**. Peacos pointed out that the facility was located in northeastern United States. January through March are generally the coldest and driest months of the year, which corresponds to the lowest contamination rates shown in **Figure 1**. Temperatures generally remain cool through early June. Beginning in late June, however, temperatures rise significantly.

“Our hottest months are usually July to September,” she said. “The operators are sweating and there is a lot more shedding. Then in October through December, it starts to cool off, and you see this [the contamination rates] drop again.”

**Figure 1** shows counts for the viable air and floor surface samples. Consistent across five ISO 8 rooms was a significant jump in the contamination rates for viable air in Q3, the hottest months of the year.

“The seasonal variation was there, but I could not see it before when I was trending by excursion only,” Peacos said. “Contamination recovery rates provided a higher level of granularity. They showed us things occurring in the background that we could not see by trending by excursion only.”

The study also showed that excursion rates and contamination recovery rates were not directly proportional. This was crucial as contamination recovery rates fluctuated while excursion rates generally did not.

“This is important,” she explained, “because when you consider that the operators pass through the less clean areas into the cleaner areas, they are going to pick up contaminants and take them along with them. If the overall contamination recovery rates is higher...there is a greater likelihood that manual transmission of contamination into a cleaner area will occur simply because more is present.

“Contamination recovery rates began to supersede the excursion rates in terms of what we used to make general decisions regarding routine controls, such as when we sanitized, or whether we had to do any extra monitoring,” she said, further adding that she did not wholly abandon excursion rates as this data also provided critical information.

“They [excursion rates] provided a frame of reference for the acceptable range we wanted to operate in. They also signaled when a process was operating outside of the normal parameters.” Peacos said. “So, the alert and action levels were not changed when the contamination recovery rates were added. Instead, we used the contamination recovery rates to mitigate

before we exceeded those limits, and thus increased our level of control.”

There were a number of payoffs resulting from adding contamination rates to environmental monitoring. Because of the ability to proactively mitigate, fewer excursions occurred, so there were fewer investigations to conduct.

“This resulted in substantial savings in time, labor and material costs,” Peacos said.

When investigations were needed, she found that they were of better quality since the contamination recovery rates provided additional information that ensured better root cause analysis. Subsequently, impact assessments were also of higher quality, and CAPAs were more efficient and effective. Trending reports became more useful due to the increased granularity of the data.

“Adding the contamination recovery rates to the traditional facility trending program substantially increased its power,” Peacos said. “The proactive mitigation—and I cannot say it often enough—led to better microbial control and lower risk. We had greater and earlier visibility of changes to the existing state of control.

“This can be applied to any type of environment, sterile or nonsterile or anything in between, as it is just a simple calculation that is incredibly easy to implement,” she concluded.



**[Editor’s Note:** Watch Peacos explain the use of contamination recovery rates in an “On the Issue” video on the *PDA Letter* website.]

### Reference

1. Denoya, C., and Dalmaso, G., “USP <1116> and its Implications for Measuring Microbial Recovery Rates.” *PDA Letter* 51 (2015): 26–29.

### About the Expert

**Paula Peacos**, Associate Director of Microbiology, Global Pharmaceutical Quality, Bristol-Myers Squibb, has been supporting the industry for over 25 years as a microbiologist. 🍷





# Vaccine Makers Face Tech Challenges

**Cristiana Campa, GSK Vaccines, and Nancy Cauwenberghs, MSD**

Due to the wide variety of possible vaccine categories, complexity of products and processes, and aggressive timelines for vaccine development and lifecycle management, there needs to be greater investment in technical capabilities by manufacturers.

In this context, it is critical that manufacturers, regulators and suppliers work together to understand common challenges and opportunities. Companies must understand new CMC trends, including greater use of platform technologies, emphasis on prior knowledge, development of novel therapeutic and cancer vaccines and accelerated development.

The 2018 PDA Europe *Vaccines* conference will address these and other new trends in vaccine development and lifecycle management. Dedicated sessions will explore novel developments, product understanding and analytics, manufacturing and technical innovation.

In addition, the conference will provide an overview of the applicability of quality-by-design in various aspects, from product, analytics and process standpoints, and considerations during lifecycle management. Newer trends in the regulatory field will also be discussed, such as the impact of post-approval changes on vaccines supply.

Prevention and control of infectious diseases requires continued efforts aimed at effective development, manufacturing and supply of vaccines. The realization of this important objective requires passion, resilience and broad technical competence. PDA's vaccines conferences and work-

shops have proven to be a key resource in this journey. 🧹

## Vaccines

Malaga, Spain

April 24–25

[www.pda.org/eu/vaccines2018](http://www.pda.org/eu/vaccines2018)

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# 2018 PDA Upcoming Events

## SAVE THE DATE for PDA's 2018 Events



### MARCH

**19-21**

**2018 PDA Annual Meeting**

Orlando, FL  
[pda.org/2018Annual](http://pda.org/2018Annual)

**21-22**

**2018 PDA Manufacturing Intelligence**

Orlando, FL  
[pda.org/2018MI](http://pda.org/2018MI)

**22-23**

**2018 PDA Annual Meeting Course Series**

Orlando, FL  
[pda.org/2018AnnualCourses](http://pda.org/2018AnnualCourses)

**27-29**

■ **Airflow Visualization Techniques and Practices – Option 1**

Bethesda, MD  
[pda.org/2018MarAir](http://pda.org/2018MarAir)

**27-29**

■ **Validation of Biotechnology-Related Cleaning Processes – Option 1**

Bethesda, MD  
[pda.org/2018MarValBiotech](http://pda.org/2018MarValBiotech)

### APRIL

**4-5**

**NEW COURSE**

**Temperature Sensitive Packaging and Distribution for Biopharmaceuticals**

Franklin, MA  
[pda.org/2018TempSensitive](http://pda.org/2018TempSensitive)

**10**

🌀 **Particle Identification in Parenterals**

Berlin, Germany  
[pda.org/EU/TCParticleID2018](http://pda.org/EU/TCParticleID2018)

**11-12**

🌀 **An Introduction to Visual Inspection**

Berlin, Germany  
[pda.org/EU/tc-visual2018](http://pda.org/EU/tc-visual2018)

**11-12**

🌀 **Mastering Automated Visual Inspection**

Berlin, Germany  
[pda.org/EU/AutoVI2018](http://pda.org/EU/AutoVI2018)

**13**

**Interest Group Meeting: Visual Inspection**

Berlin, Germany  
[pda.org/EU/IGVisual2018](http://pda.org/EU/IGVisual2018)

**17-18**

**2018 PDA Biopharmaceuticals: From Drug Substance Manufacturing to Final Product**

Seoul, South Korea  
[pda.org/2018Biopharma](http://pda.org/2018Biopharma)

**17-18**

**Quality Culture Transformation Resources**

Mainz, Germany  
[pda.org/EU/AprTransform2018](http://pda.org/EU/AprTransform2018)

**19-20**

**SOLD OUT**

**PDA Quality Culture Transformation – Regulators Only**

London, UK  
[pda.org/2018AprTransform](http://pda.org/2018AprTransform)

**23-27**

🌀 **Freeze Drying in Practice**

Osterode am Harz, Germany  
[pda.org/EU/fdp2018](http://pda.org/EU/fdp2018)

**23-27**

■ **PDA Visual Inspection Course Series – Option 1**

Bethesda, MD  
[pda.org/2018AprVI](http://pda.org/2018AprVI)

**24**

**2018 PDA Packaging Science Interest Group Workshop**

Bethesda, MD  
[pda.org/2018PackagingIG](http://pda.org/2018PackagingIG)

**24-25**

**Vaccines Conference**

Malaga, Spain  
[pda.org/EUVaccines2018](http://pda.org/EUVaccines2018)

**25**

**2018 PDA Visual Inspection Interest Group Workshop**

Bethesda, MD  
[pda.org/2018VisualIG](http://pda.org/2018VisualIG)

### MAY

**1-4**

**Regulatory and Compliance Course Series**

Bethesda, MD  
[pda.org/2018RCCS](http://pda.org/2018RCCS)

**7**

**Interest Group Meeting: Advanced Virus Detection Technologies**

Florence, Italy  
[pda.org/EU/ADVT2018](http://pda.org/EU/ADVT2018)

**7-11**

■ **PDA Aseptic Processing – Option 3**

Week 2: Jun. 4-8  
Bethesda, MD  
[pda.org/2018aseptic3](http://pda.org/2018aseptic3)

**8-9**

**Virus Forum**

Florence, Italy  
[pda.org/EU/Virus2018](http://pda.org/EU/Virus2018)

**14-15**

**2018 PDA Sterile Medicinal Products Manufacturing Conference**

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**15-17**

■ **Validation of Moist Heat Sterilization Processes – Option 1**

Bethesda, MD  
[pda.org/2018MayVMH](http://pda.org/2018MayVMH)

**21-24**

■ **Fundamentals of Aseptic Processing – Option 2**  
 Bethesda, MD  
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**21-25**

**PDA Lyophilization Course Series**  
 Bethesda, MD  
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**Pharmacopoeia Conference**  
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**5-6**

**Advanced Therapy Medicinal Products Conference**  
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**7**

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**PDA Quality Culture Transformation**  
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**13-14**

**2018 PDA Container Closure Performance and Integrity Conference**  
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**18-21**

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 Bethesda, MD  
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**25**

**Interest Group Meeting: Freeze Drying**  
 Berlin, Germany  
[pda.org/EU/IGFreezeDrying2018](http://pda.org/EU/IGFreezeDrying2018)

**25**

**Interest Group Meeting: Quality Systems**  
 Berlin, Germany  
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**25-27**

**PDA Quality Course Series**  
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**26-27**

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**28-29**

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**28-29**

**Best Compliance Practices at the GMP Testing Laboratory**  
 Berlin, Germany  
[pda.org/EU/Compliance2018](http://pda.org/EU/Compliance2018)

## ADDITIONAL SIGNATURE EVENTS IN 2018

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- 24-26** **2018 PDA/FDA Joint Regulatory Conference**  
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- 26-27** **2018 PDA Biosimilars Workshop**  
 Washington, DC | [pda.org/2018biosimilars](http://pda.org/2018biosimilars)

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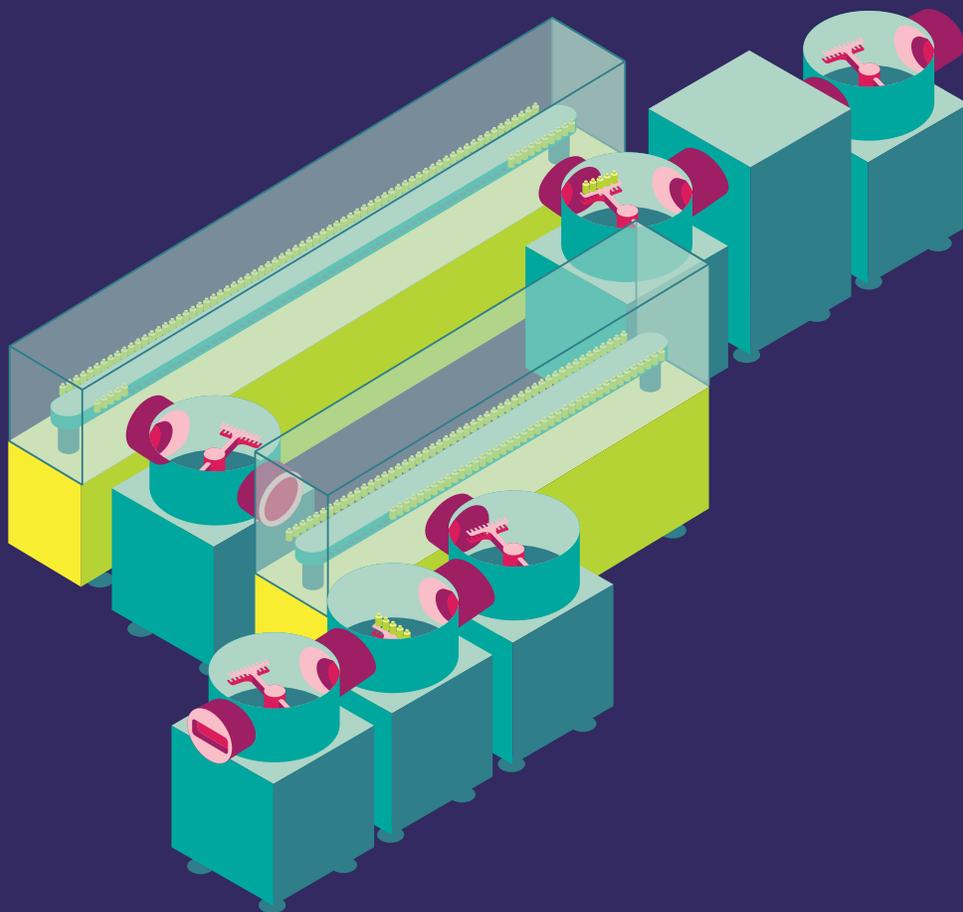
- 8-9** **2018 PDA Universe of Pre-Filled Syringes and Injection Devices**  
 Orlando, FL | [pda.org/2018PFPS](http://pda.org/2018PFPS)
- 10** **2018 PDA Combination Products Workshop**  
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- 15-16** **PDA Europe Pharmaceutical Microbiology**  
 Berlin, Germany | [pda.org/EU/PharmaMicro](http://pda.org/EU/PharmaMicro)  
*(Some sessions simulcast with PDA North America)*
- 15-17** **13th Annual PDA Conference on Pharmaceutical Microbiology**  
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- 17-18** **2018 PDA Endotoxins Workshop**  
 Bethesda, MD | [pda.org/2018Endotoxins](http://pda.org/2018Endotoxins)

### NOVEMBER

- 6-7** **Outsourcing & Supply Chain: A 360° View**  
 Seville, Spain | [pda.org/EU/Outsourcing2018](http://pda.org/EU/Outsourcing2018)
- 27-28** **11th Workshop on Monoclonal Antibodies**  
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- 27-28** **Pharmaceutical Freeze Drying Conference**  
 Seville, Spain | [pda.org/EU/FreezeDrying2018](http://pda.org/EU/FreezeDrying2018)

# New Approach Suggests Continuous Lyophilization is Possible

Pieter-Jan Van Bockstal, Ghent University, Jos Corver, RheaVita, Thomas De Beer, Ghent University



Conventional batch freeze-drying has long been the mainstay for stabilizing biologic drug products in storage and distribution, but it presents many challenges. An innovative continuous process for freeze-drying has been developed, however, that may offer a view of the future of freeze-drying for biologics.

The market for biologic drug products, like therapeutic proteins and vaccines, continues to grow. The stability of these products, however, is often limited when formulated as an aqueous solution. Water-mediated degradation pathways can lead to decreased potency or even to toxicity of the drug molecule. Freeze-drying (lyophilization) is a commonly applied low-temperature drying process used to improve the stability of these products during storage and distribution (1). Approximately 50% of the biologic drug products approved by regulators are freeze-dried formulations (2,3). Yet, freeze-drying has a long processing time and carries high costs.

## Step-by-Step, Batch-by-Batch

Conventional pharmaceutical freeze-drying of unit doses is a batchwise process during which all vials of the same batch are processed through a sequence of consecutive process steps: 1) freezing, 2) primary drying and 3) secondary drying (3). Vials containing the aqueous drug formulation (i.e., unit doses) are loaded onto temperature-controlled shelves in the drying cham-



**Figure 1** A Typical Industrial-scale Pharmaceutical Batch Freeze-dryer



## Conventional pharmaceutical freeze-drying of unit doses is a batchwise process



ber (Figure 1). During the initial freezing stage, most of the water crystallizes to ice while the solutes also crystallize or form a rigid amorphous glass.

For the subsequent primary drying step, ice crystals are removed via sublimation under vacuum, leaving a porous matrix. Energy is supplied to the frozen product to enhance ice sublimation (endothermic process). Finally, during secondary drying, most of the remaining unfrozen water (i.e., water dissolved in the amorphous phase) is removed by diffusion and desorption until the desired residual moisture content of the dried end product is achieved.

At the end of the lyophilization process, the aqueous drug formulation is transformed into a solid and rigid dried cake with an increased shelf life. The most important critical quality attributes (CQAs) of the freeze-dried end product are the (i) API state (e.g., protein conformation); (ii) residual moisture content; (iii) freeze-dried product cake appearance and (iv) reconstitution time. After freeze-drying, these CQAs are evaluated for vials selected at random positions of the batch via offline analytical techniques.

For more than 80 years, pharmaceutical freeze-drying has been conducted using this unchanged batchwise approach. This traditional batch approach, however, is inherently associated with several disadvantages:

- Batch freeze-drying is inefficient and consumes a lot of time and energy with cycle times that can vary from one to as many as seven days

- The huge size of industrial batches leads to scale-up issues; initial development of freeze-drying cycles is performed in lab-scale equipment, and subsequent steps in the development process, beginning with lab-scale to pilot-scale and, finally, to industrial-scale freeze-dryers
- The freezing stage is uncontrolled, leaving a significant impact on consecutive drying steps; this can cause vial-to-vial variability in the sublimation rate within a batch and between batches (4).

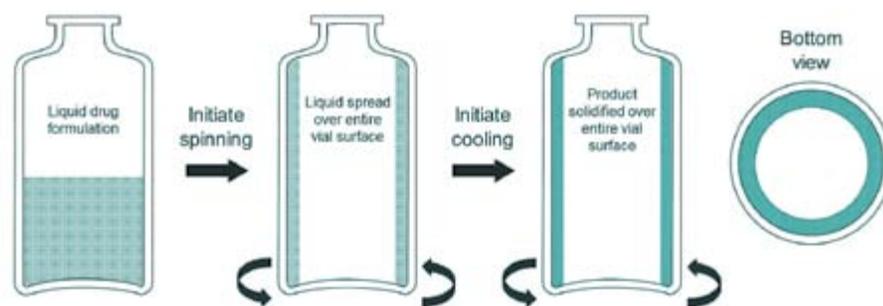


Figure 2 Illustration of the Spin-Freezing Step

- The heat transfer in the freeze-drying chamber is uneven, resulting in a difference in energy transfer to vials located at different positions on the freeze-dryer shelves (for instance, vials situated at the edge of the shelves are exposed to additional radiant heat coming from the warmer surroundings compared to the vials situated in the middle of the shelves, leading to a higher product temperature for these edge vials that is associated with faster drying rates and a higher risk for collapse) (5)

Both the uncontrolled freezing and the uneven heat transfer culminate in different process conditions for each individual vial in the batch, leading to uncontrolled vial-to-vial and batch-to-batch end product variability. Yet product quality is only

determined by testing a limited fraction of vials before releasing the complete batch.

### A Fresh Look at Freeze-Drying

To overcome the disadvantages associated with conventional batch freeze-drying, an innovative continuous and controlled freeze-drying concept for unit doses has been developed (6,7). In this approach, all unit operations are integrated in a single production line with continuous feeding of raw materials and the concomitant removal of finished products. This manufacturing approach offers several advantages—avoidance of scale-up issues, reduction in cycle times, lowered production costs, smaller manufacturing installations and improved product quality (process uniformity).

At the start of the continuous freeze-drying process, sterile glass vials are aseptically filled with the aqueous drug formulation

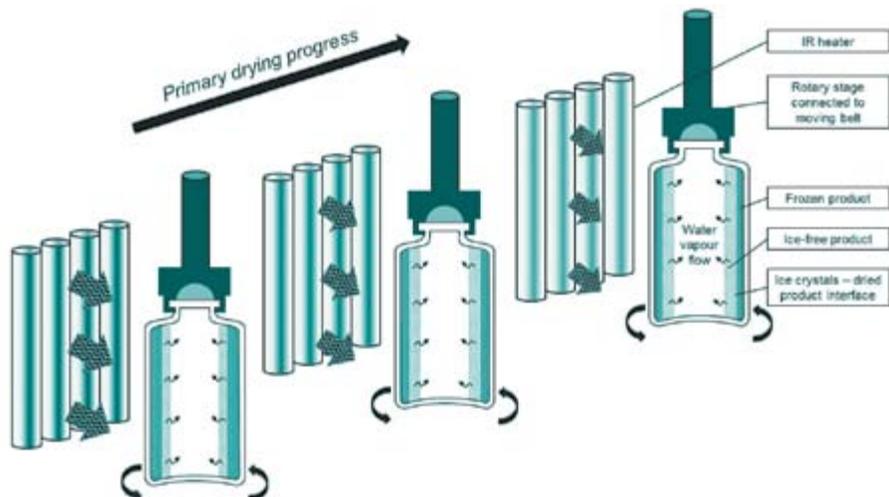
before they are transferred to the freezing unit. In the freezing unit, the vials are gripped at their cylindrical walls and rapidly rotated along their longitudinal axis to form a thin layer of product which is spread over the entire inner vial wall (i.e., spin-freezing, see Figure 2). When a homogeneous product layer is obtained, the flow of a cold, inert and sterile gas leads to the cooling and freezing of the solution. Both the temperature and the flow of the gas can be adapted to obtain a specific cooling regime, varying from very fast to slow cooling.

At the end of the spin-freezing step, the product solidifies over the entire inner vial wall resulting in a thin product layer of a uniform thickness (a large surface area and thin product layer). Annealing can be

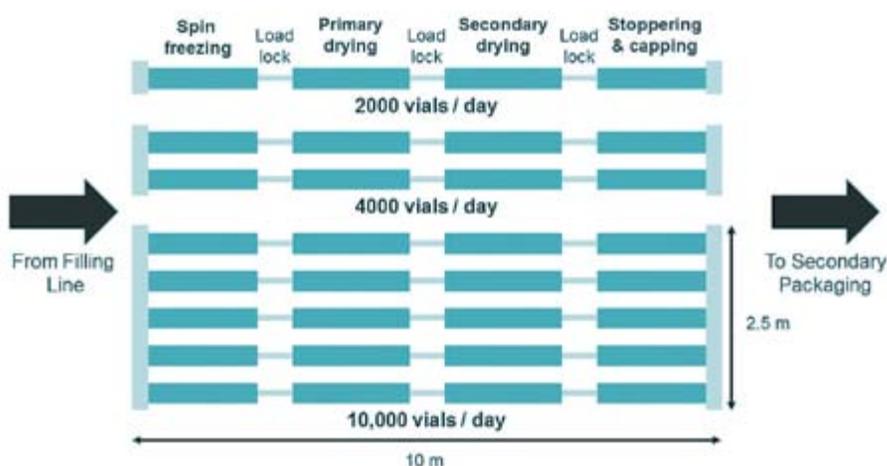
#### Article at a Glance

- As more biologics enter the market, freeze-drying is ever more critical
- Traditional freeze-drying methods have many drawbacks
- Two prototypes suggest possibilities for continuous freeze-drying

## In the GMP-like engineering prototype, all process modules are integrated



**Figure 3** Illustration of IR-assisted Continuous Primary Drying of Spin-Frozen Vials Rotating Along their Longitudinal Axes in Front of Individual IR Heaters (7)



**Figure 4** Parallel Lines in the Continuous Freeze-drying Technology Avoiding Scale-up Reoptimization and Validation

performed by transferring the vials to a chamber with a controlled temperature.

An appropriate load-lock system is used to rapidly transfer the spin-frozen vials between the continuous freezing and the continuous drying units without disturbing the specific conditions of pres-

sure and temperature in each chamber, thereby, guaranteeing the continuity of the process. In the drying chamber, an endless belt system allows the transport of the spin-frozen vials in front of individually controlled radiators which provide a uniform and adequate heat transfer to the entire vial surface to achieve efficient and

homogeneous drying behavior (Figure 3). This vial transport takes place in discrete steps. Each vial is rotating very slowly in front of a single radiator, hence, allowing for individual temperature-regulation which enables an optimal drying trajectory for each spin-frozen vial.

In a conventional freeze-dryer, sublimated ice and desorbed water is collected using cryogenic ice condensers. In the new continuous approach, an appropriate condenser system is used to continuously remove the condensed water. The vial throughput can be increased simply by adding parallel lines in the continuous freeze-drying technology modules, as schematically shown in Figure 4.

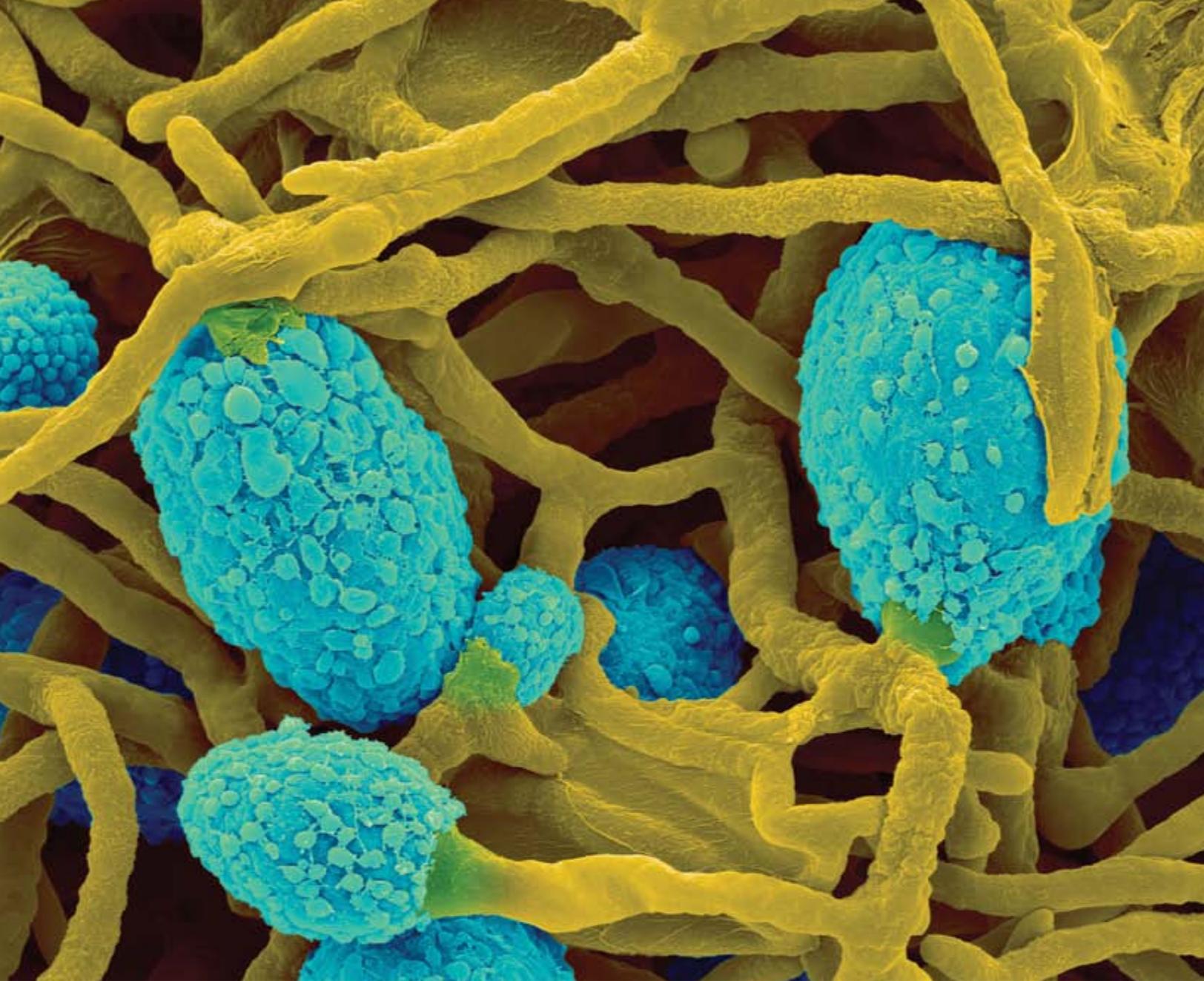
### Many Benefits to Being Continuous

The continuous freeze-drying technology offers the possibility of implementing process analyzers that allow real-time measurement and control of critical process parameters at the level of the individual vial. Several process analytical tools (PAT), such as near-infrared (NIR) spectroscopy and thermal imaging were evaluated and considered promising. Both techniques also proved highly complementary. NIR spectroscopy can provide detailed in-line information about several quality attributes like residual moisture content, protein conformation or the solid state of different components.

In turn, infrared (IR) thermography allows contactless, real-time and spatial monitoring of the product temperature at the sublimation interface, an essential parameter regarding the cake appearance of the end product.

This integrated approach strongly reduces the variability of CQAs and consistently guarantees the predefined quality of the end product. Hence, the continuous technology meets recent quality-by-design and PAT guidelines issued by global regulators, as opposed to the conventional batch freeze-drying process.

Currently, two different types of continuous freeze-drying prototypes have been built: a single-vial prototype and a GMP-like engineering prototype. The single-vial prototype allows the imitation of the



## Can you identify this organism?

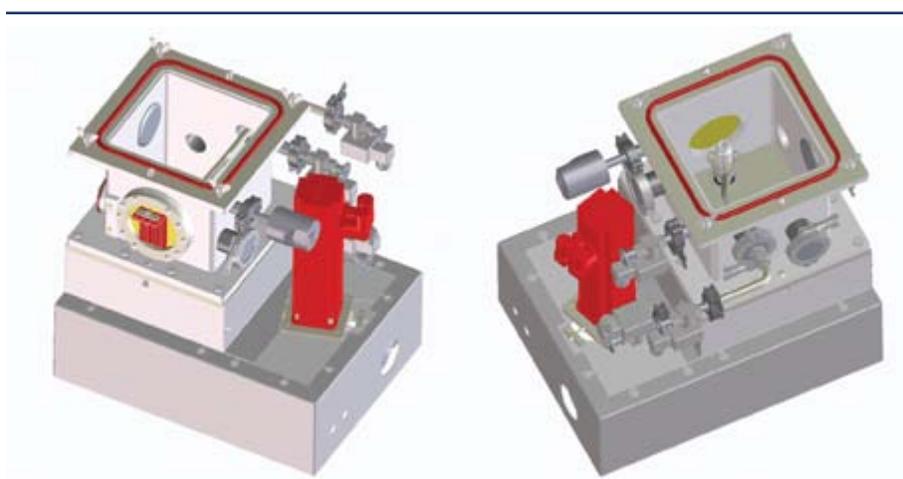
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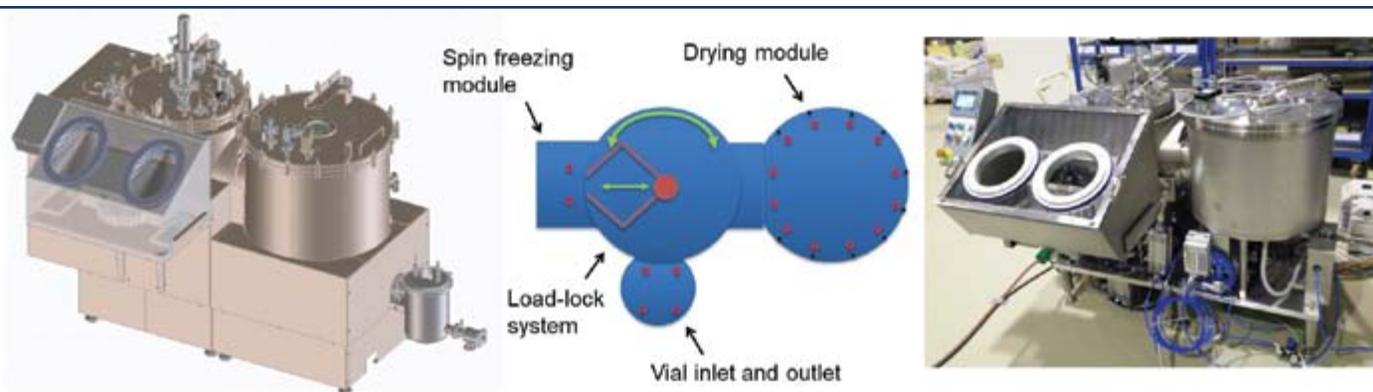
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continuous freeze-drying process for one single vial, as identical process conditions can be obtained similar to industrial-scale continuous freeze-dryers (**Figure 5**).

In case only a very limited amount of drug product material is available, such as at an early stage during development, this prototype allows initial development and optimization of the process and (drug) formulation. In addition, the ability to process small amounts of product makes the single-vial prototype suitable for producing personalized medicines. From a commercial point of view, the single-vial prototype is the perfect tool for



**Figure 5** Single-Vial Prototype For Simulation of Continuous Freeze-drying Process of Unit Doses



**Figure 6** GMP-like Engineering Prototype for Continuous Freeze-drying of Unit Doses

R&D laboratories within pharmaceutical companies to gain experience regarding the continuous freeze-drying process.

In the GMP-like engineering prototype, all process modules are integrated, and freeze-drying is executed in continuous fashion (**Figure 6**). This prototype is engineered around the implementation of needs to create and keep a sterile environment by choosing the proper materials and design principles.

Both prototypes allow the implementation of relevant PATs, including, NIR spectroscopy and thermal imaging, and the practical implementation of mechanistic models leading to optimal process conditions via individual temperature-regulation of IR heaters (7).

Biologic products will play an ever-increasing role in the future of healthcare.

And the freeze-drying for these products will be ever more crucial. The two continuous prototypes described here suggest new possibilities to ensure adequate freeze-drying beyond the traditional batchwise process.

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### About the Authors

**Pieter-Jan Van Bockstal** is pursuing his PhD at Ghent University. His research project aims at developing a continuous and controlled freeze-drying technology for unit doses based on non-contact energy transfer via infrared radiation.





**Jos Corver** has a degree in Applied Physics with specialization in transport phenomena of momentum, mass and energy. He has developed many solutions in the fields of printing, semiconductor, automotive and pharmaceuticals, leading to more than 20 patents.



**Thomas De Beer, PhD**, is a professor in Process Analytics & Technology at Ghent University. His research goals include the development of continuous manufacturing processes for drug products (e.g., continuous freeze-drying). 🍷



## Batch versus Continuous Freeze-Drying

### What Do the Experts Think?

The *PDA Letter* editors reached out to the two coleaders of PDA's Lyophilization Interest Group for their thoughts on the new technology presented in the cover story. Their responses are below:

#### Yves Mayeresse, Director, GlaxoSmithKline Vaccines

In general, I think this new technology would make a good improvement for the industry. At the same time, I do not think the picture is so bleak for batch freeze-drying. I agree batch freeze-drying can be inefficient in that it can take a few days, but that is usually after obtaining 100.000 vials at a time. The throughput of both technologies should be compared in terms of vials/units of time. There have also been more efforts at easing the revalidation required for each step of the batchwise process.

In my opinion of this technology, there needs to be further study on how the gas is filtered at low temperature with the right flow, and how the filter is tested afterward (frequency, typical temperatures and pressure).

Additionally, I want to point to personalized medicines. Here, small-scale, batchwise freeze-dryers have been used to produce personalized medicines for patients.

#### Edward Trappler, President, Lyophilization Technology

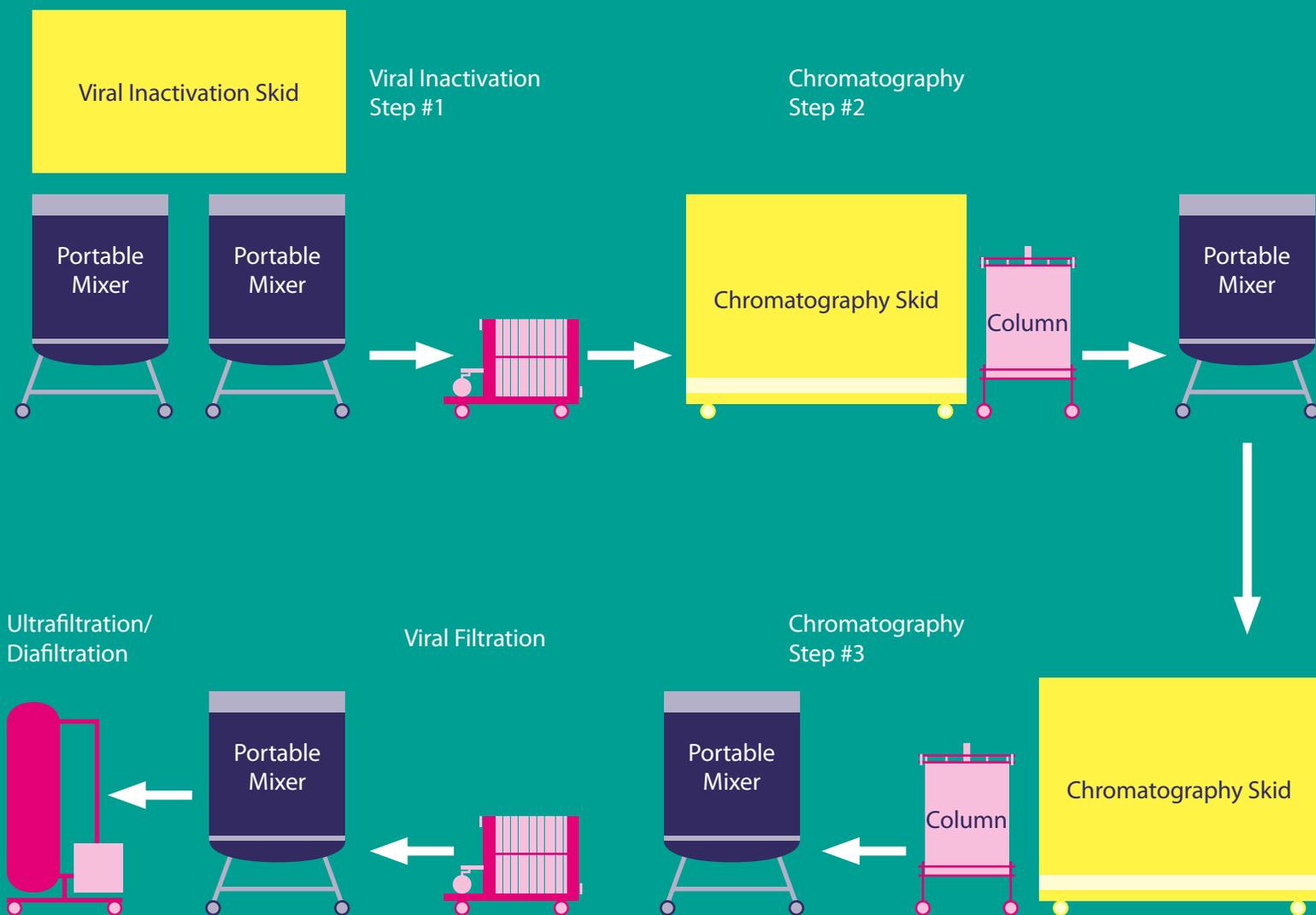
The cover story presents some interesting and thought-provoking possibilities. Pursuit of continuous processing for lyophilization is an ambitious feat, and an illustration that even the most complicated of pharmaceutical product processing can be pursued with innovative approaches. Though this new approach does not eliminate the potential for failure and other challenges of lyophilization, it is a stepping stone to further improvements and innovations. An example is the opportunity to progress from random sampling after completing the batch, to statistics-based sampling by extracting a sample from continuous processing based on the number of product units processed, similar to the approach taken to variation for dispensing with on-line weight checks on filling lines.

One of the advantages of such technology is eliminating the influence of variability in the primary packaging (vial/cartridge/syringe respective heat transfer coefficient) and its effect on the process. With the process being the same for a single presentation for the lab scale unit as large batch commercial manufacturing, application in producing personalized medicines becomes a realistic option. There would also be a great opportunity not just for biologic drug products, but also in reducing unit cost for classical small molecule product as well as for high volume production of products such as vaccines.

What do you think? The Managing Editor of the *PDA Letter* welcomes your feedback on the technology presented in this article. Submit your Letter to the Editor by email to [stauffer@pda.org](mailto:stauffer@pda.org) or by post to **Rebecca Stauffer**, PDA, 4350 East West Hwy, Suite 600, Bethesda, MD, 20814, USA. Your feedback on our content is always welcome! 🍷

# A Possible Model for Downstream Continuous Biomanufacturing

Many biologics manufacturers wonder if continuous manufacturing is achievable for downstream processing. Below is a sequence showing the operations of a discrete operation process for downstream batches taken from a recent article in the *PDA Journal of Pharmaceutical Science and Technology* (1).



**Source**

1. Garcia, F.A., and Vandiver, M.W., "Throughput Optimization of Continuous Biopharmaceutical Manufacturing Facilities." *PDA Journal of Pharmaceutical Science and Technology* 71 (2017): 189–205.

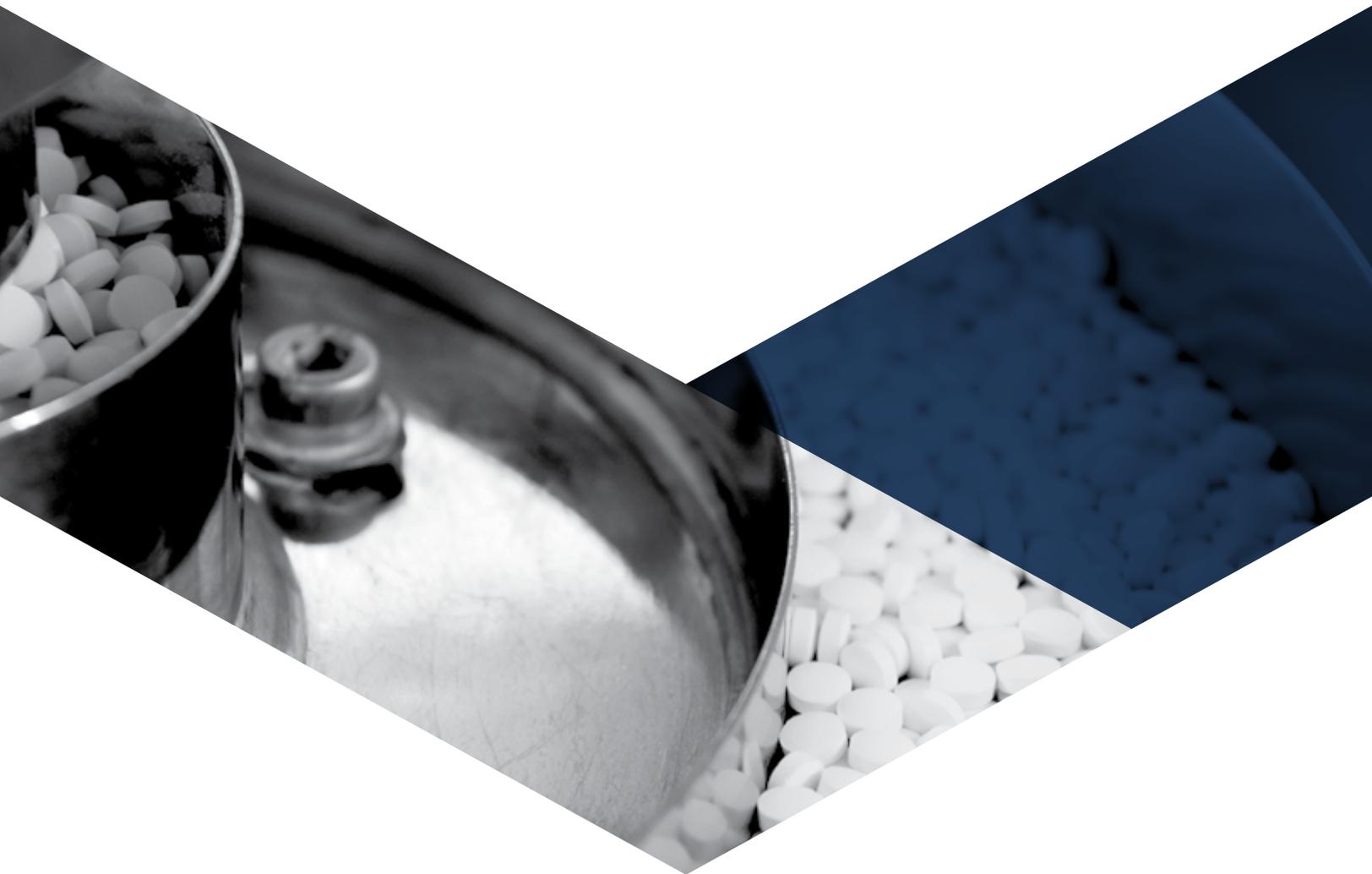


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# Smoke Signals

## One Plant's Secret for Assuring Aseptic Control

Tony Pavell, Fresenius Kabi

Airflow visualization testing, conducted as part of a routine review program, can help assure that aseptic filling areas remain under a state of proper control.

In fact, ISO standards recommend frequent airflow measurements. ISO standard 14644-2 requires “specifications for testing and monitoring to prove continued compliance with ISO 14644-1,” i.e., periodic measurements of airflow (1). The recommended tests to prove continued compliance include particle concentration testing, air volume or velocity and air differential pressure. Other recommendations suggest a maximum time interval of 24 months (1,3). This time interval may be extended based on the installation of instrumentation for continuous monitoring or other environmental control schemes based on a risk-based approach and area-specific data.

One process for conducting periodic airflow visualization testing is the tracer injection method, commonly referred to as the “smoke study.” An aseptic facility used this method for a routine airflow visualization program to provide assurance of unidirectional airflow in a critical part of the filling area.

### Visualization Offers Assurance

Airflow visualization studies were being performed in the lyophilizer loading area of an aseptic filling facility to verify that there had been no change in the ISO 5 area airflow since the last airflow visualization study date, approximately seven years prior. There had been no change in the room design, equipment configuration and the routine semiannual recertification had not identified any changes in room air change rate or filter velocities. The airflow visualization testing was initiated with the lyophilizer loading room in static conditions. With the lyophilizer door closed, the airflow was downward as expected.

When the lyophilizer door was opened, the airflow was observed to move horizontally away from the lyophilizer near the midpoint of the chamber. This did not meet the airflow visualization study acceptance criteria for unidirectional downward airflow visualized in front of the lyophilizer. It was confirmed that the airflow farther out

from the lyophilizer (underneath the next row of HEPA filters) was unidirectional and downward, therefore, it met acceptance criteria. Clearly, this was an anomaly.

After visualizing the area of horizontal airflow in front of the lyophilizer, an investigation was conducted into potential causes. The investigators reviewed maintenance activities that occurred on the equipment, integrity of the HEPA filters, airflow velocity testing 6 inches from filter face, filter life and room pressure at the time of testing. The investigation found none of these contributed to the airflow anomaly.

The filters were then returned to the vendor to perform pressure drop testing at rated airflow and velocity uniformity testing. The pressure drop testing did not identify an issue with the filter. Face velocity uniformity testing was performed using a TSI Anemasonic™ UA6 Ultrasonic Anemometer instrument to record velocity readings at 18 points on each filter (approximately 10 inches from the face of the filter).

Velocity uniformity testing showed a decrease in measured velocity from one side of the filter to the other. The decrease was approximately 30% on Filter 1 and approximately 50% on Filter 2. This is likely the result of uneven air supply to the filter inlet resulting in more particles loading on one side of the filter. This data suggests there are limitations to substituting air velocity measurements for periodic airflow visualization testing, necessitating further in-process monitoring.

Additional in-process monitoring may include differential pressure measurement or measurements of work surface velocities to help identify potential issues. The differential pressure across the filter membrane could be measured periodically and trended to indicate filter loading and potential flow issues. The differential pressure, however, can only be performed where the filters are installed with individual air supply to accurately measure the pressure across the single filter instead of the plenum to the room. The measurement of airflow velocities near the work surface/lyophilizer loading height could

be measured and trended. Airflow velocity readings near the work surface, however, have inherent issues with repeatability.

A review of previous requalification studies of the airflow visualization was performed to determine if there were any initial signs of the airflow anomaly that were not detected initially. The previous requalification studies were performed using the velocity distribution method to demonstrate that the airflow in the area being tested had not significantly changed since last airflow visualization testing using a smoke study. The ISO 14644-3 method of measuring velocity distribution for airflow visualization is commonly used to confirm airflow direction and/or airflow visualization in cleanroom areas.

During the review of previous requalification studies, it was found that the method in use (which relied on trending of air velocity values obtained for each filter) was an overinterpretation of the ISO standard. Substituting velocity measurements for visualization testing requires obtaining velocity measurements at different heights.

### Conclusion

Airflow pattern studies are an important component in the periodic review and recertification of aseptic processing areas.

Airflow measurements should be taken periodically in an area sufficiently below the filter face as to observe differences in actual supply velocities and also high enough above the work surface as to remain within “first air” that has not been influenced by the equipment in the working plane.

Alternatively, proper design on supply air filtration and in-process controls for airflow monitoring can be used to prevent issues that have an impact of air flow visualizations. These design methods may include prefiltration of supply air to reduce the amount of particulate loading on the terminal HEPA filter. In-process monitoring of the differential pressure across a terminal HEPA filter or air velocity measurements and trending of air velocity in the work surface area instead of only at the filter face may be used for trending purposes and identification of an issue that may impact airflow. Implementing these methods can be used to provide assurance of unidirectional air flow in the critical zone during routine use of the area and proactively prevent failures.

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### About the Author

**Tony Pavell** has over 20 years of compliance experience primarily focused in production and technical services.



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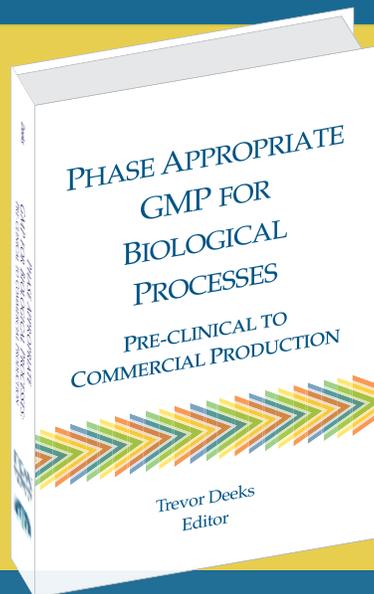
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- Systems and System Integrity in the Analytical Laboratory
- Phase Appropriate GMP in the Laboratory
- Phase Based Approach to Quality Assurance in Pharmaceutical Manufacturing - Big Pharma Perspective
- Phase Appropriate cGMPs: The Virtual Company
- Deviations, Change Control, Process Improvements
- Creating a Culture and System for Learning when using a Phase Appropriate Model
- Cell Line Characterization
- Considerations for Viral Clearance Studies
- The Impact of Single-use Systems on the Application of Phase Appropriate GMP in Bioprocessing
- Regenerative Medicine Advanced Therapies: Phase Appropriate Good Manufacturing Practices
- Microbiological Control and Testing for Phase Appropriate GMP
- The Evolution of Process Validation
- Sterility Assurance in Early Phase Development

[go.pda.org/PGBP](http://go.pda.org/PGBP)

## SNAPShot

### Regulatory Changes in China to Impact Many Areas

Hongyang Li, Novartis, PDA Regulatory and Quality Advisory Board (RAQAB) member

Recently, I had the pleasure of providing an update on Chinese regulatory trends to PDA's Regulatory Affairs and Quality Advisory Board (RAQAB). In general, while there are many new regulations coming from the China FDA, it appears Chinese regulators are striving to make sure their regulations are more aligned with international practices.

This reflects statements made by CFDA Director **Bi Jingquan** on Oct. 10 following release of the document, *Opinions on Deepening the Review and Approval System Reform and Encouraging the Drug and Medical Device Innovation*. In his remarks, he pointed to the need to expand China's development of innovative drug products as well as increase importation of new drugs from abroad for serious diseases, noting that, from 2001 to 2016, the U.S. FDA approved 433 new drugs, yet only 133 of them have been marketed in China. At the same time, safety and quality of drug products should be ensured.

Below are the highlights I shared with RAQAB:

- All post-approval changes (PAC) must be submitted online as of Dec. 1, 2017; these will be reviewed centrally by CFDA's Center of Drug Evaluation (CDE) as provincial CFDA offices will no longer accept nor review PAC submissions
- The Market Authorization Holder program will be implemented in China in the future (right now, only ten provinces/cities are allowed to participate the MAH pilot program); this change could have a dramatic impact on the Chinese pharmaceutical industry, for example, the term "imported drug" will now refer to drugs manufactured outside China but marketed in China, which may mean reduced testing at customs (some provinces have already dropped the testing fee for imported drugs in China)

[pda.org/2018VisualIG](http://pda.org/2018VisualIG)

## 2018 PDA Visual Inspection Interest Group Workshop

**If you work in visual inspection, either manual human inspection or automated machine inspection, you won't want to miss the 2018 PDA Visual Inspection Interest Group Workshop!**

The open-discussion atmosphere of this Workshop creates a forum in which to connect with colleagues and peers for an in-depth exploration of important topics, including:

- Identifying unique testing requirements for difficult-to-inspect products found in USP <790>, such as suspensions, freeze dried powders, colored solutions, biopharmaceuticals with inherent particles and those products in non-transparent containers
- Developing practical implementation strategies for automated inspection methods
- Understanding the current proposal to revise EC Annex 1, including the proposed requirements for visual inspection and container integrity testing

Participants are invited to suggest, in advance of the Workshop, additional topics for discussion.

Space is limited – Secure your spot today!

**To learn more and register, please visit [pda.org/2018VisualIG](http://pda.org/2018VisualIG)**

Extend your learning experience by attending PDA's *An Introduction to Visual Inspection* course, Apr. 26-27. This course will cover the fundamentals of visual inspection and their application to injectable products.

**To learn more and register, please visit [pda.org/2018VisualIntro](http://pda.org/2018VisualIntro)**



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- APIs will be reviewed in conjunction with NDA and ANDA applications, and there will no longer be a separate CDE review of API applications; API manufacturers are encouraged to file Drug Master Files with the CFDA, and there will be no “pharmaceutical production license” issued to API manufacturers in China
- The “GMP Certificate” issued by CFDA will cease; the intent is that preapproval inspections (PAI) will cover general GMP inspections as well
- The five-year GMP recertification for onsite inspections will be converted to routine onsite GMP inspections based on a risk model being developed by CFDA
- A revision to the Drug Administration Law is expected to be passed in the next Chinese Congress sometime in Q1 2018 so as to enable the above changes
- A new piece of Chinese regulation pertaining to “Drug Data Governance” has been published for comment—this is the third version published for commenting (PDA commented on the first version of the regulation), and the contents are now more aligned with current international guidelines regarding data integrity; this regulation is intended to govern data integrity and reliability in the whole lifecycle of pharmaceutical products in China, covering GxP, not only GMP

Anyone interested in learning more about Chinese regulations is encouraged to contact **Denyse Baker** at [baker@pda.org](mailto:baker@pda.org). 🌍

[pda.org/2018CCPI](http://pda.org/2018CCPI)

## 2018 PDA Container Closure Performance and Integrity Conference

The *2018 PDA Container Closure Performance and Integrity Conference* will address the complexities and challenges to container closure performance and integrity.

Broaden your understanding of holistic requirements related to performance and protection by identifying potential failure modes throughout the life of a product and de-risking container closure design during development.

At the Conference, experts will cover a wide range of topics, including:

- Best practices for container closure design
- System engineering approaches for performance optimization
- Container closure integrity testing
- Critical secondary/tertiary packaging and cold chain development
- Regulatory requirements in the combination product platform space

**To learn more and register, please visit [pda.org/2018CCPI](http://pda.org/2018CCPI)**



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# Awareness Key for Container Closure Components: Part I

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

The most important takeaway for participants of PDA's *2017 PDA Container Closure, Devices and Delivery Systems: Compatibility and Material Safety Workshop* can be summed up in one word: awareness. As the complexity of delivery systems and drug/device combination products increases, the task of qualifying components fit for use becomes especially challenging, necessitating greater awareness of regulatory requirements and current trends.

At the workshop, cosponsored with the Product Quality Research Institute (PQRI), Oct. 2–3, in Washington, D.C., the most pressing topics in container closure were featured: particulates, biocompatibility, leachables/extractables, biologic stability, container closure integrity, etc.

Below are summaries of each session of the workshop, written by each of the session moderators.

### Plenary 1: The Future of Drug Delivery

**Moderator: Diane Paskiet, Director, Scientific Affairs, West**

The workshop opened with a view of the future of drug delivery captured from two perspectives: integrated drug/device development and opportunities for emerging pharmaceutical technologies. **Didier Pertuy**, Vice President, Global Head Drug Device Integrated Development and Device Strategy, Sanofi, described how the increase in device-mediated injectable delivery systems is due to the significant growth of self-administered biologics for chronic diseases. The drug and the device

must be integrated, from discovery all the way to commercialization. The probability that a device is needed in combination with a drug should be raised as soon as possible during the research phase in order to select the appropriate route of administration. An integrated approach also helps in the design of a device-able biopharmaceutical candidate and for building the drug-device combination development strategy.

A good drug and formulation device-ability profile allows developers to design the best user interface and injection experience. Implementing a Phase 0 study could help to shape patient/user preferences. Drug product development must be based on a patient-centered integrated system design approach with a device-able bio- ➤

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pharmaceutical candidate. When possible, it is best to screen out nondevice-able molecules at risk for interfacial and/or leachable-induced interactions, or poor device performance, rather than attempting to alleviate the problem. A cross-functional team that can understand both the drug and device sides of the business is necessary. After all, a combination product is an integrated system and no one component is more important than another. Understanding and controlling the product and process requires a true partnership.

Following Pertuy's talk, a U.S. FDA representative emphasized the need for innovation to develop and manufacture quality medicines. **Sau Lee**, PhD, Office of Testing and Research, CDER, introduced his Center's Emerging Technology Team (ETT). The goals of the ETT are to address underlying causes of product recalls, improve manufacturing efficacy and facilitate new clinical development for novel dosage forms.

The program aims to support the adoption of innovative technology through close collaboration with industry and other relevant stakeholders. Within this program, a small ETT cross-functional team is composed of representatives from all relevant quality review and inspection programs in addition to relevant subject matter experts. This team is responsible for facilitating knowledge of novel products, manufacturing processes and analytical technologies.

The sponsor is responsible for justifying that a proposed emerging technology would be novel from a pharmaceutical perspective and also advance product quality. The technology would be included in an application-associated Drug Master File. The ETT provides a forum for firms to engage in early dialog with FDA to support innovation and ensure consistency, continuity and predictability in review and inspections. There have been 32 requests accepted into the ETT program since its launch in 2014. There have already been several approvals such as 3D-printed drugs, continuous manufacturing, a closed aseptic filling system and a novel injectable container and closure system, to name a few.



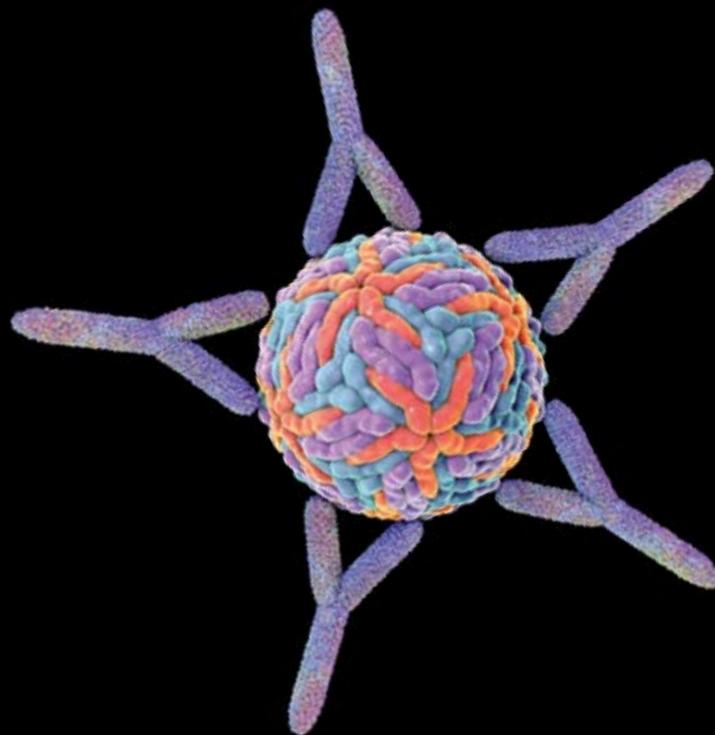
[This is the first of three installments. The article in its entirety, including figures, can be read at the *PDA Letter* website]. 🍷

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# PDA Keeps You up to Date on the Latest Advances in Packaging Science

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

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

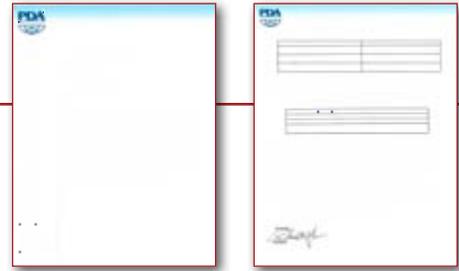
A snapshot of PDA's extensive offerings includes:

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

*To find out more about how PDA is leading the way to improved patient safety through better pharmaceutical packaging processes and practices, please visit [www.pda.org](http://www.pda.org).*

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# Changes to USP Council of Experts



January 7, 2018

Convention Governance Committee (CGC)  
United States Pharmacopeia  
2601 Twinbrook Pkwy  
Rockville, MD 20852

Reference: Notice of Proposed Change to 2015-2020 Rules and Procedures of the Council of Experts

Dear CGC Members:

PDA appreciates the opportunity to respond to the proposed change to section 7.06 of the Rules and Procedures of the 2015-2020 Council of Experts, Approval by Expert Committee. PDA and its members appreciate the challenges of a growing workload with limited resources faced by the Expert Committees under the current rules and procedures. PDA can support the delegation of certain specific Expert Committee tasks to appropriately trained and qualified USP staff as long as there is no scientific impact or risk to patients or public health. PDA would like to see the revision include more precise language on what can or cannot be delegated. For example, PDA recommends the procedure state that changes to standards, test methods or specifications for items other than editorial or format or error corrections will not be delegated. PDA agrees with the delegation to USP staff of changes due to typographical errors or editorial errors that do not change science such as already done with reference standards.

One concern PDA has with this proposal is that it creates new numbering for the various parts of section 7.06 as shown in the table below.

Structure of Current Section 7.06	Structure of USP Proposed Section 7.06
(a) New Standards and Accelerated Approvals; Balloting	(a) New Standards and Accelerated Approvals; Balloting
(b) Joint Standard-Setting Subcommittee; Approval; Balloting	(b) USP Staff; Delegation of Approval Authority with Council Oversight
(c) Responsibility for Approvals	(c) Joint Standard-Setting Subcommittee; Approval; Balloting

There are multiple issues here. First, the original section 7.06c appears to be missing in the proposal. It is unclear whether this part being deleted. Second, the renumbering of the parts (e.g., old b is new c) is problematic because other documents (e.g., Guideline for Review and Approval of Reference Standards...) directly reference these parts. The renumbering will create errors in these other documents and lead to confusion. PDA recommends the old numbering remain intact and a new sub-bullet (d) for USP Staff Delegation be created as shown below.

Structure of PDA Proposed Section 7.06
(a) New Standards and Accelerated Approvals; Balloting
(b) Joint Standard-Setting Subcommittee; Approval; Balloting
(c) Responsibility for Approvals
(d) USP Staff Delegation of Approval Authority with Council Oversight

PDA would also like to suggest alternate ways to address the constraints the ECs are facing. One approach is to split Expert Committees within the larger or more busy topics so that that workload could be divided without overlap. Advantages of this approach include involvement of more volunteers from industry bringing broader perspectives and expertise to the discussions and lowering the burden on each individual expert committee member. One challenge could be the additional considerations for the USP staff to manage and support an increased size of the Council of Experts. This approach of sub dividing current expert committees develops more experience within the volunteer base and provides increased opportunities for succession planning for expert committee leaders. One example would be the Chemical Analysis committee where the scope could be split into two groups such as spectroscopy and chromatography.

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 Regulatory Affairs and Quality Advisory Board.

If there are any questions, please do not hesitate to contact me.

Sincerely,  
Richard Johnson  
President, PDA  
Cc: USP Board of Trustees

## PDA Commenting Team

Janeen Skutnik-Wilkinson, Biogen (lead)

Norman Sesi, Eli Lilly

Susan Schniepp, Regulatory  
Compliance Associates

Karen Ginsbury, PCI

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## 2018: Greater Harmonization and Global Collaboration

*“Stability studies in Brazil have been an issue for quite some time—ANVISA’s alignment with ICH is a significant positive step forward.”*

*“We’ve got a draft set of comments on China’s PAC guidance....”*

*“Hospitals are forming their own drug company. This news article indicates who is involved....”*



Emma Ramnarine, Genentech/Roche

These are a few examples of topics that have come to the attention of PDA’s Regulatory Affairs and Quality Advisory Board (RAQAB). This advisory board serves the PDA membership by influencing science-based regulations and interpreting regulatory issues that affect the development, manufacturing and control of healthcare products. This involves regularly interacting with global regulators.

In fact, for 2018, RAQAB’s goal is to expand engagement with global regulators. A few hot topics that RAQAB specifically plans to collaborate with regulators on include:

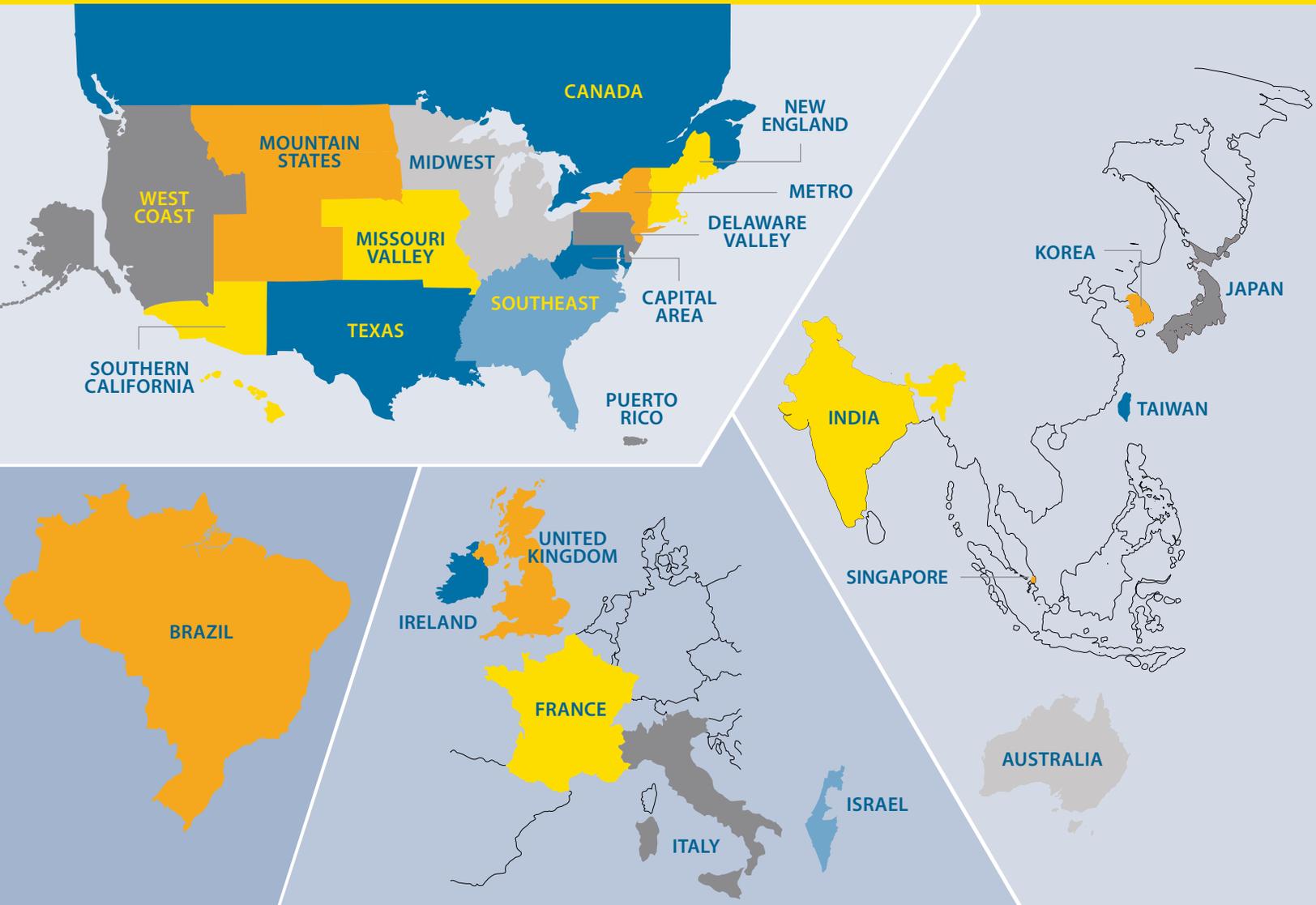
- 1. Quality Culture** — PDA is actively working with the UK MHRA and the U.S. FDA to train their regulators on PDA’s onsite assessment approach to quality culture. Additionally, there are opportunities open in both the United States and Europe for sites to enroll and compare their results with the more than 40 sites that have already completed their assessments using PDA’s quality culture assessment tool.
- 2. Post-Approval Changes** — PDA’s Post-Approval Change Innovation for Availability of Medicines (PAC iAM<sup>SM</sup>) Task Force is actively engaged in global discussions on addressing current barriers to implementation of post-approval changes (PAC) that hinder continual improvement. In addition to engaging in the development of ICH Q12: *Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management*, the task force has been active in publishing Points to Consider papers, articles, webinars, workshops, etc. A technical report on PAC is also under development.
- 3. Data Integrity** — PDA’s Data Integrity Task Force is working to clarify expectations and best practices for data integrity to help firms meet regulatory requirements. FDA is actively engaged and contributing to two technical reports. The technical report on data integrity for laboratory systems is expected to be issued in mid-2018. The technical report team working on the one focused on data integrity for manufacturing systems is firming up their outline and plans to have an initial draft completed by the end of the year. In addition, PDA has been working with FDA to find common ground regarding specific topics related to inspections that have been difficult for industry.
- 4. Pharmacopeial Harmonization** — PDA’s first ever *Pharmacopoeia Conference*, scheduled for May in Vienna, fulfills a long standing RAQAB objective to promote pharmacopeial harmonization. Pharmacopeial agencies from the United States, Europe, Japan, China, Russia, Eurasia, India and Ghana are scheduled to participate.

To learn more about these initiatives, I encourage you to visit the PDA website: [www.pda.org](http://www.pda.org).

RAQAB is integral to PDA’s mission of connecting People, Science and Regulation®, and in serving the needs of PDA members in a rapidly evolving global landscape that is becoming increasingly complex. 🌐

# PDA Chapters

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# Vaccines



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