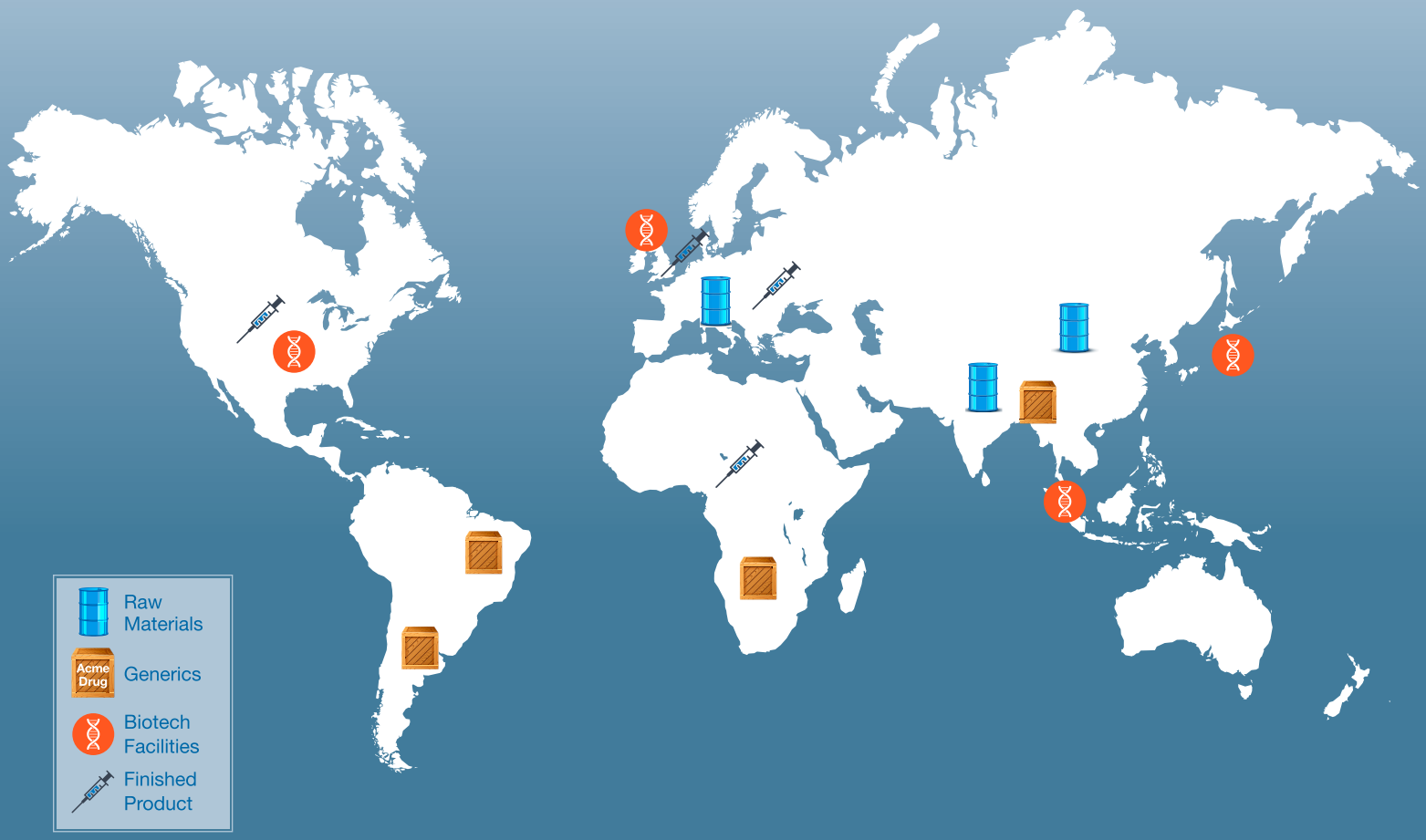
People • Science • Regulation

PDA Letter

Volume LII • Issue 10 www.pda.org/pdaletter November/December 2016



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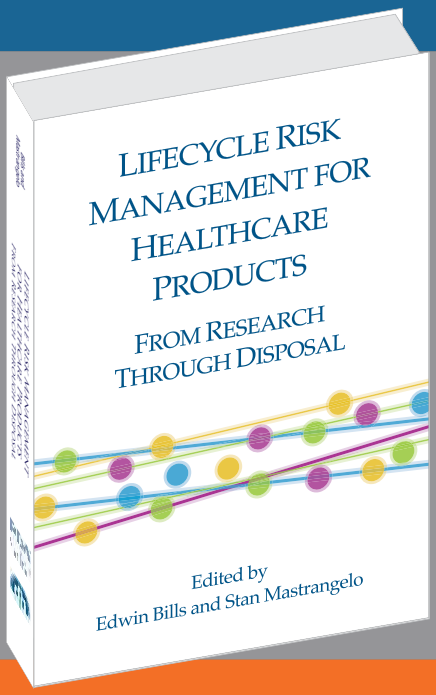

LIFECYCLE RISK MANAGEMENT FOR HEALTHCARE PRODUCTS:
FROM RESEARCH THROUGH DISPOSAL

BY: EDWIN BILLS AND STAN MASTRANGELO

PDA MEMBER PRICE: ~~$225~~ $191.25
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This book provides current information on the risk management process as it applies to health and safety of health products, drugs and biologics, medical devices and products that are a combination of two or more of these. The application of the processes will help manufacturers of these products to create and maintain products that are at an acceptable level of safety for society through the product lifecycle.

This book has been divided into two parts, part one covers healthcare risk management processes and frameworks and part two covers special topics.

In the first part, the editors provide a historical perspective of the risk management framework as well as management and its responsibilities for implementation of risk management in health product companies. You will also find an overview of combination products, use of risk traceability, criteria for risk acceptability and production and post-product risk management in this section.

In the second part, specific applications of health product risk management are examined, including clinical trials, quality system software and in vitro diagnostic devices.

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PDA Letter

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Departments

News & Notes

People

Science

Regulation

Voices of PDA

Contents

Features

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.

PDA IN THE NEWS

Below is a listing of various news articles/websites that have mentioned PDA within the past few months.

American Pharmaceutical Review

July 29, 2016

"Naturally Occurring Endotoxin: A New Reference Material Proposed By the US Pharmacopeia"
— **Radhakrishna Tirumalai, PhD**
tinyurl.com/hv7h388
[Note: For more from USP on NOE, see p. 22.**]**

July 30, 2016

"The Hottest Topics in Microbiology"
— **Karen Ginsbury**
tinyurl.com/js6mol3

BioProcess International

September 15, 2016

"Quality By Design for Monoclonal Antibodies, Part 2: Process Design Space and Control Strategies"
— **Brendan Cooney, Susan Dana Jones, and Howard L. Levine**
tinyurl.com/j4awl5w

Healthcare Packaging

September 14, 2016

"Live from PDA/FDA: Compliance to Quality: Part 1"
— **Liz Tierney**
tinyurl.com/j2y3q26

"Live from PDA/FDA: Compliance to Quality: Part 2"
— **Jim Chrzan**
tinyurl.com/guzya97

International Pharmaceutical Quality

July/August 2016

"FDA, MHRA and WHO Guidances Shed Further Light on Data Integrity Concerns"

"Industry Comments on FDA's Draft Data Integrity Guidance Reveal Regulatory Challenges"
"Regulator Expectation for Handling Data Integrity Concerns Draws Spotlight"

Pharmaceutical Technology

August 29, 2016

"PDA Issues Call to Action for Faster Postapproval Changes"
tinyurl.com/j84yhfr

The Pink Sheet

September 23, 2016

"Investigation Failures, Root Cause Problems Continue To Bedevil Manufacturers"
— **Joanne Eglovitch**
tinyurl.com/hlcaxyu

Process

October 18, 2016

"Optima zeigt Techniktrends" ("Optima displays technology trends")
— **Felix Henning and Anke Geipel-Kern**
tinyurl.com/j8tj295

Choose your Favorite Editor or Author

PDA Parenteral Drug Association

pda.org/2016authorsurvey

In recognition of the outstanding quality of his or her publications, one distinguished PDA author or editor is honored with the 2016 PDA/DHI Technical Books Distinguished Editor/Author Award, which will be presented at the *2017 PDA Annual Meeting*.

This members' choice award is **determined by you**, so please take a moment to cast your vote online for your favorite PDA author or editor. Don't wait. This survey closes on **Dec. 31, 2016**.

THE NOMINEES:

Authors: D. Scott Aldrich, Roy T. Cherris and John G. Shabushnig
Visual Inspection and Particulate Control

Author: Lynn Torbeck
Why Life Science Manufacturers Do What They Do in Development, Formulation, Production and Quality: A History

Editors: Russell E. Madsen and Jeanne Moldenhauer
Contamination Control in Healthcare Product Manufacturing, Volume 4

Editor: Siegfried Schmitt
Assuring Data Integrity for Life Sciences

Author: Tim Sandle
Risk Assessment and Management for Healthcare Manufacturing: Practical Tips and Case Studies

Check out these books and more at **pda.org/bookstore**

Commentary – PDA's Metrics Activities

Richard M. Johnson, PDA

Since the U.S. FDA first introduced and invited industry feedback on its Quality Metrics program in Feb. 2013, PDA has been engaged in the public discussion to advance the principles of the program.

PDA held three conferences on the topic (Dec. 2013 & 2014/Nov. 2015) to gather input from industry and FDA. This input helped a PDA task force develop a position paper that was published in the PDA Journal (Sept./Oct. 2014). In 2015, the task force published results of a Quality Culture Survey in the Journal (Sept./Oct.), wrote comments on FDA's draft Quality Metrics guidance, and I appeared at FDA's public meeting on the guidance to present PDA's position.

This July, FDA published its *Quality Metrics Technical Conformance Guide: Technical Specifications Document,* on which PDA is commenting independently. All PDA comments are posted on the website.

PDA is a scientific membership association. Our members are independent scientists, academics and regulators. We have no corporate memberships and do not engage in any activity that represents the interest of any specific company or group of companies. That activity is the purview of trade organizations.

On many occasions, we evaluate the possibility of collaborating with other organizations, including trade organizations, in the development of "industry" positions, but in every case we weigh the benefit of such activity against our Mission "to advance pharmaceutical/biopharmaceutical manufacturing science and regulations...."

In adherence to this mission, PDA has developed comments on the draft metrics guidance from a scientific point of view.

Several other organizations are working together on a "cross-industry group" response, but many of their comments are legal in nature and some of these groups have lobbied on this topic. As such, joining with these groups would give the appearance that PDA is lobbying. PDA has no mandate to lobby, so it does not lobby any government or regulatory agency. Based on the input of its all-volunteer Board of Directors, PDA has decided not to participate in an invitation to consolidate its comments on this topic with this "cross-industry group." We will evaluate future opportunities for collaboration on a case-by-case basis as long as they are consistent with our mission and values.

PDA Volunteer Spotlight

Horst Koller

- CEO
- *HK Packaging Consulting GmbH*
- Member Since | 2007
- Current City | Uznach, Switzerland
- Originally From | Furth im Wald, Germany

Even if it is a lot of work, it will be very rewarding

Tell us what it was like to work on *PDA Technical Report No. 73: Prefilled Syringe User Requirements for Biotechnology Applications?*

I supported the expert groups responsible for the sections covering elastomeric components and siliconization. It was really fascinating to see the existing knowledge within these groups. For me, the challenge was narrowing it down to the user level so that the information is valuable yet also understandable.

How can I become a volunteer leader like you?

Don't be shy. Go for it. Even if it is a lot of work, it will be very rewarding. And it will be quite an experience.

What did you enjoy about the inaugural PDA Europe *Annual Meeting* this year?

Playing lead guitar in the PDA band, the Parenteral Drug Addicts, at the outdoor networking party with my PDA friends and bandmates.

What is your favorite seasonal European PDA event?

It is still the *Universe of Pre-Filled Syringes and Injection Devices* but now the European *Annual Meeting* is a close second.

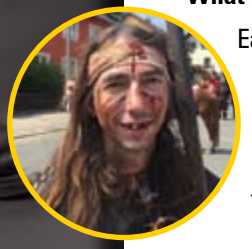
What challenge do you face most while being a team member in this industry?

Even with a lot of experience, you cannot solve some existing problems just on paper…testing also needs to be conducted. This might be more time consuming than initially thought, and, therefore, causes deviation from the original timeline. Keeping this delay as short as possible is one of the challenges.

Which superhero move are you looking forward to?

Iron Man…but only if they continue playing the right songs!

What do you like to do for fun?



Each August, I return to my hometown to play a Hussite in the *Drachenstich-Festspiele* (Slaying of the Dragon) folk play—the oldest folk spectacle in Germany!

Aseptic Processing

2017 SCHEDULE

OPTION 1
Week 1: January 23-27
Week 2: February 20-24

OPTION 2
Week 1: March 27-31
Week 2: April 24-28

OPTION 3
Week 1: May 15-19
Week 2: June 12-16

OPTION 4
Week 1: July 24-28
Week 2: August 21-25

OPTION 5
Week 1: October 9-13
Week 2: November 6-10

FOR MORE INFORMATION CONTACT:

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E-mail: mcintire@pda.org

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PDA is accredited by ACPE and offers continuing education for professional engineers.

chapter update

Brazil Chapter Approved; First in South America for PDA

On Aug. 9, PDA's Board of Directors approved our latest chapter—the Brazil Chapter. This will be PDA's first South American chapter. At this time, the chapter is still working on acquiring approval from the Brazilian government to establish a legal entity in the country. The chapter is tentatively targeting their first event for March, following the Carnival season. The officers of the chapter are listed in the box to the right.

Chapter Leaders

President: **Leonidas Orjuela,** Audisis Vale

President-Elect: **Jorge Anselmo,** Associate Director, Merck – MSD

Treasurer: **Tathiane Castro,** Quality Director, Amgen

Secretary: **Wolfgang Loscher Filho,** Quality Assurance Coordinator, Libbs Farmaceutica Ltda.

Brasilia, the capital city of Brazil

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New Committee Fosters Support for Vendors in Europe

Creixell Espilla-Gilart, PDA

The PDA Europe Exhibition Committee began its activities this January. Since then, the Committee has been advising PDA's Europe office on exhibition trends within pharma. The goal of the Committee is to help PDA improve the exhibition experience at PDA's European conferences for attendees and visitors as well as foster greater collaboration between PDA and exhibitors. The Committee meets once a month and consists entirely of volunteers. **Creixell Espilla-Gilart**, Exhibition and Sponsorship Manager at PDA Europe, moderates this Committee.

PDA would like to express its thanks for the Committee's hard work in their inaugural year.

PDA Europe Exhibition Committee

Katinka Merz, SCHOTT AG (Chair)
Willem Berends, Groninger
Sabine Duda-Schäfers, West Pharmaceutical Services, Inc.
Martin Krainz, NSF Health Sciences
Gustav-Adolf Nesemann, Bausch + Ströbel
Orfeo Niedermann, Ypsomed Delivery Systems
Thomas Uhlig, Hyglos GmbH
Rutger Vandiest, Terumo Europe


Katinka Merz


Sabine Duda-Schäfers


Martin Krainz


Rutger Vandiest


Thomas Uhlig

PDA/FDA Joint Regulatory Conference

Plenary Sessions

P1: Patient Perspective
(l-r) David Fajgenbaum, MD, Castleman Disease Collaborative Network; Peter Marks, MD, CBER, U.S. FDA; Susan Schniepp, Regulatory Compliance Associates

P2: Center Updates (FDA Panel Discussion)
(l-r) Alicia Mozzachio, CDER; William Maisel, MD, CDRH; Douglas Stearn, ORA; Michael Kopcha, PhD, OPQ, CDER; Tracey Forfa, CVM; Steven Solomon, PhD, ORA

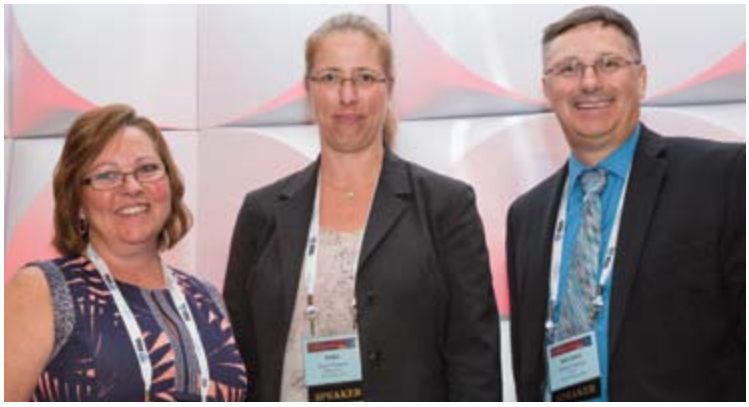
P3: Achieving Compliance by Focusing on Quality
(l-r) Thomas Cosgrove, OMQ, CDER; Michael Kopcha, PhD, OPQ, CDER; Martin VanTrieste, PDA; Steven Mendivil, Amgen

P5: Compliance Update
(l-r) Mary Malarkey, CBER; Ilisa Bernstein, PharmD, CDER; Sean Boyd, CDRH; Daniel McChesney, PhD, CVM; Douglas Stearn, ORA

P4: Quality Assurance in the Year 2016 and Beyond
(l-r) Rick Friedman, CDER; Kelly Allen, W. Edwards Deming Institute; Donna Gulbinski, Bristol Myers Squibb

PDA President Richard Johnson (left) and PDA Chair Martin VanTrieste (right) present Wanda Neal, PDA's departing Sr. VP, Programs and Registration Services, with a bouquet in recognition of her 18 years of achievement for PDA

A1: International Efforts
(l-r) Paul Hargreaves, MHRA, PIC/S; Alicia Mozzachio, CDER; Theresa Mullin, PhD, CDER



C1: Quality Submissions
(l-r) Carol Rehkopf, CBER; Kara Follmann, PhD, Pfizer; Michael Folkendt, CDER

B1: Continuous Manufacturing
(l-r) Sue Miles, Vertex; David Cummings, CDER; Michael Kopcha, PhD, OPQ, CDER

A2: The Skill of Auditing
(l-r) Thomas Arista, ORA; Anil Sawant, PhD, Merck; Susan Schniepp, Regulatory Compliance Associates; Zena Kaufman, ZGK Quality Consulting

B2: Innovation
(l-r) Christopher Weikart, PhD, SIO_2 Medical Products; Robert Langer, Massachusetts Institute of Technology; Volker Sigwarth, SKAN

C2: Supply Chain
(l-r) Ilisa Bernstein, PharmD, CDER; Brian Johnson, Pfizer; Maria Guazzaroni Jacobs, PhD, Pfizer; Lloyd Mager, AbbVie

A3: Quality Systems
(l-r) Simone Pitts, ORA; Rick Friedman, CDER; Mark Paradies, Taproot; Karen D'Orazio, CDER; David Jaworski, CDER

B3: Biosimilars
(l-r) Shane Killian, J&J; Marjorie Shaprio, CDER; Laurie Graham, CDER; Emanuela Lacana, PhD, CDER; Stephan Krause, PhD, AstraZeneca Biologics

C3: ICH
(l-r) John Ayres, MD, Eli Lilly and Company; Moheb Nasr, PhD, GSK; Robert Iser, CDER

A4: Clinically Relevant Specifications
(l-r) Laurie Graham, CDER; Mai Huynh, CVM; Marilyn Martinez, PhD, CVM

C4: Risk Based Auditing
(l-r) Susan Schniepp, Regulatory Compliance Associates; Kevin Siver, PhD, Amgen; Thomas Arista, ORA; Janeen Skutnik-Wilkinson, Biogen

B4: Process Validation
(l-r) Monica Caphart, ORA; Hal Baseman, ValSource; Grace McNally, CDER

B5: Regulatory Consideration
(l-r) Andrew Storey, AbbVie; Renee Kyro, AbbVie; Laurie Graham, CDER

Passport Drawing

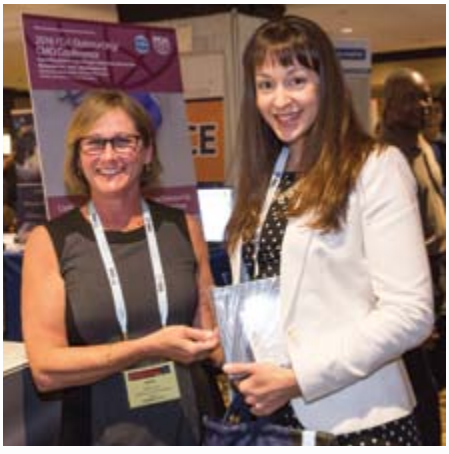
Demetria Macheras won bluetooth speakers from VR Analytical

AumVis PharmaTek awarded an Apple Watch to Beth Haas

Hanne Ziegler won a bottle of wine from Aptar

Beatriz Caceres-Gentile received a $100 Amazon gift card from Novatek

CAI awarded Margie Byrd noise-cancelling headphones



Jennifer Goodman received an Amazon Kindle from Harborview

PDA gave Pam Rood an Apple Watch

Hanne Kornoe won a $250 gift card from Associates of Cape Cod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eye on education

PDA Education Offers Intro to Working World to Intern

Ryan Morris, University of Maryland

When I first started my internship at PDA's Training and Research Institute (TRI) this summer, I was not sure what to expect. I'll be honest; I felt some trepidation as I entered the building on my first day. After all, my father, **Walter Morris,** also works at PDA, overseeing the very magazine you are reading right now. Working in the same building as my dad was a scary prospect at first. Plus, I had just graduated from high school and only had my experiences in school to draw from, so I truly did not know what to expect.

Fortunately, once I got settled in at TRI, I felt right at home, thanks to the TRI staff. I worked on many projects that became very informative learning experiences, and gave me knowledge to use in college and beyond. First, I helped **David Talmage** start a new online inventory system that simplifies how TRI organizes its stock. To fulfill this task, I had to inventory much of TRI's supplies, input this data into the new system, and organize it into easy-to-use groupings.

In addition, I had an opportunity to work in the TRI labs. My favorite responsibility there involved using the autoclave. I learned a lot about this remarkable machine—how it works, why autoclaving is important, and how to prepare items for the autoclave process. The autoclave is a very important tool for a lab because it sterilizes the equipment before it enters the lab. First the materials are packaged into autoclave-safe bags, which will not melt or catch on fire. The bags are then loaded into the autoclave which blasts extremely hot steam at temperatures upward of 250˚F onto the bags until the equipment is properly sterilized.

Finally, I helped the PDA Education staff prepare for the renovation of the original TRI office and lecture room spaces into new laboratory spaces. While it was overwhelming at first, surrounded by boxes and stacks of papers, I took the initiative and lent a hand filing old papers and scanning others into a computer. Hopefully, this means there will be less stacks of paper for the next round of renovations!

While my work was beneficial to TRI and the PDA Education staff, I believe it was equally helpful for me as I learned so much from the experience. My biggest takeaway? Working is a lot different than going to school. Until this internship, I'd never known what it was like to work in an office. I found I needed more independent thinking to complete my tasks successfully as the requirements were not as straight-forward as they would be for say, a class project. I also honed my time management skills, learning to use the time allotted to me effectively and efficiently.

I also discovered work is not always monotonous. Many parts of my internship were quite enjoyable and engaging. I want to thank PDA, and more specifically, **Craig Elliott** and the PDA Education staff for not only giving me this opportunity, but for making it a memorable experience that will benefit me going forward in my academic and professional life. I enjoyed this internship and would certainly do it again.

Ryan Morris poses in the gowning area at PDA TRI in Bethesda, Md.

PDA Who's Who

Craig Elliott, Senior Vice President, Education, PDA

Walter Morris, Senior Director, Publishing, PDA

David Talmage, Director, PDA Education

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snapshot

New Interest Group Offers Data Analysis Insights

Mike Long, Concordia ValSource

Statistics doesn't have to be scary! Proper data analysis techniques throughout the product lifecycle are critical in assuring robust product and processes. Applied statistics is a supporting element within the product lifecycle and essential to applying ICH Q9: *Quality Risk Management* and risk-based thinking. PDA created the Applied Statistics Interest Group (ASIG) to help provide guidance on the application of good data analysis techniques to manufacturing statistics.

One of ASIG's goals is to work with other PDA interest groups to provide informative webinars. Recently, ASIG held two webinars in conjunction with the Process Validation IG and the Quality Risk Management IG on the application of good statistical techniques and analysis to the process validation lifecycle. The leaders of these interest groups intend to repeat the webinar this fall for those members outside the United States.

The ASIG held a well-attended meeting at the *2016 PDA/FDA Joint Regulatory Conference* in September that featured great talks by **J. Patrick Donohue,** Senior Associate Scientist, Janssen, and the U.S. FDA's **Karthik Iyer.** Donohue spoke about sample size justification when analyzing a large molecule drug product, while Iyer offered the FDA perspective on using statistics to analyze the stages of the process validation lifecycle.

A number of questions were raised during the webinars and at the interest group meeting:

- How are CQAs defined?
- Are normality tests overused?
- What is the importance of graphing data prior to any other analysis?
- What is the rationale for the Use of Tolerance intervals?
- Why are some statistical tools used for Process Performance Qualification (PPQ) and not others?

Continued at bottom of page 26

Journal *TOC*

Virus Commentary from One of PDA's Newest Interest Groups in Latest Issue of PDA Journal

The Advanced Virus Detection Technologies Interest Group (AVDTIG) is one of PDA's newest interest groups. In the November/December issue of the *PDA Journal of Pharmaceutical Science and Technology*, read their commentary on high-throughput sequencing for virus detection. Read the whole issue at: http://journal.pda.org.

Commentary

Arifa s. Khan, Dominick A. Vacante, et al., "Advanced Virus Detection Technologies Interest Group (AVDTIG): Efforts for High Throughput Sequencing (HTS) for Virus Detection"

David Bain, et al., "Risk Management in Biologics Technology Transfer"

Research

Michael Washabaugh, Patricia Cash, et al., "Qualification of a Quantitative Method for Monitoring Aspartate Isomerization of a Monoclonal Antibody by Focused Peptide Mapping"

Tobias Werk, et al., "The Effect of Formulation, Process, and Method Variables on the Reconstitution Time in Dual Chamber Syringes"

Patrick J. Faustino, et al., "Dose Uniformity of Scored and Unscored Tablets: Application of the FDA Tablet Scoring Guidance for Industry"

Ankit Patel, et al., "A Small-scale Model To Assess the Risk of Leachables from Single-use Bioprocess Containers through Protein Quality Characterization"

Harry Yang, Steven Novick, Richard K. Burdick, "On Statistical Approaches for Demonstrating Analytical Similarity in the Presence of Correlation"

Technology/Application

Bernhard Hladik, Uwe Rothaar, Michaela Klause, "Comparative Delamination Study to Demonstrate the Impact of Container Quality and Nature of Buffer System"

Frank Günther, et al., "Sterility Testing of Injectable Products: Evaluation of the Growth-based BacT/ALERT® 3D™ Dual T Culture System"

Case Studies

Sal Giglia, et al., "Air-Water Binary Gas Integrity Test for Sterilizing and Virus Filters"

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PDA's Training and Research Institute

Lab courses are taught in PDA's Training and Research Institute (TRI) facility, the only stand-alone facility of its kind. It features an aseptic processing suite with a fill room, gowning/degowning rooms, clean staging area and a component prep room; clean-in-place lab; microbiology lab; and biotechnology lab. It is fully equipped to enable students to apply their classroom-acquired knowledge and gain experience with the operation of equipment typical of that used in the manufacture and testing of drug products.

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Visit pdatraining.org to see the complete list of PDA's course offerings.

PDA is accredited by the Accreditation Council for Pharmacy Education and is an approved provider of Continuing Professional Competency (CPC) credit by the New Jersey State Board of Professional Engineers and Land Surveyors. PDA is also an approved sponsor of CPC activities for Professional Engineers licensed in North Carolina.

USP Perspectives on LAL Assay Interference and NOE Standard

Radhakrishna Tirumalai, PhD, USP, David Hussong, PhD, ValSource, James Akers, PhD, Akers Kennedy & Associates, and Karen McCullough, MMI Associates

USP's Microbiology Expert Committee is responsible for general chapter <85> *Bacterial Endotoxin Test*. The Committee has engaged in frequent discussions regarding the assay interference issue, commonly known as Low Endotoxin Recovery (LER), since it was first reported in 2013 ***(1).*** Members of the Expert Committee collectively have over 100 years of experience in *Limulus* amebocyte lysate (LAL) and methods suitability testing, and have considerable individual experience with the development and qualification of LAL assays for use with a wide range of biologics, drugs, and devices. With this backdrop of collective experience, the Committee chose to take action to help confront and mitigate the reported LER issue by proposing a new Naturally Occurring Endotoxin (NOE) reference standard supplied by USP. This new standard will be an alternative to the Reference Standard Endotoxin (RSE) that USP has supplied since the LAL test first appeared in the compendium.

Photo by Didier Descouens

Why a New NOE Standard?

Approximately 18 months after the initial report of LER, additional information emerged indicating that:

1. When concurrent tests were conducted using RSE in parallel with laboratory derived unpurified natural samples from *E. cloacae, R. pickettii, P. aeruginosa* as well as *E. coli*, it was found that all of the natural endotoxin preparations were reactive in both the rabbit pyrogen test and the LAL assay at T= 24 hours. This indicated that naturally occurring preparations were not impacted by the so-called LER effect ***(2).***

2. The controls done in this study using RSE were nonreactive in both the LAL and rabbit test. In other words, they manifested the expected LER reaction ***(2).***

During Committee deliberations, it was noted that NOEs have been reported to have different characteristics compared to RSE or Control Standard Endotoxin (CSE) in endotoxin removal or physical depyrogenation studies. Personal communications from Committee members **James Akers** and **Karen McCullough** also confirmed, that in some cases, NOEs have proven useful in overcoming interferences in LAL testing unrelated to the LER phenomenon. The committee came to the consensus that NOE could be a useful alternative to the calibration analyte, possibly mitigating product interferences. Clearly, having such an alternative reference material possessing such properties would be useful for USP stakeholders.

A Short History on LAL

In the 1950s, **Dr. Frederick Bang** observed that the injection of marine *Vibrio* spp. into a horseshoe crab resulted in death as a result of blood coagulation ***(3).*** About a decade later, he and **Dr. Jack Levin** discovered that this coagulation resulted in *Limulus* amebocytes ***(4).*** By the end of the '60s, a prototype "LAL" test evolved into a promising replacement for the rabbit pyrogen test, which first appeared in USP <12> in 1942. In 1980, the U.S. FDA issued draft guidelines for the LAL test, and the finalized guideline was issued in 1987. In 1984, USP issued the first compendial bacterial endotoxin test using the LAL method and the use of the rabbit test quickly diminished.

It took over twenty years after the initial development of the LAL test for it to reach compendial and regulatory implementation. The reason for the slow implementation bears on the issue known today as LER. A team working at FDA in 1984 found that only 11% of the products tested demonstrated "no interference" with the LAL test ***(5).*** Fully 70% of the products tested, however, required dilution with Water for Injection, with or without pH adjustment. Additionally, 6% of the products were reported to have highly variable endpoints while 4% showed total interference and were thought to be potentially incompatible with the LAL test. This key FDA study concluded that 89% of the products evaluated required some dilution or other "adjustment," and 10% of products evaluated exhibited such ➤

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profound interference that it was suggested they may not be suitable for LAL product release testing.

Given the common reports of product inference in the LAL assay, the 2013 report of interference in specific biologic formulations was neither surprising nor alarming. This specific LER interference was associated with a category of biological products formulated in chelating buffers and polysorbate surfactants. Because the LAL test requires the presence of a sufficient concentration of divalent cations, chelating formulations had long been recognized as a potential issue in LAL testing. The circumstances of the LER interference led the Committee to hypothesize that the problem might lie in an interaction between the Westphal-extracted lipopolysaccharide (LPS) analyte and the so-called product formulation "matrix."

The use of product formulations for protein-based biologics that contain both chelating buffers and polysorbate date to roughly the time of publication of the FDA guideline on the validation of the LAL test in 1987. Over that period of time, the Committee found no reports of clusters of adverse patient reaction arising from pyrogenicity in such products. Such reports would suggest the unintended release of a product contaminated with endotoxin. This leaves no objective reason to suspect that current reports of LER reports are indicative of a public health problem associated with products formulated with chelating buffers and surfactant.

RSEs vs CSEs

From the initial publication of an official compendial LAL test in 1984, Westphal-extracted and purified LPS from Gram-negative bacteria (GNB) has served as the USP RSE. The various CSEs available commercially have been similarly extracted and purified. The original reference standard was derived from *E. coli* O113:H10:K0, a strain selected by FDA. A collaborative study published in 1985 found that generally the analytical differences among RSE and two commonly used CSEs fell within a 95% confidence interval of the two-fold dilution limits considered necessary for a valid LAL test ***(6).*** These results indicate that RSE and CSE perform as well as can be expected in LAL calibration, allowing for normal variability, which is a common feature in biological assays.

There have been discussions regarding RSE being a "well-characterized" standard. While it is a reliable and generally consistent biological calibration analyte, it is incorrect to suggest or assume that it is well-characterized in the sense of a USP product standard. The greater body of evidence suggests that there is no such thing as a "standard" endotoxin in nature. The representativeness of RSE or LSE compared to other GNB endotoxins in recovery studies should not be assumed. In fact, the Lipid A sequences ➤

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are quite variable among GNB. Characterization is not the key issue here; activity of an analyte is the only attribute that can (or will) be calibrated against the RSE. It is known that RSE and CSE have proven to be useful calibration analytes, allowing of course for inevitable biological variability

Some Final Thoughts

The term "reference standard" carries with it an expectation of special attributes including chemical purity and conservation of structure. Endotoxin analyte references, including RSE, are, however, structurally heterogeneous and known to form aggregates of various kinds. Westphal-extracted LPS may range in molecular weight from ~10^5 to several million Daltons ***(7).*** LPS is but one component of the very complex Gram-negative cell wall ***(8),*** which also includes the Lipid A fraction of LPS that is chiefly responsible for pyrogenicity. The cell wall also contains peptidoglycans, lipoproteins, as well as other associated proteins including porins. The LPS component of a cell wall cannot, and does not, exist in nature as purified material. Endotoxin, when present *in vivo* arises from the natural growth, death, and disintegration of GNB through autolysis, or phagocytic digestion or through the release of "blebs" during cell growth ***(9).*** Perhaps RSE was misnamed, and it would have been more accurate to call it a reference calibration analyte. USP will, of course, continue to make extracted LPS-derived RSE available. But an NOE reference material, as an alternative analyte, is overdue.

The USP Microbiology Expert Committee has drafted a Stimuli article that will cover the subjects covered in this brief communication in more detail. This article is expected to publish in early 2017. The Committee welcomes any questions or comments stakeholders may have regarding the NOE reference standard. These can be sent directly to USP at rst@usp.org.

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Karen McCullough is principal consultant at MMI Associates, a consulting firm specializing in endotoxin and microbiology testing compliance.

New Interest Group Offers Data Analysis Insights continued from page 20

- What is the rationale for an objective criteria for sample size selection for drug product PPQ?
- How do we assure the integrity of our data? After all, data is coming out of the system into statistical packages then presented in reports.
- How do we rightsize our data analysis not just for PPQ but for other quality system elements?

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Future projects include technical reports on continuous process verification and PPQ data analysis techniques and a joint meeting with the Process Validation IG at the *2017 PDA Annual Meeting*. The group also plans to continue working with other IGs on areas of mutual interest.

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Some Thoughts on USP's New NOE Standard

James Cooper, PharmD

USP has launched an initiative to make NOE available to the industry, requesting comments regarding a proposed reference standard that would be prepared from cell wall extracts of a well-characterized GNB. The new NOE standard will have no role in the routine release of sterile products associated with the bacterial endotoxin test (BET). This proposed standard will be a vital tool to investigate the behavior of endotoxins that might be present from a contamination event. It is critical to accept the fact that a purified LPS is not a potential contaminant.

Naturally occurring bacterial endotoxins contain the lipid, carbohydrate, and protein makeup of GNB outer cell membranes. Purified endotoxins, LPS, are generally free of nucleic acids, proteins, phospholipids and other cell constituents. Although the terms "endotoxin" and "LPS" are used interchangeably, each refers to a different entity. In contrast to LPS, endotoxin is constantly shed into the environment by GNB in a cell-associated/free state. During growth, GNB may release endotoxin in the form of spherical vesicles or tubular blebs. The advent of the LER/LPS phenomena brought to light the differences in the two types of endotoxin.

In 2011, two Pfizer scientists reported their experience with NOE preparations ***(1).*** They prepared NOE from several GNBs to assess the stability of endotoxin across various matrices, production processes, and containers. They were concerned that LPS might not be representative of endotoxin present during biopharma production. Preparation of high-concentration NOEs enabled them to add endotoxin to starting pharmaceutical processes and follow its presence through a given process. They reported that NOE stock solutions were stable for long periods of time.

My experience has shown that natural endotoxin is more stable and less prone to BET interference conditions than CSE or LPS. During the past 25 years, I used NOE in inhibition/enhancement studies to better understand the nature and causes of problematic interference conditions. The proposed standard will benefit BET labs that develop BET methods for starting materials, and for understanding ways to control endotoxin in production processes—a regulatory expectation ***(2).***

The current controversy regarding LLR/LER in certain biologics exemplifies the urgent need for an NOE ***(3–5).*** Under specific, experimental conditions, low recovery affects LPS but is far less likely to impact natural endotoxin recovery. Clearly, we need an alternative analyte to confirm that LPS-inhibitory conditions in a citrate buffer and polysorbate solution do not potentially mask natural endotoxin. The cell fragments that make up natural endotoxin are less susceptible to interference conditions than micelle formation that generally applies to purified LPS. Reference NOE will enable the many labs working on LLR/LER and other recovery projects to use uniform methods and compare results.

The availability of NOE as a consistent positive control could provide manufacturers and testing laboratories with a tool to evaluate extraction techniques appropriate for devices. The naive assumption that LPS and endotoxin are identical has led to artifacts in LPS recovery studies with devices. NOE is stable in solutions over a wide temperature range, with little to no vortex mixing. Requirements for temperature-controlled extraction and vigorous mixing for recovery of natural contamination from surfaces of medical devices/combination products are not science-based nor justified.

There will be suggestions to include rabbit pyrogenicity as part of NOE characterization. But there have been countless studies over the past 40 years documenting that LAL activity correlates with pyrogenicity ***(6).*** Rabbit testing is highly variable and relatively insensitive qualitatively, adding no meaningful data for NOE characterization. Further, the testing is inconsistent with animal welfare.

Finally, the regulatory concern for LLR/LER to date has focused on why LPS is altered and cannot be recovered. More recent studies address a far more relevant issue—the structural characteristics of NOE that make it more stable in the presence of chelating buffers and detergents. This proposed reference standard will be a powerful tool the meet the regulatory expectation to fully understand endotoxin risks in new products.

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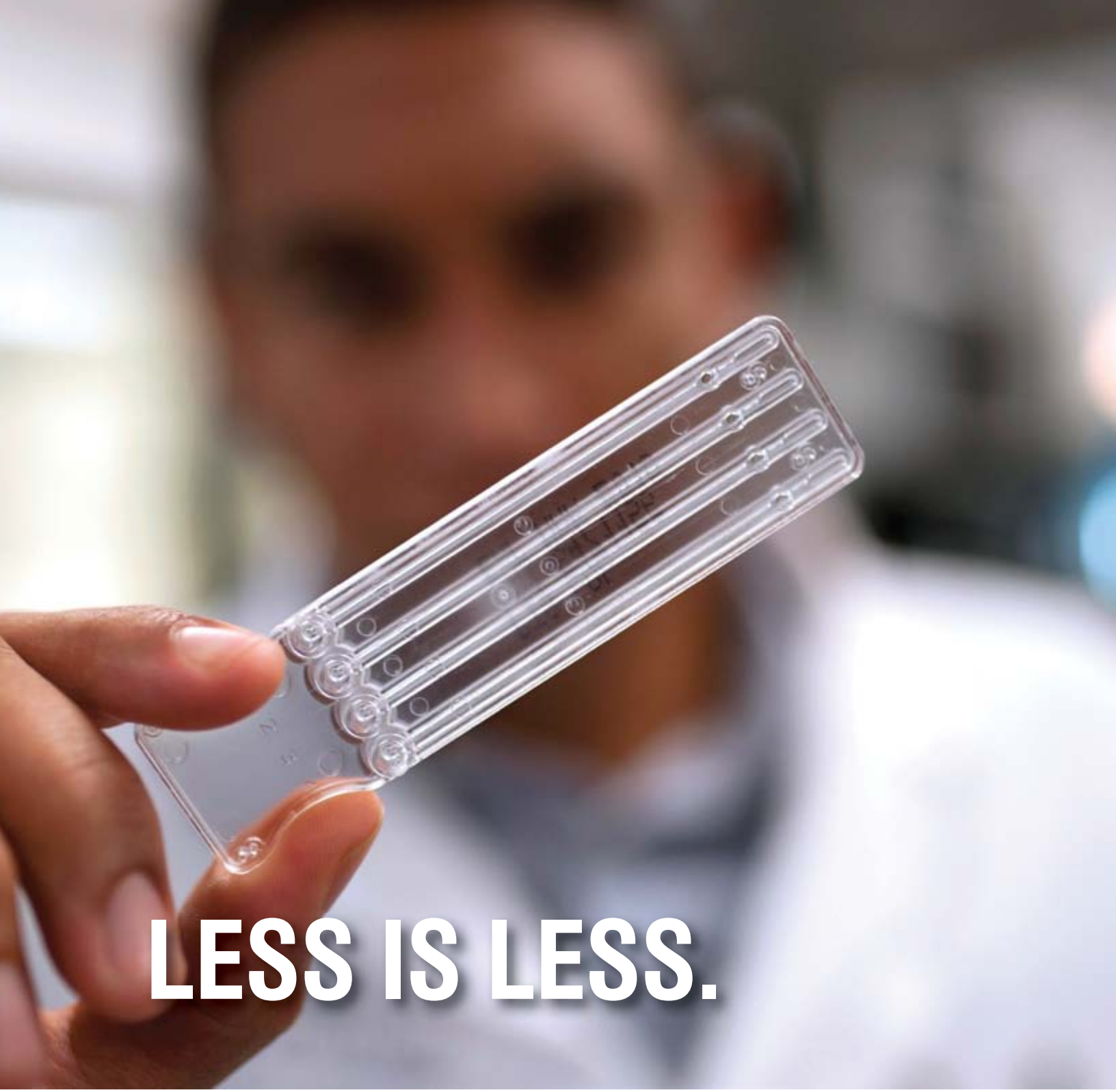
About the Author

James Cooper, PharmD, consults on depyrogenation, BET methods, endotoxin issues, and root cause investigations.



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Bethesda, MD
pda.org/2017Aseptic1

26-27
Die Basis für das erfolgreiche Auditieren: Erfahre die Kraft der Kommunikation
Berlin, Germany
pda.org/ErfolgreicheAuditieren2017

FEBRUARY

14-15
PDA Europe Pharmaceutical Microbiology
Porto, Portugal
pda.org/EU/Micro2017

16-17
Practical Guide for Root Cause Investigations – Methodology & Tool Kit
Porto, Portugal
pda.org/EU/RootCI2017

16-17
Rapid Microbiological Methods
Porto, Portugal
pda.org/EU/MicroMethods2017

21-22
2017 PDA Pharmaceutical Quality Metrics Conference
Bethesda, MD
pda.org/2017Metrics

28-3
Train the Trainer Week
Bethesda, MD
pda.org/2017Trainer

MARCH

13
Elastomers
Barcelona, Spain
pda.org/EU/Elastomers2017

13
Secondary Packaging for Parenterals
Barcelona, Spain
pda.org/EU/SecondaryPack2017

14-15
Parenteral Packaging
Barcelona, Spain
pda.org/EU/ParPack2017

16
Container Closure Development
Barcelona, Spain
pda.org/EU/CCD2017

16-17
Container Closure Integrity: Regulations, Test Methods, Application
Barcelona, Spain
pda.org/EU/CCI2017

16-17
Track and Trace: How to Implement Pharma Serialization, Tamper Evidence and the EU-Falsified Medicines Directive
Barcelona, Spain
pda.org/EU/Track-and-Trace2017

16-17
Extractables & Leachables
Barcelona, Spain
pda.org/EU/EL2017

20
Particle Identification in Parenterals
Berlin, Germany
pda.org/EU/TCParticleID2017

22-23
An Introduction to Visual Inspection: A Hands-on Course
Berlin, Germany
pda.org/EU/TCVisual2017

27-31
PDA #100 Aseptic Processing Option 2
Week 2: Apr. 24-28
Bethesda, MD
pda.org/2017Aseptic2

APRIL

3-5
2017 PDA Annual Meeting
Anaheim, CA
pda.org/2017Annual

3-7
Praxis der Pharmazeutischen Gefriertrocknung
Osterode, Germany
pda.org/EU/Gefriertrocknung2017

5-6
2017 PDA Cell and Gene Therapy Workshop
Anaheim, CA
pda.org/2017CGT

6-7
2017 PDA Annual Course Series
Anaheim, CA
pda.org/2017AnnualCourses

26-27
Current Trends in Aseptic Fill & Finish of Pre-filled Syringes
Ravensburg, Germany
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MAY

15-19
PDA #100 Aseptic Processing Option 3
Week 2: Jun. 12-16
Bethesda, MD
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30-1
Virus & TSE Safety Forum
Dubrovnik, Croatia
pda.org/EU/Virus2017

JUNE

13-14
2nd PDA Europe Annual Meeting
Berlin, Germany
pda.org/EU/Annual2017

15
Quality by Design for Biopharmaceuticals
Berlin, Germany
pda.org/EU/QBD2017

26
Practical Application of GMP for Development of ATMPs
Valencia, Spain
pda.org/EU/TCATMPs2017

27-28
Advanced Therapy Medicinal Products
Valencia, Spain
pda.org/EU/ATMPs2017

JULY

24-28
PDA #100 Aseptic Processing Option 4
Week 2: Aug. 21-25
Bethesda, MD
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SEPTEMBER

19-20
Pharmaceutical Freeze Drying Technology
Cologne, Germany
pda.org/EU/FreezeDrying2017

26-27
10th Workshop on Monoclonal Antibodies
Berlin, Germany
pda.org/EU/Monoclonals2017

OCTOBER

9-13
PDA #100 Aseptic Processing Option 5
Week 2: Nov. 6-10
Bethesda, MD
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10-11
Pharmaceutical Cold & Supply Chain Logistics
Rotterdam, The Netherlands
pda.org/EU/ColdChain2017

16-18
12th Annual PDA Global Conference on Pharmaceutical Microbiology
Bethesda, MD
pda.org/2017Micro

18-19
2017 PDA Microbiology Post Workshop
Bethesda, MD

23-24
2017 PDA Visual Inspection Forum
Bethesda, MD
pda.org/2017Visual

NOVEMBER

7-8
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Personalized Meds: There's Something for Everyone

Ghada Haddad, Merck & Co., Inc.

There is "something for everyone," as the expression says. It certainly seems so today, in many ways. You probably have your own personalized music playlist, recommendations for movies and television programs based on your viewing history from your streaming service, and you may even have your own news app set up on your phone that provides you with the news updates most pertinent to your region, sports teams, and interests.

This is all pretty awesome, if you ask me.

But as we're entering an age of greater personalization, what does this mean for healthcare? Well, the emerging fields of immunotherapy, gene, and cell-based therapies offer considerable promise in bringing personalized treatments to the forefront of medicine.

At the *2017 PDA Annual Meeting*, a number of talks will look at how we, as an industry, can bring these innovative products to the patient**. Xu-Rong Jiang,** MD, Quality and Technical Director, AstraZeneca, will speak about advances in assessment and control of effector functions in therapeutic antibodies in the breakout session, "B2: Immunotherapies." Using therapeutic antibodies to treat disorders like cancer has led to the field of "targeted medicine"—drug products that interfere with specific molecules to block the growth and spread of diseases. And related to this is the field of personalized medicine. Here, treatments are developed based on a patient's own genetic makeup. The session "B3: Genomic Profiling" will highlight the knowledge gained on why some individuals are susceptible to certain diseases compared to others and why patients can have different reactions to the same drug.

If you want to learn more about the personalization of healthcare, come to the *2017 PDA Annual Meeting.* And bring your family! The conference will be held only three-blocks from the ticket booths for Disneyland! Come to Anaheim for the weekend before the meeting, because April is a fabulous time to be in Anaheim and share the Disneyland experience with your family before you immerse yourself in this great meeting (and yes, there are apps/tools available to personalize your Disneyland experience too!).

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14 – 15 March	Parenteral Packaging	Barcelona, Spain
25 – 27 April	Current Trends in Aseptic Fill & Finish of Prefilled Syringes	Ravensburg, Germany
30 May – 1 June	Virus & TSE Safety Forum	Dubrovnik, Croatia
13 – 14 June	2nd PDA Europe Annual Meeting	Berlin, Germany
27 – 28 June	Advanced Therapy Medicinal Products	Valencia, Spain
19 – 20 September	Pharmaceutical Freeze Drying Technology	Cologne, Germany
26 – 27 September	10th Workshop on Monoclonal Antibodies	Berlin, Germany
10 – 11 October	Pharmaceutical Cold & Supply Chain Logistics	Rotterdam, Netherlands
7 - 8 November	The Universe of Pre-filled Syringes and Injection Devices	Vienna, Austria
21 – 22 November	Outsourcing & Contract Manufacturing	tbc

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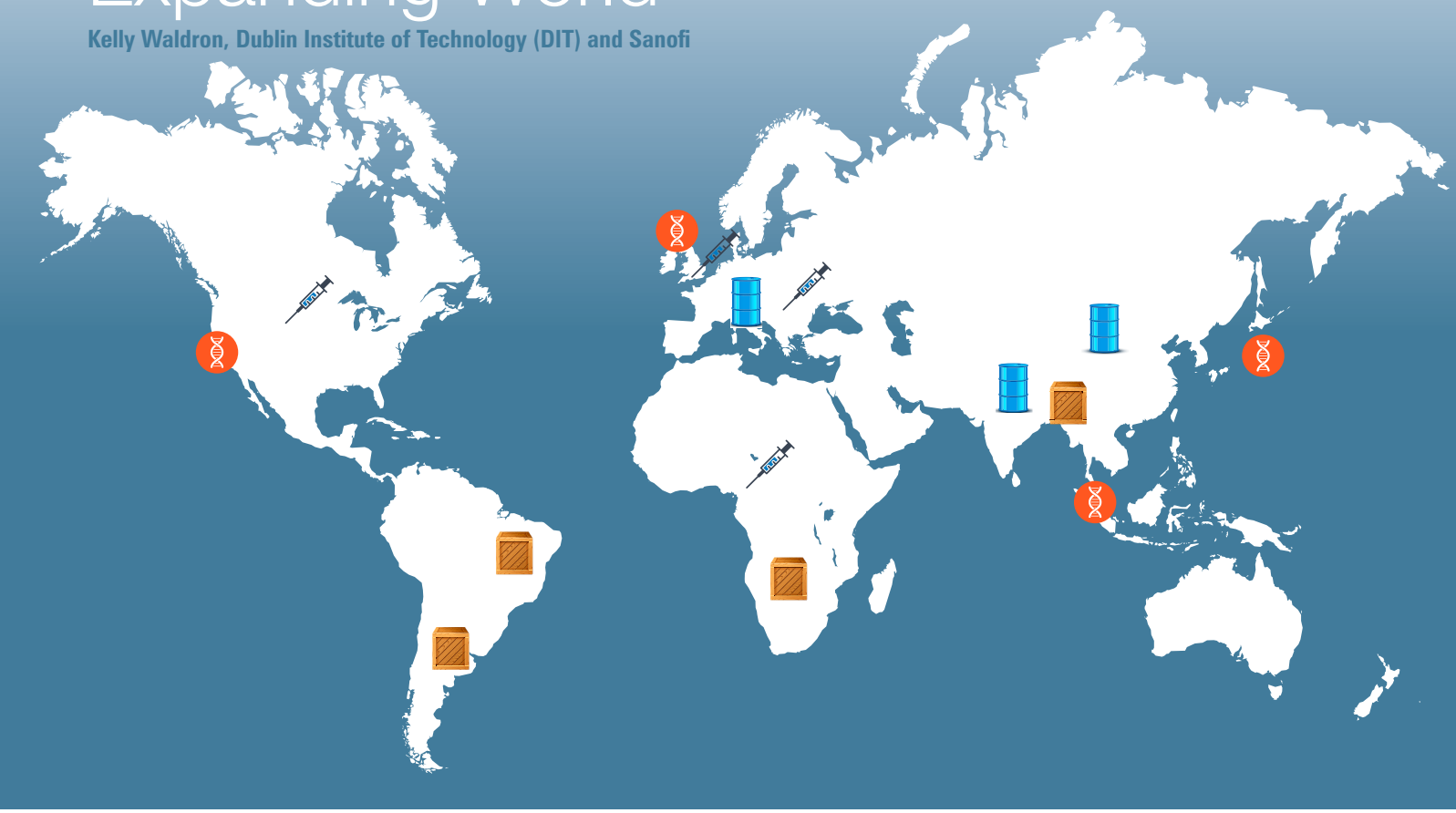
Four Global Pharma Concerns in an Expanding World

Kelly Waldron, Dublin Institute of Technology (DIT) and Sanofi



Globalization of the pharmaceutical, biopharmaceutical, and medical device industries offers numerous benefits, but brings increased complexity. Seasoned industry practitioners can attest to this evolution, as evidenced by new challenges in navigating the international regulatory climate, the intricate nature of the supply chain, and an increase in the number/diversity of patients reached. In particular, four key issues face the global pharma industry: drug shortages, aging infrastructure and technology, data integrity, and product lifecycle management.

1 Drug Shortages

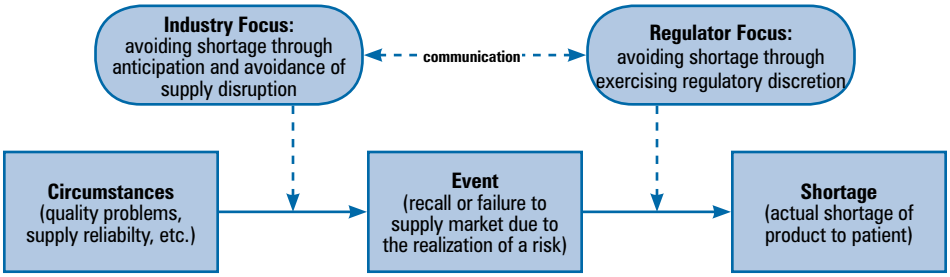
Drug shortages have become a primary focus for industry and regulators across the globe due to their impact on patient care. The number of drug shortages increased dramatically in the late 2000s and early 2010s, grabbing international attention as the issue became a worldwide public health crisis. Patients were forced to make difficult decisions regarding their quality of care as a result of these shortages, potentially impacting treatment outcomes. In a welcomed example of solidarity, international regulatory agencies collaborated with multiple industry associations, including PDA, to characterize the extent of the drug shortage crisis, improve communication between regulators and industry with respect to potential or actual shortages, and define strategies to prevent and mitigate the impact of shortages on patients ***(1–3).***

Research conducted throughout the world indicates that quality issues are the primary cause of drug shortages, followed by interruptions in the supply of raw materials and components ***(4–6).*** Various industry publications and regulatory guidances, including *PDA Technical Report No. 68: Risk-based Approach for Prevention and Management of Drug Shortages* ***(7),*** emphasize the importance of applying quality risk management principles and practices within an overarching prevention plan, acknowledge that transparency and communication are critical to the success of any resulting program, and stress that each stakeholder possess competencies that allow for targeted improvements to be made at different points in the applicable chain of events, as indicated in **Figure 1**. While drug shortages affect different regions in different ways, the problem

Article at a Glance

- Global regulators are increasing oversight of aging infrastructure
- Industry seeks a common approach to data integrity
- ICH Q12 may hold relief for post-approval change headaches

Figure 1 Areas of international collaboration focused on preventing drug shortages to patients



remains a global concern that requires a global response.

2 Aging Infrastructure and Technology

Closely linked to drug shortages is the pressing issue of an aging manufacturing infrastructure. Regulatory attention on aging facilities, equipment, and technology has increased as quality problems and inspection findings have been linked to these issues. International regulators have called into question the general state of facilities/equipment, wondering if outdated sites and equipment can adequately support production of product. Lack of investment in recapitalization and modernization is pervasic across the industry ***(8,9).*** In some instances, critical infrastructure has aged past the point where spare parts are available. Often, external service providers no longer support legacy technology. Some industry experts attribute this to resource pressures in an expanding industry, i.e., the drive to minimize costs and maximize runtime to meet growing international demand.

The consequences of this reluctance to invest in modernization are grave—aging facilities correlate to upticks in quality problems, such as particulate and microbial contamination. Antiquated technology also limits industry's ability to embrace prevailing cGMP concepts ***(10–17).*** Aging infrastructure and technology constrain effective control of process and product risk, often jeopardizing the ability to consistently supply product to patients due to the unreliability of the infrastructure. The global community is actively seeking to minimize obstacles that may impact progress in this space.

3 Data Integrity

Discussions regarding breaches of data integrity began to emerge in early 2014 when several U.S. FDA inspectors found instances of falsified laboratory and production data at foreign firms. As inspectors continued to uncover falsified data, regulatory and industry focus increased in this area, expandeding beyond purposeful data falsification to other concerns, such as electronic data capture, electronic signatures and system usage, manual transcription of raw data, and the preservation of and distinction between dynamic and static data ***(18,19).***

The topic of data integrity is applicable to any and all personnel working in a GxP environment, irrespective of region, particularly those involved with the creation or management of raw data related to production and product quality. Because the reliability of scientific data is integral to decisions around quality, the issue has garnered international attention. Industry as a whole is working to develop a common vocabulary with regard to data and its management. Industry is also working on sharing best practices among firms and with regulators to ensure the reliability of data is assured ***(20–27).***

4 Product Lifecycle Management

The challenges associated with product lifecycle management, and more specifically, the implementation and regulatory approval of changes to marketed products, have likewise been the subject of much discussion throughout industry circles. There are two main challenges:

- Ensuring that changes result in a comparable product with respect to clinical equivalency (meaning that no new or increased risks related to safety or efficacy profiles are introduced with the change), and
- Navigating global regulatory approvals to ensure that product manufactured with the change(s) in place is not distributed in markets that have not yet approved that particular product/process presentation

Key leaders within industry have called for collaboration with international regulators on this topic, pointing out that the processes associated with post-approval changes may unwittingly discourage companies from meeting regulatory expectations regarding continuous improvement. The regulatory community, as embodied by ICH, responded to these concerns with the publication of a concept paper and business plan for the forthcoming guidance, Q12: *Technical and Regulatory Considerations For Product Lifecycle Management* ***(28,29).*** The excitement throughout the world is palpable; global regulatory collaboration on this topic is expected to enable higher quality product to be delivered to patients ***(30–37).***

Increased globalization has brought with it new challenges and complexities that must be addressed in order to protect patients. Likewise, a global perspective may prove to be the key to transforming these challenges into opportunities. By engaging with multiple stakeholders, including regulators, healthcare providers, and patients, and by tapping into the field's greatest asset—the expertise and passion of those working in the industry—pharma can ensure that globalization becomes a strength underpinning its collective success.

The views and opinions expressed in this article are those of the individual author and should not be attributed to any company with which the author is now or has been employed or affiliated.

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Research conducted throughout the world indicates that quality issues are the primary cause of drug shortages

About the Author

Kelly Waldron has over twelve years of experience in various quality functions in the biopharmaceutical industry, with eight years focused on Quality Risk Management.

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Latin America: Moving from Importer to Exporter

Luis Caveda, PharmaBioServ

The Latin American pharmaceutical industry has traditionally been an importer of medicinal products, unable to generate revenue through exporting drugs or medical devices. There are many obstacles to be overcome to reverse this situation.

Latin America has a population of 582 million people, and the pharmaceutical market in the region has been growing at an annual average of 7%, reaching $80 billion dollars in 2014. It is expected to cross $100 billion in the next three years. Yet the Latin American industry is primarily represented by foreign companies operating in the region, while the local market, despite the potential, does not export their products outside their countries' borders. The difference between imported and exported pharmaceutical products is almost six times—in fact, only Mexico, Brazil, Chile, and Argentina export products.

In 2012, the region contributed only 3.3% to global pharma production, while the United States, China, Japan, France, and Germany combined contributed 63.5%. Latin America exported $7.2 billion in pharma products to foreign markets in 2013. Mexico was the first exporter with 25% of that total.

To illustrate, in 2013, Mexico was the leading pharmaceutical exporter in Latin America. The country exported $1.8 billion worth of product with 22.1% of exports going to the United States. That same year, Mexico imported $5.0 billion in pharmaceutical products. Mexico´s main suppliers were the United States (23.4%), Germany (15.9%), France (9.4%), Puerto Rico (8.6%), and Switzerland (5.8%). In 2012, this sector recorded a $3.111 million balance of trade deficit.

There are seven problems inhibiting the region from introducing products into other markets. These include:

1. No standardized regional regulations, only national regulations, which vary in stringency:
   - Countries with established, stringent regulations (Brazil, Mexico, Argentina, Colombia, and Cuba) recognized as reference authorities in the region by the Pan American Health Organization (PAHO)
   - Countries with less stringent regulations than above (Chile, Ecuador)
   - Countries with insufficient drug regulation (Peru, Bolivia, Nicaragua)
2. Young agencies with limited experience in exigent markets
3. Increasing trend toward standardized regulations in the United States and Europe
4. Lack of quality manufacturing capacity and uniformity in labeling
5. Lack of qualified personnel with experience in international registration
6. Political instability
7. Distinct medical needs with a need for drug products not used in developed countries

One potential solution to these problems? Joining forces to increase the Latin American presence in the international pharmaceutical marketplace. Already, strategic discussions are underway among various countries in the region on how to address the differing regulations and the various components required for registering a product from country to country.

In order to alleviate some of those difficulties and promote trade between Latin American countries, several regulatory bodies have entered into reciprocity agreements. In Jan. 2013, one such agreement covering the regulatory agencies in Argentina, Brazil, Colombia, and Cuba went into effect. This agreement allows GMP inspection reports to be accepted based on the GMP certificate of any member country.

Several similar reciprocity agreements have been reached, including one between Mexico and Chile and a recent one involving Mexico, Chile, Colombia, and Peru. The Mexican regulatory agency, the Federal Commission for the Protection from Sanitary Risks (COFEPRIS), has also been in talks with EMA regarding mutual recognition of GMP information as well, indicating a strong interest in pursuing more regulated markets.

Latin America has the potential to increase its role in the global pharmaceutical industry, but political resolve is needed to organize a structure capable of addressing current regulatory challenges and reducing existing inequality among countries in the region. First steps should include: increasing the region's R&D capacity to reduce the dependence on generic products and grow the number of innovators; improving manufacturing, particularly, production of quality raw materials and intermediates; designing a road map toward harmonization; considering the creation of a common regulatory agency similar to EMA; strengthening pharmacovigilance across all countries in the region; and expanding efficiency in management/organization by increasing the training of key personnel in local agencies similar to the U.S. FDA and EMA. For Latin America to shift from being an importer to an exporter of drug products requires cooperation and collaboration among all the regulatory bodies in the region.

About the Author

Luis Caveda, PhD, is the Sr. Regulatory Affairs Lead for Pharma-BioServ US, Inc, a consulting company that provides a wide array of services to the life sciences industry.

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How Global Orgs Can Achieve Process Validation Success

Ajay Pazhayattil, Apotex Inc.

The pharmaceutical market has transformed into a global industry within the span of just a few decades. Many companies have sites across the globe, presenting challenges when it comes to harmonizing process validation approaches among sites. There are numerous solutions available to ensure effective process validation at sites within a global network. No matter the solution, a comprehensive process validation strategy is necessary to achieve success.

When developing a global process validation strategy, it helps to review existing regulatory guidance. The U.S. FDA guidance on process validation outlines three stages: process design (Stage 1), process qualification (Stage 2), and continued process verification (Stage 3) ***(1).*** EMA's guideline describes traditional, continuous process verification, and hybrid approaches to process validation ***(2).*** WHO's guidelines recommend using a risk-based, circuitous technique for validation ***(3).*** And the PICS/S GMP Guide requires manufacturers control the critical aspects of an operation with validation throughout the product lifecycle ***(4).*** These regulatory guidelines boil down to one common point: a lifecycle approach.

In fact, the industry has collectively adopted the lifecycle concepts presented in ICH Q8, Q9, Q10, and Q11. This noticeable consensus, built around this approach, opens up opportunities for organizations to apply a global process validation strategy accepted by the major regulatory bodies.

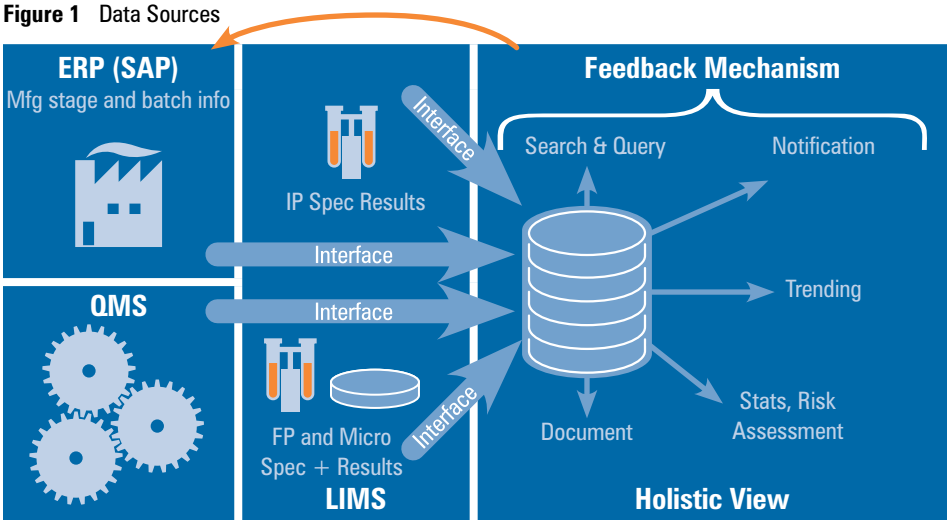
Multiple solutions have evolved over the last few years to address global regulators' recommendations. When it comes to selecting and implementing lifecycle solutions, it is critical to understand which important elements should be factored. Then, functional tools applicable for global organizations should be implemented, such as an appropriate Risk Assessment Tool.

Companies perform risk assessments to make process control decisions during Stage 1 and further along in the process after gaining additional experience. Regulators prefer data-driven risk assessments. Process knowledge of unit operations, which serves as the basis for establishing a comprehensive process control strategy, is also tied into risk assessments. So is Knowledge Management (KM).

ICH identifies KM solutions as enablers; development of a KM solution is critical but requires companies to first map and understand gaps in data. Special attention needs to be provided to ensure use of product development data from global sites. Availability and easy access to product development information of sufficiently similar products and processes across sites is also of great interest. This knowledge could help minimize the number of experiments conducted during QbD-based product development efforts for similar products. Such powerful KM systems integrate data from multiple sources (e.g., the Laboratory Information Management System, Quality Management System, ERP platform, etc.) leading to data-driven and science-based decisions captured, and shared across the organization **(Figure 1).**

Statistical tools that provide objective measures are also available to address elements described in all three stages of the process validation lifecycle. There are approaches available for determining the number of Stage 2 batches ***(5).*** An article in the *PDA Journal of Pharmaceutical Science and Technology* provides a statistically sound method for determining when a valid number of batches have been acquired based on risk assessment and calculation of process capability ***(6).*** Another approach recommends using previously collected product-specific and historical batch-to-batch process information ***(7).*** FDA's quality metrics guidance ***(8)*** and *Quality Metrics Technical Conformance Guide* suggest providing evidence of manufacturing robustness/process performance capability. Traditional process capability measures are sometimes inadequate for general application due to requirements for complex stagewise acceptance criteria (e.g., dissolution acceptance criteria). Therefore, selection of the appropriate tool is critical. An alternative approach of Acceptance Probability (P_a) offers a clear and more precise measure for quality attributes with stage wise acceptance criteria ***(9).*** Such statistically based methods should be developed with current global regulatory requirements in mind, and an eye toward application across a global ➤

Figure 1 Data Sources



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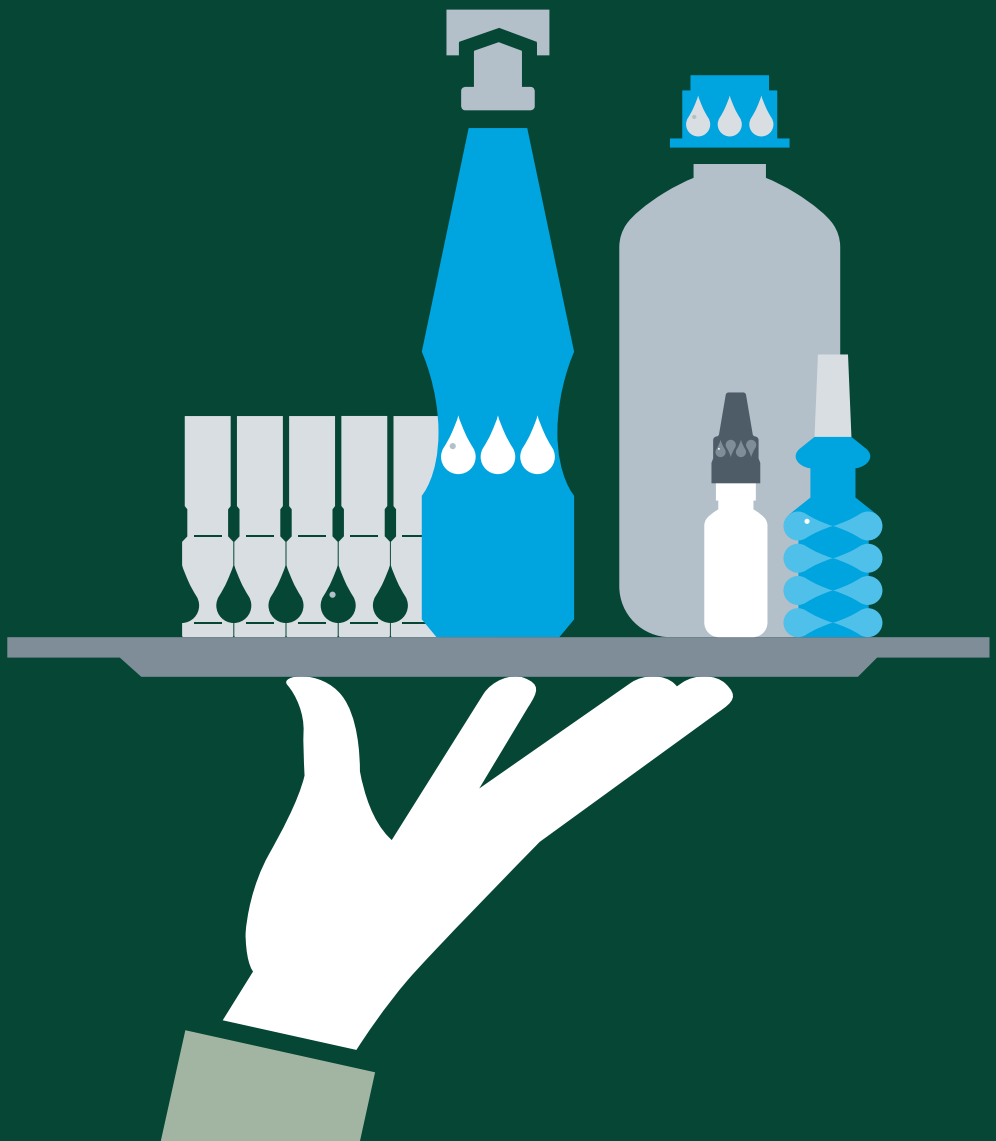
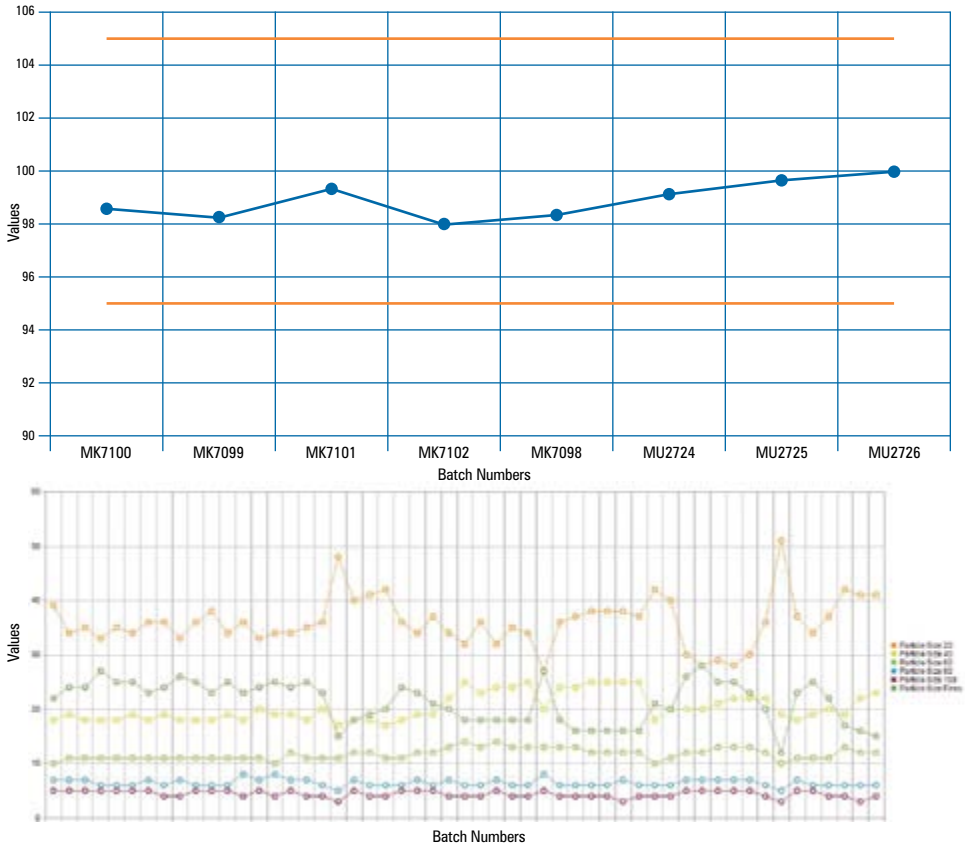


organization. The process validation guidance also recommends that a statistician develop the data collection plan and statistical methods/procedures used in measuring and evaluating process stability and process capability ***(1).***

It is important to use a harmonized data collection plan across all sites when evaluating process stability and capability during ongoing or continued process verification in Stage 3 (for an example see **Figure 2**). A globally applied organizational procedure for trending, signal detection, and action guards against overreaction as well as against failure to detect unintended process variability at sites. The continued process verification program identifies variability in the process and signals potential improvements. Outcomes of a well-implemented continued process verification program include production lines with higher throughput and an uninterrupted product supply. Additional fit-for-purpose matrices or indices are also useful for monitoring product robustness ***(10).*** If the goal is to reduce variability impact on critical quality attributes, all agencies encourage adoption of innovative technologies, such as Process Analytical Technology, where applicable. Stage 3A of process validation (expanded sampling and testing to fully understand variability) applies to newly launched products globally as well, since the assessment outcome demonstrates an organization's compliance in establishing a high level of product understanding.

A well-integrated process validation strategy across multiple global sites is essential due to the synergistic advantage it provides to the organization when it comes to product development and site transfer efforts. Certain activities, such as continued process verification can be performed by a central function instead of a site-specific function. Harmonization of the process validation lifecycle enhances global collaboration and site compliance status. But this requires the right leadership and vision to identify globally applicable process validation solutions. A global process validation policy based on lifecycle elements supports an organization's continued business success across multiple markets.

Figure 2 Statistical Process Control for Continued/Ongoing Process Verification



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PDA Member Reports from the *2016*

Day 1 | Why We Do What We Do

Sharon Ayd, PhD, Regulatory Compliance Associates

After an uneventful flight from Chicago to Washington, D.C., I eagerly headed to the *2016 PDA/FDA Joint Regulatory Conference* in the heart of downtown D.C. For many executives in the pharmaceutical industry, this conference presents a valuable opportunity to listen to and interact with key regulators within the U.S. FDA. For me, not only were each day's sessions an invigorating exploration of the current state of the industry, they also presented a chance to view the industry through the eyes of a patient.

The plenary talks of the day began with a focus on novel therapies. In the first plenary session, CBER'S Director **Peter Marks,** MD, gave the keynote address which focused on genetically modified cell therapy and the current regulatory framework surrounding it. To give a simple example describing how complicated this field is, he used a small molecule as a point of reference. If a small molecule contains 10^2 atoms, he explained, then consider the complexity of a cell composed of 10^{14} atoms. Autologous, or allogenic modified cells, redirect the effector function of the cell and represent a controlled method for delivering gene therapy. This means there is the possibility of providing therapeutic benefit with extended duration of effect. Still, the challenge for researchers is to develop, manufacture, and characterize autologous cells with each cell line representing a different product. Using the same cell line is preferable, because administration of different cell lines or therapies may be associated with both short- and long-term side effects.

I ended Day 1 by attending the breakout session on auditing in the "Product Quality" track. FDA investigator **Thomas Arista** covered how companies can achieve compliance without getting a 483 citation. He wants companies to put him out of a job by conducting effective internal audits. **Zena Kaufman,** Sr. Consultant, ZGK Quality Consulting, talked about "The Skill of Auditing," and how she leverages a site's knowledge about itself. To her, a corporate auditor must be able to establish a rapport and sense of trust throughout the audit and afterward with the group being audited. Internal audits should be viewed as a "site" program, not just a "QA thing."

After a long and tiring but information-packed day, I retired to my hotel room. As I reflected on the day and my interactions with the presenters, I felt more informed than when I stepped off my flight from Chicago. I also felt more connected to the patients we ultimately serve. It was a very good experience and I encourage others in the industry to attend next year's *PDA/FDA Regulatory Conference.* **[Editor's Note:** The full version of this article is on the *PDA Letter* website**.]**

About the Author

Sharon Ayd, PhD, is Chief Scientific Officer and Senior Vice President of Pharmaceuticals at Regulatory Compliance Associates.

Day 2 | Building a Culture of Quality

Karen Luzzi, B. Braun Medical, Inc.

Quality culture must have been on the minds of many speakers on Day 2 of the conference due to the number of talks referencing it. In particular, the first plenary session looked at "Achieving Compliance by Focusing on Quality." **Michael Kopcha,** PhD, Director, Office of Pharmaceutical Quality, U.S.FDA/CDER, and **Martin VanTrieste,** PDA Chair, discussed how companies can foster a mindset that achieves compliance through the development of a strong quality culture.

Kopcha said that FDA will try to gain better understanding of the limitations and challenges involved with building a strong quality culture through its own continuous improvement process for the FDA Quality Management System, and development of an internal quality culture, dubbed "one quality voice." The Agency embraces this approach as quality issues account for 2/3 of all drug shortages worldwide.

VanTrieste further explained that emerging technologies like handheld spectrometers are predicted to shift the quality paradigm from the industry to the hands of the consumers. The industry must work together with regulators to foster a quality culture.

In the "Quality Systems" session **Karen D'Orazio,** Consumer Safety Officer, CDER, presented, "The Problem with Investigations," generously sharing her trials and errors as an investigator. She elaborated on how she learned to become both more effective and efficient in her methods by taking a step back, involving the right people, and identifying critical factors. Taking a deeper dive into investigations, **Mark Paradies,** President of System Improvements, TapRoot, shared his "7 Secrets of Root Cause Analysis." These are:

1. Root cause analysis is only as good as the information collected
2. Understanding what happened before can help understand why something has happened
3. Knowledge (or lack of it) can get in the way of a good root cause analysis
4. Interviews are not about asking questions

6 PDA/FDA Joint Regulatory Conference

5. Human performance problems cannot be solved with discipline, training, and procedures
6. Often, people can't imagine effective corrective actions even if they can find the root causes
7. All investigations do not need to be created equal (but some investigation steps can't be skipped)

The "Process Validation" session also emphasized the importance of quality culture. **Hal Baseman,** Chief Operations Officer, ValSource, provided a brief history of process validation and two case studies stressing the importance of good planning, good design, process control, testing of worse case scenarios, monitoring, and being ever watchful for process improvements. **Grace McNally,** Acting Branch Chief, CDER, followed up with "Process Validation/Verification: Findings From Pre-Approval Inspections," covering preapproval inspections and the importance of good design with emphasis on a robust process.

Preapprovals and expedited approvals were discussed in the final session of the day. During this session, **Laurie Graham,** Acting Director, CDER, FDA, explained that with great risk comes greater benefits. Accelerated programs cover lifesaving drugs (i.e., oncology drugs) and due to the risk to the patient, this accelerated designation may be rescinded at any time should the need become met by another means, or if the efficacy or safety of the drug comes into question. She emphasized predetermining the amount needed for launch, ensuring that facilities are where they need to be for inspection, being aware of regulatory expectations, and knowing the critical quality attributes. **Andrew Storey,** Vice President, Global Regulatory Strategy, AbbVie, then gave an example of how the expedited process can work. **[Editor's Note:** View a video interview with Storey on the *PDA Letter* website**.]** He highlighted that, in order to be considered, these products must show significant improvement on existing therapies. Once that was established, AbbVie could expedite this process by allocating their best resources, creating tools on the company Web page to ensure open communication, keeping time schedules for individuals flexible, and planning ahead for error. This also meant keeping the patient in mind, making a culture of quality paramount.

All in all, the Day 2 talks covered how quality culture touches on many aspects of our industry from compliance to breakthrough therapies. These sessions illustrated how quality culture is the foundation for ensuring the quality of drug products used worldwide and the importance of maintaining it within an organization.

About the Author

Karen Luzzi has over 20 years in the pharma/biotech industry in various roles in operations, validation and quality assurance.

Day 3 | The Past, Present, and Future of QA

Kelly Thomas, Glenmark

Over the last century, significant technological and scientific advances have driven the complete evolution of manufacturing industries. Numerous QA strategies and continuous improvement methodologies have emerged to aid manufacturers in the pursuit of quality. These strategies are aimed at reducing defects, improving operating efficiency, and relying on statistical process control.

Kelly Allan, Chairman of the Advisory Board at the W. Deming Institute, said it best in his talk on Day 3 of the *2016 PDA/FDA Joint Regulatory Conference*, "Align the voice of the customer with the voice of the process." It is essential to develop and track metrics and key performance indicators to determine the health of the quality system, and to ensure appropriate actions are established in order to maintain product quality and customer satisfaction. But understanding metrics and process capability will only take an organization so far. **Donna Gulbinski,** Senior Vice President at Bristol Myers Squibb, referred to this as the "Arc of Quality," in her talk following Allan's presentation. Until culture is addressed, quality improvements will be limited.

Therefore, the challenge facing QA in this era is how to improve quality culture. So, how does an organization motivate people to act? Two very distinct answers were given at the conference. The first step? Make sure the entire organization understands the Cost of Poor Quality. Quality must shift from being viewed as "overhead" or "sunk cost" to being viewed as a profit center. Reducing deviations, defects, and nonconformances not only improves turnaround time and operating efficiency but also has a real impact on the company's financial performance. Therefore, QA professionals must learn to clearly articulate this value to the entire organization in terms of real dollars.

The second step to developing a quality culture? Ensure the entire organization is accountable for quality. In other words, everyone must have some skin in the game.

Continued at bottom of page 48

PDA Then and Now

1940

1946
PDA Founded

1947
Bulletin of the Parenteral Drug Association
(PDA Journal) issued

Now known as the *PDA Letter* at

48
pages

1951
1st Annual Meeting
at New York Academy of Sciences

1963
Washington Letter issued with just 4 pages

1970
First **non-U.S. meeting** held in Montreal, Canada

1971
PDA celebrates **25 years**

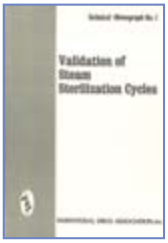
123

courses in 2016

1976
First set of **PDA regulatory comments** drafted

1977
First two **PDA Education** courses developed

1978
First **Technical Report** published



1988
Chapters established

1990
First ***PDA/FDA Joint Regulatory Conference*** held

1992
PDA moves from Philadelphia to Bethesda, Md.

1996
PDA celebrates **50 years**

1997
Training and Research Institute (TRI) Opens

2006
PDA Europe office established in Berlin, Germany

2007
Training and Research Institute (TRI) opens at Bethesda headquarters

2009
PDA Journal of Pharmaceutical Science and Technology online-only

2015
PDA Europe office moves to larger building

2016

2016
New Headquarters opens in Bethesda, Md.

Nov. 18 marks PDA's 70th anniversary. That's 70 years of connecting people, science and regulation®. In light of this momentous occasion, the *PDA Letter* wanted to highlight significant milestones in PDA's history, and compare where we were then to where we are today.

1946 70TH ANNIVERSARY 2016

80

members in 1946, all in U.S.

10,000

Members Worldwide in 2016

First Annual Meeting: Two days, 8 Sessions, 5 speakers, 3 panel discussions

2016 Annual Meeting:
2.5 days,
22 sessions, 40 Talks,
37 speakers

81

Technical Reports published since

9 chapters in North America and Japan

PDA Today

25

International Chapters

snapshot

New RAQAB Chairs Plan for a Fruitful 2017

Rebecca Stauffer, PDA

The PDA Letter *reached out to the new Regulatory Affairs and Quality Advisory Board (RAQAB) Chair* ***Jeff Broadfoot,*** *Director, Corporate Quality Compliance, Emergent BioSystems, and Vice-Chair* ***Jackie Veivia-Panter,*** *Consultant, and asked them a few questions about their plans for the RAQAB.*

PDA Letter: What are some of your overarching goals as the new co-chairs of the RAQAB?

Jeff and Jackie: First, we want to be proactive in identifying significant emerging regulatory and compliance issues, and then provide advice to the Board of Directors so that PDA can mobilize resources to support PDA's membership.

We also plan to develop a robust succession plan for RAQAB in order to ensure we have the global and diverse knowledge available to meet the needs of ever-expanding and changing regulations.

And we will engage with PDA members about RAQAB's role by communicating the benefits of RAQAB and understanding the needs of PDA members. This includes collaborating with PDA chapters, providing articles for the *PDA Letter* and PDA Journal, and reaching out to interest group members.

PDA Letter: What experience do you bring to RAQAB? Both from industry as well as from being members of RAQAB?

Jeff: I've been in QA/QC in the pharma industry for almost 25 years in facilities manufacturing everything from medicated ointments and creams to tablets and capsules to biologics and parenterals. I've been in management for about 15 years. I've covered a lot of ground in that time and understand the complexity of making pharmaceuticals, as well as the day-to-day challenges of running a manufacturing site. I've been a member of RAQAB since 2009 as the Canada Regional Rep. I spent the last three years as Vice-Chair before becoming Chair in July of this year. That experience has given me a great appreciation for the role that industry can and does play in shaping both the regulatory environment and the concept of quality.

Jackie: I have over 25 years of experience in pharmaceutical quality. My experience is in R&D and Operations in many aspects of the pharmaceutical quality system. Much of my time has been spent improving quality systems and ensuring regulatory requirements are met. This will be the first year as a co-chair on the RAQAB and I am really looking forward to it! I have learned so much from all the members and past chairs. It will be a great opportunity to continue the great work established and ensure improvement to meet the needs of the industry.

PDA Letter: What topics will RAQAB address in 2017?

Jeff and Jackie: RAQAB will continue to work on hot topics such as data integrity, post-approval changes, and quality culture metrics.

PDA Letter: What are you most looking forward to as co-chair?

Jackie: I have enjoyed being a member of the RAQAB. The breadth of knowledge within the RAQAB is incredible and has really challenged me to grow and learn. I am looking forward to continuing this and helping the RAQAB and its members succeed in their mission.

Jeff: One of my favorite quotes says, "If I have seen further it is by standing on the shoulders of giants." There really have been some giants that have led RAQAB. I'm looking forward to building on their successes.

PDA Member Reports from the 2016 PDA/FDA Joint Regulatory Conference continued from page 45

Organizations tend to set goals for each department without including a cquality component. For example, production goals tend to focus on number of units produced and meeting production timelines; but no mention of defect rates or corrective action implementation. Quality goals tend to focus on defect reduction and effective CAPA implementation. In order to improve quality culture, it makes more sense to change the production focus from overall numbers produced and packaged to the number of good units produced and packaged. This provides a motivation for production to stop when issues are observed and to correct the problem prior to proceeding with the production run.

In conclusion, understanding performance metrics, quality culture and motivating staff to act served as a common focus of several sessions at the *2016 PDA/FDA Joint Conference.* Despite the changes in manufacturing and technology that have occurred over the last 100 years, QA professionals must focus on implementing a strong quality culture across the entire organization in order to achieve operational excellence.

About the Author

Kelly Thomas is the Director of Quality for Glenmark Pharmaceuticals USA, Inc.

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PDA Recommends FDA Clarify Scope in Compounding Doc

For the comments grid, visit www.pda.org/regulatorycomments

October 3, 2016

Division of Docket Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Reference: FDA Draft Guidance: Insanitary Conditions at Compounding Facilities
Docket ID: FDA-2016-D-2268

Dear Sir/Madam:

The Guidance for Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug and Cosmetic Act, Issued July 2014, cites section 501(a)(2)(B) as not applicable to compounded product under Section 503A, but according to the Guidance for Industry Current Good Manufacturing Practice – Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B, does apply. This draft guidance identifies section 501(a)(2)(A) as being applicable, and provides the FDA's current thinking on the topic. Further, Guidance for Industry Current Good Manufacturing Practice – Interim Guidance for Human Drug Compounding Outsourcing Facilities under Section 503B is focused on those aspects that relate to sterility assurance of sterile drug products. The FDA Guidance for Industry, Insanitary Conditions at Compounding Facilities, Draft Guidance does not contain a similar statement that narrows the focus, however the majority of the content of the Guidance is drawn from FDA experience with sterile compounded products.

The inference from the flow of the document is that the only section which would be applicable to non-sterile compounding would be Section III., A., 1, Insanitary Conditions Applicable to the Production of Sterile and/or Non-Sterile Drugs. PDA recommends that FDA clarify scope to ensure that other products requiring sterile preparation such as ophthalmic products and wound care products are clearly included. Some comments are identified as "critical" in the attachment because these recommended changes to the text would specifically address and prevent conditions noted in recent FDA Warning Letters to compounding facilities.

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 and biological manufacturing, as well as training in compounding and pharmacy practices including members representing the Regulatory Affairs and Quality Advisory Board and Board of Directors.

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

Sincerely,
Richard Johnson
Cc: Denyse Baker, PDA; Richard Levy, PDA

PDA Commenting Task Force

Christopher Smalley, PhD, Merck (lead)
Susan Schniepp, Regulatory Compliance Associates
Bob Dana, Elkhorn Associates
Karin Baer, Teva
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Anticounterfeiting Rules Add to Complexity of Global Regs

Walter Morris, PDA

Guarding against counterfeit medicines remains a serious challenge for regulators and pharmaceutical manufacturers around the world. The onslaught of fake medicines endangering patients worldwide has led to the proliferation of regulations requiring companies to implement countermeasures on packaging to improve tracking, tracing, and identification, and reduce tampering of legitimate product.

While these measures are necessary, their proliferation at a national and regional level only adds to the regulatory complexity of a globalized industry. The latest additions to the growing list of rules are the EU's serialization and tamper-evident packaging requirements, published earlier this year.

The EU requirements were covered in depth at the inaugural PDA Europe *Annual Meeting* in Berlin this past June. PDA Director, **Veronique Davoust,** PharmD, Sr. Manager, Global Quality Strategy, Pfizer, and **Michael Ritter,** Global Project Manager, Serialization and Product Tracking, Novartis, provided in-depth analysis of the rules. **[Editor's Note:** Watch **Martin VanTrieste** discuss the new regs in a *PDA Letter* "On the Issue" video: www.pda.org/pda-letter-portal/multimedia/videos.**]**

The EU regulations specify a two-pronged approach to patient safety. First, they require the use of a unique identifier, or serial number, for each packaged product that will be uploaded to a centralized hub, known as the European Medicines Verification System (EMVS). At the point of sale, the package will then be scanned and authenticated through a national verification repository connected to the EMVS. Second, an anti-tampering device must be placed on each individual package. These requirements become effective in February 2019.

This "end-to-end" verification system varies from the model promulgated in the United States, which is a full "track-and-trace" system, meaning that a product can be traced all along the supply chain. Just before the PDA conference, the EU Commission issued a comprehensive Q&A on these safety features, providing significant detail on how to implement the rule.

Ritter provided details on the challenges involved with meeting these emerging regulations. He outlined six "key success factors" for compliance with the regulations:

- Clear regulations
- Standards
- Supply continuity during installation
- Governance
- Capable operations and people
- Data integrity

Next, Ritter detailed some of the challenges Novartis overcame in setting up its internal system to meet the serialization rules. First they had to ensure the various monitoring cameras and infrared readers along the packaging lines could read the "artwork" where the serial/other unit numbers and barcode are printed on each package in real time. To achieve this, Novartis developed a standard for artwork placement on its various carton sizes. Improving the durability of carton materials to withstand the constant readings from the laser readers proved to be another challenge. The company experienced a high reject rate (44%) due to "burning" and realized that increasing the chemical kaolin in the paper improved its durability and readability. After the fix, rejects plummeted to under 1%.

Ritter then discussed the firm's quality best practices for unique identifiers that span every step from the creation of randomized number series (process order) all the way to managing unique identifiers for recalled, withdrawn, stolen, returned, and destroyed product. Ritter said the U.S. FDA should require randomized serialization numbers, in line with the EU rules, to improve patient protection. He urged PDA to make this recommendation to the FDA.

Davoust provided a comprehensive overview of the EU rule, including how Notifications are to be handled for existing market authorizations. If a regulatory procedure affecting the Product Information Annex, such as a Renewal or one of the various Variations, is to be submitted within three years, notification can be provided in those. If none are expected in three years, companies need to submit a Notification 61(3). For the antitampering device, if there is no impact on the container/closure (or it is on the outer packaging), no regulatory procedure is needed. If it does impact the container closure, mock-ups must be submitted.

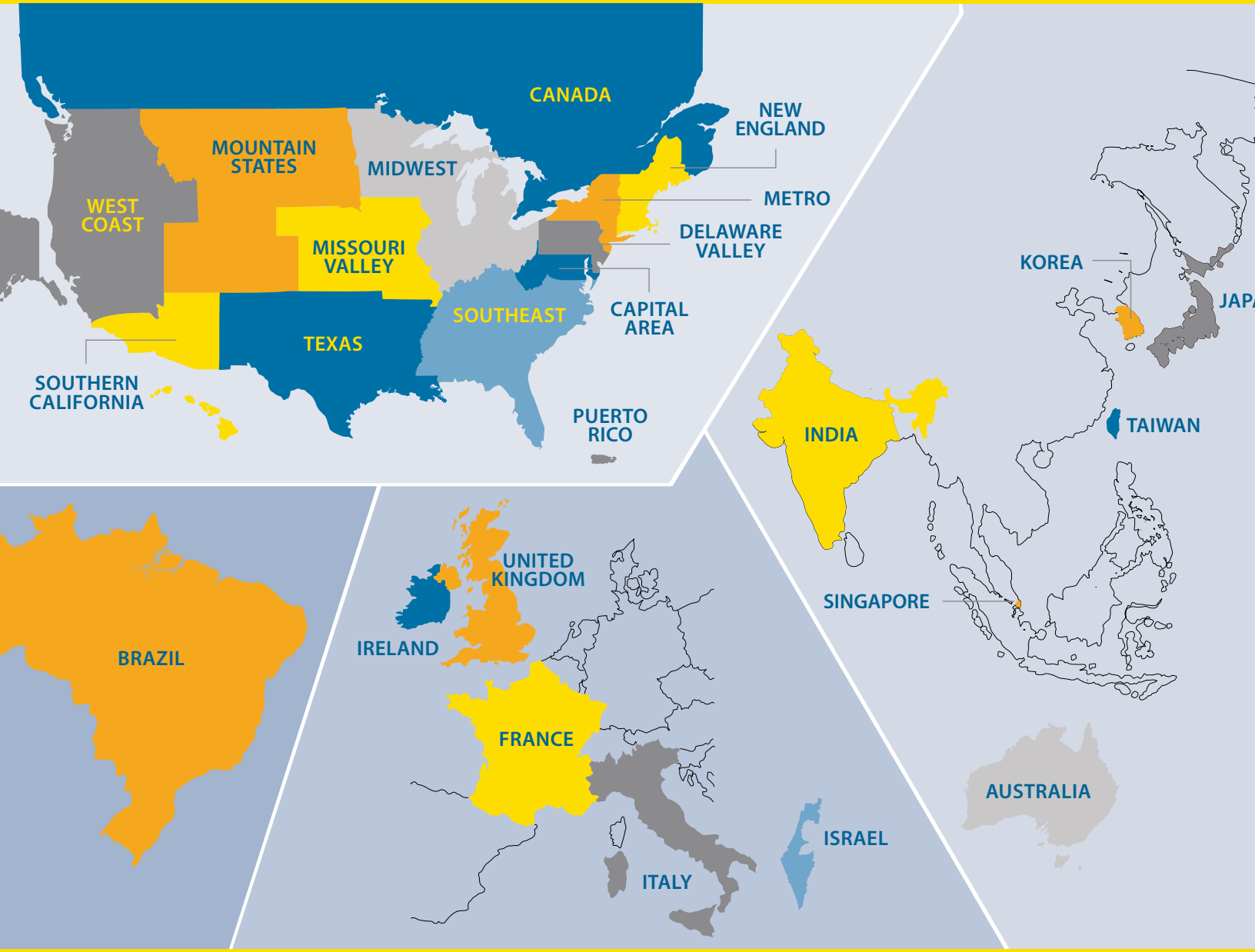
Both Ritter and Davoust presented slides showing the various national laws on serialization, with laws now effective in a dozen countries and draft laws in the works in five more countries.

Iran is one of the nations with serialization requirements, and session participants heard from **Akbar Abdollahiasl,** General Director of Pharmaceutical Affairs, Iran FDA. The Tracing, Tracking and Authentication Control system requires all imports to be opened and labeled with a 2-D serial ID and an authentication code.

The session provided valuable insights into the technical compliance challenges presented by these necessary anticounterfeiting regulations. It is up to manufacturers to develop solutions to address the challenge of monitoring a product throughout its supply chain journey.

PDA Chapters

Your Local PDA Connection



Are you curious about the issues unique to your region?

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

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

PIC/S and ICH Reps Talk Global Pharma at PDA/FDA JRC

Rebecca Stauffer, PDA

Both PIC/S and ICH have proven to be strong entities in the push for global harmonization across the industry. At the *2016 PDA/FDA Joint Regulatory Conference,* representatives from PIC/S and ICH provided background on their respective organizations as well as updates on current activities.

Paul Hargreaves, the current PIC/S Chair, provided an overview of PIC/S and its current and future projects ***(1).*** Commencing in 1995, PIC/S operates through arrangements among regulatory agencies. The founding members of the organization sought to develop a standard system for inspections.

"We wanted a uniform inspectorate system where, no matter which inspectorate was inspecting, you had the same inspection with the same standards," he said.

The goal of PIC/S is to lead development and implementation of harmonized GMP standards and quality systems across the international pharmaceutical industry. To achieve this goal, PIC/S supports development of harmonized GMP standards, training of inspectors, assessments and reassessments of inspectorates, and cooperation among global regulatory agencies. As of August, there were 49 members within PIC/S.

Hargreaves emphasized that while PIC/S has adapted to meet evolving challenges, its goal of international harmonization remains key. Currently, PIC/S working groups are involved in a number of initiatives. One group has drafted a preliminary guidance on the harmonization of risk classifications of GMP deficiencies. Another is working on a document standardizing terminology that covers cross-contamination in shared facilities. The Advanced Therapy Medicinal Products (ATMPs) Working Group is developing a document covering inspection of ATMPs. The Data Integrity Working Group recently developed the first draft of a guidance document for inspectors. A group comprised of both PIC/S and EMA representatives is working together on the revision of Annex 1 in the PIC/S-EU GMP Guide. And finally, PIC/S is also working on a Q&A document covering GDPs.

Following Hargreaves' talk, FDA's ICH delegate, **Theresa Mullin,** PhD, Director, Office of Strategic Programs, CDER, offered an update on ICH's restructuring and future plans ***(2).*** ICH was founded

in 1990 as the International Conference on Harmonisation. Last year, following the group's reorganization into a non-profit entity under Swiss law, the name was changed to International Council for Harmonisation. But ICH's goal of ensuring international harmonization of public health efforts through technical guidelines implemented by participating regulatory authorities has not changed.

"It remains something pretty unique for harmonization efforts where experts from the international regulatory community work closely with technical experts from around the pharmaceutical industry to develop these technical standards," she said.

Recent ICH activities include the elemental impurities guideline Q3D, scheduled to become effective 2018, a Q&A on Q11: *Selection and Justification of Starting Materials for the Manufacture of Drug Substances,* expected to become available for public comment sometime after November, and continuing work on ICH Q12: *Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management*. Mullins referred to the Q12 project as an "ambitious undertaking" on the part of ICH as it deals with post-approval changes. Multidisciplinary topics ICH expects to address in the future include bioanaltyical method validation and development of a system to classify biowaivers, which are used to show evidence of equivalence in the drug approval process in lieu of in vivo testing.

During the Q&A, both Mullins and Hargreaves stressed their respective organizations' dedication to expanding harmonization across the pharma industry. Whether it's attempting to work together with regulators from Taiwan and mainland China or developing standards for the Common Technical Document, both organizations are at the forefront of a globalized field.

References

1. Hargreaves, P. "PIC/S - What it Means for You." Presented at the 2016 PDA/FDA Joint Regulatory Conference, Sept. 12, 2016, Washington, D.C.
2. Mullin, T. "ICH - Restructuring and the Future." Presented at the 2016 PDA/FDA Joint Regulatory Conference, Sept. 12, 2016, Washington, D.C.

About the Experts

Paul Hargreaves has been the Deputy Chair of PIC/S for the past two years, and in January 2015 became Chair.

Theresa Mullin, PhD, directs strategic programs including business informatics for CDER.

Stephan Rönninger, Amgen (Europe) GmbH

Globalization of Pharma: What Does That Mean for PDA?

"Globalization" has been a buzzword since the 1983 publication of the *Harvard Business Review* article, "The Globalization of Markets." But how do we define what it means to be truly "global?" One look at any dictionary entry of the term tells us that it means something "involving the entire world."

Our industry now encompasses this "entire world," with business in over 50 countries. And PDA is no exception. Some might still identify PDA as a U.S.-based organization but it is much more than that. In 2006, PDA established its overseas operations with a headquarters in Berlin, Germany. **Georg Rössling** has done an outstanding job of offering a wide variety of conferences and activities for PDA members in Europe and beyond. At the end of this year, I want to take the opportunity to thank him for all his contributions to making PDA a recognized global organization. He and other staff members in the Europe office have strived to establish local and regional support for PDA members in Europe and elsewhere.

In addition to the Berlin office, PDA has chapters in 14 different countries. Recently, we founded PDA's Brazil Chapter—our first chapter in Latin America (see story on p. 10). These chapters are connecting people and science, and promoting harmonized understanding of regulations on a regional and local basis.

Nowadays, globalization has accelerated issues requiring cross-functional thinking, including in areas no one could have even imagined years ago. The complexity of the supply chain continues to trigger major challenges, e.g., counterfeiting and drug shortages. Traditionally, our industry has worked closely with regulators and control laboratories. But as we look ahead and start to think holistically, this means working with enforcement agencies, justice departments, and customs officials as well.

Most companies are global players. In contrast, regulations generally only cover a specific locale or multistate region. So, our industry seeks global guidelines and harmonized interpretation of requirements. Certainly, more and more countries are implementing similar regulations to guarantee and enforce the quality of the drugs on their market. Activities by WHO, ICH, and more recently, the Asia Pacific Economic Cooperation (APEC) have been successful to some extent. One obstacle to a harmonized understanding? The different languages mean that a literal translation is not always possible, and there can be multiple understandings of terminologies. One term can have different meanings; the word "process" can mean "procedure" or "manufacturing process." Naturally, this can result in unintended interpretations (e.g., ICH Q10: *Pharmaceutical Quality System*).

To help you, your companies, and regulators continuously improve understanding of terminologies, regulations, and expectations, PDA offers conferences, education courses, and interest groups, such as the Inspection Trends Interest Group. Members of this interest group discuss implementation issues identified in inspections by using examples of good and bad practices from the findings of international inspectors. I encourage you to join the group's discussions by using the PDA Connect® tool (community.pda.org).

Additionally, PDA's Regulatory and Quality Advisory Board (RAQAB) provides intelligence from emerging countries' regulators. Further, PDA's collaboration with PIC/S has led to joint training on ICH Q7 in South Korea, South Africa, Brazil, the European Union, and the United States to facilitate harmonization. And, last but not least, PDA Education offers courses at its Training and Research Institute (TRI) in the United States as well as in Europe. PDA can also provide in-house training opportunities adapted to address the specific needs of companies *and* individual regulatory agencies.

PDA members are also encouraged to volunteer on efforts to harmonize understanding. Consider writing an article for the *PDA Letter*, participating on a Points to Consider paper, or getting involved in a technical report team.

As you can see, PDA offers a unique opportunity for members of industry, manufacturers, distributors, suppliers, contractors, and regulators worldwide to connect on important topics and share best practices and sound science in a globalized environment.

Acknowledgement: The author wants to thank PDA staff and volunteers for support, and especially **Zena Kaufman** for her leadership of the Inspection Trends Interest Group and innovation of the "speed-dating" exercise at interest group meetings.

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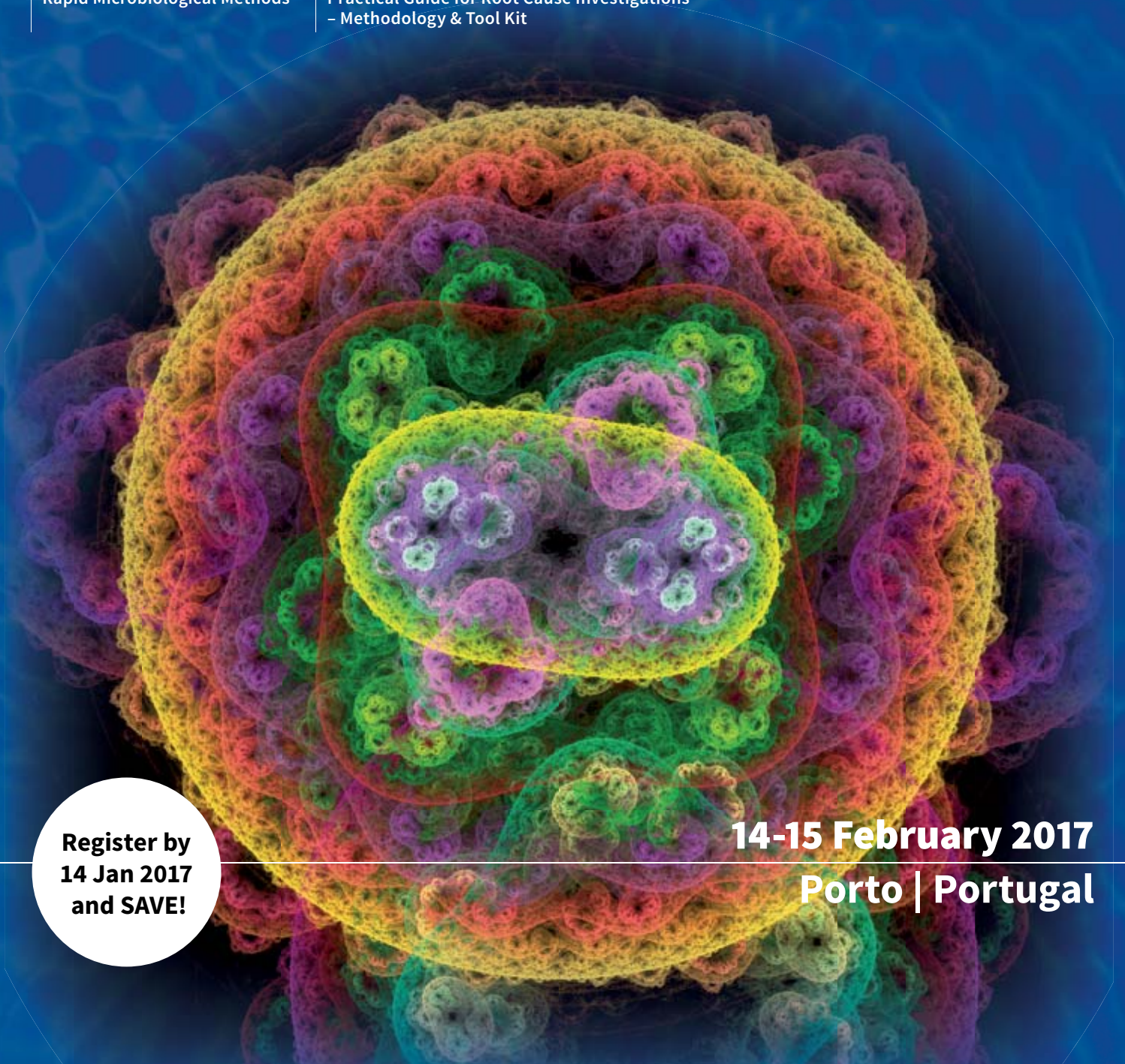

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PDA at 70 Years: A Global View

PDA celebrates its 70th Anniversary this fall. It was on the 12th of November 1946 when the Association's Certificate of Incorporation was signed in New York by its six original directors: **Harold London, Rudolph Price, A. Lincoln Konwiser, Max Gold, Arthur Herrick,** and **Abraham Wagner.** The Association was formed to:

1. Foster and advance, in the interest of public health, the art and science of parenteral therapy, and to preserve and improve the integrity and stability of the parenteral drug industry
2. Provide and disseminate information relating to parenteral drugs and parenteral therapy
3. Foster and encourage a spirit of friendly cooperation among its members and the medical and pharmaceutical professions
4. Cultivate and maintain cooperative relations with governmental departments and agencies, medical and pharmaceutical organizations, and other branches of the drug and related industries; and to originate and participate in cooperative enterprises and undertakings with them
5. Collect and disseminate, for the benefit of members, such business and scientific information as may be of value to them
6. Sponsor research projects into matters of scientific and technical interest in the field of parenteral medication
7. Review the labeling and advertising of its members in the light of current regulations and advances in medical science, and dispel uncertainty in such matters
8. Promote higher standards in the production of parenteral drugs

Many of these goals apply to this very day. You may note, however, the original charter did not mention anything about a global industry or global challenges. That is because for its first 40 years, PDA was a U.S.-centric organization. That began changing in the 1990s as the industry started down the road of rapid globalization.

In this issue, the *PDA Letter* Editorial Committee wanted to shine a light on various challenges faced by the industry after three decades of globalization. While not a "new" story, the ramifications of rapidly expanding supply chains, marketplaces, labor forces and regulatory requirements continue to ripple through the industry and will do so for years to come as more expansive and comprehensive trade agreements become effective.

These challenges drive PDA's members to come together on a variety of activities to help their colleagues throughout the global industry. In just the last few years, PDA volunteer members have formed task forces to provide guidance on the following topics directly related to a globalized industry: data integrity, post-approval changes, drug shortages, and quality metrics/culture. While PDA is the leader in providing technical information and training on sterile drug processing, our members' efforts in these and other global areas make PDA a strong leader on these fronts, too.

Globalization is also changing the demographics of PDA's membership. Twenty years ago, PDA's international activities were concentrated in Europe and Japan. Today, PDA hosts five additional chapters in the Asia Pacific region: India, Australia, Korea, Singapore, and Taiwan. In addition, PDA is entering South America by cultivating a chapter in Brazil.

It has been an amazing and highly successful 70 years for PDA. While many of its founding goals remain relevant, the globalized industry has changed PDA's constituency and its members' impact on the industry at large for the better.

PDA Letter

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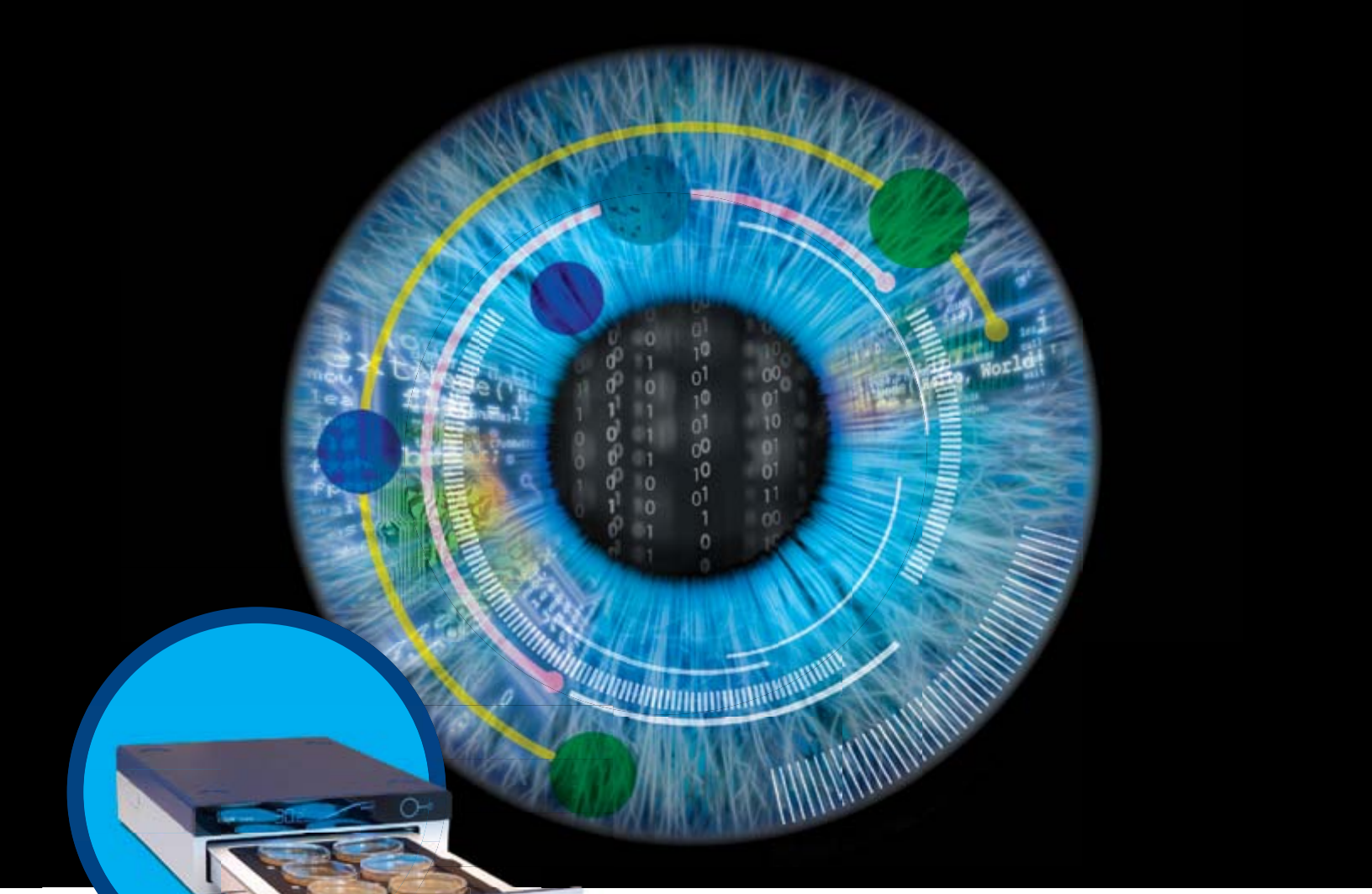

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