People • Science • Regulation

PDA Letter

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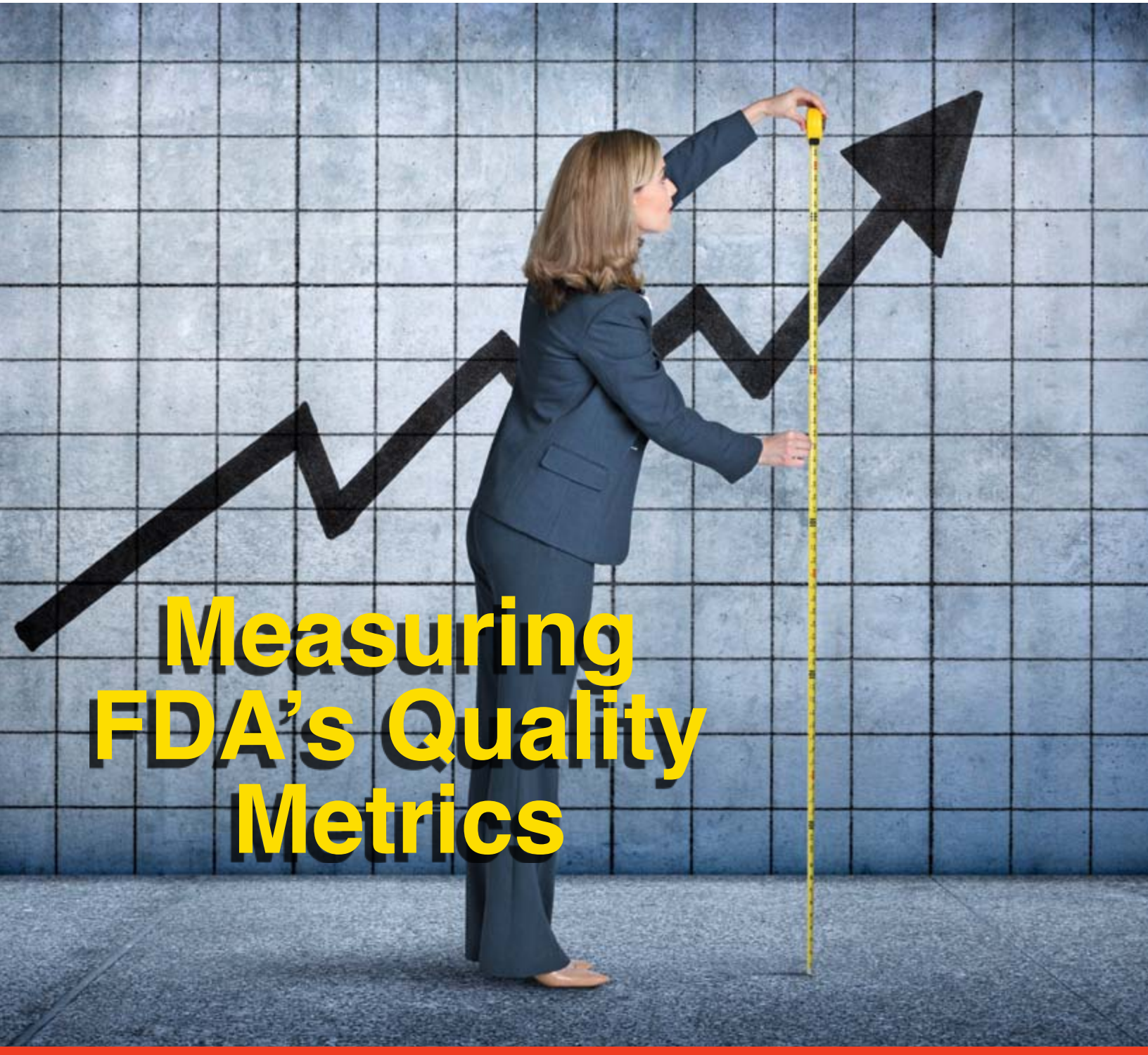

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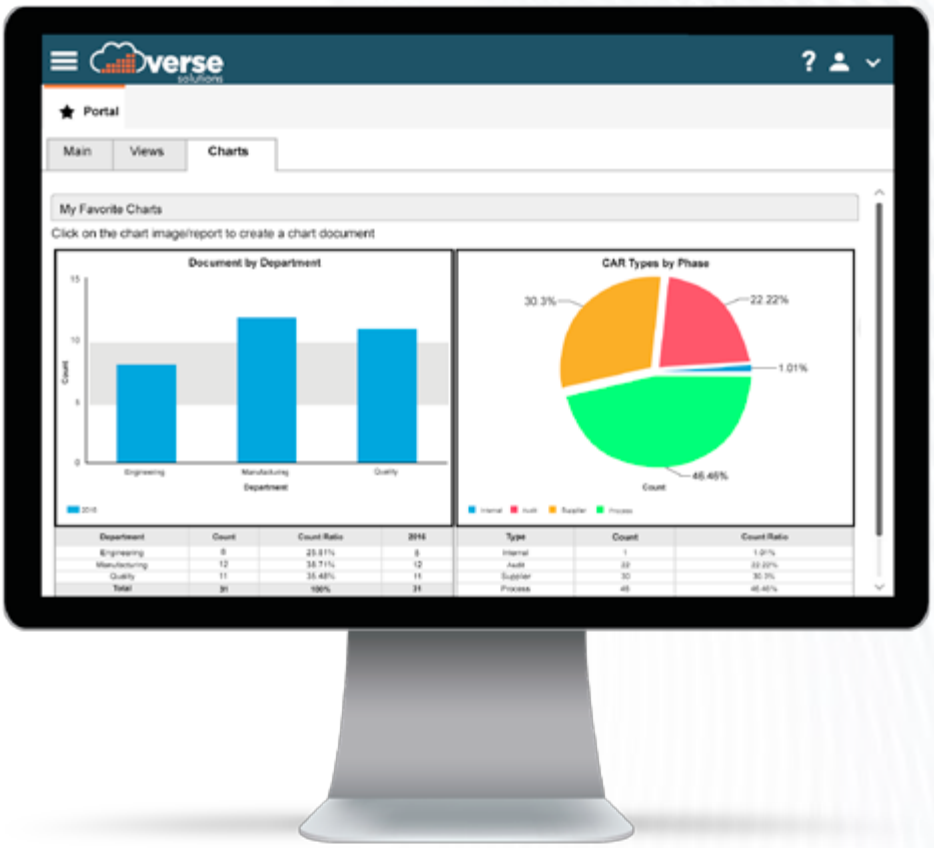

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July/August 2017 PDA Letter

2017 PDA/FDA Joint Regulatory Conference

PDA/FDA JRC Show Issue

This year's *PDA/FDA Joint Regulatory Conference* in Washington, D.C., features a slate of sessions covering product quality in an era of innovation. For a preview of these sessions, look for articles with this banner at the top of the page.

PDA's 4th Metrics Conference: Measuring the State of Quality Metrics

Stephanie Gaulding, DPS Engineering

The *2017 PDA Quality Metrics and Quality Culture Conference* offered an overview of FDA's recently revised quality metrics guidance and discussion. This summary of the two-day meeting showcases some of the highlights.

32

Cover Photo by DNY59

36

U.S., UK Regulators Share Passion for Quality Culture

Rebecca Stauffer, PDA

Find out what the FDA's **Jeffrey Baker** and MHRA's **David Churchward** had to say about quality culture at PDA's February metrics conference.

Industry Expert Weighs in on Quality Metrics

40

Rebecca Stauffer, PDA

The *PDA Letter* talks to Regulatory Compliance Associates' **Susan Schniepp** about the FDA's quality metrics initiative.

InfoGraphic

44

Grounded by Post-Approval Changes

Post-approval changes (PAC) present one of the biggest challenges for our industry. Long approval timelines and lack of collaboration hinder innovation. But how does this impact the industry?

PDA Letter

Volume LIII • Issue 7 www.pda.org/pdaletter

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Departments

Digital Exclusives

> **On the Issue** | Cell & Gene Therapies: Five Keys to Industrialization
Seattle Genetics' Karen Walker discusses how a CAR-T cell therapy was realized

> PQRI Establishes Thresholds for Leachables & Extractables Identification
Find out what PQRI is doing to establish threshold limits for identifying leachables and extractables

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18-19 October 2017 | Training Course

18–19 October 2017
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QRM and Hamburgers

I recently had the pleasure of attending the *2017 PDA Quality Risk Management for Manufacturing Systems Workshop* in Chicago. All in all, it was a very productive and insightful meeting with enthusiastic participation and discussion. Two presentations, in particular, I want to highlight.

Irish regulator **Kevin O'Donnell** offered an extensive overview of quality risk management (QRM), including its history, present and future. ICH Q9: *Quality Risk Management* came out in 2005 but 12 years later, he continues to see the same manufacturing quality issues occurring. In fact, quality defect investigations by the Irish Health Products Regulatory Authority (HPRA) have risen from 125 investigations in 2002 to 835 in 2016. Interestingly, many of the batches deemed defective by HPRA were manufactured using qualified equipment, validated processes and trained staff.

Following O'Donnell's presentation, **Elizabeth Zybczynski,** Director, Risk Management, provided an overview of Baxter's risk management program. A point she made that resonated with me was: "when everything is special, nothing is." By this, she means that companies need to be strategic in their risk management programs, expending the most time and resources on high risks.

Throughout the workshop, I could not help but think back to a movie I watched recently, *The Founder.* If you haven't seen it, I highly recommend it. The film is a biopic of **Ray Kroc,** the man who basically made McDonald's into what it is today. A good portion of the film focuses on his efforts to ensure the quality of the restaurant's food offerings as the chain expands across the Midwest and then throughout the United States and the world. In one scene in the movie, Kroc is shown outside a new franchise sweeping to make sure the restaurant maintains his strong standard of cleanliness. While this may not have happened in real life, it's well known cleanliness was part of his motto of "Quality, Service, Cleanliness, and Value" ***(1).***

I couldn't help but wonder what Kroc would think of our industry and QRM, quality systems, quality metrics, etc. Now, I admit sterile injectables are certainly more complex than hamburgers and fries; however, ensuring a quality injectable carries a greater impact than fast food fare. We're not injecting hamburgers into patients!

Anyway, if you weren't able to make it to Chicago (which was lovely, by the way), I did talk to Kevin and Elizabeth about turning their presentations into *PDA Letter* articles for future issues. And if you're attending the *2017 PDA/FDA Joint Regulatory Conference,* PDA's Quality Risk Management Interest Group will convene Sept. 11 at 5:30 p.m. I'm sure it will also come up as a topic during Q&A discussion at other points in the meeting as well.

In fact, if you're attending the *2017 PDA/FDA Joint Regulatory Conference,* make it a point to say hi if you see me and tell me what you think of the Letter.

Reference

1. Gross, D. *Forbes Greatest Business Stories of All Time.* Hoboken, NJ: Wiley, 1996. www.wiley.com/legacy/products/subject/business/forbes/kroc.html.

Rebecca Stauffer

25 FDA Speakers Confirmed for PDA/FDA JRC

So far, 25 representatives of the U.S. FDA are confirmed to speak at the *2017 PDA/FDA Joint Regulatory Conference*.

CBER Director **Peter Marks,** MD, PhD, will launch the meeting by offering an FDA perspective on innovation for medical products in the opening plenary, Sept. 11 at 8:30 a.m. Confirmed FDA speakers consist of the following:

- **Carmelo Rosa,** CDER
- **Brooke K. Higgins,** CDER
- **Deborah A. Hursh,** PhD, CBER
- **James Coburn,** CDRH
- **Linda J. Ricci,** CDRH
- **Debra Y. Lewis,** Office of Orphan Products Development
- **Patricia Y. Love,** MD, Office of Combination Products
- **Amy E. McKee,** MD, Oncology CoE
- **Francis Godwin,** CDER
- **Robert D. McElwain,** CBER
- **Paula Katz,** CDER
- **Theresa M. Mullin,** PhD, CDER
- **Joan W. Blair,** CBER
- **Shannon M. Hoste,** CDRH
- **Tamara L. Ely,** CDER
- **Christopher Joneckis,** PhD, CBER
- **Robin Newman,** CDRH
- **Steven Solomon,** CVM
- **Douglas Throckmorton,** MD, CDER
- **Donald Ashley,** CDER
- **Sean Boyd,** CDRH
- **Martine Hartogensis,** CVM
- **Mary Marlarkey,** CBER
- **Douglas Stearn,** ORA

Continue to check the website for the meeting as new speakers are added to the agenda: www.pda.org/2017pdafda.

PDA in the News

Below is a sampling of articles that have mentioned PDA in the past few months.

American Pharmaceutical Review
March 16, 2017
"Establishing a Contamination Control Strategy for Aseptic Processing"
— Tim Sandle
goo.gl/Quh8iU

BioProcess International
May 18, 2017
"Scaling Considerations to Maximize the High-Area Advantage"
— Sal Giglia, Songhua Liu, and Ryan Sylvia
goo.gl/qZfjl2

European Pharmaceutical Review
April 12, 2017
"Single-use systems for biotechnology products"
— Scott Rudge
goo.gl/hRKXpC

Healthcare Packaging
April 4, 2017
"PDA Becomes an ANSI Accredited Standards Developer"
— Keren Sookne
goo.gl/tVj9jO

Maas & Peither GMP Newsletter
June 28, 2017
"Manufacturing Innovation – PDA Annual Meeting, 2017, Anaheim"
— Thomas Peither
goo.gl/KrcgUF

Pharmaceutical Manufacturing
May 1, 2017
"PDA Annual Meeting Recap"
— Karen Langhauser
goo.gl/i03Ivd

May 30, 2017
"ET Phone Home, Then Call the FDA"
— Katie Weiler
goo.gl/5xZtP7

Pharmaceutical Online
February 3, 2017
"PDA Position Paper: A Call For Reform In Global Post-Approval Change Processes"
goo.gl/iwHCO5

Pharmaceutical Technology
April 2, 2017
"FDA Quality Metrics Initiative Challenges Manufacturers"
— Jill Wechsler
goo.gl/cIZgWm

May 2, 2017
"Combination Products Raise New Manufacturing Challenges"
— Jill Wechsler
goo.gl/a8d6jp

PDA to Take Quality Metrics Course Global

This September, PDA Director of Education **David Talmage** will travel to Australia, Singapore and India, to teach the PDA Education course, "Quality Metrics and Quality Culture for Pharmaceutical Manufacturing," as part of an effort to expand PDA's educational offerings beyond the United States and Europe.

The course will be held in conjunction with PDA chapter events in those regions. In Australia, the course will be offered Sept. 14–15 at the Victoria University Convention Centre in Melbourne. The Singapore course will be offered Sept. 18–19 at NUSS Suntec City Guild House and the course in India will be offered Sept. 21–22 at the Novotel Hyderabad Airport in Hyderabad.

"I am excited by the opportunity to deliver a PDA Education course to industry and regulatory professionals around the globe," Talmage said. "This fulfills the requests from our members and I am looking forward to providing training on quality metrics and quality culture as well as other courses in PDA Education's extensive course catalog."

To learn more about these courses and to register, visit www.pda.org/global-event-calendar/-in-eventtype/event-types/education.

PDA Volunteer Spotlight

Randy J. George

- **Area Director Sales/Business Development**
- ***Rescop US***
- Member Since | **2012**
- Current City | **Huntington Beach, California**
- Originally From | **Little Falls, NY**

Challenges Are Only A Bump In The Road

Why did you decide to volunteer for PDA?
Volunteering for PDA and being actively involved in PDA's Southern California Chapter has offered me excellent opportunities to gain exposure in the life sciences industry, meet new people, develop relationships and create new opportunities through the programs, task groups, conferences and initiatives available to PDA members.

As a service provider, PDA is a great forum to stay current with trends and best practices in the regulatory, product quality, manufacturing and science areas. With this information, I can ensure Rescop's products and services meet the needs and demands of the life sciences industry.

Of your PDA volunteer experiences, which have you enjoyed the most?
Giving back to the community through the Southern California Chapter's philanthropy initiatives and knowing we're doing something good to assist others on behalf of PDA.

What was it like to work on the *2017 PDA Annual Meeting?*
It was a great opportunity to work closely with, and meet, many of the key people at PDA. Through the efforts of the Annual Meeting, I gained a greater appreciation for the care and importance PDA places on the Annual Meeting to ensure members, as well as sponsors, benefit from their participation, and that all the values PDA stands for are achieved—from the program to the speakers to the location. Balancing the above is not an easy task for any organization, and PDA does it well. As Southern California Chapter board member **Stephanie Powers-Kurtz,** coined it, "PDA cares."

What lessons has your work life taught you?
My career has taught me a lot and I've learned quite a few memorable lessons. Good communication is essential to a successful work environment. Challenges are only a bump in the road and determination to succeed is the motivation to overcome them. Patience is a learned behavior, not a gift. Change is okay. Every day you learn something new. Quality is essential. As a service provider, "no" means ask me again later. Understand before you're understood. And always think with the end in mind first.

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

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

ANDERS YNNERMAN
JAMES AGALLOCO
JAMES AKERS
DENNIS JENKE
JAMES COOPER
IRVING PFLUG
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India Chapter Holds Successful Biologics Workshop

Biny Joseph, PDA India Chapter Coordinator

The PDA India Chapter held a successful workshop on right-first-time principles and quality for vaccines and biologics manufacturing in the city of Pune, March 23 and 24. Forty people participated, with interests spanning from formulation and development to operations to product development. Naturally, with senior professionals from the vaccine and biologics side of the industry gathered under one roof, the level of energy was very high.

On Day 1, following opening remarks from the India Chapter's President-Elect **Ivy Louis, Rustom Mody** spoke on the need for right-first-time practices within parenteral manufacturing organizations. Following that session, **Reinhard Gluck** covered the different scale manufacturing techniques for vaccines and biologics. In the same session, **Rajeshkumar Singh** covered the regulatory expectations for vaccines and biologics. Other presenters that day included **Akshay Goel,** who spoke about good review practices for biologic manufacturing, and **Gopi Vudathala,** who covered "Managing Post-Approval Changes and ICH Q12 (draft) in Biologics" and "Managing Post-Approval Changes and ICH Q12 (draft) in Vaccines." He and Louis also covered "Approaches in Deviation Management and Investigations in Manufacturing Lines."

(Back l-r) India Chapter members: Vishal Sharma, Umesh Baikunje, Ivy Louis, Biny Joseph, S.G. Belapure, Ranjit Menon
(Front l-r) Gopikrishna Vuduthala, Ricky Bithar, Dr.Ranjana Pathak, Ravi Menon, Swapnil Ballal

The next day, **Harish Shandilya** opened the workshop with a presentation on right-first-time metrics. **Ravi Menon** provided a practical case study on approaches for using quality risk management (QRM) in vaccine manufacturing—a topic also covered by **Amit Jogi** in the same session—followed by **Ranjana Pathak's** talk on Good Documentation Practices and data integrity concerns. The other talks that day featured **Swapnil Ballal** ("Integrity of Operations for Quality Teams"), **Ricky Bithar,** and **Vishal Sharma** (both Bithar and Sharma covered cold chain distribution).

Interspersed throughout the workshop were lively, interactive sessions. Attendees were split into small groups for these sessions to ensure cross-organizational learning.

Ultimately, the workshop brought together different facets of biologics and vaccines manufacturing for two days of vigorous discussion. Questions that emerged during these discussions covered Quality by Design, risk mitigation, changes in submission documents, continuous validation/verification principles, batch sizes for various phases of clinical studies and many others. The participants also offered specific feedback about the need to discuss case studies in depth, and to provide live examples, backed up with the practical details, as outlined in specific PDA technical reports. Considering the majority of attendees were not PDA members, this illustrates the considerable influence these reports have on the global pharma industry.

The India Chapter thanks the sponsors of the event, M/S Bosch and M/S Brevity, for their support.

PDA Who's Who

Umesh Baikunje, Founder, Baikunje Consultancy

Swapnil Ballal, Senior Director Quality Assurance Product Operations, Dr Reddy's Laboratory, India

S.G. Belapure, Managing Director, Zydus Hospira

Ricky Bithar, CEO, Absolute Cold

Reinhard Gluck, Chief Scientific Officer, Zydus Cadila, India

Akshay Goel, Senior VP-Technical Development, Biological E. Ltd, India

Amit Jogi, Senior Director, Pharmaceutical & Biopharmaceutical Development, Syngene International Ltd, India

Biny Joseph, PDA India Chapter

Ivy Louis, Founder, Director, VIENNI Training & Consulting LLP

Ranjit Menon, Vice President, Zydus Hospira

Ravi Menon, Additional Director, Production, Serum Institute Of India Pvt Ltd,

Rustom Mody, Senior VP and Head R&D Biotech, Lupin

Ranjana Pathak, Global Head, Quality, Cipla Ltd, India

Harish Shandilya, Senior General Manager, Enzene Biosciences, India

Vishal Sharma, Cofounder-Director, VIENNI Training & Consulting LLP

Rajesh Kumar Singh, Deputy General Manager, Regulatory Affairs, Gennova Biopharmaceuticals Ltd, India

Gopi Vudathala, PhD, Executive Director and Head, Quality Advocacy, GSK Vaccines

2017 PDA/FDA Joint Regulatory Conference

Build Your Network at the PDA/FDA JRC

One of the best parts of attending the *2017 PDA/FDA Joint Regulatory Conference* is networking with fellow attendees and making lasting connections. Each year, the meeting brings together individuals from industry and global regulators with the goal of finding solutions to common problems. And this year is no different, with a number of opportunities for attendees to connect with each other and discuss how to tackle the issues affecting our industry.

Monday, September 11

Orientation Breakfast

New to PDA? Learn more about the Association and the various ways you can volunteer with PDA. Invitation only. 7–8 a.m. *(Sponsored by Amgen)*

Networking Reception

All conference attendees are invited to attend a networking reception in the Exhibit Area and chat with exhibitors and other attendees. Refreshments will be provided. 6:45–8:30 p.m

Tuesday, September 12

Tuesday Reception (Top Secret!)

Shh. The name is PDA. PDA/FDA Joint Regulatory Conference. Join your fellow spies and spooks for a special event Tuesday night following the conference. There will be live entertainment along with food and drink (shaken not stirred, of course). Special clearance needed to attend (aka attendance is included with conference registration—passes for guests or secret informants can be purchased at the registration desk). Disguises are optional. 6:30–9 p.m.

There will also be additional opportunities for networking during refreshment breaks throughout the conference.

The Parenteral Drug Association presents the...

2017

PDA/FDA Joint Regulatory Conference

September 11-13, 2017 | Washington, DC

Renaissance Washington, DC Downtown Hotel

Exhibition: September 11-12

#2017PDAFDA

PDA will independently present:

2017 PDA PAC iAM Workshop: September 13-14, co-sponsored by IFPMA | 2017 PDA Regulatory Course Series: September 14-15

Ensuring Product Quality in an Era of Innovative Therapies

The *2017 PDA/FDA Joint Regulatory Conference* will provide you with unrivaled opportunity to dialogue face to face with regulatory and industry experts on global regulatory strategies and how they are used to improve the quality of medical products.

Hear about advancing product quality in an era of ground-breaking therapies and explore the advanced biomedical innovations leading to safer and more effective therapies for patients.

Benefit from discussions on expedited pathways, advanced therapies and current regulatory findings taken directly from the most current 483 citations. And, don't miss the ever-popular updates from the FDA and fishbowl sessions, where you will be presented with real-life situations and work with your peers to find solutions to the problem!

There's something for everyone, whether you're new to the field or a seasoned expert! Learn more and register at ***pda.org/2017PDAFDA***

PDA will also be independently hosting five courses from **Sept. 14-15** to advance your knowledge. Learn more and register at ***pda.org/2017RCCS***

PDA Photostream www.flickr.com/parenteral-drug

2017 PDA Europe Aseptic Fill & Finish Conference

April 26–27 | Lindau, Germany

Hanne Agerbaek of Novo Nordisk (left) was the winner of the Exhibition Raffle, announced by Conference Co-chair Brigitte Reutter-Haerle (right) with PDA Europe's Melanie Decker (center)

Panel Discussion:
Future Challenges for Aseptic Manufacturing

(l-r) Chi Yuen Liu, Janssen J&J; Oliver Kurz, Vetter Pharma; Aidan Harrington, DPS Engineering; Stefan Merkle, Janssen J&J; Daniel Mueller, GMP Inspector, Germany; Anil Busimi, Schott;

Panel Discussion:
Regulatory and Manufacturing Trends

(l-r) Markus Rothen, INSYS; Ian Thompson, Ypsomed

Georg Rössling (left), then SVP of PDA Europe, gave co-chair Brigitte Reutter-Haerle a Buddy Bear statue from Berlin as a thank you gift

2017 Prefilled Syringe Interest Group Meeting

May 10 | PDA Headquarters, Bethesda, Md.

Plenary Session 2
Quantification & Alternatives to Silicone Oil

(l-r) Robert Schultheis, ZebraSci; Nate Joh, Amgen; Markus Lankers, PhD, rap.ID Particle Systems; Xia Dong, PhD, Eli Lilly; Paolo Mangiagalli, PhD, Sanofi; Akshay Kamdar, PhD, Eli Lilly

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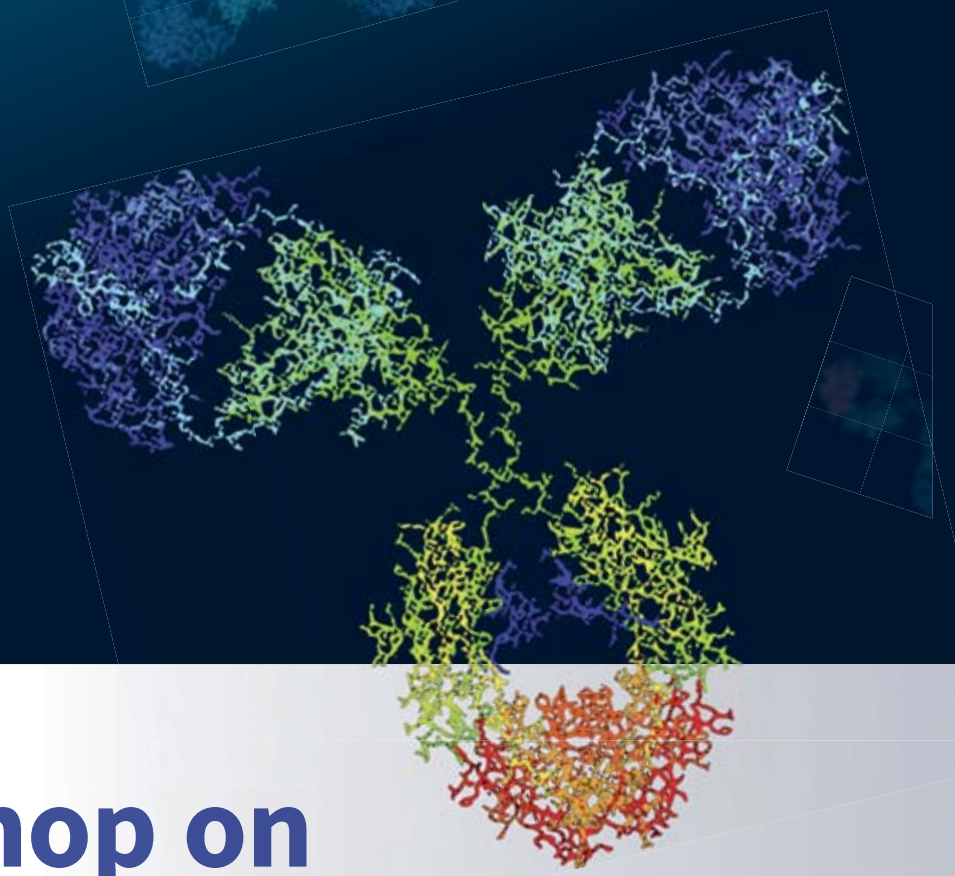

2017 PDA Europe

10th Workshop on Monoclonal Antibodies

Manufacturing & Analytics Considerations for Antibodies and Related Products – A Decade of Progress

EDUCATION PROGRAM

28 September
Tailormade Strategies for High Level Expression of Biologicals

28-29 September
Best Compliance Practices im GMP Prüflabor
– Course in German –

28-29 September
CMC Regulatory Compliance for Biopharmaceuticals

28-29 September
DoE Basics for Validation by Design

Taking place concurrently to the Particles in Injectables Conference

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Register by 30 July 2017 and SAVE!

26-27 September 2017

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SNAPShot

2017 PDA/FDA Joint Regulatory Conference

Meeting *Preview*

Interest Group Schedule

To supplement regular sessions, a number of PDA Interest Groups will convene at the *2017 PDA/FDA Joint Regulatory Conference.* Below is a schedule of interest group sessions falling under the Science and Biotechnology Advisory Boards.

Monday, September 11	Tuesday, September 12
5:30 p.m. – 6:45 p.m.	5:30 p.m. – 6:30 p.m.
Vaccines Interest Group Visual Inspection of Parenterals and Packaging Science Interest Groups (combined meeting)	Lyophilization and Sterile Processing/Parenteral Drug Manufacturing (combined meeting) Facilities and Engineering Interest Group

Journal *TOC*

July/August Issue of PDA Journal Includes Part III of the Sterile Production Gap Series

The latest issue of the *PDA Journal of Pharmaceutical Science and Technology* looks at bioburden moist heat resistance in Part III of **James Agalloco's** series on the sterile production gap. Read more at journal.pda.org.

Review

James P. Agalloco, "Increasing Patient Safety by Closing the Sterile Production Gap—Part 1. Introduction"

James P. Agalloco, "Increasing Patient Safety by Closing the Sterile Production Gap—Part 2. Implementation"

James P. Agalloco, "Increasing Patient Safety by Closing the Sterile Production Gap—Part 3. Moist Heat Resistance of Bioburden"

Robert A. Schaut, Wendell Porter Weeks, "Historical Review of Glasses Used for Parenteral Packaging"

Binbing Yu, Harry Yang, "Evaluation of Different Estimation Methods for Accuracy and Precision in Biological Assay Validation"

Research

Alberto Biavati, et al., "Complexing Agents and pH Influence on Chemical Durability of Type I Molded Glass Containers"

Technology/Application

Christopher M. Weikart, Carlo G. Pantano, Jeff R. Shallenberger, "Performance Stability of Silicone Oxide Coated Plastic Parenteral Vials"

Call for Volunteers!

Revision of Technical Report No. 45: Filtration of Liquids Using Cellulose-Based Depth Filters

A variety of our technical reports are becoming aged and require revision, including *Technical Report No. 45: Filtration of Liquids Using Cellulose-Based Depth Filters.* The current report no longer meets the standards of technological advancements in this area and PDA is forming a revision task force. Ideally, the revision will also broaden the scope of this technical report to include non-cellulose-based filter types, meaning all common forms of liquid prefilters.

To commence work, PDA is looking for volunteers to form a revision task force and present a formal proposal outlining the scope and major points of focus of the revised technical report. To volunteer, please send an e-mail with your contact details to **Maik Jornitz** (mjornitz@gconbio.com) and note whether you are able to be a coleader of the task force.

Thank you in advance!

Can Single-Use Components Be Commodities?

Qualifying Single-Use Components with a Design Space

Sabrina Restrepo, PhD, Merck, and Christopher J. Smalley, PhD, ValSource

Manufacturers implementing single-use components often face challenges brought about by three factors: **(1)** every introduction of a single-use component is treated as unique, therefore, implementation becomes cumbersome since qualification and implementation activities are performed at the same level of thoroughness every single time; **(2)** regulatory filings specify the manufacturer and model of many of the single-use components, complicating single-use lifecycle management within GMP and quality management systems; and **(3)** the industry lacks the needed motivation to drive standardization in terms of design, material of construction and supplier qualification.

By making these components unique, studies and regulatory submissions are required for implementing changes. Can there be a change to this paradigm? Many single-use components, such as silicone tubing, thermoplastic tubing, basic connectors and storage bags, can be interchangeable between suppliers. The important element is that they meet qualification.

This begs the question: What is the appropriate qualification? A good way to answer this would be to establish a basic qualification approach that essentially provides a first pass sorting of eligible single-use components. Each component would then be evaluated against Design Space criteria.

The first pass of basic qualification should ensure there is no impact to patient safety and should include:

- A BSE/TSE statement (EMA 410/01) to indicate no introduction of Bovine Spongiform Encephalopathy (BSE) and Transmissible Spongiform Encephalopathy (TSE) to the process stream
- Biocompatibility testing (USP <88> Class VI, USP <87>, ISO 10993-3/-5/-6) to assure no possibility of eliciting local or systemic responses from a living system or tissue by the single-use component
- Physicochemical testing (USP <661>), to ensure that the ingredients used in the manufacturing of the single-use component do not impose a risk to the patient or product quality
- Extractables testing (ideally, BPOG Standardized Extractables Protocol since it covers more conditions frequently used in the manufacturing of biopharmaceuticals) ***(1)*** to facilitate the impact assessment of the reported chemical identities on the quality of the product and patient safety

Manufacturers would greatly benefit from standardization of the basic qualification packages compiled by suppliers. Setting a Design Space is one way to achieve this standardization.

So, what is a Design Space? It is a multidimensional parametric space based on acceptable qualification criteria that allows a single-use component or system to be used for a specific product and/or process with minimal or no additional qualification activities in terms of extractables/leachables or physical performance.

Widely used platinum-cured silicone tubing provides a good example to illustrate this point. Recently, a team of researchers developed a Design Space encompassing more than 90% of possible applications. (For these applications, the Design Space covered the ranges for each use, with set limits so that the setpoints or targets of the processes did not fall on the "fringes.") The Design Space consists of:

- Temperature – 2-40 degrees °C
- Duration of Contact – 0 to 30 days (to embrace the use of tubing as part of storage bags)
- pH – 3 through 11

Supplier	Max Temperature (°C)	Max Number of Days	pH Range	Solvents
A	50	120	2 – 12	Purified water, ethanol
B	60	120	3 – 12	Purified water, 50% ethanol
C	55	60	2 – 12	Purified water
D	70	30	3 – 12	Purified water, 50% ethanol
E	50	30	3 – 11	Purified water

Table 1 Design Space Criteria

- Pressure – based on pressure rating provided by supplier

- Solvent – aqueous-based, organic solvent; presence of surfactants or chelating agents

To assess applicability of the Design Space, information was obtained from six different suppliers regarding their platinum-cured silicone tubing. The products from all six suppliers that conformed to the first pass qualifications also met the Design Space for every attribute except "solvent." **Table 1** summarizes the criteria for the assessment of the qualification performed by the six suppliers. Three suppliers had appropriate information for both aqueous and organic solvents as defined in the Design Space; the other three did not have adequate information on organic solvents.

The conclusion drawn from this analysis was, that for the three suppliers of platinum-cured silicone tubing that met the Design Space criteria, their tubing would be considered interchangeable for the vast majority of applications. By interchangeable, the supplier/model of the component in the Design Space—in this case platinum-cured silicon tubing—could be considered standardized and used without additional qualification. Manufacturing processes would no longer need to add extra steps and controls to ensure that the a unique, designated manufacturer and model is being used for each process step. Instead, the suppliers would only need to show that they are using platinum-cured silicone tubing qualified within the Design Space.

For those processing conditions that extend beyond the Design Space, such as tubing installed on equipment subject to NaOH solution storage conditions or phenol addition, studies would still need to be conducted on those specific conditions for each supplier/model tubing considered for use.

Although this approach addresses one of the costliest and most time-consuming tasks in qualification, other challenges remain. Driving standard best practices will enable aligned understanding and expectations around single-use components but, more importantly, about qualification. For example, some of the testing cited came from records up to seven years old. Has nothing changed in tubing manufacturing since that testing was performed?

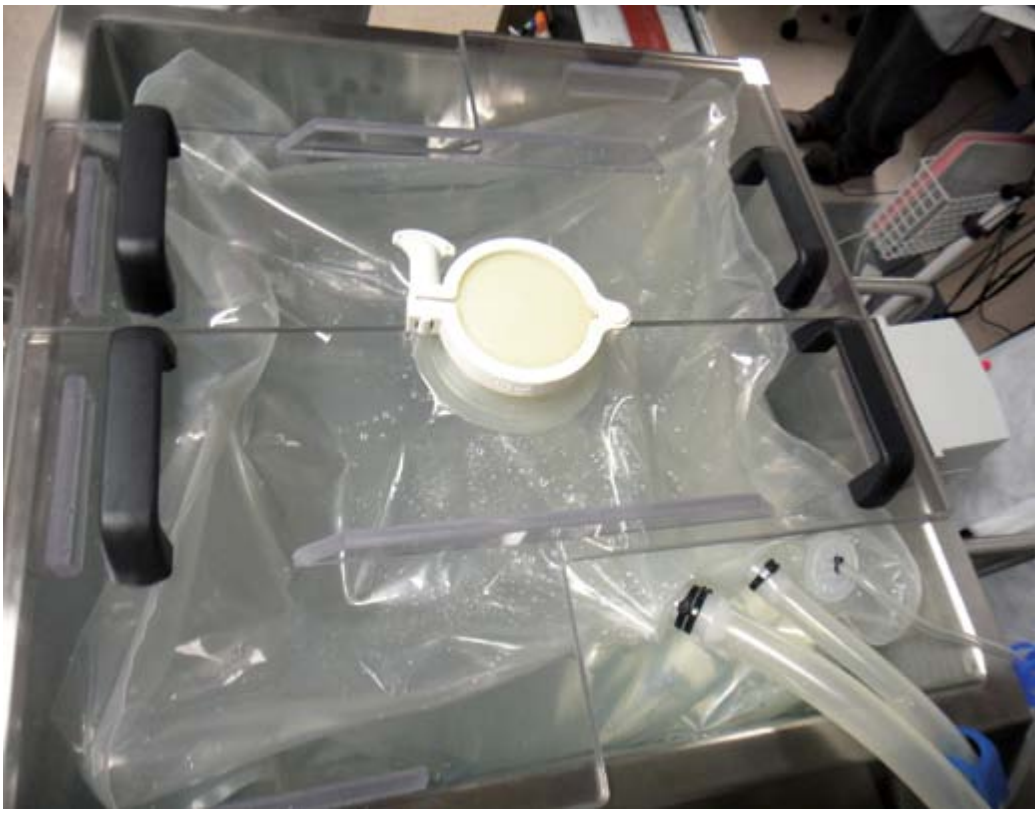

Photo courtesy of Sabrina Restrepo, Merck

Another challenge is endotoxin. Many components are sterilized with gamma irradiation; thus, endotoxin may be present. A supplier would typically perform endotoxin testing according to USP <85> or EP 2.6.14 and report those results as less than the acceptable limit. The question should be addressed as to whether this is acceptable based on standards developed for finished products.

Overall, this work with the six suppliers showed that standardization can be effected for single-use components, leaving open the possibility they could be treated as commodities in the near future.

[Editor's Note: This article is based on the *2017 PDA Annual Meeting* poster presentation "Can Single-Use Components Be Considered Commodities?"**]**

Reference

1. Standard Extractables Protocol, BioPhorum Operations Group, November 26, 2014 www.biophorum.com/standard-extractables-protocol/

About the Authors

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Christopher J. Smalley, PhD, is the Compounding Pharmacy Advisor at ValSource, working with pharmacists to design, build and operate compliant compounding facilities. He recently retired from Merck, where he worked for five years with responsibility for innovative implementation and validation, including global single-use systems.

PDA Summer Reading

The summer vacation season is upon us, so now is the perfect time to crack open a good book. This edition of the *PDA Letter* includes an expanded "In Print" of recently published PDA literature. All the publications mentioned are available for purchase at the PDA bookstore: www.pda.org/bookstore. In addition, find out what some PDA staff plan to read for fun this summer. References and graphics have been removed from the excerpts.

***Effective Implementation of Audit Programs* — Miguel Montalvo**
Excerpted from the chapter: **"Key Aspects to Audit in Particular Systems/Areas"**

I have seen numerous occasions where there is an inadequate control on official copies of procedures and, while some of the obsolete copies are retrieved, personnel in some areas will keep their own copies without knowing that there is a revised copy and they will be using an obsolete version. There are two typical situations:

• The company decides to have "official" binders with controlled copies of procedures in each area. This could be combined with a computerized system which keeps "controlled copies" of the procedures and personnel can access them at any time from any terminal/PC. The concern with a computerized system is that the organization has to be sure that only the official copy of the procedure is available for personnel to use – therefore, they cannot print additional copies at any time or, if printed, the copy will be identified as being a copy and only valid for a limited time (usually 24 hours). They can verify that it is the official copy by looking at the signatures and noting the effective date and the revision due date. Recently, during an audit, I asked for a procedure and I was shown a copy printed from a computerized system with no signatures – clearly not the official copy. I asked how personnel had these copies available and it was clear to me that they had no control on these documents and personnel were not adequately trained on how to look for the official procedure copy and to follow that version.

• Use only a computerized system for providing the controlled copies for personnel to use in all areas. The question with this option is the availability of the documents to all personnel in all areas. On many occasions I have seen areas where the access to the procedures is extremely limited – no terminals or PCs in the area, long distances to any location where they may be available and physical barriers (different classifications/segregation) where the employee cannot access the systems without going out of his working area.

The problem is even more pronounced with the forms. Many departments will make numerous copies of the forms for their own convenience. When there is a change to the form, they will keep using an obsolete copy until someone discovers that a new version is available. These are issues that can only be resolved with adequate training of personnel to understand the criticality of keeping adequate controls on these procedures/forms.

Specifically, on forms, the following controls should be applied:
• In addition to form number, a revision indicator (letter or number) must be assigned.
• Copies must be controlled – allow only one or two copies to bemade one or two copies each time.
• Unique identifiers if computer-generated.
• Or supervisors maintain and issue.

The auditor must ask for the logbooks or system log for the control of procedures and forms – these will have a history of new/revised procedures and forms and the process of development, revision, approval and the effective date. Then, the auditor will select some of these documents and follow the process with the corresponding documentation to verify that the applicable procedures were followed and were adequately documented.

While doing the tour or during additional visits to the operational areas, ask where the procedures are kept or where they can be accessed and assess the availability of these documents to the personnel. Also, ask where are the forms that they use in the area and see how they are controlled. In most cases, in my experience, this is an extremely weak area where the personnel will keep copies of forms in varied storage systems including a personal file or different types of form holders in their work area where numerous copies are typically found. Ask the personnel how they verify that they are using the correct version of the forms.

DEVIATIONS AND CORRESPONDING INVESTIGATIONS

In the 21 CFR 211 there is a short mention of the deviations as:

"Sec. 211.100 Written procedures; deviations.

(a) There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Such procedures shall include all requirements in this subpart. These written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit.

(b) Written production and process control procedures shall be followed in the execution of the various production and process control functions and shall be documented at the time of performance. *Any deviation from the written procedures shall be recorded and justified."*

Even when this is the only formal mention of the term "deviation", it has been established as a standard concept that a deviation applies to any situation where any type of procedure cannot be followed as written.

***Method Development and Validation for the Pharmaceutical Microbiologist* — Crystal Booth**
Excerpted from the chapter: **"Understanding Container Closure Integrity Testing"**

STABILITY TESTING

The routine testing SOP should be utilized when performing CCIT for stability testing. Container/closure integrity should be demonstrated as part of the stability program over the shelf life of the product for new and existing products.

Stability studies are performed at different temperatures, storage positions, and humidity requirements. Stability studies are designed to observe the stability of a product's formulation or activity over a period of time and at room temperature conditions throughout the world. As different areas of the world have different climates, the "room temperature" of the stability study will vary to simulate those climate changes.

"For drug substances with a proposed re-test period of at least 12 months, the frequency of testing at the long term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed re-test period."

Microbiological assays are different from chemical assays when it comes to stability testing frequencies. Microbiological assays could potentially take up to six weeks from the beginning of an assay to the finalized report. This makes monthly stability testing impractical (Sutton, 2007).

"The sterility testing or alternatives (e.g. container/closure integrity testing) should be performed minimally at the initial time point and at the end of the proposed shelf-life."

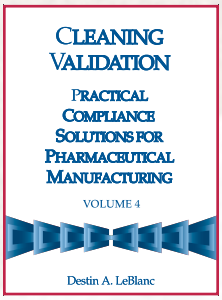
However, this does not provide adequate data points for trending or investigations if the terminal point fails the analysis. The testing should be frequent enough to establish a stability profile. Most companies successfully perform microbiology testing at the initial time point, and then yearly until the end of the stability protocol (or shelf-life of the product). Sutton, states that:

"In general, microbiological assays should be performed no more frequently than the initial time point, 6 month, 12 month, and 24 month time points. This provides sufficient assurance of the microbiological quality of the product, and allows trending of the data (as appropriate)."

The most conservative approach would be to test every time point. However, scientific rationale and risk assessments may be used to justify a decreased testing frequency.

When designing the program, take into account the product formulations, strengths, and packaging configurations. ICH Q1D provides guidance to utilizing bracketing and matrixing strategies for stability testing. Bracketing or matrixing can greatly reduce the test samples needed for the stability program. This strategy will save time, money, product, and room in the stability chambers.

Container closure integrity testing may not replace the sterility test for release testing. However, container-closure integrity testing can be used to replace sterility testing in stability protocols. If a non-destructive test has been validated for the specific container-closure system, it is useful during stability studies. The same container can be used throughout the stability period. This saves money and allows for more meaningful profiles of container-closure integrity.



***Cleaning Validation: Practical Compliance Solutions for Pharmaceutical Manufacturing, Volume 4* — Destin A. LeBlanc**

Excerpted from the chapter: **Special Cases in Determining "Visually Clean"**

It is well known that there are many variables in determining whether a surface is visually clean or not. Those variables include lighting, distance, surface roughness, angle of viewing, residue sheen, residue color, operator eyesight, and the contrast between the residue and the surface. This chapter focuses on the last issue in that list, the contrast between the residue and the surface. It covers two specific cases, and possible ways to deal with appropriate evaluation as to whether the surface is "visually clean" or "visually soiled".

In the *first* situation, suppose we are dealing with a residue that is clear (transparent), and further that the residue has a sheen (and that sheen is different from the sheen on the surface itself). If the residue is only on a small portion of the surface, then the visual presence of that residue may be established by the difference in sheen of the surface itself in contrast to the sheen of the residue on the surface. That's the easy case. The more difficult case is what happens if the residue covers the entire surface, remembering that the residue is transparent. We may look at the surface and not be able to identify it as visually soiled; that is, the surface looks the same over all areas viewed. How do we deal with that situation?

One way is to take a swab and wet it with a solvent the residue is known to be soluble in. The swab is then moved across a relatively small portion of the surface (back and forth several times). The surface is then allowed to dry. If the swabbing dissolves and removes the residue on the surface, it may now be possible to see any contrast between the surface itself (the portion of the surface swabbed) and the cleaned (or spiked) surface. If there is no difference in appearance between the swabbed area and the non-swabbed area, then the surface (before swabbing) could be considered visually clean. On the other hand, if there is a visual difference between the swabbed area and the non-swabbed area, then the surface (before swabbing) was not visually clean.

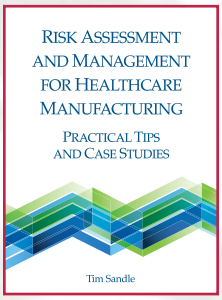
There may be some variation on this procedure, such as flipping a wetted swab over for a second pass or using two solvent-wetted swabs in succession. The reason for two swabs might be that one might only remove 70% of the residue on the surface, and the second swab might provide an assurance of > 90% removal of residue, thereby enhancing the difference (if any) in appearance between the two areas.

A *second* situation involves a residue that is the *same color* as the surface. The most common example of this is where the residue is white and the surface itself is also white, such as would be the case with PTFE

(polytetrafluoroethylene). In that situation, there may be large amounts of residue on the surface (> 20 µg/cm2), but the surface appears visually clean. One way to deal with this is to use an artificial situation to examine the surface, such as wiping it with a black (or other dark color) cloth or swab. If the cloth appears visually soiled with white residue, then perhaps the surface is not visually clean. I include the word "perhaps" because whether I see a white residue on the cloth depends on the surface area wiped and the surface area of the cloth the residue is transferred to. It certainly is possible to increase the ratio of wiped surface area to cloth (or swab) surface area such that the cloth will *always* appear soiled. It would be appropriate to control (for consistent results) the area wiped and the cloth or swab surface area. It also may be appropriate to do some spiking studies (with the white residue spiked at different levels in terms of µg/cm2) to determine at what level the cloth would be visibly soiled.

For this second situation, remember that the regulatory requirement (or at least my understanding of the regulatory requirement) is not that the cloth be visibly clean; it is that the *equipment* be visually clean when viewed by the unaided eye. If you use a "black cloth" evaluation, make sure you carefully define the objective and what is acceptable (or what is unacceptable) in such an evaluation. For example, it might be used in routine monitoring of a process, whereby a visibly soiled cloth wipe requires that the equipment be sampled with measurement by a validated analytical method (such as Ultrahigh Pressure Liquid Chromatography (UHPLC) or TOC). On the positive side, if the cloth is visually clean, it might be a measure of the consistency of the cleaning process.

The purpose of this chapter is not to advocate for use of either of these options in determining if a surface is visually clean. It is to present alternatives that may be useful in certain situations, and to provide some cautions in their use.



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

Excerpted from the chapter: **Risk Considerations for Aging Pharmaceutical Facilities**

RISK 6: MICROBIOLOGICAL CONTAMINATION

The aging facility presents various microbiological contamination risks (and some more recent pharmaceutical product recalls associated with microbial contamination have related to older facilities). These risks include:

Poor facility management

General poor upkeep, leading to peeling paint or torn lagging, presents opportunities for microbial contamination to occur. Risks are more acute for spore forming organisms, such as *Bacillus* and related genera and with fungal spores.

Changes to facility use

Changes to facility use, in terms of people and equipment, present potential risks. For example, if a facility was designed for a specific number of personnel and the operational level increases, this could present new challenges for contamination control, especially where cleanroom occupancy rates increase (given that people are the primary contamination source within cleanroom environments).

Furthermore, changes to production equipment and layouts can affect airflow directions, especially in relation to aseptic processing. The addition of more equipment to a working space can cause greater heat generation, placing a greater heat load upon air conditioning. If environments are not suitably controlled, this can cause personnel to shed higher levels of skin and thus increase the microbial load into the cleanroom. Additionally, as amounts of equipment increase this can make areas more difficult to clean and disinfect simply because operators cannot maneuver around the equipment footprint. Poor air circulation also brings with it other risks, such as undetected fungal growth A related area is with the air supply system from variable air volume boxes. Here the air volumes supplied into cleanrooms may not be as originally designed. This not only affects air supply volumes but also air exchange rates and clean-up times. These physical parameters are essential for keeping particles (viable and inert) in suspension and for removing them from cleanrooms. This factor can be overlooked because most cleanroom monitoring systems assess pressure differentials rather than air supply volumes.

Degradation to fabric

Cracks in walls, tears to vinyl, and the degradation of construction joints can lead to microbial contamination events. Here unclean areas can become exposed to cleanrooms and microorganisms can

reside in cracks. Where cracks occur, cleaning solutions will often not be able to penetrate.

A further risk with weakened or broken joints is that high airflow velocities can drag unsuitable air into cleanrooms from plant areas. This can lead to turbulent mixing and the potential entailment of contamination. This can be assessed through airflow visualization.

Regular inspection and a sound repair program can overcome these problems, together with the fitting of high quality seals such as compressed rubber gaskets.

Building void spaces

The voids between adjacent cleanrooms or between cleanrooms and the outside environment will accumulate dust, and within the dust there will be spore-forming microorganisms. Such environments will not have any impact unless they are disturbed. Here contamination will arise when facilities are modified, such as knocking through a wall in order to expand a cleanroom. Good control measures should be in place when modifications take place including partitioning off areas, vacuuming dust and regular cleaning followed by sporicidal disinfection.

Technical Report No. 60-2: Process Validation: A Lifecycle Approach — Annex 1: Oral Solid Dosage/ Semisolid Dosage Forms

5.0 APPLICATION OF THE PROCESS VALIDATION LIFECYCLE TO OSD PRODUCTS

5.1 Stage 1: Process Design

This section discusses the major points to be considered during Stage 1of the process validation lifecycle defined in PDA TR 60, as applied to OSD forms. One of the main goals of this stage is to determine CQAs and CPPs that will be used to define the commercial manufacturing process and to ensure the CQAs and CPPs are documented in the development report. In addition, the design of the sampling plan/technique/technology must be

defined at this stage. The following studies are conducted with compendial as well as R&D sampling methods (which typically require many more samples than compendial methods). The sampling plan is further refined as the control plan is developed.

For the purposes of this discussion of Stage 1, the unit operation of powder blending will be discussed. Two of the most prevalent characteristics (powder characteristics and flow patterns) are described below. In addition to the specific areas of study outlined in this section, common process design characteristics such as cleanability and microbial control should also be evaluated.

5.1.1 Powder Characteristics

Manufacturing of OSD forms is contingent upon proper powder-blending processes to consistently produce uniform finished dosage units. There are many characteristics of the materials and process that impact particle–particle interactions. For the formulation eing studied, it is important to understand those interactions that have the potential to impact the quality of the finished dosage form. Properties that are subject to study may include:

- Particle size distribution
- Powder density (bulk and tap)
- Powder angles of repose
- Particle morphology
- Moisture
- Stability
- Dissolution

5.1.2 Flow Patterns

Process design should consider powder flow pattern and its impact on material segregation in a vessel (i.e., blender, hopper, storage container, drum, etc.).The powder characteristics described above are linked, such that changing one property may have an impact on one or more flow characteristics. Flow pattern characteristics subject to study may include:

- Bulk powder flow properties, e.g., mass flow or funnel flow
- Impact of outlet orifice size, e.g., formation of arches
- Powder shear strength
- Agglomeration
- Sifting or percolation
- Air entrapment
- Microbial control and cleanability
- Particle entrapment

5.1.3 Effect of Scale on the Powder Flow and Segregation

In general, the types of processes involved in both OSD and SSD manufacture, particularly the mixing/blending steps, could typically present some challenges when being scaled up throughout the lifecycle of the product. It is important to carefully examine scale-up considerations and plan process control strategies appropriately. The scale-up modeling and actual studies could be considered to achieve consistent processing and transfer to a larger or smaller scale. These scale-up considerations apply to all three stages of the process validation continuum.

Technical Report No. 77: The Manufacture of Sterile Pharmaceutical Products Using Blow-Fill-Seal Technology

6.2 Evaluating Critical BFS Process Parameters for Quality and Sterility

The expected outcome of a BFS critical process parameter study is a complete understanding of an in-control process, achieved with a machine design that can produce a high-quality product in a reliable and qualified manner.

The objective of any process parameter study is to develop and differentiate the noncritical process parameters from the critical process parameters and learn if or how these parameters will affect the process when pushed to the edge of failure. Through this approach, optimum parameters can be selected to develop and perform future process validations.

Critical processing parameters are a subset of overall process parameters for the entire machine cycle. Critical process parameters in BFS consist of two categories: quality attribute processing parameters and sterility assurance-related processing parameters.

Key to this process is maintaining quality output while ensuring consistent production volume. Critical quality attribute process parameter ranges can be successfully implemented without inhibiting the ability to operate the equipment at high-quality standards and efficiency levels. Batch yields typically have low reject rates. The user would need to determine what the critical processing parameters are and determine their relationship to the quality attributes, and then establish timer ranges/values for each vial and bottle configuration since these will have a direct effect on the formation of the final container.

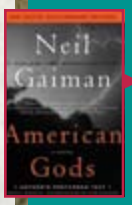
Sterility assurance and particulate matter control/reduction are the two most critical quality requirements for sterile products produced by aseptic processing. Current advanced aseptic BFS technology has been shown to provide distinct advantages over earlier BFS systems, as well as over traditional aseptic processing. These advantages include controlling the air pressure cascade within the nozzle shroud by employing HEPA filtration or other sterilized air supply to ensure ISO 4.8/5 requirements are met under dynamic filling conditions. Such improvements provide enhanced sterility assurance, product safety, and regulatory compliance.

During aseptic processing using BFS technology, the most likely opportunity for product contamination occurs briefly when the container is open to the environment prior to sealing. This time is identified as the "critical process time." The duration of the critical process time is controlled by the sum of a number of sterility critical machine process (timer) parameters and defined as the time from parison cut to container closure.

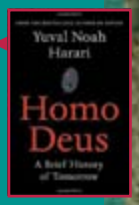
When performing media fills, as a worst case scenario, the sum of the critical process time parameters needs to be greater than or equal to the sum documented during a normal production run. This will ensure that the limits of process capability are adequately challenged by exposure to the internal machine environment and the process in general.

The user should develop a machine parameter set-up sheet that adequately addresses QA/QC requirements. The set-up sheet requires accurate development to establish appropriate set-points for each of these parameters. This will provide the BFS operator with the information necessary to stay within an acceptable range as previously determined from these engineering studies. The machine parameter set-up sheet should incorporate a table to document any changes to the critical process parameter timer values during production. This form can easily be incorporated into a batch record or used as a stand-alone form maintained by engineering, maintenance, or any other department deemed responsible.

PDA's Personal Reading List



American Gods, Neil Gaiman
— **Richard Johnson,** PDA President



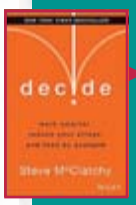
Homo Deus: A Brief History of Tomorrow, Yuval Noah Harari
— **Falk Klar,** PhD, VP, PDA Europe

Wish Lanterns: Young Lives in New China, Alec Ash
— **Rich Levy,** PhD, PDA SVP, Scientific and Regulatory Affairs

Mercy, Jussi Adler-Olsen
— **Elke von Laufenberg,** Manager, Training and Education, PDA Europe

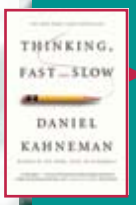
Masters of the Air: America's Bomber Boys Who Fought the Air War Against Nazi Germany, Donald L. Miller
— **Marilyn Foster,** PDA Technical Editor

JFK and the Unspeakable: Why He Died and Why It Matters, James W. Douglass, and *Microbes and Man,* John Postgate
— **David Hussong,** PhD, ValSource, appeared in "USP Microbiology General Chapters" *On the Issue* video



Decide, Steve McClatchy
— **Claire Fritz Briglia,** MilliporeSigma, *PDA Letter* Editorial Committee member

1491: New Revelations of the Americas Before Columbus, Charles C. Mann
— **Mary Carver,** Pharma Microbiology Consulting, appeared in "Cleaning and Disinfection for Pharmaceutical Manufacturing" *On the Issue* video

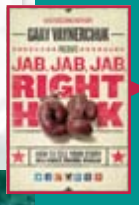


Thinking, Fast and Slow, Daniel Kahneman
— **Chris Hanff,** Concordia ValSource, *PDA Letter* Editorial Committee chair

Give and Take, Adam Grant
— **Cylia Chen-Ooi,** Amgen, appeared in "Defining the Quality Culture" *On the Issue* video

Command and Control, Eric Schlosser
— **Robert Darius,** Sanofi, *PDA Letter* Editorial Committee member

Make Your Bed, William McRaven, and *Year of Yes*, Shonda Rhimes
— **Lisa Sykes,** Merck, appeared in "Straight Through Processing" *On the Issue* video



Jab, Jab, Jab, Right Hook, Gary Vaynerchuk
— **Mina Mitry,** Marcyrl Pharma, *PDA Letter* Editorial Committee member

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PDA Europe Conference, Exhibition

Pharmaceutical Freeze Drying Technology

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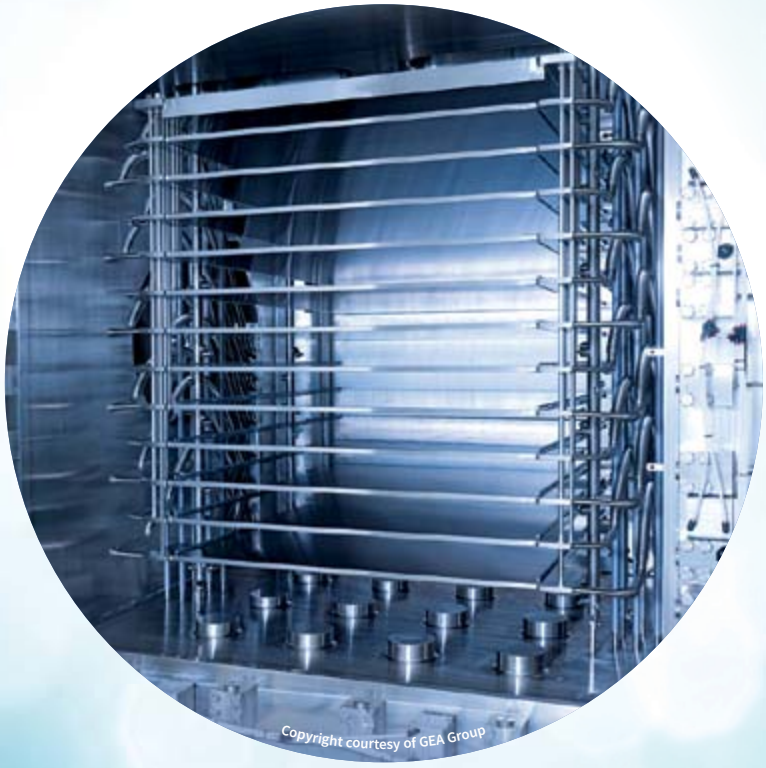
21-22 September
Development of a Freeze Drying Process

21-22 September
Einfache und Prozessorienterte Qualifizierung

COURSE IN GERMAN



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When Microbiologists Collaborate, Great Things Happen

Marsha Steed (Hardiman), ValSource

There are numerous challenges that are not always easy for pharmaceutical microbiologists to resolve on their own. Quality management. Microbial control. Environmental monitoring. How can microbiologists address these challenges?

Collaboration is the answer. For example, a successful investigation can never be performed by one department. It requires cross-functional support and collaboration to ensure that true root causes are found and that corrective actions are put in place to prevent recurrence of unwanted events.

To highlight the importance of collaboration in microbiology, the theme of this year's *12th Annual PDA Global Conference on Pharmaceutical Microbiology* is "Solving Microbiological Challenges and Sustaining Success through a Culture of Collaboration."

Concurrent sessions will focus on current hot topics and challenges in microbiology such as mold contamination and contamination control, combination products, nonsterile products, environmental monitoring, quality management, innovations, biotechnology, and data integrity. Plenary sessions will cover U.S. FDA and USP updates, human drug compounding regulations, emerging leaders in microbiology, a patient perspective and the challenges of antibiotic resistance. Throughout these sessions will be opportunities for attendees to discuss and collaborate on solutions to these topics of concern.

Successful collaboration also includes cooperation between regulators and industry; therefore, the tradition of closing the meeting with an "Ask the Regulators" session will continue as this session offers attendees the opportunity to ask regulators questions directly.

Recent graduates, benchtop microbiologists, supervisors, managers, directors, executives, vendors and regulators will all collaborate at this year's conference. Mark your calendars and come collaborate and network with us in October.

12th Annual PDA Global Conference on Pharmaceutical Microbiology and Related PDA Education Courses

Bethesda, Md.
Oct. 16–20
www.pda.org/2017micro

2017 PDA Upcoming Events

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JULY

24-28
PDA #100 Aseptic Processing Option SOLD OUT
Week 2: Aug. 21-25
Bethesda, MD
pda.org/2017Aseptic4

31-1
Sterile Pharmaceutical Dosage Forms: Basic Principles
Bethesda, MD
pda.org/2017Sterile

AUGUST

2-3
Fundamentals of Cleaning and Disinfectant Programs for Aseptic Manufacturing Facilities
Bethesda, MD
pda.org/2017Clean

8-9
Mold Identification for Quality Control
Bethesda, MD
pda.org/2017QC

9-10
Assessing Packaging and Processing Extractables/ Leachables
Bethesda, MD
pda.org/2017APP

15-17
Airflow Visualization Techniques and Practices
Bethesda, MD
pda.org/2017AugAir

SEPTEMBER

5-8
Fundamentals of Aseptic Processing
Bethesda, MD
pda.org/2017SeptFundAP

11-13
2017 PDA/FDA Joint Regulatory Conference
Washington, DC
pda.org/2017PDAFDA

13-14
2017 PDA PAC iAM Workshop
Washington, DC
pda.org/2017PAC

14-15
2017 PDA Regulatory Course Series
Washington, DC
pda.org/2017RCCS

14-15
Quality Metrics and Quality Culture for Pharmaceutical Manufacturing
Melbourne, Australia
pda.org/2017QMQC-AU

18-19
Quality Metrics and Quality Culture for Pharmaceutical Manufacturing
Suntec City, Singapore
pda.org/2017QMQC-SG

19-21
Validation of Biotechnology-Related Cleaning Processes
Bethesda, MD
pda.org/2017SeptBio

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

21
Application of a Risk-Based Approach to Freeze Drying Processes
Cologne, Germany
pda.org/EU/RBP2017

21-22
Development of a Freeze Drying Process
Cologne, Germany
pda.org/EU/FDProcess2017

21-22
Einfache und Prozessorientierte Qualifizierung
COURSE IN GERMAN LANGUAGE
Cologne, Germany
pda.org/EU/EPQ2017

21-22
Quality Metrics and Quality Culture for Pharmaceutical Manufacturing
Hyderabad, India
pda.org/2017QMQC-IN

25
Particle Identification in Parenterals
Berlin, Germany
pda.org/EU/ParticleID2017

25-28
Filtration Processes in the Pharmaceutical and Biopharmaceutical Industry
Bethesda, MD
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25-28
Sterilization Course Series
Bethesda, MD
pda.org/2017SterilizationCS

26-27
Particles in Injectables Conference – PDA Exchange
Berlin, Germany
pda.org/EU/Particles2017

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

28
Tailormade Strategies for High Level Expression of Biologicals
Berlin, Germany
pda.org/EU/HLE-of-Bio2017

28
Testmethoden für vorbefüllte Spritzen
COURSE IN GERMAN LANGUAGE
Berlin, Germany
pda.org/EU/Test-Methoden-PFS2017

28-29
Extractables & Leachables Workshop
Berlin, Germany
pda.org/EU/E-and-L2017

28-29
An Introduction to Visual Inspection
Berlin, Germany
pda.org/EU/TC-Visual2017

28-29
Best Compliance Practices im GMP Prüflabor
COURSE IN GERMAN LANGUAGE
Berlin, Germany
pda.org/EU/GMP-Prüflabor2017

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28-29
CMC Regulatory Compliance for Biopharmaceuticals
Berlin, Germany
pda.org/EU/CMC-Regulatory2017

28-29
DoE Basics for Validation by Design
Berlin, Germany
pda.org/EU/DoE-Design2017

28-29
Mastering Automated Visual Inspection
Berlin, Germany
pda.org/EU/AutoVI2017

OCTOBER

2-3
2017 PDA Annex 1 Workshop
Washington, DC
pda.org/2017Annex1

2-3
2017 PDA Container Closure, Devices and Delivery Systems: Compatibility and Material Safety Workshop
Washington, DC
pda.org/2017CC

5-6
PDA Italy Chapter – Manufacturing Trends in Parenterals, a Glance to the Future
Bari, Italy
pda.org/2017Italy-MT

9-13
PDA #100 Aseptic Processing Option 5
Week 2: Nov. 6-10
Bethesda, MD
pda.org/2017Aseptic5

10-11
Pharmaceutical Cold & Supply Chain Logistics
Prague, Czech Republic
pda.org/EU/ColdChain2017

12
Good Qualification Practice of Pharma Storage and Transportation Equipment
Prague, Czech Republic
pda.org/EU/GQP2017

12-13
Qualification of a Secure Cold Supply Chain
Prague, Czech Republic
pda.org/EU/Secure-Chain2017

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

17-18
Best Practices for Glass Primary Containers
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pda.org/EU/GPC2017

18-19
2017 PDA Endotoxins Workshop
Bethesda, MD
pda.org/2017Endotoxins

19-20
12th Annual PDA Global Conference on Pharmaceutical Microbiology Course Series
Bethesda, MD
pda.org/2017MicroCS

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

25-26
An Introduction to Visual Inspection
Bethesda, MD
pda.org/2017OctVI

25-26
Temperature Sensitive Packaging and Distribution for Biopharmaceuticals
Franklin, MA
pda.org/2017Temp

NOVEMBER

1
Training Effectiveness: What's Your Design Strategy?
Bethesda, MD
pda.org/2017TE

1-3
Environmental Monitoring Course Series
Bethesda, MD
pda.org/2017NovEM

2
Strategies for Reducing Human Error Nonconformances
Bethesda, MD
pda.org/2017HE

7-8
The Universe of Pre-filled Syringes and Injection Devices
Vienna, Austria
pda.org/EU/UPS2017

9
Container Closure Development
Vienna, Austria
pda.org/EU/CCD2017

9-10
Best Practices and Points to Consider in Aseptic Processing
Vienna, Austria
pda.org/EU/BP-Aseptic2017

9-10
Container Closure Integrity Testing
Vienna, Austria
pda.org/EU/CCI2017

9-10
Rapid Microbiological Methods
Vienna, Austria
pda.org/EU/RMM2017

14-16
Validation of Moist Heat Sterilization Processes
Bethesda, MD
pda.org/2017NovMH

14-17
Facilities and Engineering Course Series
Bethesda, MD
pda.org/2017FacilitiesCS

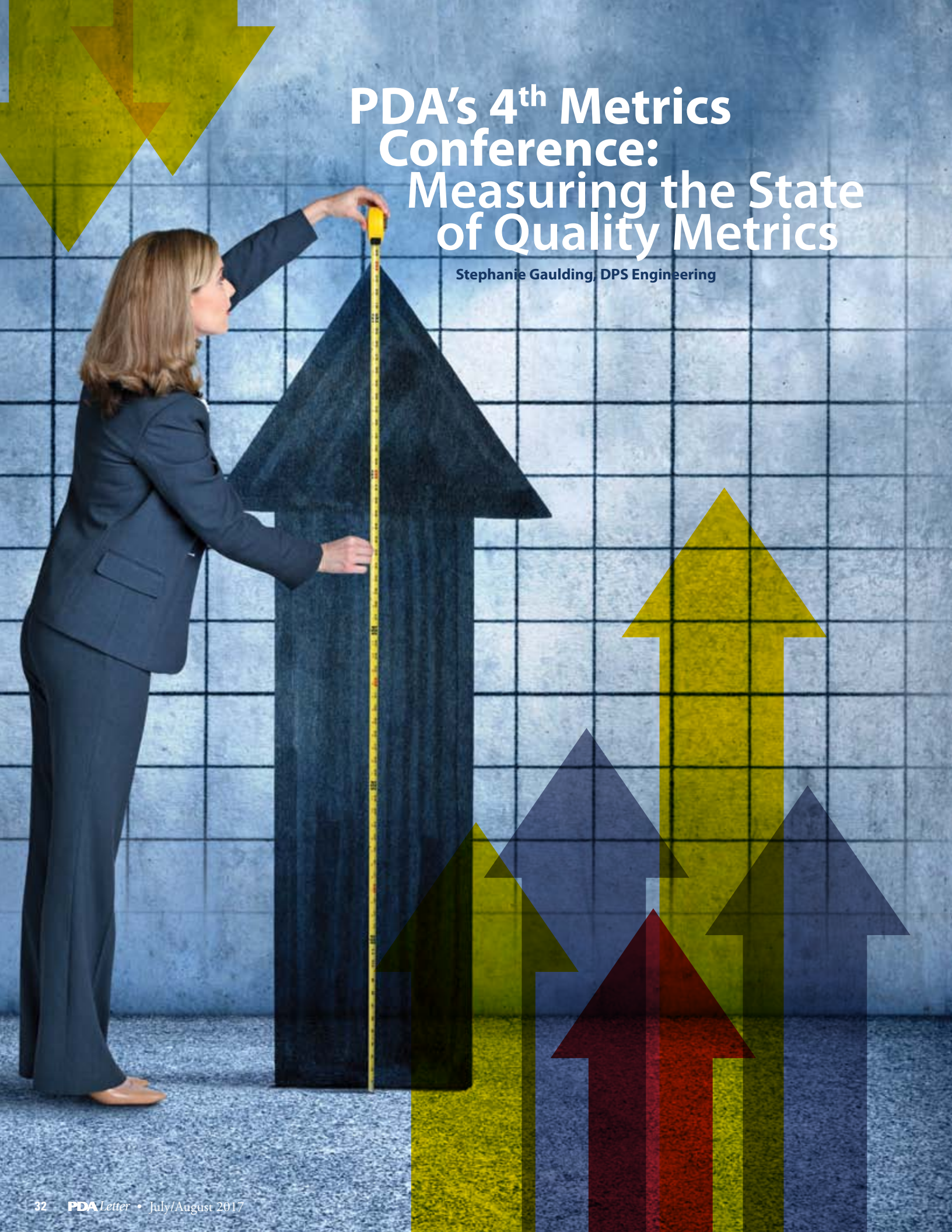
21-22
Outsourcing & Contract Manufacturing
Munich, Germany
pda.org/EU/Outsourcing2017

DECEMBER

5-6
2017 PDA Cell and Gene Therapy Conference
San Diego, CA
pda.org/2017CellGene

PDA's 4th Metrics Conference: Measuring the State of Quality Metrics

Stephanie Gaulding, DPS Engineering



It was repeatedly acknowledged that we are at a beginning of a journey

I had the pleasure of networking and discussing quality metrics and quality culture with industry and U.S. FDA leadership at the *2017 PDA Quality Metrics and Quality Culture Conference* Feb. 21–22 in Bethesda, Md. This year's conference (PDA's fourth on the topic of metrics) included some of the most candid and honest dialog that I've seen between industry and FDA, and I've attended all of the quality metrics meetings so far. I thought I would share some of my learnings from this two-day event.

Day 1: Focus on Quality Metrics

The first day focused on quality metrics and, specifically, the revised draft guidance issued by the FDA in November 2016 ***(1).*** Some of the key messages coming from FDA centered on the goals and benefits of the proposed program as well as their desire for continued feedback from industry. FDA's metrics program is intended to improve the quality of drugs, accessibility of quality drugs (i.e., minimize shortages) and effectiveness of FDA regulatory oversight. Additionally, FDA desires to foster a joint culture of dialog with industry focused on what they can learn from the data they collect as both sides share the responsibility for providing quality drugs. The Agency knows that dialog will not likely come easy at first but hopes to see improved communication over time, especially around areas that could impact the quality or availability of drugs.

Article at a Glance

- FDA seeks to create a culture of dialog around quality metrics
- Although not mentioned in current guidance, quality culture still important
- Pilot of PDA quality culture assessment tool underway

Many "technical" aspects of the program were discussed, including:

- An overview of the key changes between the first and second drafts of the metrics guidance, and recognition of the valuable feedback FDA received from industry on the first draft
- Details on who will be doing the reporting and comparison of the benefits of site reporting versus product reporting, as the proposed program is geared to collect either.
- Phases of the program—based on industry feedback, there will be a voluntary phase prior to implementation of the mandatory program for drugs and some biologics (see scope information in the draft guidance); currently, there is no defined endpoint for the voluntary phase (In my opinion, this means we could see several years of voluntary metrics reporting before the program is finalized)
- Timing of the program—the voluntary phase will be launched using notification through the *Federal Register,* approximately 1–2 months in advance of the portal opening, and the announcement will include the details on what to submit, how to submit, and how long the portal will remain open; while not mentioned in the guidance, FDA indicated at the conference that the portal would likely be open for approximately 1–3 months, anticipating launch of the voluntary phase in early 2018
- Metrics and data to be collected—the draft metrics were simplified from the first version and focus on collection of data which will be used to determine Lot Acceptance Rate (LAR), Invalidated Out-of-Specification Rate (IOOSR), and Product Quality Complaint Rate (PQCR); these metrics were selected because the Agency feels they are indicators of robustness of commercial manufacturing processes (LAR), robustness of lab operations (IOOSR), and voice of the customer (PQCR)
- Recognition of participation via the reporters list, including discussion of the pros and cons of the proposed tier-based approach in the voluntary phase

A couple of interesting questions were discussed during the first panel session. One of the first questions, as you might expect, was around the potential impact of the new U.S. government administration on this program. I found it interesting that their perspective was aligned with my own. There is always new policy in association with a new administration in the United States (every four or eight years). With that said, FDA still feels this program is important to achieve many of the objectives set out in the Food and Drug Safety and Innovation Act (FDASIA) and the 21st Century Cures Act, as well as being a smarter and more innovative way to provide regulatory oversight to industry.

Another interesting question for the FDA panel centered on why quality culture was not mentioned in the new guidance (in the first draft, it was mentioned nine times). The panelists clearly indicated that just because the term "quality culture" is not written into the current draft of the guidance does not mean it is not important. The draft guidance document clarified and focused on a program that would be executable by both industry and the agency. They also believed that the proposed metrics can be very predictive of the future and are driven by an organization's quality culture.

There was also an entire session devoted to discussion of the analytical approaches from both Agency and industry perspectives.

Alex Viehmann, Operations Research Analyst at CDER, presented an overview of the work going on at the agency in preparation to receive and analyze the requested data. Much of the groundwork has been around defining data structures ➤

and processes for validating the data from both internal and external sources. They are anticipating a testing phase later this year (likely in the fall) for the submission portal in order to help test the assumptions made to date.

> **"…people are still at the center of what we do"**

Industry representatives also presented their experience in analysis of quality metrics for their own internal programs. Some of what they learned from their experiences included:

- Acknowledgement that the tools to automate data collection and analysis are out there; organizations do not have to invent something in order to perform robust analytics and reduce the burden on the organization
- Metrics programs are inherently complex, namely due to inconsistency in definitions and the variety of sources for the data; the complexity of these programs should not be underestimated
- Metrics programs should aim to "find it once, fix it everywhere," especially when there are signals of a larger issue or the potential for an issue to pop up elsewhere in the organization by working on impacting the "drivers of the drivers"
- In a related comment, several speakers emphasized the need to not "sweat the red" when looking at a dashboard, but also cautioned not to get too comfortable with the green (a great analogy was provided for this: think of a watermelon, the surface is all green and looks good but you never know what lies beneath… it may be good, or it may be bad)
- Understanding that whatever you decide to measure changes behavior—sometimes for the better but, potentially for the worse
- Don't forget to understand the context around a metric as this can help you determine if a blip is just a blip or if it is indicative of a more serious issue
- Don't get overly focused on the tools (e.g., dashboards) but, instead, focus on making information transparent and the flow in an organization
- Don't expect your metrics to stay the same year after year; after all, a robust quality metrics program requires continual improvement and will evolve

It was clear that both the FDA and industry understand that the benefits of the program may not be realized immediately. It was repeatedly acknowledged that we are at a beginning of a journey. We have a

lot to learn in order to achieve the ultimate goals of improving the quality of drugs, accessibility of quality drugs (minimize shortages), and effectiveness of the FDA regulatory oversight (specifically around inspections and post-approval changes).

Day 2: Focus on Culture

On the second day, the focus shifted to quality culture, starting with presentations from both FDA and MHRA representatives discussing their perspective on quality culture. From the FDA's **Jeffrey Baker,** we heard about culture as both a noun and a verb which begs an interesting question: Are you looking at culture as a thing (something you possess) or a behavior (something you can grow and influence)? And, if culture is more of a behavior, then we were reminded of the way adults learn behaviors via the ladder of inference, a theory that describes how we go from a fact to a decision or action.

The MHRA perspective indicated that quality culture requires knowledge, diligence, vigilance, management commitment and transparency. Based on their 2015 inspection experience, many of the serious failures resulted from an absent or over-controlling senior management. In fact, they still find that many of the conclusions from the Clothier Report issued in 1972 still hold true, reminding us that people are still at the center of what we do. **[Editor's Note:** For more on this session, see p. 36**.]**

When industry presented their perspectives on quality culture, I must admit, I was quite pleasantly surprised with what I heard from industry's senior leaders. A significant portion of the time was spent on the need to return to **W. Edwards Deming's** 14 Points for Management (first presented in his book *Out of the Crisis*) and, in particular, point No. 8— drive out fear in order to build and sustain healthy and robust quality culture***(2).*** I couldn't agree more.

Then we heard about the progress that the PDA team is making on their quality culture assessment tool including perspectives shared by one of the participants. The tool provides a structured framework aimed at assessing the quality culture of an organization. There are approximately 50 sites from 26 firms participating in the pilot of the tool, and 64 assessors have been trained. PDA hopes to finish the pilot this year and roll it out formally soon after.

Machelle Eppler, Vice President and Head of Global Quality Compliance and Regulatory at Patheon, shared the company's experience so far in using the tool (five sites from several regions of the world participated). She reemphasized that the tool provides consistent language, framework, and scoring method as well as a road map for improvement. She also discussed the need to create the right environment (i.e., make people feel safe to be open and honest and that there are not right and wrong answers) and to spend the necessary time planning (i.e., several weeks not days). She stressed the key role senior leadership engagement plays. In fact, all communications around the process came from plant general managers and not quality teams. The communication of results, action plans and successes, and the implementation of best practices were also important. After all, she reminded us, improving quality culture is a journey.

The conference concluded with one final panel discussion where we were reminded of the goals of the quality metrics program discussed the previous day:

- Improve the quality of drugs
- Decrease drug shortages by detecting signals earlier
- Decrease inspection frequency and/or duration
- Increase dialog between industry and FDA

As can see, there was a lot of information shared over the two days, and it would be difficult to capture everything discussed in one summary. I found this a great learning experience that I am excited to share with readers of the *PDA Letter.*

[Editor's Note: A version of this article was originally published by the author on her personal LinkedIn site on Feb. 23**.]**

References

1. Guidance for Industry: Submission of Quality Metrics Data, U.S. Food and Drug Administration, November 2016 www.fda.gov/downloads/drugs/guidances/ucm455957.pdf

2. Deming, W.E. *Out of the Crisis*. Cambridge, MA.: The MIT Press, 1982.

About the Author

Stephanie Gaulding is a Principal Consultant at DPS with over 20 years' quality and regulatory compliance experience in the pharma, biotech, and medical device industries. In her role, she helps clients develop, redesign, and implement efficient and sustainable quality systems as well as successfully preparing for and navigating regulatory inspections.

U.S., UK Regulators Share Passion for Quality Culture

Rebecca Stauffer, PDA

Quality culture has often been characterized as the driver behind effective quality systems ***(1),*** and it has become even more important as the U.S. FDA seeks to collect quality metrics data from pharmaceutical manufacturers.

The *2017 PDA Pharmaceutical Quality Metrics and Quality Culture Conference* in Bethesda, Md., Feb. 21-22, provided insight into both the U.S. and UK regulatory perspectives on quality culture. **Jeffrey Baker,** Deputy Director, Office of Biotechnology Products, CDER, FDA, and **David Churchward,** Expert GMP Inspector, UK MHRA, represented these agencies in the session, "Quality Culture and What We Are Learning as an Industry."

Baker opened his talk by acknowledging that quality culture can be interpreted in many different ways.

"This is something where everyone has passionate opinions because it's very close to our hearts and our day-to-day lives," he said. "But that's okay, because it makes for a very rich marketplace of ideas."

His presentation offered a different take on quality culture, taking a more etymological approach, starting with the word "quality" itself. While there are books and publications that list different types of quality, Baker worries that "we're using the same word but in very nuanced ways." He then cited CDER Director **Janet Woodcock,** who in 2014 defined the quality of a pharmaceutical product as "fitness for use," meaning it "delivers the properties described on the drug label and is not contaminated." The rest of his talk explored the meaning of "culture" and its relation to "quality." He noted that in 2014, according to Merriam-Webster, "the No. 1 word was culture." And this word carries many connotations: Cultivation; development of intellectual abilities through education; familiarity with the fine arts and humanities; shared values within social groups; and the act of cultivating living material such as bacteria or viruses in nutrient media. He focused the last portion of his talk on this last connotation.

In his presentation, Baker used the analogy of quality culture as living cells on a petri dish, to which many of the microbiologists in the audience could relate. To culture healthy cells, a microbiologist requires an appropriate growth medium, a stable environment, and must guard against the accumulation of dead cells and contaminating cultures.

Turning the analogy to quality culture, Baker said a healthy one requires a stable environment that supports ➤

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it and protection from contamination by "viruses." The "viruses" that can impact a healthy quality culture are just as fast-growing as the ones in the lab.

"Culturing quality is an exercise in providing experiences that promote and support healthy stable cultures of behaviors we value," he said. "Just as with 'management,' when we refer to 'quality culture,' we need to understand whether we are talking about the noun or the verb. One of my great frustrations is when 'management' becomes what you are rather than what you do. I want management the verb."

When it comes to quality culture as a noun, Baker pointed out that "acceptable" is always relative in the viewpoint of the assessor. And the assessor could be a regulatory agency, large company, small biotech firm, etc. Either way, the culture conforms to who is looking.

"When we think about quality culture the verb, we get to a much better place. The culturing of quality is about us going and making something really good and stable happen."

> **When we think about quality culture the verb, we get to a much better place**

By taking the active stance of "let's go culture some quality," this makes all involved with quality the actors instead of observers, he explained. In other words, it's a decision of action.

Quality: Embedded at All Levels

While Baker's talk ended with a call to action, Churchward's presentation offered a look back into quality culture's past and its impact on MHRA, the UK regulatory agency.

"Quality culture, it's nothing new," he said. "In 1972, a failure to sterilize a batch of intravenous fluids led to a public health emergency in the United Kingdom. These products weren't just killing patients, there were 500 units in the supply chain that nobody could locate. And at the time, the UK Department of Health initiated a 'life or death' search to find those units before they were administered to patients."

This incident led to the Clothier Report, an enquiry into the contamination of intravenous fluids. It also led to the UK's GMP regulations. While the report contained a number of conclusions, Churchward pointed to a few that specifically related to quality culture. First, there was no technology available that eliminated "the need for skillful men devoted to their work." Second, too many in the

field believed that sterilization of fluids could be easily achieved by unskilled workers operating under minimal supervision. And third, that "public safety depends ultimately on untiring vigilance by both industry and government." At the same time, regulations and inspections are not necessarily a panacea from similar events occurring.

"So we need that quality mindset," he said.

When MHRA looks at a company's quality culture, the Agency wants to see:

- Confidence that the company is (and remains) in control
- Understanding of how quality attributes impact patients
- Quality-related decision-making
- Mature organizational mind-set, i.e., avoiding a compliance-driven mind-set of "I do this because I have to"

MHRA expects a firm's quality culture to manifest in a number of ways. "First of all, we require knowledge by personnel of what is important…We need diligence by personnel at all levels of an organization, so that everybody understands their contribution to quality," Churchward said.

No matter how removed someone is from the patient, they need to understand that their actions impact the patient and the organization. This awareness should extend across the organization so that employees are empowered to bring quality issues up with all levels of management.

Second, management should be committed to promoting this holistic view of quality and be transparent about that support."This is more than just the mission statement," he said. "This is senior management walking the talk. Otherwise, no one's going to report things."

Churchward suggests companies send personnel out to see their products administered to patients. Prior to joining MHRA, Churchward managed a manufacturing unit in a hospital that produced a range of aseptic products, some of it for the hospital's pediatric intensive care unit. To instill a greater awareness of the importance of the product's quality, he established a program in which technicians had to go to the unit and see the infants receiving the medicine.

"The effect was remarkable," he said. "It turned an acceptable technician into a good technician, because they really 'got' the importance of what they were making."

Metrics Tied to Quality Culture

Regarding quality metrics, MHRA looks for flexible metrics based on compliance that augments existing regulatory practices.

"Some of the indicators we are looking for are the ones that we feel foster an environment of commitment, diligence, vigilance and knowledge of staff," Churchward said. "And clearly that requires strong leadership, but it also needs empowerment for staff at all levels."

Both talks illustrated that quality culture is a crucial underpining for any successful quality metrics plan. A company's quality metrics are only as good as the culture that supports them. And that support has to be ingrained at all levels of the organization, starting from the top.

[Author's Note: Learn more about PDA's quality culture activities in the "On the Issue" video, "Defining the Quality Culture," featuring Amgen's **Cylia Chen-Ooi,** available on the *PDA Letter* website.**]**

Reference

1. Morris, W. "Want to Make the FDA Quality Dean's List? Take a Look at Your Metrics."*PDA Letter.* 51 (March 2015) 22 –29.

About the Experts

Jeffrey Baker, PhD, worked in bioprocess development and manufacturing for over 20 years at Eli Lilly and AstraZeneca before being appointed Deputy Director in the Office of Biotechnology Products, CDER, at the U.S. FDA.

David Churchward is an Expert GMDP inspector at MHRA. In his current role, he is the MHRA's representative at the EMA Inspectors Working Group.

Industry Expert Weighs in on Quality Metrics

Rebecca Stauffer, PDA

Quality metrics remain a focal point of discussion within industry. In session "A3: Quality Metrics" (Sept. 12, 10:45 a.m.) at the 2017 PDA/FDA Joint Regulatory Conference, *there will be a panel discussion on quality metrics featuring industry leaders. One of the panelists,* ***Susan Schniepp,*** *Distinguished Fellow, Regulatory Compliance Associates, offered her views on quality metrics for the* PDA Letter.

PDA Letter: It's been just over four years since **Janet Woodcock** issued her call for quality metrics and the first PDA conference on the topic. What has industry learned over the past four years?

Schniepp: I think we have learned that quality metrics are complicated, and that reliability of these metrics is dependent upon an organization's quality culture. And quality culture is a very aspect of metrics.

We have to also realize that companies are already collecting metrics and, in many cases, they are collecting the metrics specifically asked for by the U.S. FDA.

PDA Letter: How does quality culture relate to metrics?

Schniepp: The culture of an organization relates directly to the reliability of the metrics being reported. When there is a functioning quality culture, the information can be assumed to be reliable and accurate. When a good quality culture is not forthcoming, then there could be issues with the metrics. Some of the metrics may be suspect because a poor culture will drive undesired behavior and that might result in inaccurate metrics where not all the information is reported.

PDA Letter: What are industry's main concerns about the FDA's quality metrics program at this point?

Schniepp: The main concerns I've heard seem to be the amount of time and man-hours needed to gather, review and submit the information to the Agency. And the larger, unanswered question is how the Agency intends to use the information once it has been submitted by a company.

PDA Letter: What has changed with regard to metrics since the first PDA metrics conference in 2013?

Schniepp: Since PDA's 2013 metrics conference, the FDA guideline has been issued twice along with a technical guideline. I think the Agency is also now looking at this to be a voluntary program instead of mandatory. Industry is still not that accepting of the program, so that is one aspect that has remained the same. The requirements for reporting have changed and it seems, with the last version of the guideline, that reporting will be voluntary.

PDA Letter: For a small company that is starting out on the quality metrics journey, what three things should the organization consider?

Schniepp: First, establish a positive culture. Second, establish meaningful metrics that drive continuous change. And three, establish goals that measure product quality. These should be realistic and constructed so they do not drive undesirable behavior.

PDA Letter: The FDA has added a voluntary reporting phase of the quality metrics program, and there has been additional industry feedback after the most recent revised FDA draft guidance. What would you recommend companies do today in regards to the metrics program?

Schniepp: I think companies should be receptive to the metrics program and accept it for what it is trying to accomplish. The point of the program is to monitor and correct potential issues before there ➤

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is a drug shortage. Companies should review their data and see if they can't do some self-correcting before there is a drug shortage. And companies should not be afraid to work with the Agency to solve problems in their quality systems or manufacturing systems before they result in drug shortages.

PDA Letter: Could a company tie the FDA's metrics in with their overall metrics, ensuring the process is scaleable as more metrics are expected to be reported? Or should another approach be taken?

Schniepp: I think it would be advantageous for a company to tie their metrics to the FDA program, but I would not limit the metrics to only those called for in the guideline. The metrics specified in the guideline are *lagging* metrics. It would be wise for companies to establish *leading* metrics so they can react faster to problems.

PDA Letter: What are PDA's next steps when it comes to quality metrics and quality culture?

Schniepp: We are still working on a quality culture tool because we feel that this is an important part in making the metrics meaningful for both the company and the Agency.

About the Expert

Susan Schniepp is a Distinguished Fellow at Regulatory Compliance Associates. As an active member of PDA, she is on the Board of Directors and has been a member of the planning committee behind the *PDA/FDA Joint Regulatory Conference* since 2001.

Want to Learn More About Metrics?

Consider attending Session A3: "Quality Metrics," Sept. 12, 10:45 a.m.–12:15 pm. at the *2017 PDA/FDA Joint Regulatory Conference*. **Steven Mendivil,** Senior Advisor, International Quality External Affairs at Amgen will be moderating this session. **Valerie Whelan,** Amgen's Vice President of Corporate Quality, will provide an industry case study on using metrics to drive quality and prevent drug shortages. Her talk will then be followed by the panel discussion on metrics featuring the following representatives from industry: **Barbara Allen,** PhD, (Eli Lilly), **Deborah Autor** (Mylan), **Harry Jeffreys** (Catalent Pharma Solutions,) and **Susan Schniepp** (Regulatory Compliance Associates). U.S. FDA representatives have been invited to speak as well.

Allen, Autor and Jeffreys, along with **Guy Villax** (Hovione), **Carol Montandon** (Johnson & Johnson Consumer), and **Melissa Seymour** (Biogen) offered their opinions on the impact of FDA's quality metrics on different segments of pharma at the *2017 PDA Pharmaceutical Quality Metrics and Quality Culture Conference* in Bethesda, Md., Feb. 21. An excerpted transcript of their talking points was published in the April *PDA Letter* ("Quality Metrics to Impact Pharma Sectors"). The article can also be found on the *PDA Letter* website.

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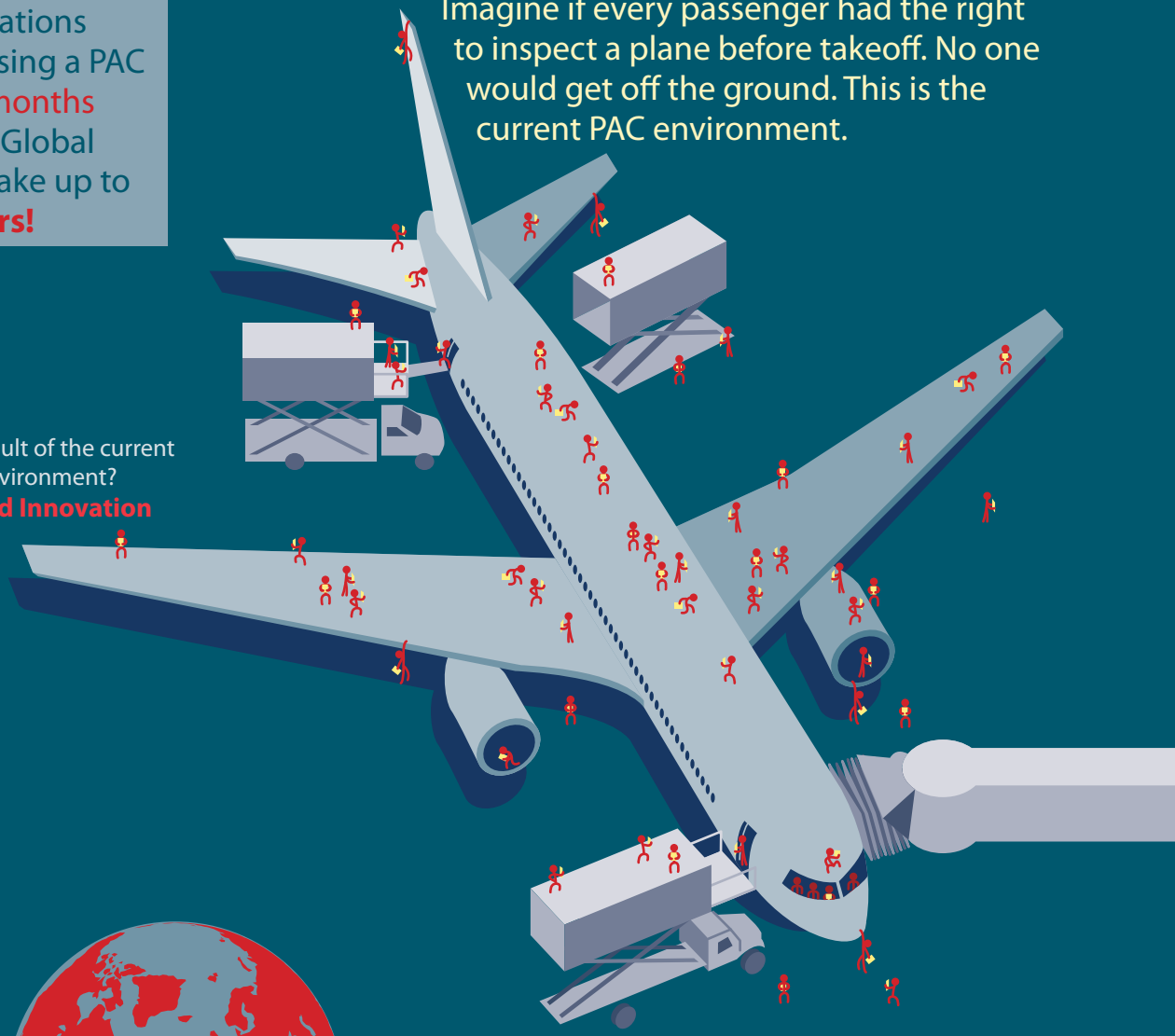
Grounded by Post-Approval Changes

Global Complexity is Slowing Down Innovation and Supply

Post-approval changes (PAC) present one of the biggest challenges for our industry. Long approval timelines and lack of collaboration hinder innovation. But how does this impact the industry?

35% of organizations indicate processing a PAC can take 6–12 months in one country. Global approvals can take up to **5 years!**

Imagine if every passenger had the right to inspect a plane before takeoff. No one would get off the ground. This is the current PAC environment.



The result of the current PAC environment?
Stifled Innovation

Majority of companies are submitting changes to 25 or more countries

Country-specific requirements lead to the most regulatory complexity

Learn more at the *2017 PDA PAC iAM Workshop*

www.pda.org/2017pac

Source

1. PDA PAC iAM 2017 Survey on Post Approval Change

The Parenteral Drug Association presents the...

2017 PDA PAC iAM Workshop

September 13-14, 2017 | Washington, DC

Renaissance Washington, DC Downtown Hotel

Exhibition: September 13-14

#2017PAC

Science- and Risk-Based Approaches to Technical Change Management

The *2017 PDA PAC iAM Workshop* will provide overviews and insights on how industry and regulatory authorities are working together to streamline and harmonize post-approval changes (PACs). It will also include updates on the development of a new guidance, ICH Q12.

At this Workshop, take part in interactive plenaries and small group discussion sessions that will explore global harmonization of post-approval change including use of change management protocols and lifecycle management. Members of the ICH Q12 Expert Working Group will be in attendance to listen to your current PAC management challenges and discuss future concepts. Contribute to the discussion of the latest on topics such as:

- Why is a Global Dialog Important? Why Now?
- Established Conditions and Change Categorization
- Elements of Lifecycle Management Strategy
- Pharmaceutical Quality System and Change Categorization
- Perspectives on PAC Regulatory Convergence and Manufacturing Innovation

Learn how an effective pharmaceutical quality system can streamline change reporting requirements and contribute to reducing regulatory burden.

Learn more and register at *pda.org/2017PAC*

SNAPShot

Meeting *Preview*

Interest Group Schedule

As always, relevant interest groups will meet for the first two days of the *2017 PDA/FDA Joint Regulatory Conference.* Below is a schedule of interest group meetings falling under the Regulatory Affairs and Quality Advisory Board (RAQAB).

Monday, September 11	Tuesday, September 12
5:30 p.m. – 6:45 p.m.	5:30 p.m. – 6:30 p.m.
Quality Systems Interest Group	Regulatory Affairs Interest Group
Supply Chain Management Interest Group	Inspection Trends Interest Group
Quality Risk Management Interest Group	GMP Links to Pharmacovigilance Interest Group
Pharmacopeial Interest Group	Technology Transfer Interest Group

OPQ Establishes Manufacturing Science CoE

Kurt Brorson and Sau L. Lee, U.S. FDA

As the pharmaceutical and biopharmaceutical industries become increasingly globalized and manufacturing processes grow ever more complex, the U.S. FDA relies critically on the latest manufacturing science research to inform the Agency's decision making. For this reason, FDA's Office of Pharmaceutical Quality (OPQ) has established a Manufacturing Science and Innovation Center of Excellence (CoE) to promote internal and external scientific collaboration in manufacturing science, facilitate research communication and management and advance OPQ's research culture and capabilities in manufacturing science. Individuals from across OPQ, including the Offices of Biotechnology Products (OBP) and Testing and Research (OTR) are key members of this CoE. Reviewers, investigators and other disciplines both within OPQ and from other offices within CDER will also participate as appropriate.

Manufacturing science is critical for biotech products because their APIs are larger and they also use more complex molecules compared to traditional small molecule drugs produced by chemical processes. Proteins are predominantly manufactured in a batch mode using living cells. In batch mode bioprocessing, unit operations are followed in series to produce a final protein product free of raw materials like media components, contaminating molecules, potential viruses and endogenous viruslike particles, column ligands and protein aggregates. Even before OPQ was established, biomanufacturing science has played a large role in CDER research for over 15 years, with an in-house focus on viral clearance, Quality by Design, bioreactor control and unit operation linkage. By organizing this effort into the Manufacturing Science and Innovation CoE, OPQ can build on this past history of research success.

The mission of the new CoE is to promote biopharmaceutical science and innovation by addressing cross-cutting science and regulatory issues in bioprocessing through research that supports guidance and policy development. To define the focus, the CoE will identify potential technological gaps in biomanufacturing methods based on internal expertise and external stakeholder input. The input, which will be gathered and evaluated on an ongoing basis, will help direct research on gap areas, such as windows of robustness or potential failure modes of typical biotech unit operations. The CoE's strategy will be to select and design project areas based on the ongoing gap assessment, all to support the mission goal of assuring drug quality and product safety. New projects can be generated as additional information reaches the CoE team. Examples of project areas within the CoE scope (see **Table 1**) include novel analytical technology, single-use bioreactor systems, new virus removal/inactivation methods or equipment, and progress toward more fully integrated continuous-mode production of biopharmaceuticals. The project areas will determine if individual, more specific projects are within scope of the CoE. By establishing the Manufacturing Science and Innovation CoE, OPQ is poised to keep pace with advances in biomanufacturing to bolster the science behind high quality, safe and consistent biopharmaceuticals that benefit patients.

FDA believes that the CoE can help address industry competitiveness as

Manufacturing Area	Perceived gaps	Project Areas
Upstream Bioprocessing	Real-time monitoring of protein critical quality attributes (CQAs) in complex process fluids	Near-IR for complex process fluids
	Strategies for consistency of complex CQAs like glycan profile	2-D chromatography
	Control/monitoring of low level media components	Single-use systems
	Adventitious agent control	Barrier methods
		DoE approaches to link of culture inputs to product CQAs
		Persistence and measurement of metals in culture
		Control strategies for perfusion cultures
Downstream Bioprocessing	Viral clearance robustness and failure modes	Virus filtration
	Consensus standards for biotech unit operations	Multimodal media
	Risk attuned process validation approaches	Continuous mode chromatography
	Context for deviation impact	Mycoplasma persistence
	Linkage to upstream	
Formulation/Dosage Forms	Product or process factors that impact protein stability	Minimization of aggregates
	Product degradation impact on potency or PK/PD	Lyophilization
		Bioseparations and impurity modeling
Oligonucleotides	Synthesis of complex specialty oligonucleotides	Cellular internalization of phosphorothioates
	Delivery of transfection reagents	Highly parallel screening of oligos

Table 1 Manufacturing Science and Innovation CoE Areas of Lab Research Focus

advanced manufacturing can potentially reinvigorate some sectors of the U.S. pharmaceutical manufacturing sector that have been moving overseas. This concept was validated in December 2016 by the U.S. Department of Commerce, which established the National Institute for Innovation in Manufacturing Biopharmaceuticals as part of the Manufacturing USA network ***(1).*** The advancement of processing technologies can bring efficiencies to manufacturing of both drug substances and drug products. While these advancements are welcomed, they could present a regulatory challenge as FDA reviewers must fully understand them as part of preparations to evaluate their impact and implementation in various product classes. OPQ seeks to encourage these developments while also identifying gaps and potential pitfalls to avoid so that OPQ continues to build a strong science and research presence in the field of manufacturing science. By standing up the Manufacturing Science and Innovation CoE, OPQ will bring this effort to the next level.

Although the Manufacturing Science and Innovation CoE was founded and led by OPQ scientists, the Agency is confident that it will facilitate collaboration between OPQ, other elements of CDER and the external scientific community. The CoE intends to be agile, interactive, and adaptive to leverage resources and advance science critical for drug product development, manufacturing and regulatory evaluation.

Reference

1. US Department of Commerce. *U.S. Secretary of Commerce Penny Pritzker Announces Biopharmaceutical Manufacturing Institute Joining Manufacturing USA Network,* 2016. https://www.commerce.gov/news/press-releases/2016/12/us-secretary-commerce-penny-pritzker-announces-biopharmaceutical (accessed May 25, 2017)

About the Authors

Kurt Brorson, PhD is a Lab Chief in CDER's Division of Biotechnology Research and Review II, Office of Biotech Products. In addition to review, inspection, training and policy activities, he conducts research on bioprocess monitoring and viral safety of biotechnology products.

Sau (Larry) Lee is a Senior Biomedical Research Scientist (SBRS). He is a Deputy Director of the Office of Testing and Research in the Office of Pharmaceutical Quality (OPQ), and the chair of the OPQ Emerging Technology Team. He is leading the effort in advancing OPQ research and in manufacturing science, complex drug substances and products, as well as in developing the regulatory policy, scientific standards as well as computational and modeling tools supporting quality review and inspection in OPQ.

2017 PDA/FDA Joint Regulatory Conference

A Maturing Model of Quality

Jacqueline Kunzler, PhD, Baxter International Inc.

"Measurement is the first step that leads to control and eventually to improvement…If you can't measure something…you can't improve it."
— H. James Harrington

How do we assess the effectiveness of our quality system?

An appropriate response may be captured within the above quote by **H. James Harrington,** a American author, lecturer, consultant, international performance improvement and quality guru, entrepreneur, engineer and businessman. Throughout his long career, he developed many concepts. Some of the more important ones are poor-quality cost, total improvement management and business process improvement. He has authored 35 books and created ten software packages on performance improvement. Harrington's career in quality and performance improvement spans more than 65 years. During this time span, the quality system has evolved tremendously from then to now.

Traditionally, at the end of management review, a signature was requested from Management with Executive Responsibility (MWER) and those involved in Quality Management Review (QMR), attesting to the suitability and effectiveness of the quality system. Traditional management reviews typically consisted of a collection of data tables, charts and graphs trying to explain the quality system's performance since the last management review. These charts and graphs, (which usually portrayed things like how many complaints were received, how many nonconformances were generated, how timely were CAPAs being executed, what were the outcomes of significant audits, etc.,) tried to paint a picture of the health of the quality system. The challenge with this scenario is that it was difficult to make a *subjective* leap from a collection of data, to the statement that the quality system is suitable and effective (see red line in **Figure 1).**

Today, quality systems are transitioning from a heavy focus on data and looking at past performance through charts and graphs, to a systematic review of each quality system element, using Maturity Model methodology. With this methodology, each quality system element has criteria starting at Level 1 (just getting started) to Level 5 (world class). Systematic assessments are performed at each manufacturing facility to determine relative maturity level for each element, as well as the gaps to achieving the next maturity level. The manufacturing sites then prepare quality plans to close those gaps. At the corporate level, a review of maturity levels for all quality system elements across all sites enables objective assessment toward progress in growing a quality system's maturity. In addition, this approach allows the identification of areas of weakness and proactive work toward improvement (see blue line in **Figure 1).**

To learn more about the continuous expansion of quality system maturity level modeling, register to attend the *2017 PDA/FDA Joint Regulatory Conference,* Sept. 11–13, 2017, at the Renaissance Hotel in Washington, D.C. In "Session B1: Quality Systems: Maturity Models and Continuous Improvement," representatives from industry and the U.S. FDA will team up to describe maturity model methodology within a broader quality system and provide examples of inspection findings from various quality systems.

2017 PDA/FDA Joint Regulatory Conference and Related PDA Education Courses

Washington, D.C.
Sept. 11–15
www.pda.org/2017pdafda

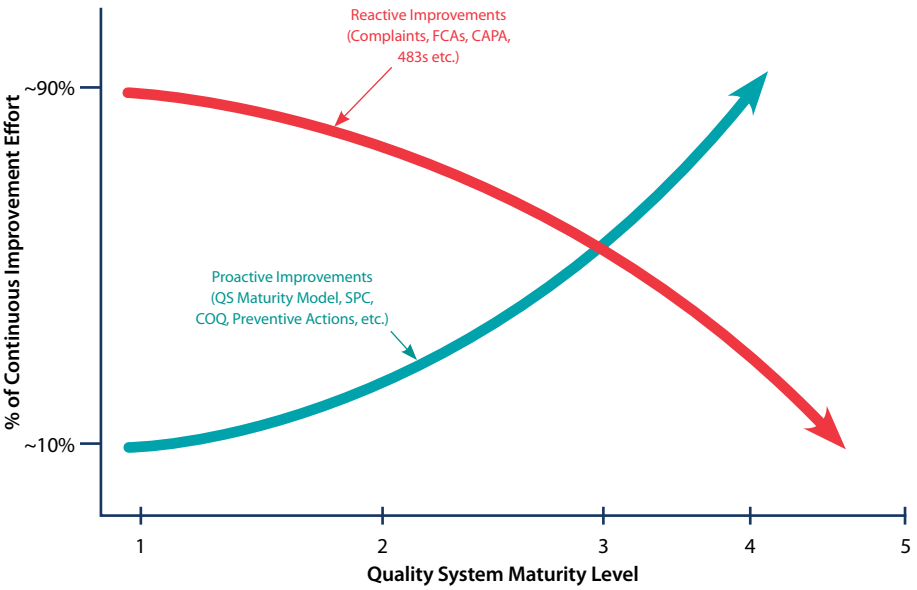


Figure 1 Maturity Model (SPC=Statistical Process Control, COQ=Cost of Quality, CAPA=Corrective and Preventive Action, FCA= Field Corrective Action)

Make PDA Your Bio/Pharmaceutical Manufacturing Resource

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Parenteral Drug Association

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

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

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

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

PDA – *Connecting People, Science and Regulation®*

Difficult-to-Inspect Drugs Require New Processes

Rick Watson, Merck & Co., Inc.

Developing a robust visual inspection process along with comprehensive particulate controls for parenterals has long been a significant challenge, and the increased introduction of difficult-to-inspect product formats and evolving guidance is adding to that challenge.

As an increasing number of biologic products are introduced, more companies are dealing with the challenge of discriminating between extraneous visible matter and inherent drug matter. In addition, products that require lyophilization and products filled as suspensions add significant complexity to visual inspection process design and qualification. These difficult-to-inspect products require new developments in both manual and automated inspection processes.

While the new guidance established in USP Chapter <790> Visible Particulates in Injections provided long needed definition on "essentially free of visible particulates," there are still many challenges and questions regarding visible particulate control requirements. USP Chapter <1790> Visual Inspection of Injections becomes official August 2017 and provides more detail on the USP <790> requirement for "a complete program for the control and monitoring of particulate matter."

The *2017 PDA Visual Inspection Forum* provides an excellent opportunity to learn how the pharmaceutical industry is evolving to more effectively inspect challenging product formats and how industry is changing to meet the new particulate guidance. Presentations are scheduled to discuss the status of USP <790> and <1790>. Multiple case studies will be presented on processes for inspecting difficult-to-inspect product formats as well as approaches for comprehensive particulate control. Lastly, the Forum is the best opportunity to connect and network annually with industry experts and industry peers on the topic of visual inspection.

2017 PDA Visual Inspection Forum and Related PDA Education Courses

Bethesda, Md.
Oct. 23–26
www.pda.org/2017visual

Knowledge is Power

Regulatory Awareness is Key to Supply Chain Success

Rafik H. Bishara, PhD, Eli Lilly and Company (retired) and Erik van Asselt, PhD, MSD

The industry's ability to maintain a secure temperature-controlled supply chain continues to receive increased global attention from regulators, manufacturers and solution providers. The major goal in this endeavor is to ensure the proper handling, storage and transportation of medicines until they reach the end user—the patient. Knowing the regulatory requirements and current best practices should be a top priority for all involved.

EU GMP Annex 16 requires companies to map their specific supply chains in order to determine the various partners involved as well as to assess the weakest links. This enables companies to improve their supply chains through risk analyses and mitigation measures. Risk management in the pharmaceutical supply chain encompasses quality risk management (QRM), data integrity, supply chain security, medicine verification systems and protection from theft, loss, tampering,, and diversion by employing multifaceted anti-counterfeiting measures.

Global regulations and quality standards covering GDP are also on the rise. Regulators want to see that patients are protected by ensuring that the quality, integrity, potency and efficacy of a medicine has not been compromised during its movement through the supply chain—from API to finished product. This is achieved through communication and knowledge transfer among regulatory agencies, manufacturers and distributors. The recent reciprocation between the U.S. FDA and EMA

on regulatory inspections is one positive example of shared knowledge across the supply chain.

Serialization and security in the end-to-end supply chain will soon be a global regulatory requirement. This will cover manufacturers, packaging sites, wholesalers and third-party logistics. Aggregation at packaging sites, best practices in preventing counterfeiting, tampering, theft and mapping the pharmaceutical supply chain should also be addressed.

To learn more about effective temperature-controlled supply chains, consider attending PDA's 2017 *Pharmaceutical Cold & Supply Chain Logistics* conference. Here, regulators, industry experts and solution providers will offer the latest case studies, advances and success stories. This conference has proven to be the ideal event to learn, debate, and exchange ideas about how to safeguard a secure temperature-controlled supply chain.

Pharmaceutical Cold & Supply Chain Logistics

Prague
Oct. 10–11
www.pda.org/eu-ColdChain2017

Regulatory Briefs

Regulatory briefs are compiled by PDA member volunteers and staff directly from official government/compendial releases. Links to additional information and documentation are available at www.pda.org/regulatorynews.

North America

Supply Chain Pilot Commenting Period Extended

The U.S. FDA has extended the commenting period relating to supply chain elements of the Drug Supply Chain Security Act (DSCSA). The Agency is requesting comments on product identifiers for product tracing, supply chain technical capabilities, and identification of system attributes needed under the DSCSA.

Comments now close April 30, 2018.

Europe

EMA Addresses UK Exit

On May 2, EMA released a Q&A document in response to the United Kingdom's withdrawal from the European Union. This document covers procedures for marketing authorization holders currently established in the United Kingdom, orphan designation procedures, role of Qualified Persons, etc. EMA expects to update this document in the future.

In addition, a recent meeting of EMA's Management Board covered how the Agency will handle the UK's plans to exit the European Union. The Agency is working on the assumption that the UK will be considered a third country outside the EU and European Economic area as of March 30, 2019, and will continue to participate in all formal meetings and retain its speaking and voting rights.

MHRA Publishes Inspection Data

MHRA released its annual report covering inspection findings of facilities producing drug product for the UK market in May. This report covers 324 inspections in 2016, of which 34% were of overseas facilities. Top deficiencies noted in the report included issues with quality systems, sterility assurance concerns, production problems, complaints/recalls, and more. MHRA releases this data publicly so companies can use it as part of continuous improvement.

Counterfeit Enters German Drug Supply Chain

According to a June press release from the German Federal Institute for Drugs and Medical Devices, a batch of hepatitis C drug, Harvoni®, has entered the German drug supply chain. A patient notified authorities of a difference in the color of the product. Gilead Sciences, the manufacturer, recalled the batch; analysis showed that the product had been repackaging and relabeled.

Counterfeit Harvoni® batches have also been discovered in Israel, Japan and Switzerland over the past 18 months. The Federal Institute for Drugs and Medical Devices is working with EMA and other regulatory agencies to determine if other European markets have been affected.

Key Regulatory Dates

Comments Due

April 30, 2018 — Supply Chain Pilot Commenting Period Extended

Asia-Pacific

CFDA Releases GMP Inspection Data

In early June, the China FDA released its annual drug inspection report for 2016. The Agency conducted 431 total inspections, including GMP inspections. The report shows another year of growth in the number of inspections of overseas manufacturers ordered by CFDA; however, the Agency only performed a fraction of these planned visits.

Toolkit to Support Supply Chain

Recently, the U.S. FDA led a collaboration effort with participating Asia Pacific Economic Cooperation (APEC) regions to create a Supply Chain Security Toolkit for Medical Products. This toolkit contains training materials to educate regulators and industries in the Asia-Pacific region on best practices for ensuring the security of medical products in the supply chain. Training materials cover GMP, GDP, track and trace systems, surveillance/monitoring, etc. To further establish best practices in the global supply chain, APEC plans to also develop Training Centers of Excellence for Regulatory Science which will be responsible for furthering training on the toolkit.

The Parenteral Drug Association presents the...

2017 PDA Visual Inspection Forum

October 23-24, 2017 | Bethesda, MD

Bethesda North Marriott Hotel & Conference Center

Exhibition: October 23-24 | Courses: October 25-26

#PDAVisual

Register by **Sept. 8** and save up to $200!

Photo courtesy of John Shabushnig, *Insight Pharma Consulting LLC*

The 2017 *Visual Inspection Forum* is an excellent opportunity to learn more about visual inspection and to discuss inspection challenges with the experts, including representatives from the U.S. FDA.

At the forum, you will hear topics on:

- Regulatory Compendial Issues
- Particle Control and Characterization
- Challenging or Difficult-to-Inspect Products
- Lyophilized Product Inspection
- Manual, Automated and Biopharmaceutical Inspections
- Primary Packaging Materials

And, as in past years, the Forum will feature an exhibition where attendees can see the latest in commercial inspection hardware and discuss production needs with key suppliers of inspection systems and services.

Learn more and register at *pda.org/2017Visual*

Following the Forum, PDA Education will hold a two-day *Introduction to Visual Inspection* course, **Oct. 25-26**, where you can develop practical inspection skills that can be applied to both manual human and automated machine inspection.

Discover more about this course at *pda.org/2017OctVi*

2017 PDA/FDA Joint Regulatory Conference

Regulatory Submissions: No Longer Paper-Based

Matthew M. Lowe, MasterControl

Last year, the U.S. FDA granted 22 novel drug approvals for conditions ranging from eczema and asthma to spinal muscular atrophy and certain types of ovarian cancer ***(1).*** New treatment options like these happen, in large part, due to faster and more efficient technology-driven clinical trials and approval processes.

R&D has always been closely linked with technological advances, but such has not been the case for regulatory compliance. Those of us who have been in the life sciences a long time will remember a time when the FDA required truckloads of paper submissions. Regulatory compliance used to entail color-coded stamps for various documents, countless binders of paper documents, gigantic cabinets for storing files in a room, and even an entire floor dedicated to file storage, etc.

These oppressive manual processes compelled many life science companies to partly or completely automate their quality systems,. In the early 1990s, a group of pharmaceutical companies met with FDA to find out how they could submit voluminous documents electronically. This ultimately led to the development of 21 CFR Part 11, which established the criteria for the use of electronic records and electronic signatures by organizations under FDA jurisdiction ***(2)***.

The regulation went into effect in August 1997, but it took FDA two guidances (issued in 2001 and 2003) to explain the regulation's scope and application. The 2003 guidance signaled that, at last, FDA had embraced technology for compliance purposes. As such, Part 11 is one of the key regulations that helped modernize the compliance process for life science companies.

In addition to Part 11, other highly important laws and initiatives have led to increased use of technology in the area of compliance for the past 13 years. Each one has served, piece-by-piece, to advance the modernization of compliance into the evolving, technological practice it is today.

Key Initiatives in Growth of Electronic Compliance Documents 2003–2016

2003: FDA issues the second guidance for 21 CFR Part 11, meant to allow the widest possible use of electronic technology for FDA submissions and compliance purposes.

2004: PhRMA (Pharmaceutical Research and Manufacturers of America) issues the Signatures and Authentication for Everyone (SAFE) digital signature standard for pharmaceutical, biotech and healthcare industries worldwide. It is intended to encourage the use of digital signatures as part of an electronic environment within the industry.

2005: FDA issues a guidance on the use of structured product labeling (SPL) format, a Health Level 7 (HL7) international standard, for submissions containing establishment registration and drug listing information.

2007: Congress passes the FDA Amendments Act, expanding ClinicalTrials.gov submission requirements.

2008: FDA launches the Sentinel Initiative, a national electronic system designed to track the safety of drugs, medical devices and biologics once they reach the market. The project is planned to be implemented in stages. So far, FDA has implemented a mini-Sentinel.

2008: In the pharmaceutical industry, the electronic common technical document (eCTD) becomes the standard for electronic submission to CDER and CBER. The eCTD specifies how electronic submissions should be created, reviewed and archived.

2010: The Physician Payments Sunshine Act is passed, requiring drug and medical device manufacturers that participate in U.S. federal healthcare programs to report payments and items of value they give to doctors and providers. The reporting is to be done electronically through the Open Payments Program.

2011: FDA introduces the Innovation Pathway pilot, a priority review program for pioneering medical devices. Under this program, the FDA can conduct premarket reviews within 150 days of submission, about half the time of approval for non-priority products.

2012: Congress creates a new category of "breakthrough therapy" in the Food and Drug Administration Safety and Innovation Act (FDASIA), which becomes law in July 2012. This category refers to an expedited process of review and approval of new drugs for life-threatening illnesses. This is in addition to expedited approval processes already in place: priority review designation (1992), fast track designation (1997), and accelerated approval (1997).

2013: FDA releases a final rule establishing a unique device identification (UDI) system to identify medical devices through distribution and use. A UDI is a unique numeric or alphanumeric code.

2014: FDA requires device manufacturers and importers to electronically submit mandatory reports of adverse events (known as eMDR).

2014: FDA's 510(k) eSubmissions Pilot Program offers a pathway for the construction and submission of a premarket notification application electronically without the requirement of a hard copy or a compact disk. It becomes known as "turbo 510(k)" because it's similar to the Turbo Tax® electronic process for taxpayers.

2015: FDA finalizes its guidance requiring most eCTD submissions to be submitted electronically, including new drug applications (NDAs), biologic license applications (BLAs), and investigational new drug applications (INDs).

2015: FDA's Adverse Reporting System/MedWatch requires that applicants electronically submit all MDRs, MDR attachments, and periodic safety reports.

2015: FDA's Center for Devices and Radiological Health (CDRH), along with its Offices of Device Evaluation (ODE) and In Vitro Diagnostics and Radiation (OIR) participate in the International Medical Device Regulators Forum's (IMDRF) Regulated Product Submission (RPS) Pilot Program. FDA's goal with this program is to implement a standards-based fully electronic receipt, review, dissemination and archival environment. The RPS program is meant to harmonize electronic submission methods for pharmaceutical and medical device industries.

2016: The 21st Century Cures Act, which addresses a wide range of healthcare concerns, includes important technology-related provisions, such as creating a reporting system on the electronic health record usability, interoperability and security by stakeholders and setting up an electronic provider directory to facilitate data exchange.

All of the initiatives and regulations outlined above has served to advance the field of regulatory compliance. While technology helped spur the development of medical products, as well as expedited clinical trials and approval processes like never before in the past decade, it has also enhanced the ways these are regulated. Technology will continue to play a significant role in the future, both in regulatory compliance and in fostering continued growth of the life science industry.

[Editor's Note: Learn more about compliance from representatives of the author's company at Booth 13 in the Exhibit Hall at the *2017 FDA/PDA Joint Conference.*]

References

1. Novel Drug Approvals for 2016, *U.S. FDA*, (January 26, 2017) http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm483775.htm (accessed May 31, 2017).
2. Rothke, B. "21 CFR Part 11—The Biggest Security Regulation You've Never Heard of." *ISSA Journal* 2 (2004): 16.

About the Author

Matthew M. Lowe, Executive Vice President at MasterControl, is a mechanical engineer with over a dozen years of medical device experience in product development, product management, and regulatory compliance. He is also the author of *Convergence of Compliance and Technology: How Technology Has Changed Regulatory Compliance in the Past Decade.*

The Parenteral Drug Association presents...

2017 PDA Annex 1 Workshop

October 2-3, 2017 | Washington, DC
Omni Shoreham Hotel
Exhibition: October 2-3
#2017Annex1

Register by **Aug. 21** and save up to $200!

Photo courtesy of Sartorius AG

The much-anticipated revision to *Annex 1: Manufacture of Sterile Medicinal Products* will require changes on the part of pharmaceutical manufacturers. At The *2017 PDA Annex 1 Workshop*, experts involved in the development of the Annex 1 revision will provide background, interpretation and expectations related to the revision and how it will impact the industry.

This informative Workshop will focus on the most challenging aspects of modern aseptic processing facing globally oriented companies. **Andrew Hopkins**, Chair of the PIC/S EMA working group for the revision of Annex 1 will present the opening address.

Other topics of interest include:

- Expectations for and effective use of risk-based decision making and planning
- Design, classification and operation of clean room facilities
- Better use and interpretation of environmental monitoring
- Advantages and disadvantages of the revisions as they relate to pre-use post sterilization integrity testing (PUPSIT) of sterilization filters, vapor phase hydrogen peroxide sterilization, container closure integrity and reaction to microbial excursions

Don't miss this opportunity to engage with colleagues, industry experts and regulatory leaders and to provide feedback for the health authorities on this important and influential document!

Visit *pda.org/2017Annex1* to learn more and register.

From a Compliance to a Quality Mindset

Melissa Seymour, Biogen

PDA is recognized as a technical leader and voice for industry in the field of pharmaceutical science and technology. One of the goals of PDA's 2020 Strategic Plan is to provide both regulators and industry the knowledge and tools needed to drive a new mindset—one that goes beyond compliance toward continuous improvement, quality performance and true quality innovation. PDA's passion for modern quality systems covers a wide range of activities including development of technical reports, responses to regulatory initiatives and collaboration with regulators as the industry moves toward modernization. These are all crucial to PDA's strategy to "lead the dialogue for new topics and improvements with regulators worldwide." In fact, PDA is doing just that in multiple areas.

PDA has been actively involved in the discussion of quality metrics and quality culture since 2013, holding multiple successful workshops on the topic and contributing comments to the U.S. FDA based on discussion from the workshops. In January, the FDA announced an extension of the commenting period for its revised quality metrics guidance document. PDA was one of several organizations urging FDA to extend the deadline for comments, and in March, PDA submitted a response to the draft guidance. In February, PDA held an interactive conference on quality metrics/quality culture, featuring FDA speakers and panelists. Another upcoming opportunity to hear from FDA will occur at the *PDA/FDA Joint Regulatory Conference* in Washington, D.C. on Tuesday, Sept. 12, in session "A3: Quality Metrics."

Data integrity is another area where PDA has taken a lead in driving industry thought processes and regulatory collaboration. In April 2016, PDA collaborated with MHRA on a workshop in London followed by three additional workshops in Washington, D.C., Berlin and San Diego. PDA also commissioned the book, *Assuring Data Integrity for Life Sciences*, which was published in 2016. This year, in March, PDA responded to the China FDA's draft data integrity guidance. PDA is also creating a series of technical reports intended to provide technical tools for addressing data integrity. These are being created by teams of volunteers from both industry and regulatory agencies. The first one in the series will focus on data integrity within the laboratory system. In addition, the *2017 PDA/FDA Joint Regulatory Conference* in Washington, D.C. will include an FDA perspective on data integrity from **Carmelo Rosa**.

Last year, PDA established a task force with the official title of Post Approval Change Innovation for Availability of Medicines, or PAC iAM℠. This task force seeks to transform the current paradigm for post-approval changes (PACs). Two Points to Consider documents on the topic have already been published in the *PDA Journal of Pharmaceutical Science and Technology.* One focused on communication and knowledge exchange between regulators and marketing authorization holders, and the other focused on pharmaceutical quality system effectiveness as a key aspect of innovation for PACs. The task force has also delivered an industry survey, the results of which were provided at a breakfast session during the *PDA Annual Meeting*. The task force also anticipates publishing an article on the survey results in July 2017. The *2017 PDA PAC iAM Workshop* will provide insights on how industry and regulators are working together to support PACs through the development of a new guidance, ICH Q12. The goal of this task force is to identify, assess and address current barriers to implementation of PACs, and how companies can ensure continued operations and drive innovation and continual improvement.

Collaboration between industry and regulators is key in driving the industry to move from a compliance mindset to a quality mindset in order to provide quality medicines to patients in need. PDA and its technically diverse members have the ability to influence the future course of the pharmaceutical industry.

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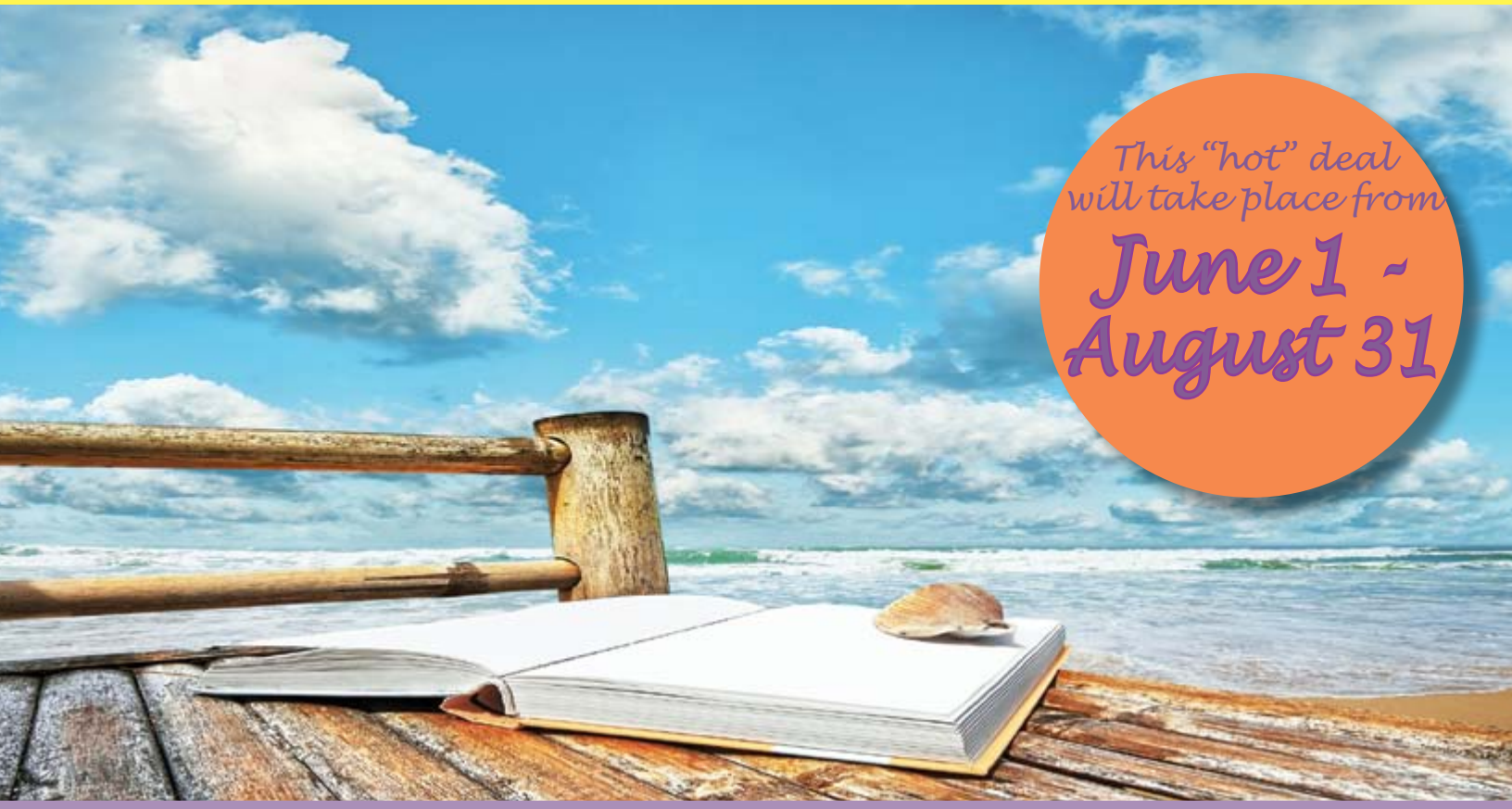

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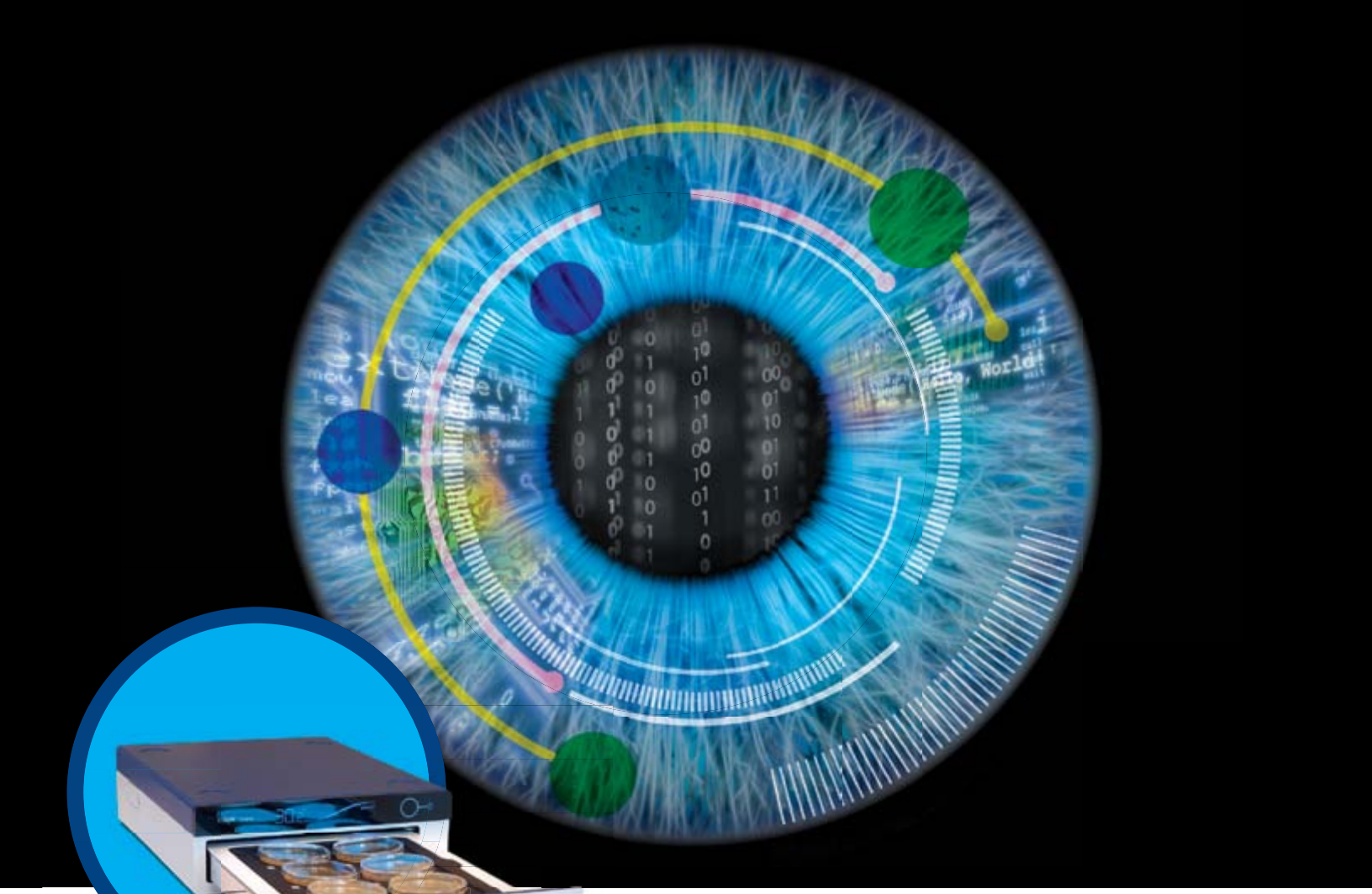

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