People • Science • Regulation

PDA Letter

Volume LIV • Issue 6 www.pda.org/pdaletter June 2018

Can ICH Q12 Unlock Manufacturing Innovation?

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PDA
Parenteral Drug Association

On the Issue Videos by the *PDA Letter*

Interviews with leading industry experts on the issues important to you

Watch the following experts:

Vetter's Ute Schleyer — RABS/Isolator combination

PDA Education Instructor Elaine Lehecka Pratt — Reducing Human Error

Corning's Timothy Hunt — Updates to USP <660>

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

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

www.pda.org/pdaletter

June 2018 PDA Letter

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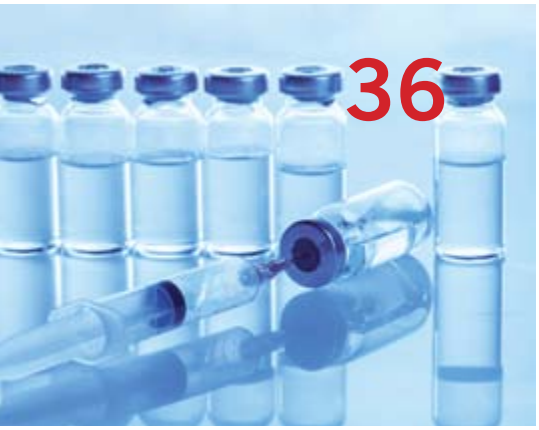
Can ICH Q12 Unlock Manufacturing Innovation?

Ursula Busse, PhD, Novartis, and Melissa Seymour, Biogen

Human medicine has come a long way in the last 100 years. Paradigm-changing therapies have made their way into the clinic since the end of the last century, nurtured by better understanding of the underlying causes of various diseases.

Cover Art Illustrated by Katja Yount

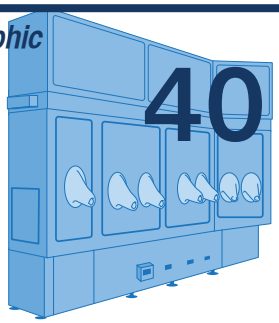


Prospects for Post-Approval Change Management

Naheed Sayeed-Desta, Apotex, Ajay Babu Pazhayattil, and Ivy Louis, Vienni Training and Consulting LLP

As new types of biologic products enter the market, the need for innovative processes continues to grow. This requires improvements in post-approval change management. *ICH Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* offers a solution to post-approval change challenges in the form of a post-approval change management protocol (PACMP).

InfoGraphic



A Post-Approval Change for an Aseptic Filling Isolator

When a manufacturer implements a new isolator as part of a post-approval change, a Process Design and Characterization Study is required.

A Wealth of New Tech Possibilities

Annual Meeting Showcases the Latest in New Drugs, Manufacturing Technology

Scott Bozzone, PhD, Pharm Lifecycle Validation LLC

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Healthy patients are always the end goal for PDA members. This means it is now more important than ever for industry to modernize existing processes. This year's Annual Meeting in Orlando, Fla., provided no shortage of sessions highlighting the importance of producing quality parenteral medicines for patients while also maintaining top-notch manufacturing systems.

PDA Letter

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

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

Subscriptions are not available.

Departments

Digital Exclusives

> **On the Issue | 3 Questions on a New RABS/Isolator Combination**
Annual Meeting speaker **Ute Schleyer** from Vetter discusses the company's new isolator/RABS technology

pda.org/letter

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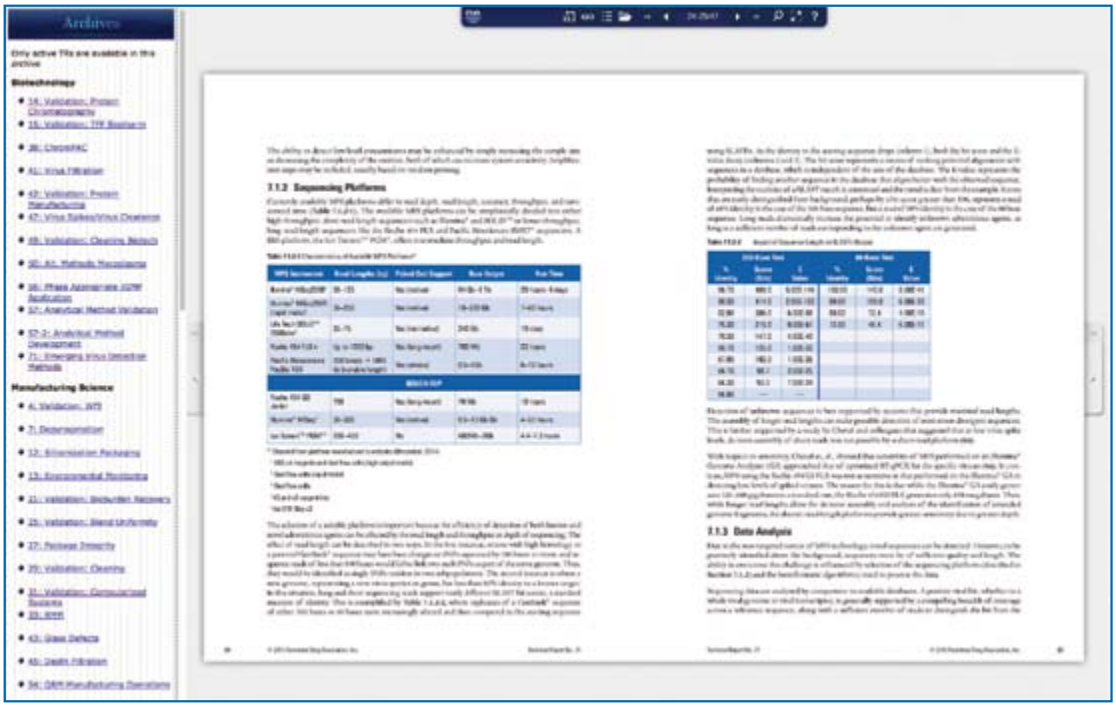
PDA's Technical Report Portal



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trarchive.pda.org/t/26426

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

2018 PDA/FDA Joint Regulatory Conference

Putting Patients First: Ensuring Innovation, Quality, Compliance, and Supply in an Evolving Environment

Register by July 16 and save up to $400!

Continuing a nearly 30-year tradition, the *2018 PDA/FDA Joint Regulatory Conference* offers unique opportunities to interact directly with regulators and to gain insight into key regulatory issues and solutions.

This year's conference marks 10 years since the heparin supply chain crisis, and the Conference will take stock of lessons learned and remaining challenges, focusing on practical approaches implemented by companies to better manage risks in their increasingly complex supply chains, and case studies relating to CMOs and ingredient suppliers.

Through plenary sessions, including the ever-popular Compliance and Center updates; breakout sessions in three concurrent tracks covering lifecycle management and innovation, quality and compliance, and supply chain; and breakfast sessions on "hot industry topics," this premier Conference will provide you with the tools you need to ensure innovation, quality, compliance, and adequate supply in an ever-evolving manufacturing and regulatory environment!

Learn more and register at pda.org/2018PDAFDA

FDA

PDA Parenteral Drug Association

September 24-26, 2018 | Washington, DC
Exhibition: September 24-25
#2018PDAFDA

CONNECTING PEOPLE SCIENCE AND REGULATION®

New Publishing Tech Means New Processes for PDA Letter Staff

Rebecca Stauffer

Not only has covering post-approval changes exposed me to innovations in parenteral manufacturing, but it has also made me think about how my role as editor of the *PDA Letter* has changed over time as PDA has embraced new publishing technologies.

When I started, my primary focus was reviewing and editing content strictly for the print magazine. The editorial team had a specific process with even more specific checklists to help in putting together the print magazine. But that process has changed over time as we have revamped the Letter website, published more digital exclusive articles, and produced "On the Issue" and "Editor's HotSeat" videos. For example, we post new content to the website every Tuesday, which is a big departure from our previous, monthly routine. Now we must prioritize and accelerate the editing process for articles slated for online publication. the editing process for articles slated to appear online ahead of print.

Now, along with writing and editing, I also work with members of the *PDA Letter* Editorial Committee (PLEC) to identify subject matter experts to interview and develop questions and a script. This is another change. In the past, the PLEC only had one subcommittee, the Art Subcommittee. This subcommittee was tasked with reviewing cover art and infographics. Now, there is a Multimedia Subcommittee that helps us with our video and other multimedia content. I want to thank the members of this year's Multimedia Committee for assisting with this year's slate of videos: **Christopher Hanff, Claire Briglia, Joanne Beck, Stephanie Gaulding** and **Valeria Frigerio-Regazzoni.**

Speaking of our videos, we continue to try new things to make them ever-more compelling and tackle new subjects. At this year's Annual Meeting in Orlando, Fla., we filmed PDA board member **Masahiro Akimoto** interviewing Japan PMDA regulator **Issei Takayama** about his poster presentation, "Current Regulatory Considerations for Continuous Manufacturing of Pharmaceuticals in Japan." The interview was conducted in Japanese and will be subtitled in English. Look for it in the next few months on the Letter website (https://www.pda.org/pda-letter-portal/multimedia/videos) and the PDA YouTube channel (https://www.youtube.com/user/ParenteralDrugAssoc).

We also continue to expand the Letter website. Earlier this year, we published a lengthy overview of the *2017 PDA Container Closure, Devices and Delivery Systems Workshop*. Each of the workshop moderators summarized their session of the workshop. The online version includes selected slides from the workshop and includes special navigation for accessing sections of the article. In print, the article appeared in three parts. If you have not already, I urge you to check out the article at https://www.pda.org/pda-letter-portal/awareness-critical-for-container-closure-components. We are also planning a similar article later this year. This article also required adjustments in our processes, particularly when it came to reviewing and selecting the accompanying slides for the online version.

While you contemplate how to implement a post-approval change for a new isolator, RABS, etc., take comfort in the fact that the *PDA Letter* staff also face the sometimes-challenging task of developing new processes for innovative technologies. Addressing these challenges, however, is worth it for providing PDA members the content and information they want in the most appropriate medium.

Rich Levy, PhD, to Lead PDA Journal as Editor

PDA Thanks Dr. Govind Rao and Associate Editors

On May 21, **Rich Levy,** PhD, PDA's former Senior Vice President of Scientific and Regulatory Affairs, began his new role as the Journal Editor for the *PDA Journal of Pharmaceutical Science and Technology.*

Dr. Levy looks forward to keeping the Journal relevant to the members and making it one of the most valued PDA member benefits. As part of his duties, he will be assembling a volunteer editorial committee. If interested in joining, please contact Dr. Levy at journal@pda.org with the subject line "editorial committee."

PDA thanks the previous Journal editors for their contributions to the peer-reviewed journal:

- Journal Editor **Govind Rao,** PhD
- Associate Editor **Antonio Moreira,** PhD
- Associate Editor **Anurag Rathore,** PhD
- Associate Editor **Beth Junker,** PhD

Drs. Rao, Moreira and Rathore served for nearly nine years. The entire editorial team helped ensure the content of the PDA Journal was tailored to the needs and interests of our community.

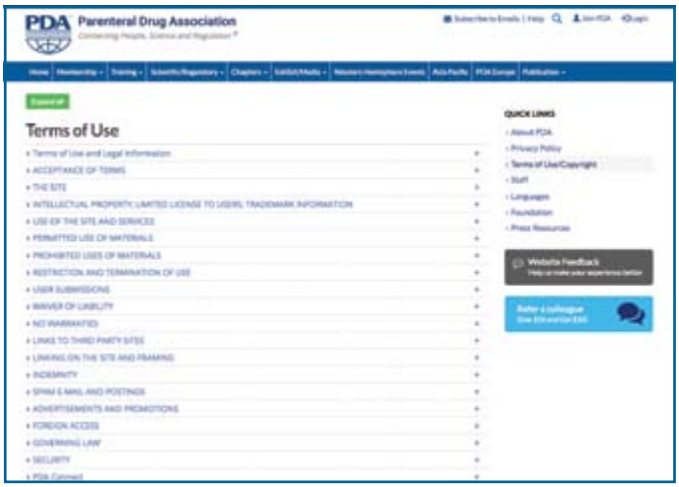
The *PDA Journal of Pharmaceutical Science and Technology* can be accessed at journal.pda.org.

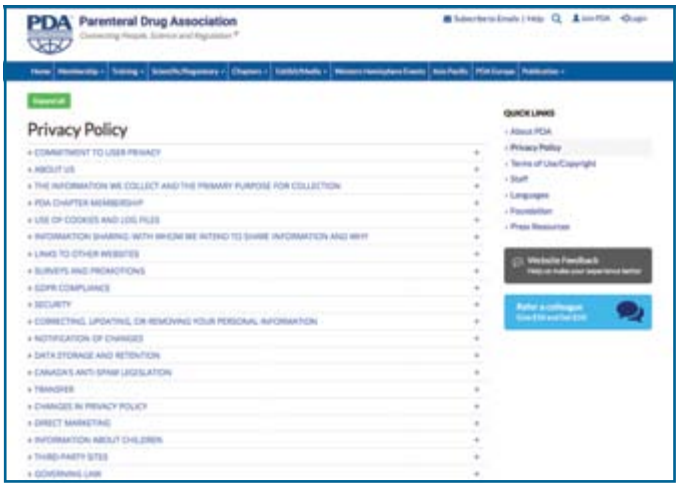
PDA Cares About Your Data Privacy

The protection of your privacy and your data is of the utmost importance to PDA. Therefore, we have changed the Terms of Use for the website and our Privacy Policy to better ensure the privacy of your personal information.

The EU's General Data Protection Regulation (GDPR) went into effect on May 25 and we have taken the necessary steps to ensure that we are in compliance with GDPR.

Both the Terms of Use (www.pda.org/terms-of-use-copyright) and Privacy Policy (www.pda.org/privacy-policy) can be accessed on the PDA website.





PDA Volunteer Spotlight

Julie Barlasov-Brown

- **Associate Director of Sterile and Microbiology QA, Global Quality**
- ***Merck & Co.***
- Member Since | **2003**
- Current City | **Slatington, Pennsylvania**
- Originally From | **Moscow, Russia**

I have had opportunities to share my experiences

Why did you decide to volunteer for PDA?
I first learned about PDA in Israel during a trade show in 2002. I quickly realized PDA is a great resource for learning about recent updates, current practices, etc. When I moved to the United States in 2003, I became a member of PDA. This led me to learn about volunteering and all the exciting opportunities that could help me advance in my field.

I started to volunteer as soon as I had an opportunity and I am glad that I can help others by coauthoring technical reports or organizing conferences as a member of a planning committee.

Of your PDA volunteer experiences, which have you enjoyed the most?
I am not sure I can decide which one is the best! All the experiences have been very different, creating amazing opportunities for learning and collaboration. While working on technical reports, I have had opportunities to share my experiences, and also learn from other team members.

When it comes to planning committees, such as for the *Annual PDA Global Conference on Pharmaceutical Microbiology,* I like how an idea leads to a theme, which then leads to a cohesive set of presentations, resulting in a well-planned meeting. It is always a great collaborative effort.

What is your favorite place to visit?
Anywhere with a view of mountains and very dark nights. I love photographing landscapes, and night photography is my favorite.

When you were a child, what did you want to be when you grew up?
I wanted to be a dentist.

Tell us something surprising about you.
I am an avid backpacker and when I have the time, I want to hike every long trail out there. In particular, there is one trail that just got finalized; it is about 15,000 miles long and runs between the east and west coasts of Canada.

PDA
Parenteral Drug Association

Where do leading experts turn to communicate with the PDA community?

The *PDA Letter* and *PDA Journal of Pharmaceutical Science and Technology*

RICHARD FRIEDMAN
STEPHAN ROENNINGER
JANET WOODCOCK
ANDERS VINTHER
JAMES AGALLOCO
JAMES AKERS
DENNIS JENKE
JAMES COOPER
IRVING PFLUG
MAIK JORNITZ
KURT BRORSON
JEANNE MOLDENHAUER
MICHAEL MILLER
SUSAN SCHNIEPP

You can too!
Authors wanted

For more information on PDA publishing please visit:

www.pda.org/pdaletter **http://journal.pda.org**

Eyeing the Future of Biomanufacturing

New England Chapter Learns About Two Promising New Processes for Biologics Production

Victoria Hayes, ICQ

New visions are on the horizon for the future of biologics manufacturing, and the field is on the cusp of great change.

Two of these changes were showcased at the March 14 PDA New England Chapter dinner meeting, "Future Trends in Manufacturing." **Kathleen Souza, Stephanie Ferrante** and **Donald McCarthy** graciously hosted the meeting at the newly completed MilliporeSigma facility in Burlington, Mass. Attendees were able to tour the facility prior to the evening's presentations.

After a buffet dinner meeting in the site's café, Chapter President-Elect **Laurie Masiello** and MilliporeSigma's **Willem Kools** delivered the opening remarks to the 115 attendees.

Ventakesh Natarajan then provided the first presentation, "Can Non-Mammalian Hosts be the Future Expression System of Choice for Antibodies?" His talk explored the notion that scientific vision can improve the economics of therapeutics production, pointing out that, while Chinese hamster ovary cells are commonly used, other modalities are being explored that could potentially offer lower media costs. The yeast *Pichia pastoris,* filamentous fungi, microalgae and protozoa, among others, were included in the study. Results have been promising and further studies will continue. Interestingly, the Gates Foundation is a sponsor of this project.

Scientific vision can improve the economics of therapeutics production

Next, **Aaron Noyes** presented "Manufacturing Process Development Challenges for Exosomes, a New Therapeutic Platform for the Delivery of Biomolecules." He talked about exosomes, a subclass of extracellular vesicles, and how a technology akin to cell therapy is being developed in which siRNA and miRNA can be delivered to cells. This is a new area that has, for the most part, only received coverage in journals within the last five years. While much remains unknown, great hope for the viability of this technology in the treatment of can-

cers or other diseases based on the natural delivery mechanism of exosomes continues.

These two talks covered some innovative approaches to manufacturing currently under development and, not surprisingly, stirred considerable discussion during the Q&A session that followed.

The chapter thanks the following volunteers for their assistance: Kathleen Souza, Stephanie Ferrante, Don McCarthy, **Elisabeth Piquet** (Chapter Events Coordinator), **Steve Jones** (Communications Chair), **Shawn Sherry** (Chapter Treasurer) and **Tayaba Naz.** The chapter also thanks Aztec Technologies, Particle Measuring Systems, Commissioning Agents and Steris for sponsoring the meeting.

PDA Who's Who

Stephanie Ferrante, Associate Director, Technology Management, MilliporeSigma

Steve Jones, Manager, Validation Support LLC

Willem Kools, Head, Process Solution Technology Management, MilliporeSigma

Laurie Masiello, President and CEO, Masy BioServices

Don McCarthy, Senior Application Specialist, MilliporeSigma

Ventakesh Natarajan, Principle Process Engineer, Biogen

Tayaba Naz

Aaron Noyes, Codiak BioSciences

Elisabeth Piquet, Events Coordinator, PDA New England Chapter

Shawn Sherry, Overlook Industries

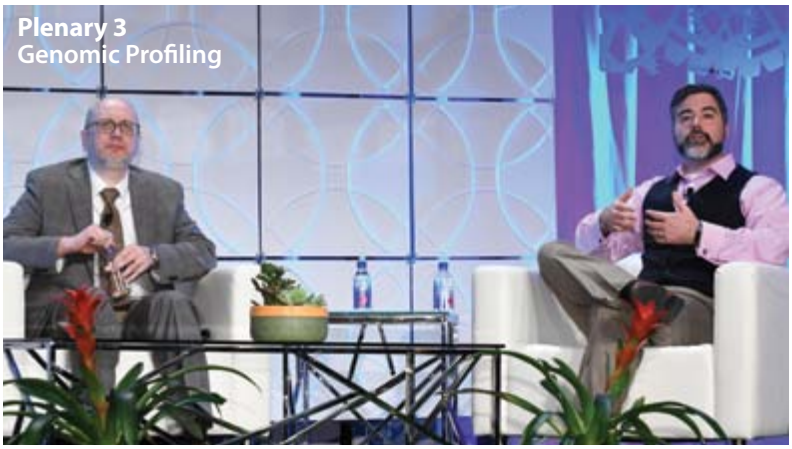
Kathleen Souza, R&D Manager, Virology and Microbiological Sciences, MilliporeSigma

2018 PDA Annual Meeting
April 19–21 | Orlando, Fla.

(l-r) PDA Chair Rebecca Devine, PhD; PDA President Richard Johnson; Annual Meeting Co-chair Ghada Haddad, Merck; Annual Meeting Co-chair Morten Munk, NNE

(l-r) Stephen Kingsmore, MD, Rady Children's Institute for Genomic Medicine; Lori Richter, ValSource

(l-r) Tia Bush, Amgen; Steven Spear, PhD, Massachusetts Institute of Technology; Sharmista Chatterjee, PhD, U.S. FDA



(l-r) Vadim V. Romanov, MD, Novartis; Victor Weigman, PhD, IQVIA

(l-r) Amy Wilson, PhD, Biogen; Arleen Paulino, Amgen

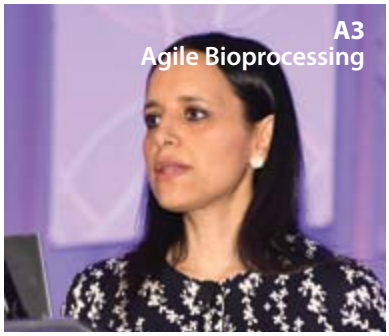
(l-r) Ghada Haddad, Merck; Rainer Mueller, PhD, Roche; Matthias Gromeier, MD, Duke University Medical School

(l-r) Thomas Seewoester, PhD, Amgen; Michele D'Alessandro, Merck

(l-r) Jeffrey Gelwicks, PhD, Eli Lilly; Jay Buchanan, Takeda; Marcia Baroni, Eli Lilly

(l-r) Melissa Seymour, Biogen; Erwin Irdam, Biogen

(l-r) Ute Schleyer, PhD, Vetter; Shelley Preslar, Azzur Group; Terrence Hollis, Patheon; Ross Gold, Vanrx



Suzanne Farid, PhD, University College London

(l-r) Patrick Gammell, PhD, Amgen; Austin Caudle, IQVIA; Paul Stey, Brown University; Malcolm Postings, IQVIA

(l-r) Suzanne Farid, PhD, University College London; Karen Walker, Seattle Genetics; Kirstin Powel, Novartis; Jeffery Odum, NNE

(l-r) Michael Long, PhD, ValSource; Ajay Pazhayattil, PhD; Scott Bozzone, PhD, Pharm Lifecycle Validation

(l-r) Russell Madsen, The Williamsburg Group; Maik Jornitz, G-CON Manufacturing

(l-r) Ghada Haddad, Merck; Lori Richter, ValSource; Amanda Bishop McFarland, ValSource; Kelly Waldron, ValSource

Arleen Paulino

(l-r) Michael Blackton, Adaptimmune; Marsha Steed (Hardiman), ValSource; Karen Walker, Seattle Genetics

Terrence Hollis, Patheon

(l-r) Ghada Haddad, Merck; Melissa Seymour, Biogen

pda.org/conferences

Engage, Connect, and Convert Valuable Leads at PDA's Fall 2018 Conferences!

Gain direct access to PDA's global community of leading professionals in the field of bio/pharmaceutical manufacturing by exhibiting at or sponsoring one of PDA's Fall 2018 events. With Conferences and Workshops on a variety of exciting industry hot topics, you'll be sure to reach your target audience.

SEPTEMBER 24-26	***2018 PDA/FDA Joint Regulatory Conference*** | Washington, DC
SEPTEMBER 26-27	***2018 PDA Biosimilars Workshop*** | Washington, DC
OCTOBER 8-9	**LIMITED SPACE AVAILABLE** ***2018 PDA Universe of Pre-Filled Syringes and Injection Devices*** | Orlando, FL
OCTOBER 10	***2018 PDA Combination Products Workshop*** | Orlando, FL
OCTOBER 15-17	**LIMITED SPACE AVAILABLE** ***13th Annual PDA Global Conference on Pharmaceutical Microbiology*** | Bethesda, MD
OCTOBER 17-18	***2018 PDA Endotoxins Workshop*** | Bethesda, MD
OCTOBER 23-24	***2018 PDA Cell and Gene Therapy Conference*** | Bethesda, MD

PDA® Parenteral Drug Association

For more information on all sponsorship and exhibit opportunities for PDA events in the U.S., contact **David Hall**, Vice President, Sales, PDA, at hall@pda.org

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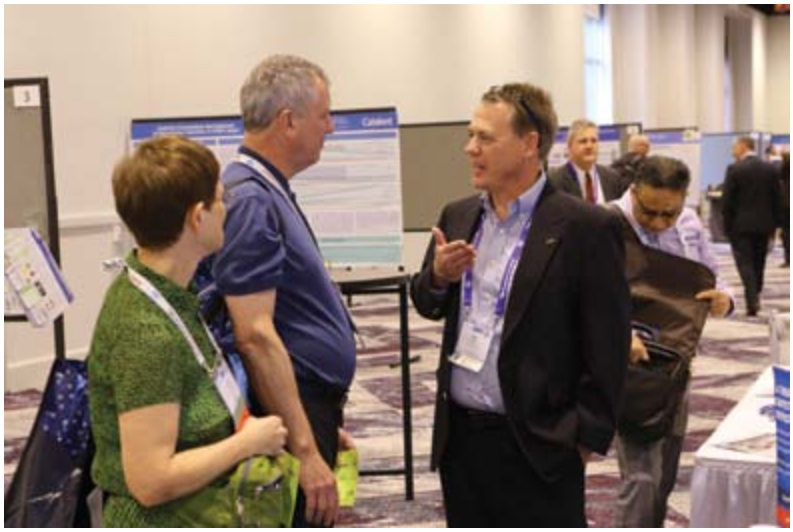

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PDA Europe Conference, Exhibition, Education

3rd PDA Europe Annual Meeting

Global Healthcare of the Present & the Future

Register by 29 April 2018 and SAVE!

pda.org/EU/Annual2018

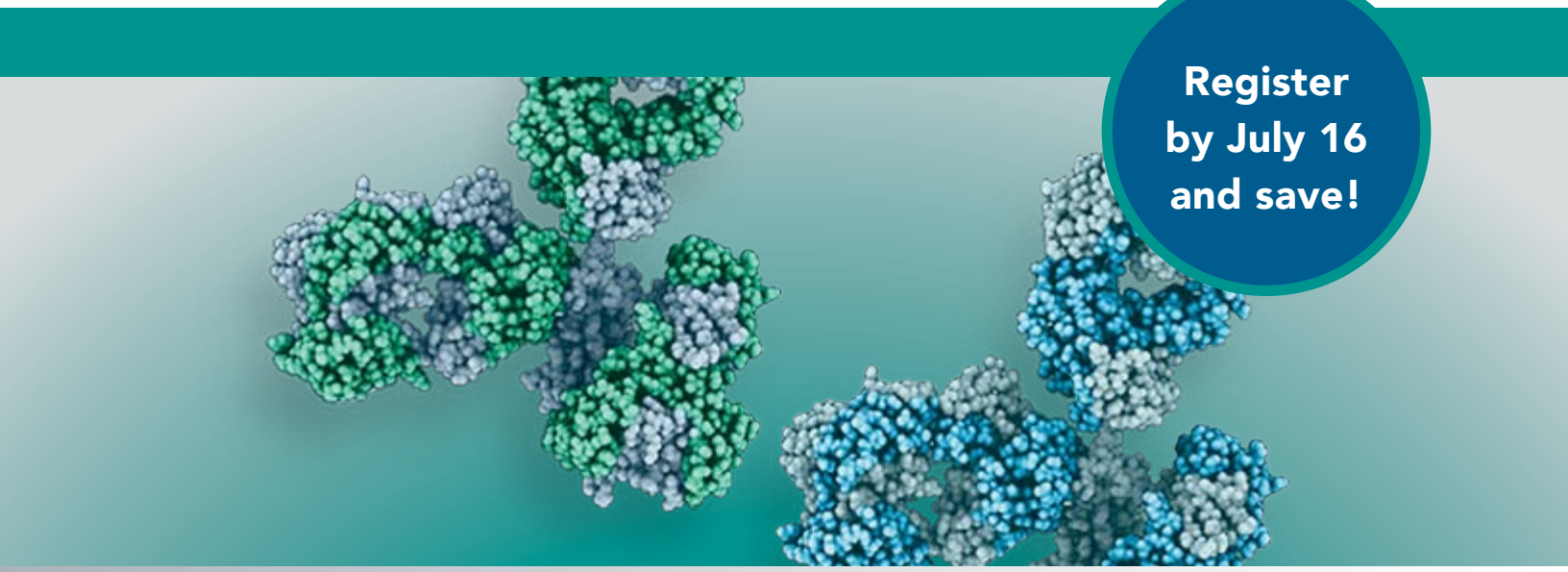
26-27 June 2018

Marriott Hotel

Berlin | Germany

2018 PDA Biosimilars Workshop

Getting It Right the First Time for Biosimilar Marketing Applications



Register by July 16 and save!

Has your company entered the field of biosimilar development? Has your company encountered challenges with your biosimilar application? If so, PDA's Biosimilars Workshop has valuable tools and information for you!

Representatives from the U.S. FDA, EMA, and Health Canada will share the most common challenges they've identified in biosimilar applications, both in established requirements and in more progressive areas, such as statistical tools.

Learn ways to tackle technical obstacles and gain practical approaches to avoid the pitfalls frequently encountered during biosimilar candidate development, including:

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

Whether you work in the development, manufacture, or marketing of biosimilars, you don't want to miss this Workshop!

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

PDA® Parenteral Drug Association

September 26-27, 2018 | Washington, DC
Exhibition: September 26-27
Courses: September 27-28
#PDABIOSIMILARS

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SNAPShot

New Book Compiles Ten Years of Glass Research

Are you aware of the latest glass research from the previous ten years? Do you want to learn more about new developments in glass composition? Are you still concerned about the effects of delamination?

The recently published *PDA Technical Series: Pharmaceutical Glass* might prove valuable. This book collects 19 articles previously published in the *PDA Journal of Pharmaceutical Science and Technology* between 2007 and 2017. The articles are organized into four categories: Overview, Material Composition, Delamination and Quality Methods.

Topics covered include vial breakage, chemical durability of Type I molded containers, effects of subzero temperature exposure, accelerated testing with different extraction media and more.

Ten years ago, a series of product recalls due to glass particulates found in finished product sharpened the industry's focus on pharmaceutical glass. *PDA Technical Series: Pharmaceutical Glass* addresses quality issues pertaining to glass and offers manufacturers a way to understand these issues in full. The publication of this book is part of an initiative PDA launched in 2017 to connect pharmaceutical manufacturers and glass suppliers to prepare for future developments. It can be purchased in the PDA Bookstore.

Journal *Top 10*

Particulate Matter Still a Popular Topic in the PDA Journal

Below are the top ten articles from the *PDA Journal of Pharmaceutical Science and Technology* (journal.pda.org) for the month of April.

1. **PDA Paper**
   Deborah M. Autor, et al., "PDA Points to Consider: Best Practices for Document/Data Management and Control and Preparing for Data Integrity Inspections," Feb. 14, 2018 (Accepted Article)

2. **Review**
   Stephen E. Langille, "Particulate Matter in Injectable Drug Products," May/June 2013

3. **PQRI Special Section – *Research***
   Dennis Jenke, et al., "Extractables Characterization for Five Materials of Construction Representative of Packaging Systems Used for Parenteral and Ophthalmic Drug Products," September/October 2013

4. **PDA Paper**
   Stan Bukofzer, et al., "Industry Perspective on the Medical Risk of Visible Particles in Injectable Drug Products," January/February 2013

5. **PQRI Special Section – *Review***
   Diane Paskiet, et al., "The Product Quality Research Institute (PQRI) Leachables and Extractables Working Group Initiatives for Parenteral and Ophthalmic Drug Product (PODP)," September/October 2013

6. **Review**
   Anil K. Rattan, "Data Integrity: History, Issues, and Remediation of Issues," March/April 2018

7. **Technology/Application**
   Bert Gunter, et al., "A Risk Index and Data Display for Process Performance in the Pharmaceutical Industry," March/April 2018

8. **Research**
   Qingyu Zeng and Xia Zhao, "Time-Dependent Testing Evaluation and Modeling for Rubber Stopper Seal Performance," March/April 2018

9. **Research**
   Benson Gikanga, Ada Hui and Yuh-Fun Maa, "Mechanistic Investigation on Grinding-Induced Subvisible Particle Formation during Mixing and Filling of Monoclonal Antibody Formulations," March/April 2018

10. **Research**
    Ganapathy Gopalrathnam, et al., "Impact of Stainless Steel Exposure on the Oxidation of Polysorbate 80 in Histidine Placebo and Active Monoclonal Antibody Formulation," March/April 2018

2018 PDA Upcoming Events

SAVE THE DATE for PDA's 2018 Events

JUNE

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

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

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

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

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

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

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

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

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

JULY

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

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

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

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

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

AUGUST

2
NEW COURSE
Addressing Biofilm and Other Non-Routine Microbial Events
Bethesda, MD
pda.org/2018Biofilm

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

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

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

SEPTEMBER

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

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

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

17-21
■ **PDA Aseptic Processing – Option 5**
Week 2: Oct. 15-19
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18-19
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Cologne, Germany
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1-3
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10
2018 PDA Combination Products Workshop
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pda.org/2018Combo

11-12
PDA Universe of Pre-Filled Syringes and Injection Devices Course Series
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15-17
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17-18
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17-18
Best Practices and Points to Consider in Aseptic Processing
Berlin, Germany
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22-25
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pda.org/EU/IntroVisual2

29-2
PDA Validation Course Series
Bethesda, MD
pda.org/2018VCS

30-31
2018 PDA Annual Singapore Conference
Singapore, Singapore
pda.org/2018Singapore

A Tale of Two Vials

Large Pharma Company Introduces New Vial Type to Filling Process

Rebecca Stauffer, PDA

Recently, a number of innovative parenteral packaging products have entered the market. These include Corning's new Valor™ glass, an entirely aluminosilicate glass vial ***(1),*** Schott's polymer syringe line, TopPac ***(2),*** and Bormioli's Delta vials ***(3).***

So, what happens when a drug manufacturer seeks to implement one of these new packaging options? How does a manufacturer ensure that the packaging product is compatible with existing filling lines? **Dawn Watson,** Director, Sterile Technology and Commercialization, Merck, offered her insights, based on the company's introduction of Valor™ glass vials into existing processes, in her talk, "New Vial Technologies for Pharmaceutical Products," Jan. 23, at the *2018 PDA Glass Quality Conference.*

Ensuring successful introduction of the vial required a consistent plan to compare the performance of the Valor™ vial with the vial then being used by the firm.

"We established a global, cross-functional team in order to make sure that we had subject matter expertise and good operations experience," she said. "We also set up a standard approach."

The team's first task involved filling trials to assess machinability and vial performance. The team analyzed the performance of the vial across multiple sites for a variety of products. Line trials varied from two hours to one week. Despite these variances, similar observations resulted from the line trials.

"That was across the board," explained Watson of the line trials. "Depending on where we were on the globe, we did see similar observations."

All in all, the team saw a 25% improvement in line speed, a 61% reduction in interventions and a 92% reduction in nonviable particles at in-feed.

Valor™ vials are composed of aluminosilicate glass with no boron in the composition, which gives the glass greater inherent strength. Additionally, an external coating reduces friction ***(4).*** According to Watson, the reduced friction helped with machinability, but also necessitated timing adjustments to accommodate the new flow pattern of the vials. For example, where the previous vials moved via backpressure from the transition plates, the Valor™ vials flowed more readily. This necessitated making changes to the washer, tunnel and fillers.

An unexpected yet valuable finding: the comparison of the two vials helped the team detect improper setups, such as misaligned transitions causing impacts to the heel of the vial, capper setups resulting in damage to the neck of the vial and needle strikes occurring at the top of the vial. All of these led to vial breakage but did not result in significant checks or cracks.

Enter the Freeze-Dryer

After analyzing the performance of the Valor™ vial on the various filling lines, the next step involved assessing the vial's lyophilization performance through a comparability assessment of the existing vial and the Valor™ vial. A lab-scale run showed that the Valor™ vial had a slightly lower coefficient for heat transfer but made no impact to the lyophilization product cycle with the existing drying time.

When it came to the commercial-scale run, the results were similar. The freezing profile and chamber pressure were comparable, moisture results were within specification, appearance of the lyophilization cakes were not changed and no changes to the lyophilization cycle parameters were needed. Ultimately, the lyophilization performance of the Valor™ vial was deemed equivalent.

So, what can other manufacturers learn from this experience?

Watson pointed out that this analysis of a new vial would not have been possible without the efforts of a good team.

"It is important to have the right individuals pulled together on a cross-functional team," she said. "The types of individuals we had included were those involved with glass manufacturing and handling, of course, those involved in our product stability programs, those...familiar with the manufacturing processes and all the steps and sequences to achieve our final container package, quality and risk management, of course, and then regulatory [individuals]."

[Editor's Note: Watch Corning's **Timothy Hunt** discuss USP packaging chapters in an "On the Issue" video: https://youtu.be/xxr6lWJy_Bs**.]**

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About the Expert

Dawn Watson oversees sterile technology engineering at Merck. She was also one of the authors of *PDA Technical Report No. 76: Identification and Classification of Visible Nonconformities in Elastomeric Components and Aluminum Seals for Parenteral Packaging.*

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A Not-So-Sweet Smell: Part I

A Review of Contamination Concerns for Wooden Pallets

Siegfried Schmitt, PhD, and Anthony Newcombe, PhD, PAREXEL Consulting

The humble wooden pallet continues to play a vital role in the pharmaceutical industry. Production materials and consumables transported to a production facility are often received and stored on wooden pallets before they are sampled, tested and transferred onto metal or molded plastic pallets for use in production areas. In addition, finished products leaving the production facility are often transferred back on to wooden pallets in the warehouse for shipping and distribution.

With an estimated 1–2 billion wooden pallets currently in circulation in the United States alone ***(1),*** wooden pallets remain an intrinsic part of pharmaceutical supply chain management. But wooden pallets possess several innate chemical and physical characteristics that may present potential challenges within the pharmaceutical warehouse. These undesirable characteristics include the possibility of splintering and shedding particles. Additionally, as wooden fibers are inherently absorptive, liquids can affect the wood, potentially resulting in the growth of microorganisms, such as fungi. This article provides an overview of the potential compliance issues associated with the use of wooden pallets in the warehouse, some of the best practices for their management and the associated controls that should be considered as part of GMP/GDP.

Different Standards Available

U.S. FDA cGMP regulation 21 CFR 211.56(c) requires written procedures for sanitation designed to prevent the contamination of equipment, components, drug product containers, closures, packaging, labelling materials and drug products. A similar recommendation for manufacturers of APIs is also described in the internationally harmonized guidance for industry, *ICH Q7: Good Manufacturing Practice for Active Pharmaceutical Ingredients* (section 4.72) ***(2)***. An effective pallet management program should therefore be considered essential to minimize potential contamination of warehouse materials that could be affected by chemical taints or contamination.

It also helps to look at standards not just specific to pharma. International standards, such those set by ASTM and the International Standard for Phytosanitary Measures (ISPM), have been established for regulating the movement of timber through international trade, aimed at preventing the global spread of timber pests ***(3,4).*** The ISPM standard for wooden packaging (ISPM 15) has been adopted by several countries, including the United States and the European Union, to prevent the international transport and spread of pests when shipping wooden materials greater than six millimeters in thickness between countries. Pallets heat-treated with conventional steam or a dry kiln heat chamber (typically observed with pallets used within pharmaceutical warehouses) should be heated to a minimum core temperature of 56 °C (132.8 °F) for at least 30 continuous minutes throughout the entire profile of the wood, including the core (***4).*** Pallets treated by this method bear a Heat Treated (HT) stamp as part of the pallet marking. Wooden pallets may also be treated using methylene bromide (MB) fumigation following a specific temperature/time-based schedule. Although fumigation is an effective method, the use of MB as an acceptable treatment, according to ISPM 15, is no longer permitted in many countries. Heat treatment of pallets is intended to control invasive species and not bacteria and fungi; therefore, moisture content should be considered an important pallet specification.

Fungicide and Funny Odor Concerns

When fresh wood is used to construct pallets, the moisture content may vary between 20 and 60 %. A maximum surface moisture content of 20 % for heat-treated pallets was proposed as early as 1946 as necessary to prevent mold growth ***(5)***,

The impact of TBA odors appears to be associated with a behavioral reaction of the consumer

and a residual moisture content of 20 % or less is generally considered the industry standard for kiln-dried pallets ***(1).*** In warehouse environments with suitable airflow, the moisture content is likely reduced significantly, but in reduced-airflow environments, the moisture content of new pallets may result in potential mold growth, particularly when stored outside or in wet, damp or humid conditions, such as near warehouse doors.

Pallets may also contain wood that has been treated with the fungicides 2,4,6 tribromophenol (TBP) or 2,4,6 trichlorophenol (TCP), both of which have a phenolic smell ***(1).*** TBP is used as a wood preservative in some parts of the world, including Central and South America, Eastern Europe and Northern Asia, and is commonly used in hot, humid climates to control mold growth on freshly cut wood ***(1)***. The use of halogenated phenolic compounds to preserve wood is becoming increasingly rare, as this practice is either discouraged or prohibited by most countries since the chemicals may be converted to 2,4,6, tribromoanisole (TBA) and 2,4,6, trichloroanisole (TCA), both of which have an unpleasant earthy, musty and moldy aroma ***(6).*** TBP treatment of wood, however, continues in some regions that supply wood to the United States and other countries ***(1).***

Another risk involves material transported on wooden pallets in nondedicated shipments. This may result in contamination from untreated pallets in the same vehicle or transporter. Through naturally occurring processes (methylation by ubiquitous fungi) ***(7),*** the fungicides TBP and TCP adsorb onto materials stored near the TBA source. Due to their volatility, low levels of halogenated anisole compounds can adversely affect a large quantity of product in a single contamination incident ***(8).***

Many pharmaceutical products have been recalled due to moldy odors, with fungicide-treated wooden pallets identified as a likely cause of product contamination ***(1).*** Although nausea has been reported by consumers sensing a musty or moldy odor, adverse event investigations thus far have not shown any conclusive relationship between TBA and gastrointestinal events. And, toxicological studies associated with TBA have shown no mutagenicity or systemic toxicology in rodents ***(1).*** The impact of TBA odors appears to be associated with a behavioral reaction of the consumer rather than a patient safety risk.

Due to the high volatility of the compounds TBA and TCA, contamination via migration and penetration into nonpolar materials such as plastics is another possibility. The odors attributable to the presence of a halogenated anisole compound can be detected by consumers even when the compound is present at parts per trillion (ppt) levels, with the human odor threshold for TBA as low as 0.2 ppt ***(1).*** Numerous drug product recalls have been associated with TBA taints that have been shown to permeate plastic drug product containers. Regulatory agencies are concerned that patients sensing an unusual odor, one not intrinsic to the product, will increase the likelihood of patients not taking a medication ***(1).***

[Editor's Note: Part II of this article will offer some tools for evaluating wooden pallets**.]**

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Getting Biosimilars Right the First Time

Barbara Rellahan, Amgen

Biosimilar products represent a rapidly growing sector of the biotechnology market. They have the potential to reduce the cost of biologics, resulting in expanded access to these critical therapeutics.

While a regulatory pathway has been available for biosimilars since 2005 in Europe and since 2010 in the United States, manufacturers still experience challenges when commercializing biosimilars. These include demonstration of analytical similarity to reference product, development of robust manufacturing/control processes and submission of high-quality registration submissions.

The *2018 PDA Biosimilars Workshop* will facilitate discussion between global regulatory and industry representatives on these challenges. The workshop aims to provide attendees with strategies on how to address them effectively. The one-and-a-half-day workshop will be co-chaired by **Emanuela Lacana,** Associate Director for Biosimilar and Biologics Policy, U.S. FDA, and **Stephan Krause**, PhD, Director, QA Technology, AstraZeneca Biologics.

Krause will kick-off the workshop by moderating an afternoon session on global regulatory expectations for marketing applications. As the number of biosimilar registration submissions increase, regulators are finding common gaps in the CMC sections. Representatives from three regulatory agencies—both U.S. and non-U.S.—will highlight areas where they have observed deficiencies and present agency expectations of what constitutes a high-quality biosimilar registration submission.

Starting off Day 2, **Joel T. Welsh,** PhD, Review Chief, Office of Biotechnology Products, FDA, will moderate a session on how to navigate technical concerns in biosimilar development. Session speakers will explore methods to avoid pitfalls frequently encountered during biosimilar candidate development. An FDA representative will discuss data quality expectations, including expectations for developing "fit for purpose" analytical methods and inspections. Industry representatives will cover development of an integrated control strategy, the relationship between biosimilarity and process/product control, and the critical strategic decisions during biosimilar development that can influence the quality of the biosimilar and robustness of the biosimilar process.

Bev Ingram, PhD, Senior Director, Pfizer, will moderate the closing session, addressing the role of statistical tools in demonstrating analytical similarity. Here, presentations will highlight practical challenges that arise when applying statistical tools, including reference product variability and Tier 1 attribute expectations as outlined in the FDA draft guidance, *Statistical Approaches to Evaluate Analytical Similarity.* Practical alternative solutions to current approaches will also be discussed. Experiences from regulatory agencies outside the United States will be shared to complement the details presented in the FDA draft guideline.

By participating in this workshop, biosimilar product developers can better understand the common issues experienced by multiple regulatory authorities when reviewing registration dossiers for biosimilars, share common challenges and solutions from an industry perspective and contribute to the dialogue on the most appropriate use of statistical tools.

The format of this workshop is designed to facilitate active dialogue between regulators and biosimilar developers, and allow attendees to share perspectives, clarify concerns and, ultimately, increase the quality and success of submissions.

2018 PDA Biosimilars Workshop

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

Knowledge Grows for mAb Development

Martijn van der Plas, PhD, Medicines Evaluation Board, and Michael De Felippis, PhD, Eli Lilly

Since the first product licensed in 1986, monoclonal antibodies, also referred to as "mAbs," have dominated the field of biopharmaceuticals with more than 70 products approved, and hundreds more currently under clinical evaluation. Market evaluations for these products predict continued interest for years to come.

The knowledge gained over decades of discovery research, development and manufacturing has enabled tremendous advancements in the commercialization of therapeutic monoclonal antibodies. In addition to fully human and humanized monoclonal antibodies, new related modalities have been introduced, such as antibody fragments, Fc-fusions, bi-specifics and antibody drug conjugates, all aimed at improving pharmacological properties. Technological improvements in expression systems, cell culture and downstream purification have increased productivity. The ability to apply common unit operations across multiple monoclonal antibodies has allowed manufacturers to develop platform processes and, in turn, accumulate substantial knowledge to apply to future molecules in their portfolios. Many companies are now adopting continuous manufacturing approaches to further streamline production and reduce operating expenses.

With so much accumulated knowledge related to monoclonal antibodies, the focus is now on how best to make use of all that information. The term "prior knowledge" describes this wealth of information—a hot topic among industry and regulators. With this in mind, the program planning committee behind the *11th Workshop on Monoclonal Antibodies* selected prior knowledge as this year's theme. The key objective of the workshop will be to answer questions on how process knowledge is being captured, transferred and, more importantly, how it can be used to drive continuous improvements, sustaining further advancements for this therapeutic class of products.

Workshop sessions will cover a variety of topics related to prior knowledge from research, development, manufacturing and regulation. Through presentations, case studies and panel discussions, workshop participants will learn the latest trends in applying prior knowledge to monoclonal antibodies. In addition to the planned sessions, the program will provide abundant opportunities to network and exchange ideas with regulators and industry leaders.

11th Workshop on Monoclonal Antibodies

Seville, Spain
Nov. 27–28
www.pda.org/eu/mabs2018

Can ICH Q12 Unlock Manufacturing Innovation?

Ursula Busse, PhD, Novartis, and Melissa Seymour, Biogen

Human medicine has come a long way in the last 100 years. Paradigm-changing therapies have made their way into the clinic since the end of the last century, nurtured by better understanding of the underlying causes of various diseases. These 21st century cures entail personalized therapies using genomics, targeted tumor therapies using antibody–drug conjugates along with cell and gene therapies, just to name a few. These therapies are giving hope to millions of patients. In addition, they profoundly impact multiple stakeholders in the healthcare sector, including the pharmaceutical industry.

Article at a Glance

- New therapies necessitate a new look at existing manufacturing processes
- Challenges to implementing post-approval changes remain a hindrance to innovation
- ICH Q12 offers regulatory flexibility for post-approval changes

Today's innovative therapies require a complete revision of the traditional manufacturing environment. Manufacturing of the future must become efficient, flexible and agile to adapt to rapidly changing demands and to meet evolving patient needs. Meanwhile, improvements need not compromise the quality and availability of therapies. This implies the use of innovative manufacturing and supply approaches and cutting-edge technologies. And it requires overcoming challenges and barriers to their implementation. In the words of U.S. FDA CDER Director **Janet Woodcock,** 21st century pharma should be a "maximally agile, flexible manufacturing sector that reliably produces high quality medicines without extensive regulatory oversight."

The need to revolutionize the technical sector was recognized almost two decades ago, when the first therapies based on recombinant monoclonal antibodies showed huge benefits for patients. Shortly thereafter, work began to develop harmonized guidelines outlining risk- and science-based approaches to product development and manufacturing. ICH Q8–Q11, published between 2005 and 2011, included new, groundbreaking concepts such as quality-by-design, or QbD.

Have we achieved this vision? Only partly. Application of science- and risk-based approaches throughout the product lifecycle have certainly enhanced our product and process understanding. We have also improved robustness of our quality systems and assurance of product quality. Yet we still see little of the regulatory flexibility expected from the new ICH guidelines. Our regulatory filings contain more information and raise more questions than ever before, in part, due to the lack of clarity from regulations during submission. Major challenges consist of variable timelines and submission requirements for post-approval change review and approval. Consequently, globally applicable changes are a logistical challenge that requires excessive time and resources, discouraging innovation. This increases the risk of shortages, supply mistakes and noncompliance situations.

ICH Q12 to the Rescue!

Recognizing the need for action, in 2014, ICH started working on *ICH Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* **(Figure 1).** The main objectives of ICH Q12 are to facilitate predictability and efficiency of post-approval change management, thus supporting innovation and ensuring sustained product supply. In the ICH Q12 "desired state," most manufacturing changes will be managed effectively under a company's pharmaceutical quality system (PQS) without the need for regulatory approval prior to implementation. The extent of such operational flexibility will be subject to the company's product and process knowledge and confidence in the company's quality system, which needs to include an effective change management system. This would be supported by effective knowledge and risk management.

ICH Q12 is intended to complement the existing ICH Q8–Q11 guidelines. It includes a core guideline as well as annexes. Key aspects of the Q12 core document

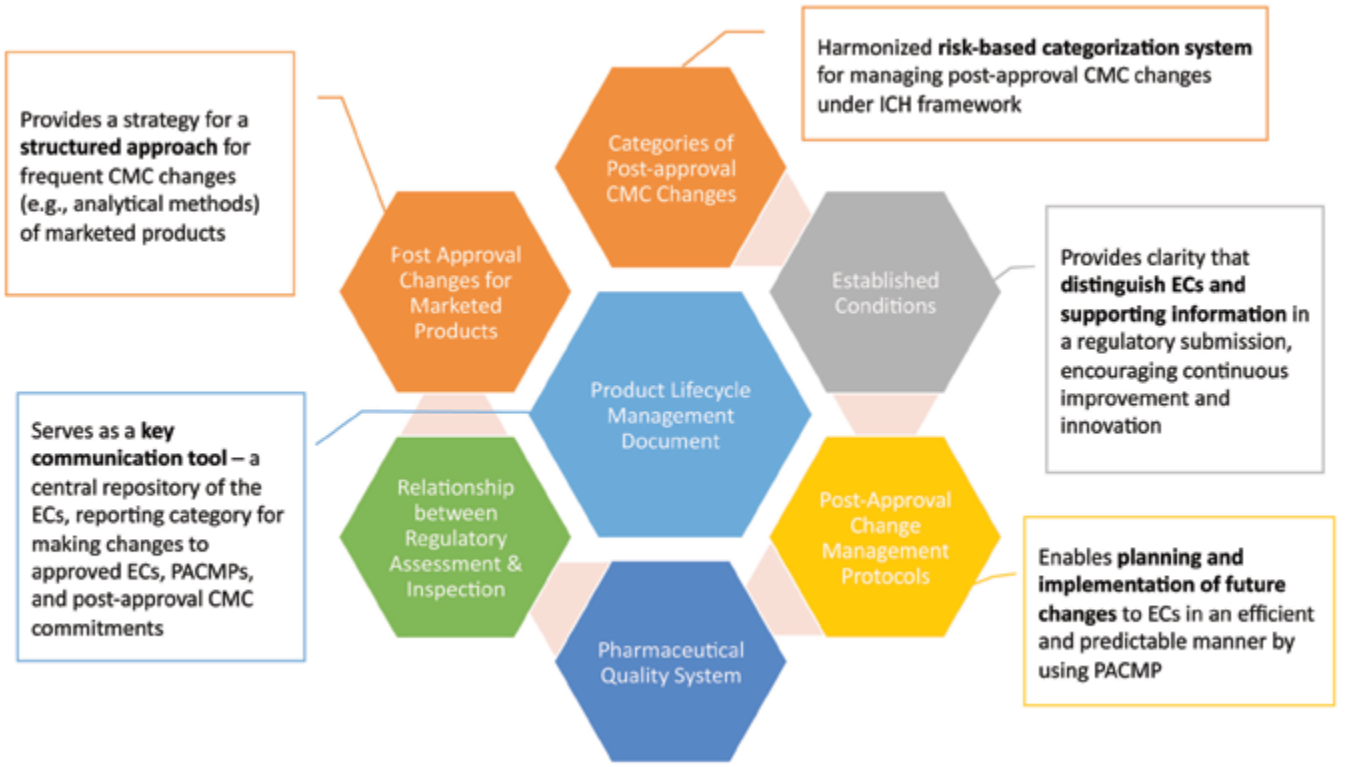

Figure 1 Main Sections of ICH Q12

cover harmonized tools for established conditions (ECs), planned changes through post-approval change management protocols (PACMPs) and proactive management of the product lifecycle through the product lifecycle management (PLCM) document **(see Figure 1).** The annexes contain illustrative examples of ECs, PACMPs and PLCM documents.

ICH Q12 also considers other important elements to change management. Notably, it explicitly addresses post-approval changes for currently marketed products. Without the ability to apply Q12 approaches to marketed products, the benefits of this guidance would be quite limited. For many organizations, regulatory complexity is the most cumbersome and difficult area to navigate, particularly in a global environment. ICH Q12 describes both a structured approach for frequent CMC changes as well as proposed data requirements. The document also reinforces the criticality of a company's PQS, particularly as it relates to change management.

This proposed ICH guideline has the potential to be truly transformational, potentially reducing unnecessary cost and time burdens on both the industry and regulators, without compromising high-quality medicines. Perhaps one of the largest gains would be for potential regulatory convergence among ICH regions with respect to defining "regulatory commitments" as opposed to "supportive information" within regulatory submissions. Additionally, implementation of the principles will improve communication and transparency among industry, regulators, reviewers and inspectors. Ultimately, this should lead to greater application of innovative technologies in a timely fashion.

Innovation in manufacturing should be at the heart of our efforts to ensure sustained supply of better, safer medicines to patients. Our industry needs to become faster in adapting the wealth of new manufacturing technologies available to enable product realization, effective control system deployment and continual improvement throughout a product's lifecycle (*ICH Q10: Pharmaceutical Quality System*). ICH Q12 will only be a starting point. We have learned from the QbD journey that it will take communication and transparency from both industry and regulators to make the concepts in this guideline a reality that will improve our industry and strengthen our commitment to patients.

About the Authors

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Seeing the Light

What a Bicycle Tour and a Rear Light Can Teach Us About Post-Approval Changes

Anders Vinther, PhD

Imagine the following scenario: You are planning a bicycle tour. For a few days, you will ride through nice scenery in 23 cities. To ensure a safe trip, you decide to install a better rear light on your bicycle. The current light can be seen from 300 feet; however, a new light on the market can be seen from as far away as 900 feet. This new light only costs $12.

If this were you, would you go out and buy the new light? I would. Only $12, easy to install, and offers improved safety as you can be seen from three times farther away. But imagine that each of the 23 cities you travel through require a permit for this new rear light. It must be approved prior to entry into each city, and each city cannot really predict how long the approval process will take. Historically, it takes 4 to 62 days. It also comes with an application fee of anywhere between $15 and $25 per city. Additionally, each city has their own individual form, and these differ not only in terms of layout, but also in the information required. With this additional information, would you now buy and install this new rear light before your trip? Probably not.

What could be done to simplify the situation and increase the likelihood of your buying and installing the new rear light?

Well, for one, each city could commit to a (short) timeline for approval of the application. Then you would be able to know exactly how far in advance you need to submit the application form to avoid a delay of your bicycle trip.

Or the cities could agree to have the same form and the same requirements for the application. This would make it easier to fill in all the forms and save time.

Even better, the cities could trust each other and rely on each other's assessments. That would hopefully reduce the number of applications you would have to submit to just one.

And, ideally, you would not have to submit an application to any of the cities. How would that work? The cities would have to trust you and your own assessment of installing an improved rear light on your bicycle. This could be achieved if the cities agree on a "self-assessment" form or guideline that ensures you asked yourself all the right questions and documented this process.

Something else to ponder. In this situation, it is obvious that the new rear light would allow cars to see your bicycle from farther away than with the current rear light. This improves your safety. For this reason, would it not be better to install the rear light right away instead of waiting anywhere between 4 and 62 days? Here, the prior-approval process delays improved safety for you.

Obviously, the case of the bicycle is hypothetical. This article is not really about bicycles; it is about post-approval changes, continuous improvement and innovation in the pharmaceutical industry. The oversimplified metaphor of the bicycle and the rear light encapsulates the current state of affairs. Even simple changes to an approved regulatory file can take years to implement from first to last country. The approval timelines are not always predictable. Change classification and documentation requirements differ from country to country. National regulatory agencies rarely rely on each other's assessment (with some exceptions).

We know that changes in the pharmaceutical industry take years, rather than months or weeks, to implement. We do not know how much innovation is hindered by the high complexity of the global regulatory framework. Colleagues across the industry have shared many examples with me, and I have even experienced it myself over the past several years.

Return for a moment to the example of the bicycle. We can all agree that installing the rear light that can be seen 900 feet away is better than the one that can be seen 300 feet away. What if we all agreed that our objective and starting point should be to continually improve and innovate our industry to ensure a sustainable supply of safe, efficacious, quality drugs. Changes that objectively improve safety, changes that reduce process variability or enhance analytical methods and changes that reduce the likelihood of drug shortages—provided there is no added risk to the patient—should be implemented as soon as possible. This would require industry, regulators and politicians to sit down and find global solutions, including a much simpler regulatory framework.

I actually did go on a bicycle tour. It was a nice ride with beautiful scenery and a rear light that can be seen 300 feet away!

Prospects for Post-Approval Change Management

Naheed Sayeed-Desta, Apotex, Ajay Babu Pazhayattil, and Ivy Louis, Vienni Training and Consulting LLP

As new types of biologic products enter the market, the need for innovative processes continues to grow. This requires improvements in post-approval change management. *ICH Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* offers a solution to post-approval change challenges in the form of a post-approval change management protocol (PACMP) ***(1).***

The PACMP is a tool that provides predictability regarding the information required to support a CMC change and the type of regulatory submission based on prior agreement between the marketing authorization holder (MAH) and a regulatory authority. Such a mechanism enables manufacturers to more efficiently plan future changes to established conditions (ECs).

Adopting the principles outlined in ICH Q12 gives industry greater operational flexibility. While ICH Q8–Q11 introduced a risk-based vision of quality ***(2),*** the regulators and the biopharma industry have adopted the product lifecycle approach ICH Q12 advocates. The ICH Q12 prerequisites, i.e., "enablers," were a challenge at one time; however, with the current innovations in applied statistics along with advancements in modeling, risk assessment and monitoring tools, there are new ways for the biopharma industry to effectively manage post-approval changes. A new level of flexibility in regulatory approval can be achieved, enabling continuous improvement in biomanufacturing.

ICH Q12 has arrived at a time when industry is being pushed toward greater innovation. Quality-by-design (QbD) principles now guide the design of products and process characteristics. Coming out of QbD, process analytical technologies (PAT) and process modeling offer opportunities for continuous improvement. Further, each segment of biologics processing is currently undergoing constant innovation, fueled by the need to enhance yield and productivity in a highly cost-conscious industry. The process efficiency push, newer process technology and PAT advancement, combined with the necessary use of multiple integrated processing technologies, calls for a need to develop a robust post-approval change management strategy. ICH Q12 provides the pathway to such strategy development and adoption.

Upstream and downstream biopharma processes typically involve cell banks, fermentation, purification and filling technologies. These are developed to suit the type of biologic product whether it be a vaccine, albumin, immunoglobulin, clotting factors fibrin sealant, proteinase inhibitor, antitoxin, antivenin, enzyme, toxin or gene-and-cell-based product. Here, an integrated process design is required in bioprocesses with multiple elements of the control strategy for assuring product quantity and quality, allowing biologics manufacturers to take a leading role in adoption of ICH Q12.

Anticipating potential processing changes in complex biologic processes is a challenge, yet there are ample opportunities to consider. Take, for example, switching a traditional aseptic vial filling operation for a biologic molecule to an isolator aseptic filling technology. Isolator technology better prevents or eliminates possible contamination opportunities as traditional aseptic filling presents inherent risks to sterility assurance. Adopting an isolator technology aids in raising the sterility ➤

assurance levels (SAL) of the product, especially during the filling operations. The proposed change involves extensive changes in processing equipment and parameters for a higher level of sterility assurance.

A PACMP In Action

A PACMP is an effective tool for adopting such a change. Below are some considerations that need to be included in the protocol:

1. Definitions for the characterization and qualification aspects of the isolators.

2. Descriptions of proposed change elements to be confirmed during process performance qualification and continued process verification.

3. Requirements concerning the quality management system (QMS), SOPs and GMPs, such as media fills or aseptic simulation studies, that need to be conducted as part of implementing the change ***(3).***

4. Information for that supports a reduced submission category, including strategies for characterizing engineering studies, meeting predefined quality and sterility attributes, conducting stability studies and performing equipment qualification activities and process performance studies.

Providing sufficient clarity on the proposed change and demonstrating commitment to performing listed activities can enable the submission and preapproval of a PACMP. An organization's established pharmaceutical quality systems (PQS) and QMS provides the framework to ensuring that changes will be implemented while also meeting the preapproved commitments. Inspectors can use this to then verify the implementation of activities as part of the routine inspection process.

Apart from the complexity and uncertainty regarding individual regulators, a few other challenges need to be addressed to effectively apply ICH Q12 concepts. One critical area is organizational harmonization. ICH Q12 strategies can help a biologics manufacturer to prepare from potential questions from regulators upon product commercialization. At the same time, this may lead some individuals within an organization to avoid including a PACMP as part of the initial submission in an effort to prevent additional questioning from regulators and requests for additional technical documents. This tendency must be addressed for manufacturers to effectively realize ICH Q12.

A holistic impact assessment is beneficial for each BLA. The standardization of the post-approval change management process can be achieved by following a stepwise procedure using a standard acceptable protocol format with required sections ***(4).*** The use of a PACMP empowers regulators and biologics manufacturers to make risk-based decisions based on scientific rationale embedded during the early stages of creating therapeutically safe and commercially viable molecules. Submission of additional supportive data from prior knowledge continues

to remain relevant due to the lack of such information for a novel process.

ICH Q12 provides an opportunity to save some of the long-term costs associated with regulatory submissions, enabling swift implementation of process-efficiency enhancement plans without supply disruptions. The guidance, currently in draft form for public consultation, would also benefit from offering additional biologics-specific examples or case studies that provide clarity for early adopters.

In addition, the value of including an all-encompassing product lifecycle management (PLCM) document in this guidance is unclear, as there are already specific sections in the eCTD that address ECs while the PACMP includes the proposed change types and submission categories. Such inconsistencies may be addressed through public commenting and feedback from the regulators to the ICH Q12 Expert Working Group. Regulatory convergence, such as the joint U.S. FDA and EMA pilot program on QbD, Canada–United States Regulatory Cooperation Council (RCC) ***(5),*** etc., will further advance process harmonization—a critical need for biologic manufacturers with products in multiple markets.

ICH Q12 solutions are the right fit for biologics due to their complexity and the current challenges they face. Novel continuous improvement changes are imminent in the biologics operations sector due to pricing concerns and the emergence of biosimilars. A PACMP paves a pathway for innovation of manufacturing, optimization of investment and maximization of effort, enabling speedier production of novel products. Biologic manufacturers have already embraced new lifecycle tools and solutions, making this field a prime candidate for adopting ICH Q12 concepts. The regulations are in place, the enablers are available, global regulatory harmonization is ongoing, industry organizations have converged and ICH Q12 is

> **Biologic manufacturers have already embraced new lifecycle tools and solutions**

in the approval process ***(6).*** Standardizing the submission of the PACMP along with every BLA will help organizations reap the benefit of implementing ICH Q8–11 and reduce operational risks ***(7).***

Adoption of ICH Q12 will promote innovation and continual improvement, ultimately, improving the accessibility of product for patients and product safety.

Note: *This article was prepared by the authors in their personal capacities, and the opinions expressed in this paper do not reflect the view of their employers, government, or any affiliated agencies.*

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About the Authors

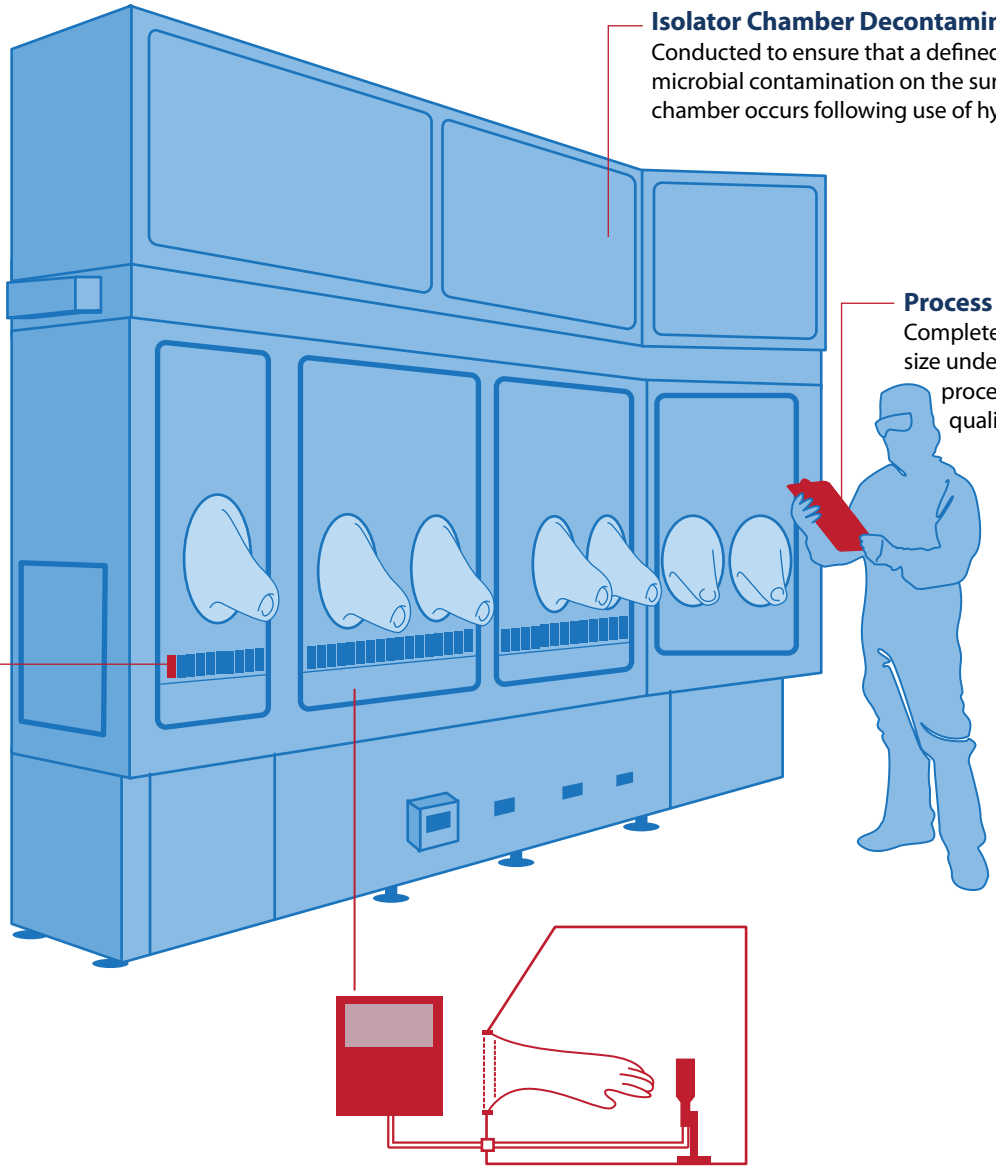
Naheed Sayeed-Desta has been responsible for providing strategic direction on lifecycle management of pharmaceuticals through delivery of science- and risk-based approaches from traditional to novel processing technologies.

Ajay Babu Pazhayattil, has held key management roles with brand name, biosimilar and contract manufacturing organizations. He is an industrial pharmacist successful in delivering tangible results across multiple segments of biopharmaceutical operations.

Ivy Louis, is a forerunner in establishing validation and support services in research, production and QA/QC areas by propagating the science and importance of filtration validation, significance of microbiology, contamination control, monitoring in aseptic processing and its regulatory requirements. She is also President of the PDA India Chapter.

A Post-Approval Change for an Aseptic Filling Isolator

When a manufacturer implements a new isolator as part of a post-approval change, a Process Design and Characterization Study* is required that features the following elements.



Isolator Chamber Decontamination
Conducted to ensure that a defined reduction of the microbial contamination on the surfaces of the isolator chamber occurs following use of hydrogen peroxide

Process Validation
Completed for each fill size under predefined process performance qualification protocols

Media Fills
Performed to requalify the filling process, the equipment and the aseptic process

Air Visualization
Conducted to confirm airflow direction in the cleanroom

*Information taken from a forthcoming PDA technical report that will address post-approval changes for drug and biologic products. Look for it in the PDA Bookstore!

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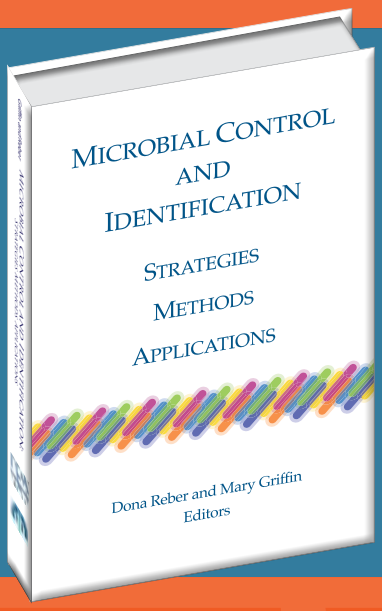

Microbial Control and Identification: Strategies Methods Applications

Edited by: Dona Reber and Mary Griffin

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In PDA's latest release, expert microbiologists and biopharmaceutical industry leaders explore the role of microbial identification knowledge as a cornerstone in the concept of microbial and contamination control programs. This book is an excellent reference for new microbiologists and seasoned professionals alike. Each chapter illustrates how microbial control programs for facilities, equipment, and personnel can have a positive impact on products and ultimately, patients.

The three sections will focus on the following topics:

- **Strategies:** Regulation, regulatory expectations, and strategies for trending, risk assessments, and risk management.
- **Methods:** Current best practices for microorganism identification methods, both conventional and emerging rapid methods for bacteria, viruses, mycoplasma, and fungi.
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A Wealth of New Tech Possibilities

2018 PDA Annual Meeting Showcases the Latest in New Drugs, Manufacturing Techology

Scott Bozzone, PhD, Pharm Lifecycle Validation LLC

Healthy patients are always the end goal for PDA members. So, it is now more important than ever for industry to modernize existing processes. This year's Annual Meeting in Orlando, Fla., provided no shortage of sessions highlighting the importance of producing quality parenteral medicines for patients while also maintaining top-notch manufacturing systems.

As always, it was exciting to hear from the world's most distinguished pharmaceutical industry scientists, over 700 of whom attended the *2018 PDA Annual Meeting.* This included a wide variety of scientists, clinicians and many others from both within the industry and outside the pharmaceutical field. All pointed to numerous accomplishments not only in new therapeutic products but also in the manufacturing space itself.

The meeting began on March 19 with a look from both the clinician and patient perspectives. **Stephen Kingsmore,** MD, President and CEO, Rady Children's Institutes for Genomic Medicine, offered a look at advances in neonatal therapies in his talk, "Clinical Perspective on Future Patient Therapies: Inventing the NICU of the Future." He spoke about his experience developing life-saving therapies for newborn babies, typically 2–30 days old, suffering from a variety of genetic diseases. In fact, he has held a Guinness record at 19.5 hours from diagnosis to treatment in the NICU. The basis of his treatment involves characterizing the genomes of the infant's family. He ultimately hopes to offer this therapy to hundreds of children's hospitals over the next couple years.

Following Kingsmore's talk, longtime PDA volunteer **Lori Richter,** Senior Consultant, ValSource, shared her experiences as a patient. At the age of 16, she learned she only had one kidney. Her condition eventually required a transplant. She put a face on the patients who receive drugs manufactured by PDA members.

Treating patients effectively means that disruptive technology will drive the future of medicine. In the second plenary, **Steven Spear,** PhD, Principal, HVE LLC and Senior Lecturer, MIT Sloan and Engineering School, described the effects of product development outside the drug industry, such as jet engines, cell phones and cars. He then outlined the advantages and disadvantages of the product lifecycle model "Design, Make and Test." Spear stressed the importance of investing in product design. He remarked that we learn best when success is measured by the value delivered to our society. In some ways, "Design, Make and Test" parallels the three stages of process validation laid out in the 2011 U.S. FDA guidance—process design, process qualification and continued process verification.

Next, **Sharmista Chatterjee,** PhD, Division Director, Office of Process and Facilities, Office of Pharmaceutical Quality, CDER, FDA, presented "Emerging Technologies and Innovative Review Approaches: Key Enablers to Meet the Needs of Patients." She described recently approved new technologies, including a digital pill and four continuous manufacturing processes approved to date. The four continuous processes pertained to small molecules, one of which involved switching an HIV drug production from batch to continuous processing. FDA's Emerging Technology Team (ETT) has also been involved in finalizing information on new technology support to industry, such as a Sept. 2017 guidance for industry and an update to the manual of policies and procedures ***(1,2).*** Chatterjee encouraged those interested in implementing new technologies and getting involved to email the group at CDER-ETT@fda.hhs.gov.

Vadim Romanov, MD, Executive Medical Director, CAR-T, Novartis, opened the second day of the meeting with a presentation on Novartis' recently approved chimeric antigen receptor T-cell therapy. Research for this groundbreaking drug spanned 12 years. During this research, the company found a variation of the "starting material" (Leukapheresis material) that led to consistent drug product. The target turnaround is 22 days for manufacturing and release. Cryopreservation has helped the company achieve individualized treatments on a global scale.

After Romanov's presentation, **Victor Weigman,** PhD, Director, Translational Genomics, IQVIA, provided an overview of the current immunotherapy landscape, including the role of biomarkers. Since different tumors have different immune profiles, this research and development required different therapeutic solutions. Genomic testing offers a wealth of data to enhance the treatment. Also, understanding a varied response is important, i.e., when tumors change, test results change.

Manufacturing Innovations Abound

The new therapies discussed above are all well and good, but what about the manufacturing technologies behind their production? The third and final day of the conference addressed this by exploring the latest advancements in manufacturing in a plenary session. **Arleen Paulino,** Vice President, Site Operations, Singapore, Am-

gen, presented "Transforming Operations with Next Generation Biomanufacturing." The introduction and transfer of a newly approved biologic to the Singapore site was described. Flexibility, speed and application of single-use systems in a new facility were key components for successful transfer. Approval of a site transfer process usually takes 25–30 months. Key elements consisted of supplier partnerships or relationships, variability and an "identify, track and control" process. Paulino also stressed the importance of adapting to change. **[Editor's Note:** Learn more about Amgen's Next Generation Biomanufacturing in an "On the Issue" video: https://youtu.be/mIbLYmkuoUQ**.]**

Amy Wilson, PhD, Director, Global Human Performance, Biogen, then covered how to improve operational performance by embracing a resilience engineering approach. This requires **1)** anticipating dynamic risk, **2)** observing work as done, **3)** applying systems thinking to investigations, **4)** learning from successes and **5)** expanding how you learn. Since Biogen has integrated this approach into its operations, unexpected outcomes have decreased, leading to great successes since its launch. **[Editor's Note:** Learn more about resilience in the article, "4 Capabilities to Operationalizing Resilience," in the Feb. 2018 *PDA Letter*.**]**

In addition to these plenary sessions, breakout sessions also covered a lot of ground. In the session, "IT: So Much More Than Technology," **Michele D'Alessandro,** CIO, Manufacturing IT, Merck, offered an overview of manufacturing 4.0 technologies while **Thomas Seewoester,** PhD, Executive Director and Plant Manager, Amgen, showed the different insights manufacturers can gain from data. The "Trends in Digital Information and Automated Technology" session featured presentations from **Patrick Gammell,** PhD, Director, Process Development, Amgen, and **Paul Stey,** PhD, Biomedical Data Scientist, Brown University ("New Approaches to Harnessing Data at a Portfolio Level") and from **Malcolm R. Postings,** Vice President, Head of Innovation and Emerging Technologies, IQVIA ("The Rise of Human Data Science in the Real World"). Additional breakout sessions touched on new strategies for continuous bioprocessing and the latest in isolator and RABS technologies.

Many innovations in both drug product and manufacturing technology were highlighted at the *2018 PDA Annual Meeting.* Overall, the conference planning committee successfully captured the latest medical and pharmaceutical topics applicable in the industry today.

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About the Author

Scott Bozzone, PhD, is a Pfizer retiree and part-time consultant with Pharm Lifecycle Validation.

Growing Acceptance of Real-Time Monitoring

Regulators Increasingly Embrace New Rapid Technologies for Viable Air Monitoring

Frank Panofen, PhD, Particle Measuring Systems

When it comes to air monitoring, manufacturers have relied on gravitational sampling by settle plates—a weak methodology. The value of data generated by settle plates is highly questionable, considering that most positive plates are generated from false-positive results. But real-time monitoring might offer a solution, driven by recent regulatory developments.

For example, regulators are turning to ISO/EN norms as reference documents detailing methods for the determination of microbiological and particulate cleanliness of air, surfaces, etc. ***(1).*** With viable air monitoring, in particular, they are looking at the ISO 14698 standard ***(2).*** ISO 14698 states that "a sampling device shall be selected according to the area being monitored. The selection for a particular application shall take into consideration the following factors: expected concentration of the viable particles, ability to detect low levels of biocontamination and time and duration of sampling" ***(2).***

This leads to a vital point: it is virtually impossible for pharmaceutical customers to validate viable air samples for biological or physical collection efficiency as required in ISO 14698. Only a few laboratories worldwide can provide the experimental design and know-how required for trial testing. Collection efficiency remains a critical measure that manufacturers of instruments should provide and demonstrate. This is where real-time solutions can help.

Rapid or alternative microbiological methods have been promoted for almost 20 years in the pharmaceutical industry. In 2003, the U.S. FDA guidance on process analytical technology (PAT) ***(3)*** and the pharmaceutical cGMPS for the 21st century gave industry a new drive. The concept of PAT implies the need for collection of process data in real-time, targeting a real-time release of drug products. The FDA guidance, updated in 2015, recommends "building quality into products" through science-based facility, equipment, process and system design for sterile drug manufacture and emphasizes the importance of the pharmaceutical industry's adoption of new technological advances.

With the continuous effort of regulatory bodies encouraging the use of alternative microbiological methods, the need to understand how these methods could be implemented in pharmaceutical

manufacturing processes grows. All major pharmacopeias worldwide now include chapters that describe the validation of those methods, e.g., USP <1223>, Ph. Eur. 5.1.60 ***(4,5).*** Those chapters continue to evolve with regular updates.

In recent years, regulators have begun creating specific pathways to facilitate the use of modern technologies such as real-time monitoring. The FDA promotes the use of "comparability protocols" and has developed an Emerging Technologies Team to evaluate change proposals. EMA has implemented a post-approval change management protocol and provides an opportunity to request a "scientific advice meeting" with experts.

Still, the adoption rate of alternative methods remains slow, whether due to hesitation, uncertainty or fear of longer validation processes. Other factors, such as difficulty in justifying the return of investment for implementation, also play a large part. The key to supporting rapid technologies lies in recognizing the costs of poor quality. Many of these technologies offer the potential to offset such costs as waste, rework, poor inspection findings, recalls and more.

The key to a strong regulatory framework around viable air monitoring lies in considering new technologies like real-time testing. Global regulators are increasingly accepting these new technologies for ISO 7 (Grade C) and ISO 5 (Grade B) critical environments. The right combination of strategies can lead to substantial improvements, contributing significantly to cost savings programs by reducing the "cost of poor quality."

[Editor's Note: This is a follow-up to the article, "Monitor Viable Air with Single-Use, Real-Time Tech," in the Jan. 2018 *PDA Letter*.**]**

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About the Author

Frank Panofen, PhD, has extensive experience in the field of applied pharmaceutical microbiology and serves as the Sterility Assurance/ Microbiology Product Line Manager at Particle Measuring Systems.

How PDA Supports the Regulatory Environment

Stephan Rönninger, PhD, Amgen (Europe) GmbH

Regulations provide the foundation for our industry to guarantee patients access to safe and effective medicines. Stepping back, let us look at the different types of regulations. In the legislative branch, the primary laws describe the value of certain regulations and the secondary laws outline the elements that need to be regulated. In the executive branch, countries issue "rules," "regulations" or "directives" to describe "what to do" requirements. Related to these, "guidances" or "standards" outline "what to implement." PDA volunteers help with these "what to do" and "what to implement" requirements through best practice documents, like our technical reports and points to consider papers, in addition to coordinating meetings and education courses focused on key regulatory topics.

Much of this work is coordinated through PDA's Regulatory and Quality Advisory Board (RAQAB). Currently, RAQAB's core of volunteers are supporting a variety of regulatory-focused initiatives. One involves development of a quality culture tool. Here, a team is doing a fantastic job of training regulators in the United States, European Union and United Kingdom, to better understand how industry actually operates beyond what is demonstrated by inspections and in regulatory dossiers. Another team is working on post-approval changes and lifecycle management (ICH Q12) while other volunteers are providing comments and feedback on the Annex 1 revision.

This work helps industry and regulators to continuously improve understanding of terminologies, regulations and expectations as well as facilitating innovation. PDA's conferences, interest group meetings and educational courses support these efforts. When I ask members about attending a PDA "regulatory conference," most refer to the ever-popular *PDA/FDA Joint Regulatory Conference.* But PDA offers other conferences addressing regulatory topics. When you read this article, PDA Europe will have just wrapped up its inaugural *Pharmacopoeia Conference* that brought together representatives of leading pharmacopoeias from around the globe to discuss opportunities for convergence. And, as more and more inspectors flag deficiencies related to outsourced operations and the supply chain, PDA has also organized a 360° view conference on the topic in Seville, Spain, for November.

Furthermore, PDA's chapters are organizing meetings with local regulators in their respective regions to understand regulatory perspectives and, most importantly, facilitate dialogue. The Brazil and Singapore Chapters are currently planning such meetings and the Japan Chapter organizes a signature conference with regulatory partners each December.

Last, but not least, PDA Education offers courses at its Training and Research Institute (TRI) located at the U.S. headquarters in Bethesda, Md., and in different languages across Europe as well. In addition, PDA also offers in-house training opportunities adapted to the specific needs of companies *and* individual regulatory agencies.

As you can see, PDA offers a unique opportunity for members of industry and regulators to connect worldwide on these important topics and to share best practices and sound science in a globalized environment, that is, addressing the "what to do" and "what to implement."

Please allow me to conclude on a personal note. This is my last year as a PDA board member. It has been, and remains, a pleasure driving PDA's strategy by focusing on the third aspect of PDA's mission: regulation. I want to close with a quote from my good friend, **Tor Gråberg,** as I believe these are *the* cultural elements for success in any regulated environment: "Collaboration, communication and trust."

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