People • Science • Regulation

PDA Letter

Volume LII • Issue 1 www.pda.org/pdaletter January 2016

Managing Post-Approval Changes in a Global Environment:

The Case for Product-Based Impact Assessments

20

PDA ***Education*** *– Where Excellence Begins*

The Parenteral Drug Association presents...

Environmental Monitoring Course Series

February 16-18, 2016 | Bethesda, MD

PDA Training and Research Institute

BACK BY POPULAR DEMAND!

Start the Year off Right – Learn strategies, methods and regulatory expectations for monitoring controlled environments at the *Environmental Monitoring Course Series*.

Give your career a boost in 2016! From Feb. 16-18, learn to identify microbial and particulate control concepts and principles as they relate to the manufacture of pharmaceutical products. The courses in this series will also address establishing new as well as reassessing current EM programs to stay compliant with industry standards.

GSA Schedule Contract GS-02F-113BA

The *Fundamentals of an Environmental Monitoring Program* course, Feb. 16-17, is based on PDA's Technical Report No. 13 (revised 2014). Through a combination of lecture and hands-on laboratory instruction, you will learn how to develop a surface and air environmental monitoring program for PDA's clean room. You will be able to utilize the information presented in the lectures to determine appropriate sampling sites and methods based on area classification, activities performed and surface type.

On Feb.18, the *Establishment of a Risk Based Environmental Monitoring (EM) Program* course will teach you how to utilize risk tools to determine microbial contamination sources in production environments and processes as well as perform EM risk assessments using tools such as Fishbone, FMEA and HACCP.

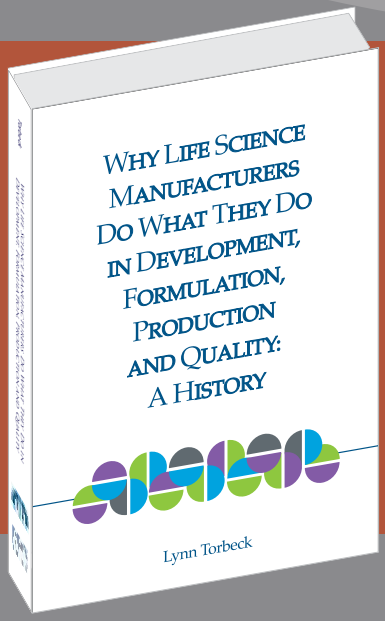
Discounts apply when you register for both courses!

Don't miss this opportunity – Register today at pda.org/2016EMCourses!

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

Denotes Laboratory Course | GSA Schedule Denotes GSA Schedule Contract

PDA Bookstore New Release



WHY LIFE SCIENCE MANUFACTURERS DO WHAT THEY DO IN DEVELOPMENT, FORMULATION, PRODUCTION AND QUALITY: A HISTORY

BY: LYNN TORBECK

PDA MEMBER PRICE: $210

ITEM NO. 17333

In a passionate retrospective of a successful career built on thinking statistically and applying that approach to quality in pharmaceutical manufacturing, Lynn Torbeck has created a "must-read" for anyone involved in product development, formulation, manufacturing and quality. Each of the 45 chapters in this book addresses a specific aspect of applied statistics and provides pragmatic applications on such topics as:

- Can we save the Technical Conference?
- %RSD friend, Foe or Faux?
- OOS, OOT, OOC and OOSC
- Can AQLbe Zero?
- Outlier Management
- Why 5%?
- Design Space Circa 1987
- Quality by Design Circa 1982
- Training Scores

Because this book is not organized in a linear fashion, Torbeck encourages readers to dip into any chapter that is of interest. This book is not a statistics text per se; however, it shares the author's passion and decades of experience for statistics applied to pharmaceutical quality by showing how they can be used in real-world pharmaceutical quality problems.

go.pda.org/dowhattheydo

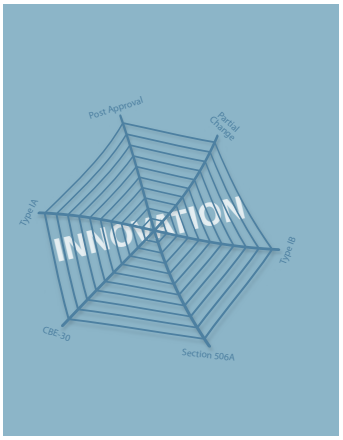
ABOUT THE AUTHOR

LYNN D. TORBECK, started Torbeck and Associates in 1988 providing training and consulting in applied statistics and experimental design for pharmaceutical and biopharmaceutical development, quality assurance and control. Specific effort was targeted to process and method validation under cGMPs. Publications include many journal articles, books and chapters. Specifically, *Trend and Out-of-Trend Analysis for Pharmaceutical Quality and Manufacturing Using Minitab®, Validation by Design and Square Root of (N) Sampling Plans* as well as a chapter in *Pharmaceutical Quality* titled *Using Statistics to Measure and Improve Quality.*

PDA Letter

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

Cover



Cover Art Illustrated by Katja Yount

Departments

News & Notes

People

Science

Regulation

Voices of PDA

Contents

Features

2016 Board of Directors

PDA is pleased to announce the results of the 2015 Board of Directors and Officers election.

Executive Committee

Congratulations to **Martin VanTrieste,** Senior Vice President of Quality, Amgen, Inc., who assumes the role of PDA Chair for the 2016–2018 cycle.

Rebecca Devine, PhD, Biopharmaceutical Consultant, has been elected as Chair-Elect.

Michael Sadowski, Director, Research, Baxter Healthcare, has been elected as Treasurer.

Jette Christensen, Principal Compliance Specialist, Novo Nordisk A/S, was elected to the position of Secretary.

Hal Baseman, Chief Operations Officer, ValSource, moves into the Immediate Past Chair position for the next two years.

PDA would also like to thank **Anders Vinther,** PhD, Chief Quality Officer, Sanofi Pasteur, for serving as PDA Chair in 2012–2014 and as Immediate Past Chair for 2014–2016.

Chair
Martin VanTrieste
Amgen

Chair-Elect
Rebecca Devine, PhD
Regulatory Consultant

Secretary
Jette Christensen
Novo Nordisk

Treasurer
Michael Sadowski
Baxter Healthcare

Immediate Past Chair
Hal Baseman
ValSource

Directors

PDA Congratulates and welcomes the following new directors to the Board: **Anil Sawant,** PhD, Vice President, Quality Management Systems and External Affairs, Merck, and **Melissa Seymour,** Vice President, Corporate Quality, Biogen.

Returning to the Board is **Susan Schniepp,** Consultant, Regulatory Compliance Associates, who previously served on the Board from 2011–2013.

Stephan Rönninger, PhD, Amgen, was reelected to the Board for a second consecutive three-year term.

PDA thanks **Gabriele Gori,** Vice President, Audit and Risk Management, GSK Vaccines, **Lisa Skeens,** PhD, Vice President, Global Regulatory Affairs, Pfizer, and **Ian Elvins,** President, Elvins & Associates, for their service to the Board.

Masahiro Akimoto
Toray

Deborah Autor
Mylan

Joyce Bloomfield

Ursula Busse, PhD
Novartis

Veronique Davoust
Pfizer

Emma Ramnarine
Genentech/Roche

Stephan Rönninger, PhD,
Amgen

Anil Sawant
Merck

Susan Schniepp
Regulatory Compliance
Associates

Melissa Seymour
Biogen

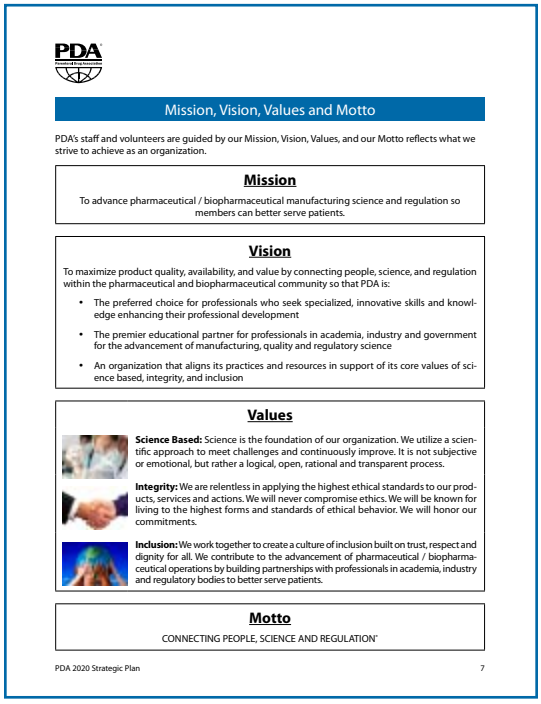
Glenn Wright
Eli Lilly and Company

2020 Strategic Plan Released

In December, PDA officially released the Association's 2020 Strategic Plan. This plan will help prepare PDA for the future by emphasizing activities supporting key strategic priorities over the next four years.

There are four strategic areas of focus outlined by the Strategic Planning Committee and the Board of Directors. These are:

- **People –** Enhancing the value of PDA membership
- **Science –** Achieving recognition as a global leader
- **Regulation –** Assisting regulators and industry by developing technically focused tools
- **Leadership and Management –** Fostering an environment that allows PDA to flourish and achieve its mission and vision



PDA

Mission, Vision, Values and Motto

PDA's staff and volunteers are guided by our Mission, Vision, Values, and our Motto reflects what we strive to achieve as an organization.

Mission

To advance pharmaceutical / biopharmaceutical manufacturing science and regulation so members can better serve patients.

Vision

To maximize product quality, availability, and value by connecting people, science, and regulation within the pharmaceutical and biopharmaceutical community so that PDA is:

- The preferred choice for professionals who seek specialized, innovative skills and knowledge enhancing their professional development
- The premier educational partner for professionals in academia, industry and government for the advancement of manufacturing, quality and regulatory science
- An organization that aligns its practices and resources in support of its core values of science based, integrity, and inclusion

Values

Science Based: Science is the foundation of our organization. We utilize a scientific approach to meet challenges and continuously improve. It is not subjective or emotional, but rather a logical, open, rational and transparent process.

Integrity: We are relentless in applying the highest ethical standards to our products, services and actions. We will never compromise ethics. We will be known for living to the highest forms and standards of ethical behavior. We will honor our commitments.

Inclusion: We work together to create a culture of inclusion built on trust, respect and dignity for all. We contribute to the advancement of pharmaceutical / biopharmaceutical operations by building partnerships with professionals in academia, industry and regulatory bodies to better serve patients.

Motto

CONNECTING PEOPLE, SCIENCE AND REGULATION®

PDA 2020 Strategic Plan 7

PDA will establish programs and initiatives to advance the key objectives in each of these areas and will regularly measure progress toward achieving the 2020 Strategic Plan through its education opportunities, conferences, publications and networking opportunities.

To access the 2020 Strategic Plan, go to https://www.pda.org/footer/about-pda.

PDA Volunteer Spotlight

Morten Munk

- Senior Technology Partner
- *NNE Pharmaplan A/S*
- Member Since | 2006
- Current City | Copenhagen, Denmark
- Originally From | Viborg, Denmark

I have met some of my best friends through PDA

At one point, Morten considered becoming a forest administrator

How has volunteering with PDA benefited you professionally?

I do not believe I would have the areas of responsibilities in my current job without having learned from my network within PDA.

Tell us about some of your volunteer work for PDA.

I have presented at numerous conferences in the United States and Europe, served as a member of the organizing committees for several conferences, chaired the recent PDA outsourcing conference in Copenhagen, provided input as a member of the Biotech Advisory Board and was involved in several technical reports.

I enjoyed all these activities as they gave me the possibility to work and share knowledge with so many talented colleagues in the industry as well as the always professional and supporting PDA staff.

How can I get started volunteering for PDA?

I would suggest getting involved in organizing a workshop or a conference within the area of your expertise. And always remember that the more you offer/give to the organization the more you get back.

What qualities do you like to see in a manager?

A person who is able to see the best in each member of their staff and to support further successful development of each individual.

What are some of the latest trends in your area?

I'm extremely excited about the growing interest in the industry for continuous manufacturing, especially within the downstream area, where one of the hot topics is continuous chromatography. The field of continuous chromatography is also supported by the relatively recent introduction of prepacked columns and other advances within single-use technology, which is another of my favorite developing technologies.

Another area where I also believe continuous manufacturing can be part of the solution, is the increased focus on finding sustainable solutions for the challenges we are facing for the future growth and welfare of all inhabitants of our world.

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

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

You can too!
Authors wanted

For more information on PDA publishing please visit:

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

chapter update

Chapter Tours United Airlines Cold Chain Cargo Facility

Jeff Cook, Baxter Healthcare Corporation

In August, PDA's Midwest Chapter hosted a special all-day event on GDPs for cold chain product that included an opportunity for attendees to tour a United Airlines Boeing 777.

Chapter Secretary **Diane Knight** opened the event, and after a quick breakfast, attendees boarded a chartered bus to visit the United Cargo Facility at Chicago O'Hare International Airport. **Jan Krems**, President of United Cargo, welcomed everyone to the facility and started the tour. The tour included multiple behind-the-scenes stops in the facility along with discussion of facility procedures that related to cold chain storage GDPs for pharma-related products. The tour culminated in the chance for attendees to examine a working Boeing 777 aircraft set aside specifically for this event.

Following the tour, attendees spent the afternoon listening to presentations and discussion on cold chain topics. These included the following speakers:

- **Karl Kussow:** "Transportation Best Practice for Medicinal Products"
- **Chris Fore:** "Where We Are As An Industry? Protecting Patients Though An Unbroken Cold Chain"
- **Jim Chrzan:** "GDPs in General"

The chapter thanks Diane Knight and United Cargo for making this a truly memorable event.

PDA Who's Who

Diane Knight, Sales Manager, Envirotainer

Jan Krems, President,United Cargo

Karl Kussow, Manager, Manager, Quality and Validation, Fedex Custom Critical

Chris Fore, Envirotainer

Jim Chrzan, Publisher, *Healthcare Packaging*

Experts Underscore Key Role of Data Integrity

Eoin Hanley, PharmOut, Committee Member and Membership Liaison, Australia Chapter

Attendees sat rapt through three talks on data integrity at a heavily attended dinner meeting hosted by PDA's Australia chapter this past summer. Data integrity is a hot topic, not just for Australian pharma companies, but for firms across the globe, particularly in light of recent regulatory actions citing firms' failure to maintain integrity of data.

Australian regulator **Stephen Hart** opened the session. His talk outlined TGA's expectations on data integrity, including data integrity principles and examples of poor data integrity. His key message? Manufacturers must always keep data integrity at the forefront and understand vulnerabilities in this area. Companies have a responsibility to detect and prevent data integrity breaches.

Next, **Trevor Schoerie** discussed the three "Fs" of data integrity failures. These are:

- Fat fingers – inadvertent data entry errors by individuals
- Falsification – deliberate data entry errors by individuals
- Fraud – collusion by two or more individuals

He also shared his experiences on how best to design systems to ensure integrity according to PIC/S recommendations and U.S. FDA 21 CFR Part 11.

Mark Dickson closed out the evening with insights on common data integrity pitfalls from his work in compliance and inspections. He also pointed out what to look for when auditing for data integrity deficiencies. Companies should perform self-audits, he recommended, and ensure that all staff working in GMP areas remain aware of the importance of good data integrity.

The evening also included a lighter moment when the chapter recognized **Malcolm Tipping** for his 11 years as a member of the PDA Australia Chapter in addition to his various roles as an officer for the chapter.

PDA Who's Who

Mark Dickson, Senior Compliance, Novartis

Stephen Hart, Senior Inspector, Therapeutic Goods Administration

Trevor Schoerie, Managing Director, PharmOut

Malcolm Tipping, Validation Manager, BioCSL

10th Annual Global Conference on Pharmaceutical Microbiology

Plenary Sessions

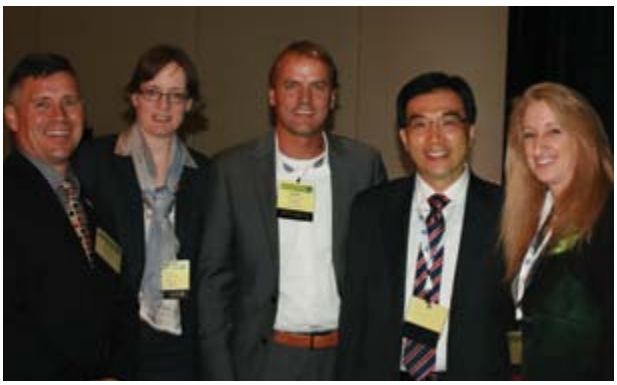
P2: Urban Myths
(l-r) Rich Levy, PhD, PDA; David Hussong, PhD, ValSource; Timothy Sandle, PhD, Bio Products Laboratory; Capt. Sharon Thoma, PharmD, U.S. FDA

P3: The Impact of an Altered Microbiome on Inflammation and Disease
(l-r) Amy McDaniel, PhD, Pfizer; Andrew Gewirtz, PhD, Georgia State University

P4: Emerging Leaders
(l-r) Osama (Sam) Elrashidy; Ayako Hasegawa, PhD, Allergan; Lia Jeffrey, PhD, Genentech; Susan Hatley, Pfizer; Jarett Scalzo, Agensys

Breakout Sessions

A1: Rapid Micro Methods: Past Case Studies and Where Are They Now?
(l-r) Michael Miller, PhD, Microbiology Consultants, LLC; Amy McDaniel, PhD, Pfizer; John Duguid, Vericel Corporation; Bryan Riley, U.S. FDA



A2: Innovative Technologies
(l-r) Jeffrey Weber, Pfizer Global Supply; Pieta Ijzerman-Boon, Merck & Co.; Geert Verdonk, PhD, Merck & Co.; Joseph Chen, PhD, Genentech; Amy McDaniel, PhD, Pfizer

B2: Applications of Risk Assessment: Case Studies
(l-r) Kalavati Suvarna, PhD, U.S. FDA; Paula Peacos, Bristol-Myers Squibb; Bryan Riley, U.S. FDA; Jim Polarine, Steris Corporation

A3: Biofilms and Endotoxin
(l-r) Mark Pasmore, PhD, Baxter Healthcare; Patricia Hughes-Troost, PhD, U.S. FDA; Cheryl Platco, Merck Research Laboratories; Vinayak Pawar, PhD, U.S. FDA

A4: Biotechnology
(l-r) Kim Sobien, Merck; Tyler Tsang, Genentech; Reyes Candau-Chacon, PhD, U.S. FDA; Leesa McBurnie, Meissner Filtration Products

B3: Quality and Microbiology
(l-r) Osama (Sam) Elrashidy; Marsha Stabler Hardiman, ValSource; Katalin Kiss, PhD, ATCC; Liz Kerrigan, ATCC; Dennis Guilfoyle, PhD, J&J

B4: Global Harmonization
(l-r) Hal Baseman, ValSource; Julie Barlasov, Perritt Laboratories; Anil Sawant, PhD, Merck

10th Annual Global Conference on Pharmaceutical Microbiology

10th Anniversary Celebration | Gala Awards Dinner

Members of the Original Planning Committee

The following individuals were recognized for serving on the planning committee for the original conference (l-r): Michael Miller, PhD, Microbiology Consultants; Rich Levy, PhD, PDA; Eric Dewhurst, Johnson & Johnson; David Hussong, ValSource; Terry Munson, PAREXEL; Tony Cundell, PhD, Microbiological Consulting; Radha Tirumalai, PhD, USP

Other Committee Honorees

The following were recongized for their service on various planning committees (l-r): John Metcalfe, PhD, U.S. FDA; Amy McDaniel, PhD, Pfizer; Julie Barlasov, Perritt Laboratories; Capt. Sharon Thoma, PharmD, U.S. FDA; Kim Sobien, Merck; Osama (Sam) Elrashidy; Ed Balkovic, PhD, Genzyme; Marsha Stabler Hardiman, ValSource; Kalavati Suvarna, PhD, U.S. FDA; Vinayak Pawar, PhD, U.S. FDA

Passport Raffle

Dave Kremer won a Fitbit charge from BioVigilant

Boston Analytical awarded an Amazon Echo to Philip Istafanos

Gretchen Brunner won an iPad Mini from bioMerieux

Charles River gave an iPad Mini to Amberly Bradberry

Chris Knutsen walked away with a GoPro from Lonza

Leticia Portalatin won a beer stein from EMD

PDA awards Crystal Booth an Apple Watch

Hilary Chan received a gift card from Novatek

Associates of Cape Cod awarded Cliff Poindexter a gift card

snapshot

Making Visual Inspection of Opaque Product Less Cloudy

Jahanvi (Janie) Miller, PDA

In recent years, regulatory authorities have increasingly focused on particulate matter and defect control. For example, USP developed guidelines for clear liquids through <790> *Visible Particulates in Injections*. Clear liquids can be 100% visually inspected, however, products which are "opaque," such as dry powders, API suspensions, etc., cannot be 100% inspected for visible particulates. This means that opaque products require a supplemental method for routine inspection. But inspection is only one issue for many opaque products, which may depend on the particle-burden of the sterile bulk API. The latter is typically produced at a different facility than the final dosage fill/finish facility.

These highly specific manufacturing processes are very different from those used for clear liquids, and require a lifecycle strategy that can control bulk API manufacturing as well as the fill/finish process. In addition, bulk API of the finished product must undergo statistically valid destructive testing in order to monitor the particle populations. Due to the lack of detailed guidance and clear best practices, PDA has established a technical report team to develop a technical report on particulate matter in difficult-to-inspect parenteral products. This team will focus on establishing a common understanding of the current particle levels found in opaque product, APIs and finished dosage. In order to develop the technical report, the team has launched a survey to ascertain current industry practices on difficult-to-inspect parenterals. The results will be analyzed and used in the technical report to support comprehensive best practices for ensuring control of particulate matter in these types of products.

If you would like to contribute your expertise in this area, please take a moment to complete the survey by Jan. 22: https://www.surveymonkey.com/r/PDAParticulateMatterDIPSurvey.

Journal *Preview*

Container Closure Topics Explored in Latest Issue of the PDA Journal

Two research articles explore container closure integrity issues in the January/February issue of the *PDA Journal of Pharmaceutical Science and Technology*. Find out the impact of vial capping on residual seal force and container closure integrity. And learn about the feasibility of fluorescence spectrophotometry for developing an immersion method for container closure integrity testing.

Review

Wei Wang, "Integration of Regulatory Guidelines into Protein Drug Product Development"

Research

Roman Mathaes, et. al., "Impact of Vial Capping on Residual Seal Force and Container Closure Integrity"

Masamitsu Izumi, et. al., "Evaluation of Bacillus oleronius as a Biological Indicator for Terminal Sterilization of Large-Volume Parenterals"

Xujin Lu, David K. Lloyd, Steven E. Klohr, "Feasibility of Using Fluorescence Spectrophotometry to Develop a Sensitive Dye Immersion Method for Container Closure Integrity Testing of Prefilled Syringes"

Technology/Application

Xiaolin Cao, et.al., "Rapid Identification and Characterization of Formulated Protein Products by Raman Spectroscopy Coupled with Discriminant Analysis"

Case Studies

Terry Wilson, et. al., "Particulate Study on NeoProfen, a Neonatal Injectable Product"

ELIMINATE PARTICULATES & FIBERS IN THE CORE.

SYNTHETIC WRITING SUBSTRATE

CleanPrint 10

- Low particulate and non-shedding
- Exceptionally durable
- Abrasion and chemical resistant
- Easy to write on
- Double bagged packaged sterile

CUSTOM DOCUMENTATION

Core2Write

- Logbooks, ID tags, Forms and Labels
- Constructed using CLEANPRINT 10
- Customized specifically per customer
- Individual unique numbering and integrity features
- RFID Technology available

HEPA FILTERED PRINTING SYSTEM

Core2Print

- Print wirelessly into cleanrooms
- Use with pre-sterilized CLEANPRINT 10
- 316L Stainless Steel Construction, can be completely disinfected
- HEPA Filter cabinet
- Sheet fed, high speed digital printer using chemical resistant ink

vai
VELTEK ASSOCIATES, INC.

15 Lee Boulevard
Malvern, PA 19355-1234 USA
(610) 644-8335

www.sterile.com

Science

Visual Inspection as Part of a Stability Program

The following blinded, unedited remarks are taken from PDA Connect℠, an online forum that allows PDA members to share some of the most challenging issues confronting the pharmaceutical industry. The discussions on PDA Connect℠ do not represent the official views of PDA, PDA's Board of Directors or PDA members. The following is taken from the Visual Inspection Interest Group Forum.

Questioner

how many of you routinely perform visual inspecton as part of the stability program? I don't mean appearance - I mean (apart from USP particulate matter testing) repeating the vis inspection performed at batch release i.e. USP black / white background or even semi-automated or automated (not sure you could do the latter for such a small sample) testing. I have a case where a company SWITCHED inspection methods mid-stability study (probably not smart) and got increased rejection rates because the new method is more sensitive. However their t0 rejection rate is around 2% for small, transient grey particles which they have never managed to isolate and around 50% after 12 months stability storage — also transient and can't be isolated. Obviously they are concerned — the vials with the grey particles pass the USP particulate matter and visual inspection method if manual. any input welcomed.

Respondent 1

The Israeli MOH expects manufacturers to test vial/ampoule for visual inspection as part of stability.

We had a case last year were this test could discover a compatibility problem between one of the product ingredients and the vial glass (not detected by particulate matter).

The visual inspection done by the QC perssonel was different from that made by the production perssonel. (no black/white background for QC). Even though the company got complaints for particles from an outsourced packaging site the investigation of the company did not revealed the problem since the visual test was done not according to the SOP in production.

Respondent 2

As directed by USP (1) and (788), physical condition and stability is evaluated at time of release and through shelf life. While it is much more common to conduct 788 assays routinely on stability, visual inspection is an important element of the program, and must be conducted in the same manner as qualified inspection on release. The situation

you describe shows why this is important. One may encounter containers with particles that have eluded detection during the initial 100% process, but will only be single to few particles near or into the Gray Zone size. Your description seems to be an intrinsic change of particle solids over time, indicating instability due to uncontrolled factor(s). Investigation by forensic methods, such as 788-2 membrane microscopy and the techniques described in USP (1787) are warranted.

Respondent 3

I agree with **[Redacted].** Here are a few more thoughts on this subject. A firm should use VI (and sub-vis particle tests) during stability studies performed during product development and for marketed product. They should focus on stability indicating visual defects (e.g., glass flakes from delamination, precipitation, agglomeration, crystallization, discoloration) and not on intrinsic and extrinsic particles (e.g., glass particles from breakage, stainless steel, elastomer, fibers) or other container and closure defects normally removed during 100% inspection after filling. The inspection method may be the same as that described in the EP and USP or an enhanced method that uses Tyndall lighting (strong light from the bottom) to enhance glass flakes and small particles. It is recommended that the sample be initially examined during a gentle swirl to see fine particles coming up from the bottom before inversion or other stronger agitation which will disperse any of these fines. This inspection is typically manual (as described in the pharmacopeias). I am not aware of anyone using semi-auto or automated inspection for this purpose.

All of this primarily applies to liquid products. Powders and lyo cakes should also be inspected but looking for particles on stability does not add much value. Here general changes in color and appearance are important.

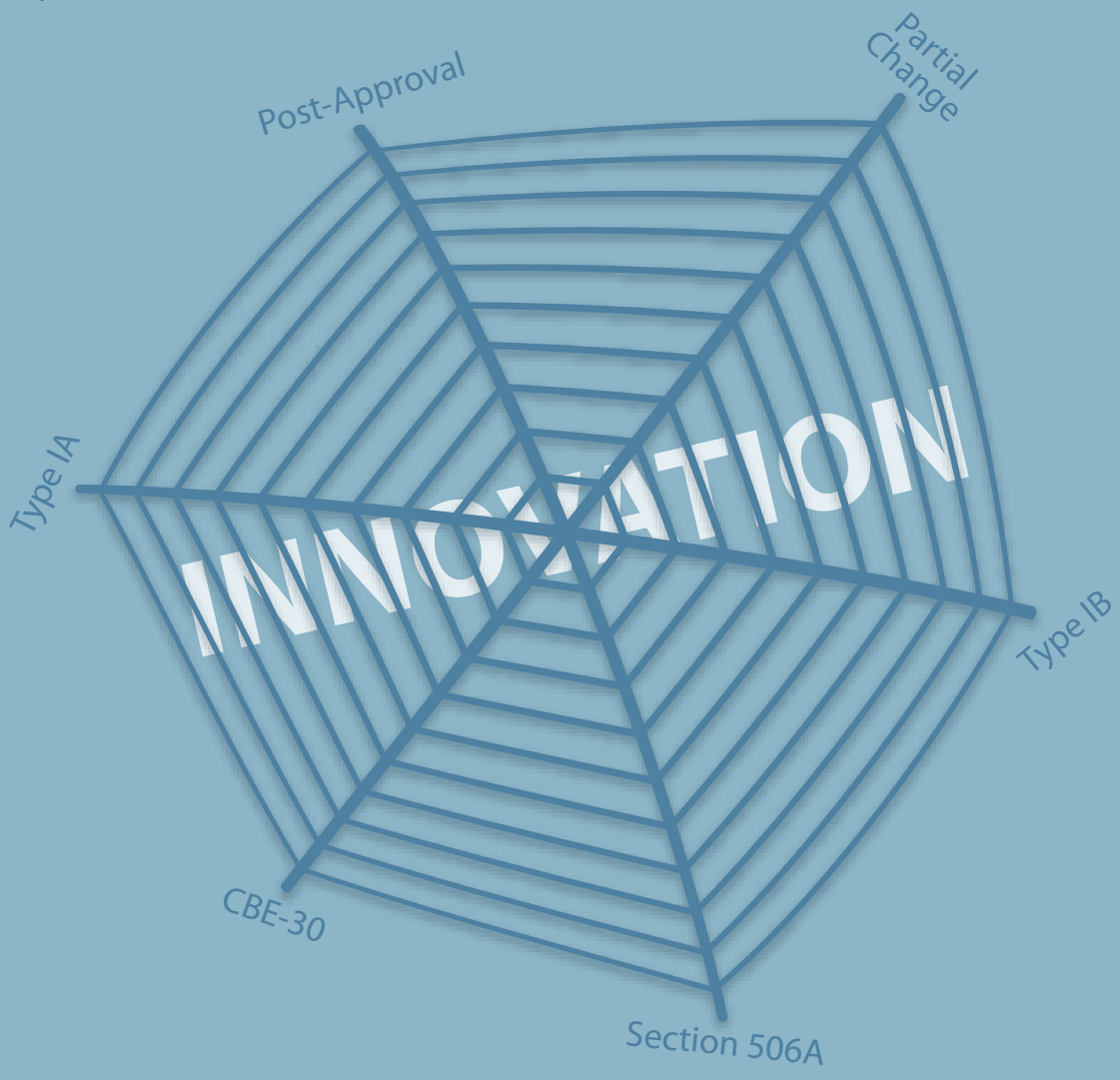
In all cases if something is detected, further investigation is needed to identify the particle. This will confirm f t is a stability indicating particle or just an extrinsic or intrinsic particle that was missed during the initial inspection. If the latter is detected, this should not be considered a stability failure, but rather an indication of the initial inspection performance. Even here, given he probabilistic nature of the inspection process, it may not be significant with regard to the quality of the batch. Here, the testing of 20 units with no further evidence of particles as described in USP <790> provides a guide. A larger sample will provide a better assessment of lot quality.

[Editor's Note: For the first time ever, PDA's Visual Inspection Interest Group will hold a one-day workshop at PDA headquarters. For more information, visit http://www.pda.org/2016visualworkshop.]

Managing Post-Approval Changes in a Global Environment:

The Case for Product-Based Impact Assessments

Jenifer Avenatti, Baxter Healthcare



As **regulatory agencies push** industry toward risk management and product design space knowledge, how can organizations with global products manage change control in a robust and efficient way? The answer to this question is multifaceted but certainly achievable.

In recent years, EMA and the U.S. FDA have rolled out major efforts focusing on quality risk management (QRM), continuous improvement and innovation with respect to product knowledge and pharmaceutical manufacturing. These two agencies have paved the way for advancement of quality-based assessments of pharmaceutical products. Both are members of the Pharmaceutical Inspection Co-operation Scheme (PIC/S), which allows these agencies to influence global regulations and trends.

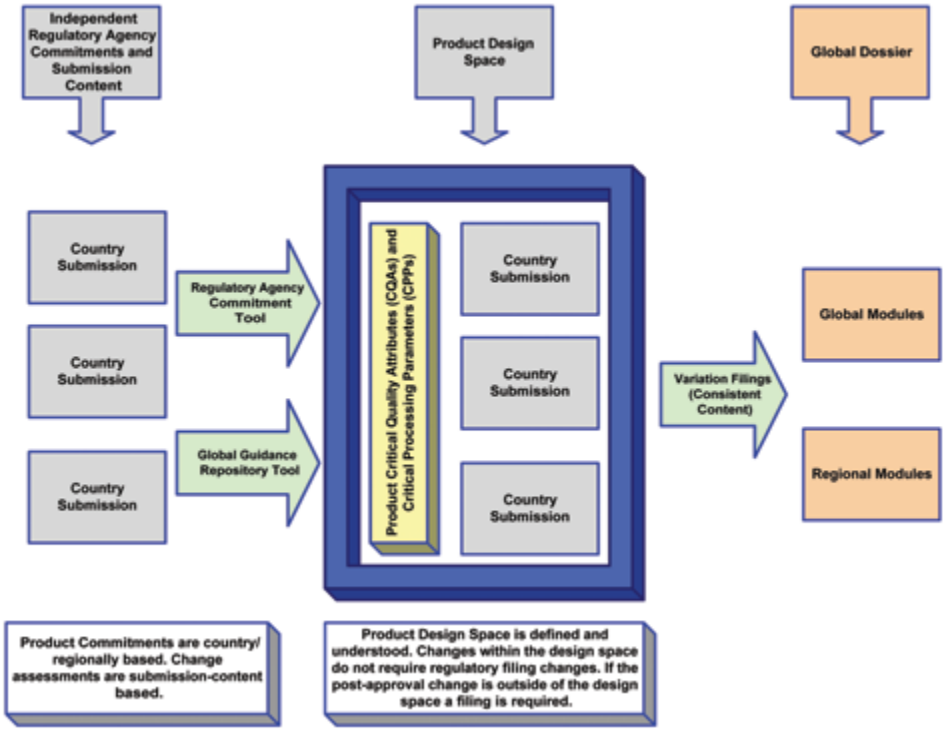
As companies continue to manage legacy products they face a laborious assessment process for post-approval changes. In particular, legacy products often have regional submissions that were authored independently, and vary in content and detail. Therefore, it makes sense to transition to a more robust process that allows for post-approval changes to be implemented in an efficient way while still maintaining regulatory compliance.

Regulatory impact assessments have traditionally been made based upon submission content that often varies across regions. If the post-approval change is not described in the submission, then the change can be deemed nonreportable. This process is not

Article at a Glance

- Product-based assessments focus more on quality of product
- Recent regulatory guidance supports new approach
- Transition may require a shift in organizational culture

Figure 1 Product-based Assessment



only time consuming, but can render assessments that vary in the level of impact identified. Plus, it does not consider product impact.

Viewing post-approval changes from a different lens, consider the use of QRM concepts. Suddenly, a new approach can be taken! This approach is a product-based assessment focused on evaluating defined product design space within the submission, or ideally, a global dossier.

Moving to product design space assessments, based upon the critical attributes and controls of the product, ensures the impact assessment is streamlined while still providing a robust impact assessment.

Not a new concept, many pharma companies have put effort into developing a global dossier that defines the product design space for newer product submissions. This quality-based approach not only provides a stronger foundation for regulatory compliance, but also saves resources since data within the submission is consistent across all regions. Implementation of global dossiers can span many years, however, and also doesn't completely solve the issue of ensuring post-approval changes are accurately evaluated for impact without seeking feedback from each region.

What does a streamlined, global change assessment look like for post-approval changes? In short, the concept can be described as switching from a "submission-based" assessment to a "product-based" assessment. **Figure 1** depicts this concept.

Product-Based Model Rooted in ICH

Currently, regulators' are leaning toward product-based assessments, particularly, in the areas of quality management and change control. As a follow-up to FDA's *Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach*, ICH guidance documents provide further explanation regarding practical application of these concepts.

ICH Q9: *Quality Risk Management* ***(1)*** defines the criteria most important for utilizing QRM in managing changes.

> *"QRM is a process that supports science-based and practical decisions when integrated into quality systems. Appropriate use of QRM does not obviate industry's obligation to comply with regulatory requirements. However, effective QRM can facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks, and might affect the extent and level of direct regulatory oversight. In addition, QRM can facilitate better use of resources by all parties."*

Table 1 Key Benefits, Challenges and Tools for Product-Based Assessments

Benefits	Challenges	Tools
Leads to consistent product design space across governing regulatory agencies and marketing regions	Global dossiers clearly defined and fully implemented for new and legacy products with consistent product design space (CQAs and CPPs)	Organizational structure that supports global alignment of regulatory affairs teams
Ensures robust, regulatory-compliant submission	Repository of translated regional submissions that include a comprehensive understanding of global regulations and their interpretations	Centralized regulatory commitment and reportable changes repository
Reduces unnecessary variation filings, resources and time required to complete assessments	Cultural shift from major markets-centric to global-centric thinking for some organizations when evaluating changes	Regulatory intelligence tools

In addition, ICH Q9 and ICH Q10: *Pharmaceutical Quality System* ***(2)*** provide specific criteria that may be utilized for performing impact assessments to post-approval changes. In summary, the focus is on quality impact to the product, while maintaining regulatory compliance—the cornerstone in the concept of implementing a product-based assessment for post-approval changes.

The following excerpts from ICH Q9 and ICH Q10 support this concept:

- *Manage changes based on knowledge and information accumulated in pharmaceutical development and during manufacturing.*
- *Evaluate the impact of the changes on the availability of the final product.*
- *Evaluate the impact on product quality of changes to the facility, equipment, material, manufacturing process or technical transfers.*
- *Proposed changes should be evaluated relative to the marketing authorisation, including design space, where established, and/or current product and process understanding.*

In 2014, regulators recognized the need to further support industry to standardize regulatory commitments within the submission. A concept paper was issued outlining a new guidance, ICH Q12: *Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* ***(3).*** This paper indicates that additional information regarding post-approval change management will be included in the new guidance; specifically:

- *Development of a harmonised approach to "regulatory commitments". Such approaches could enable post approval changes that facilitate continual improvement and encourage the adoption of innovative technologies.*
- *Delineate the appropriate level of detail and information necessary for regulatory assessment and inspection in the dossier, in order to create a more enabling post approval change management system.*

Many pharma companies have put effort into developing a global dossier that defines the product design space for newer product submissions

Reorg to Impact Post-Approval Changes

FDA's recent quality-focused reorganizaton of CDER will also impact post-approval changes, especially as the Agency recognizes the need to move beyond simply maintaining submission content, to reporting those changes that impact critical attributes of the product and process. CDER's new Office of Pharmaceutical Quality (OPQ) launched in January 2015.

A white paper on the OPQ reorganization ***(4)*** notes that:

- *OPQ will combine non-enforcement-related drug quality work into one super-office, creating one quality voice and improving our oversight of quality throughout the lifecycle of a drug product.*
- *OPQ's Office of Lifecycle Drug Products will evaluate post-approval changes to innovator drugs, as well as original abbreviated new drug applications for generic drugs, which means that knowledge about quality issues gained from review of the innovator product can be appropriately applied to the review of the generic product.*

As part of lifecycle management for approved products, OPQ will also use a risk-based approach to improve the review and management of post-approval changes. The white paper did specify two challenges for FDA and industry related to post-approval changes:

- *The number of post-approval supplements received for review has increased over the past decade, in part owing to our current practice of "locking in" an applicant's manufacturing process before it is fully optimized.*
- *OPQ will provide recommendations on approvability based on consistent drug product quality assessments.*

Table 1 provides a summary of the key benefits and challenges of the product-based assessment approach as well as tools that help to mitigate challenges.

There are many benefits of implementing product-based impact assessments. They support development and implementation of a consistent product design space across all governing regulatory agencies and marketing regions to form a global product design space. This consistent design space across products in all regions establishes the path for a robust impact assessment process. Fewer resources are required to complete the assessment and there is a reduction in unnecessary variations/supplements as changes within the design space do not require a regulatory supplement. Organizations also receive cost and time savings as post-approval change controls are processed and implemented quicker due to fewer resource requirements and reduced variations.

Most importantly, product-based assessments utilize QRM principles. Therefore, these types of assessments ensure regulatory compliance throughout the product lifecycle as regulatory assessors utilize current standards to assess post-approval changes rather than focus on the impact to the submission—which in some cases may not be up to current regulatory standards (i.e., legacy products).

May Require Change in Org Culture

With any new approach there are always challenges organizations encounter. One challenge involves implementation of global dossiers with clearly defined and consistent design space (critical quality attributes and critical process parameters) across all regions. This may prove particularly challenging for organizations with multiple legacy products. Additionally, there may not be an easily accessible central repository for regional submissions and their translations.

Some organizations may need to to undergo a cultural shift from major markets-centric thinking to global-centric thinking when evaluating changes. Postpproval changes should be assessed not only for impact, but also for an appropriate implementation strategy, i.e., understanding when a change should be implemented globally across multiple plants.

For example, if a change to the U.S. Pharmacopeia requires method validation, then this means the change needs to be implemented at all plants that manufacture the global product. The implementation strategy needs to ensure that all plants are notified, and the impact assessment performed from a global perspective. But, a change in a manufacturing plant's cleaning procedures can be managed at the plant level. If the product is marketed globally, however, then the impact assessment must be performed from a global perspective.

Finally, global assessment of post-approval changes requires a seasoned regulatory professional with a comprehensive understanding of global regulations and their interpretations.

Tools Are Available to Help with Transition

Clearly, there are many benefits to a product-based regulatory impact assessment process for post-approval changes. Yet there are also challenges to actualizing this process. As a result, an organization may consider evaluating several tools to address these challenges.

First, look at the current organizational structure. Does it support global alignment within the regulatory affairs team? This global alignment can be accomplished in several ways; one model involves one global product owner and/or global CMC owner where responsibilities are delineated based upon CTD modules. Regional or site/facility regulatory representatives may still be needed to provide global change control assessments, communicate plant and product-specific regulatory agency commitments, and perform regional agency communications and translations.

Next, utilize regulatory intelligence tools/services; these can usually be purchased for a nominal fee and provide access to the most current global regulatory requirements. Several well-recognized services include Tarius, Cortellis, RSS feeds from the Regulatory Affairs Professional Society (RAPS), and *FDANews* services.

Finally, central repository systems that house product-specific and regional specific regulatory agency commitments along with summaries of relevant global guidances and reporting categories should be developed and maintained. These systems support regulators' abilities to perform global impact assessments while also maintaining regulatory compliance. Central repository systems can be built using internal IT resources and existing database tools such as SharePoint software, or a 21 CFR Part 11 compliant electronic document management system. The latter include, but are not limited to Documentum, DocuTrack, and DocWave systems.

With the use of these tools, as well as an appropriate training program to support those on the regulatory affairs team with the appropriate knowledge to perform global assessments, implementation of a product-based impact assessment program can be quite successful.

To demonstrate how the product-based regulatory impact assessment would work, consider the following example.

An Ethylene Oxide (EO) sterilization cycle for syringe components is harmonized across multiple facilities and sterilization chambers. The new cycle meets ISO requirements; maximum temperature remains the same, but with reduced the cycle duration time.

As a sterile injectable drug product, the sterilization cycle and cycle duration for the syringe components is defined within the product's design space. Therefore, this change is reportable. The Global Regulatory Affairs impact assessor utilizes the Global Guidance Repository Tool to determine each regional reporting requirement, submission timing and data packages needed to support the change.

Practical application of these concepts is well worth the time, resources and funding required for implementation. While implementation of these tools and a global dossier program may require long-range planning, it also provides a robust impact assessment process that ensures global regulatory compliance. In addition, it can save time, effort and resources in the long-term. Organizations seeking a leaner operation model may benefit greatly from a product-based impact assessment program, while ensuring alignment with regulatory initiatives that focus on the quality of the drug product as the most essential component of a post-approval impact assessment.

References

1. ICH Harmonised Tripartite Guideline: Q9 – Quality Risk Management, International Conference of Harmonization, November 2005 tinyurl.com/6dpw73l
2. ICH Harmonised Tripartite Guideline: Q10 – Pharmaceutical Quality System, International Conference of Harmonization, June 2008 tinyurl.com/3t68uwy
3. Final Concept Paper: Q12 – Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management, International Conference of Harmonization, July 2014 tinyurl.com/j2gsvgl
4. "FDA Pharmaceutical Quality Oversight: One Quality Voice," *Office of Pharmaceutical Quality: Food and Drug Administration,* Accessed November 5, 2015 tinyurl.com/zealg6g

About the Author

Jenifer Avenatti is a Regulatory Affairs Senior Manager with Baxter Healthcare, and has expertise in pre-approval and post-approval regulatory submissions for the U.S. and global markets for INDs, NDAs, BLAs and ANDAs.

2016 PDA Upcoming Events

SAVE THE DATE for PDA's 2016 Events

For an updated PDA calendar of events, please visit:
pda.org/calendar

JANUARY

25-29

GSA Schedule Contract GS-02F-113BA

Aseptic Processing Training Program – Session 1 SOLD OUT
Week 2: February 22 – 26
Bethesda, MD
pda.org/2016aseptic1

FEBRUARY

16-18

Environment Monitoring Course Series
Bethesda, MD
pda.org/2016EMCourses

23-24

Pharmaceutical Microbiology
Berlin, Germany
pda.org/EU/Microbiology2016

25-26

Rapid Microbiology Methods
Berlin, Germany
pda.org/EU/MicroMethods2016

25-26

Control, Validation and Monitoring of Biofilms in Water Systems
Berlin, Germany
pda.org/EU/Biofilms2016

25-26

Charting and Trending Environmental Data
Berlin, Germany
pda.org/EU/EnvironmentalData2016

29 – MAR. 3

GMP Week
Bethesda, MD
pda.org/2016GMPWeek

MARCH

1

Visual Inspection IG Meeting
Berlin, Germany
pda.org/EU/IGVisual2016

2-3

An Introduction to Visual Inspection: A Hands-on Course
pda.org/EU/WSVisual2016

4

Particle Identification in Parenterals
Berlin, Germany
pda.org/EU/ParticleIdentification2016

14-16

2016 PDA Annual Meeting
San Antonio, TX
pda.org/2016Annual

16-17

Preparing for the Next Generation of Regulatory Inspections: A 2016 PDA Manufacturing Science Workshop
San Antonio, TX
pda.org/2016MSW

17-18

2016 PDA Annual Meeting Course Series
San Antonio, TX
pda.org/2016AnnualCourses

29-31

Risk-Based Qualification of Sterile Drug Product Manufacturing Systems
Bethesda, MD
pda.org/2016Sterile

PDA Session Recordings

PDA's session recordings allow you to affordably hear from today's top presenters in the bio/pharmaceutical industry with no traveling!

Session recordings from **PDA's 2015 events** are now available for purchase. The events include:

2015 PDA Annual Meeting

Recordings from the entire workshop are available for purchase for **$240 Member/ $280 Nonmember**. Price of recordings includes:

- Eight recorded sessions from the 2015 PDA Annual Meeting
- PowerPoint slides with synchronized audio
- Access to 18 downloadable presentation handouts
- Unlimited playback of the recordings for 90 days from receipt of login information.

2015 PDA Drug Delivery Combination Products Workshop

Recordings from the conference and workshop are available for purchase for **$260 Member/ $300 Nonmember**. Price of recordings includes:

- Eight recorded sessions from the 2015 PDA Drug Delivery Combination Products Workshop
- PowerPoint slides with synchronized audio
- Access to 17 downloadable presentation handouts
- Unlimited playback of the recordings for 90 days from receipt of login information.

2015 PDA/FDA Joint Regulatory Conference

Recordings from the conference are available for purchase for **$300 Member/$350 Nonmember**. Price of recordings includes:

- Ten recorded sessions from the 2015 PDA/FDA Joint Regulatory
- PowerPoint slides with synchronized audio
- Access to 21 downloadable presentation handouts
- Unlimited playback of the recordings for 90 days from receipt of login information.

For more information on all PDA session recordings please visit:

pda.org/session-recordings

EU Procedures for Transferring a Marketing Authorization

Enigma or Opportunity?

Barbara Jentges, PhACT GmbH

When it comes to the global post-approval management process, procedural and administrative differences are unavoidable *per se* in view of the various legal and political systems in the different regions of the world. Yet, simplification and harmonization could potentially reduce administrative burden ***(1).*** To illustrate the regulatory administrative hurdles faced within the European Union alone, the procedure/process for transferring a marketing authorization (MA)—also referred to as a change in ownership of an MA—is one example where harmonization of administrative procedures could significantly reduce the burden for both industry and regulatory agencies.

An MA for a drug product lists the terms under which the marketing of a medicinal product is authorized in a specific region. It generally consists of (a) the decision by the regional regulatory body granting the MA, and (b) a "technical dossier" containing the data and documents demonstrating quality, safety and efficacy.

The MA holder can be a "physical or legal entity" as further specified in *EudraLex Volume 2A* ***(2).*** A proof of establishment must be submitted as part of an initial marketing authorization application (Annex 5.3 to the EU application form).

The MA holder is responsible for marketing the medicinal product. In this respect, the MA holder must fulfill the legal obligations (e.g., ongoing pharmacovigilance of the medicinal product that is placed on the market) and is liable for damages caused by defective medicinal products under the Product Liability Directive ***(3).*** The designation of a representative (i.e., the local representative designated to represent an MA holder in a specific EU member state) does not relieve the MA holder of legal responsibility ***(4).***

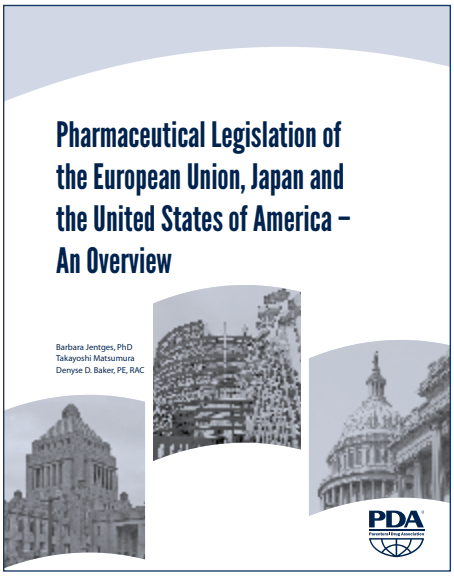
When the holder of an MA is changed, the ownership of the MA is transferred from one owner (the transferor) to another (the transferee). The MA transfer implies that the rights and the (legal) obligations placed on the MA holder are transferred to another person or legal entity.

While many initiatives and steps have been taken within the European Union to harmonize regulations and procedures for medicinal products within the region, the procedure for handling the transfer of an MA is still not harmonized.

Why is this so? The handling of post-approval changes, or "variations" for medicinal products licensed in the European Union/EEA falls under EU Variations Regulation 1234/2008 ***(5).*** While the transfer of an MA is a post-approval change, it is not covered by the EU Variations Regulation (EC) 1234/2008, Art. 1***(2):***

> *"This Regulation shall not apply to transfers of a marketing authorisation from one marketing authorisation holder (hereinafter holder) to another."*

Consequently, due to a lack of a harmonized regulation within the European Union, different MA transfer procedures apply depending on whether the medicinal product in question is a centrally authorized product (CAP), the MA was granted for several EU Member States via one of the national procedures with mutual recognition, i.e., Mutual Recognition Procedure (MPR) or Decentralised Procedure (DCP), or for only one EU member state via a purely national procedure (NP). As a result, procedural steps, timelines, fees and the documents that need to be submitted differ.



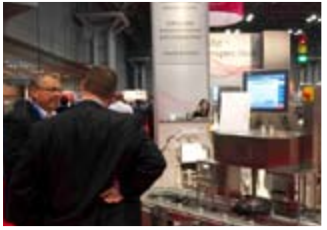
MA Transfer: A Complex Web

The MA transfer procedure for CAPs is regulated by EU Regulation (EC) N° 2141/96 ***(6)*** and follows the "procedural principle" of the centralized procedure: the transfer documentation is submitted to EMA and the decision is issued by the EU Commission. Detailed guidance for CAPs is provided on EMA's website ***(7).*** It becomes more complicated, however, for medicinal products licensed as part of national procedures. Regardless of whether the product was licensed in a national procedure with mutual recognition (MRP, DCP) or without (a purely national procedure), the MA transfer is handled as an "independent purely national application" ***(4).*** As a consequence—along with the lack of a "central point of information"—the national competent authorities (NCAs) or their websites must be consulted for further information with regard to the ➤

This article is an expansion of the chapter on post-approval changes from *Pharmaceutical Legislation of the European Union, Japan and the United States of America — An Overview Second Edition.*

Coming soon to the PDA Bookstore.





INTERPHEX

PREMIER SPONSOR:
PDA
Parenteral Drug Association

EXPERIENCE SCIENCE THROUGH COMMERCIALIZATION

April 26-28, 2016
Javits Center | New York City

STATE-OF-THE-ART TECHNOLOGIES LAUNCHES, from Industry Leaders

CUTTING-EDGE Innovation & Technologies

LEARN IT, EXPERIENCE IT with PDA-led Technical Conference

"INTERPHEX was a great experience this year! Sat in on multiple presentations and was very impressed with content, material presented, and the turnout. I also thought the layout of the show this year was great. Finally, the mobile app was awesome! Very helpful in locating companies, saving vendors I wished to visit, and much more."

- Lisa Birmingham

REGISTER TODAY AT **WWW.INTERPHEX.COM/PDA**



PDA
Parenteral Drug Association

We want You!

PDA Europe is looking for Freelancers / Consultants as Trainers in Europe

Training Topics:

- API and Drug Product
- Filling and Lyophilization
- Sterilization
- Qualification and Validation
- Contamination Control
- Quality Assurance
- Aseptic Manufacturing
- Packaging and Storage
- Cleaning and Disinfection
- HVAC and Water Systems
- Quality Control
- Regulatory Affairs

Languages:
English and local European Languages

Falk Klar
klar@pda.org

Please Contact Falk Klar at klar@pda.org

Simplification and harmonization could potentially reduce administrative burden

application procedure, the documentation needed for submission, the timelines, and the procedural fees. The gathering of information is further complicated by the fact that not all NCA websites are available in English.

Moreover, an application for the transfer of an MA must be submitted for each single drug product. Considering the merger and acquisition of companies where a large portfolio of different drug products are transferred, the differing requirements in the European Union alone result in enormous efforts and costs not only for the transferee.

Furthermore, any additional changes in consequence of the MA transfer (e.g., change in the name and/or address of the MA holder; change in the name of qualified person) must be submitted in a separate variations application according to the procedures laid down in the EU Variations Regulation ***(4).***

With this said, transfers of an MA "are not as simple as they appear" ***(8),*** and harmonization—at least at the EU level—would reduce associated costs, time, and efforts resulting from nonharmonized administrative procedures. **Gilda Gordon** discussed different possible scenarios for an EU-harmonized procedure in her master's thesis, with the inclusion of the MA transfer in the EU Variations Regulation being the most promising one ***(9).*** An EU-wide harmonization of the MA transfer procedures would be the prerequisite for the reduction of unnecessary administrative burden and costs, enabling a smooth transfer of MA ownership and prevention of "out-of-stock" situations.

To summarize, both industry and regulatory authorities can achieve significant benefits from simplifying administrative processes and harmonizing regulatory processes. In this respect, it is to be hoped that an EU-harmonized procedure for the transfer of MA ownership will be discussed in the near future.

References

1. Radzhivosky, J., Schiller, C., Gleixner, R., and Jentges, B. "Post-Approval Change Management On A Global Scale: An Inconvenient Complexity For Pharma?" *SCRIP Regulatory Affairs*, November 19, 2015.
2. EudraLex Volume 2A: Procedures for marketing authorisation, Chapter 1: Marketing authorisation, July 2015 http://ec.europa.eu/health/files/eudralex/vol-2/a/vol2a_chap1_201507.pdf (accessed Dec. 7, 2015)
3. "COUNCIL DIRECTIVE of 25 July 1985 on the approximation of the laws, regulations and administrative provisions of the Member States concerning liability for defective products." *Official Journal of the European Communities* 28 (1985): 29-33. http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31985L0374&qid=1448969315612&from=EN (accessed Dec. 7, 2015)
4. Q/A-LIST FOR THE SUBMISSION OF VARIATIONS ACCORDING TO COMMISSION REGULATION (EC) 1234/2008, Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human: November 2015, http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Questions_Answers/CMDh_132_2009_Rev37_2015_11_clean.pdf (accessed Dec. 7, 2015)
5. Commission Regulation 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisation for medicinal products for human use and veterinary use, http://ec.europa.eu/health/files/eudralex/vol-1/reg_2008_1234_cons_2012-11-02/reg_2008_1234_cons_2012-11-02_en.pdf (accessed Dec. 7, 2015)
6. Commission Regulation (EC) No 2141/96 of 7 November 1996 concerning the examination of an application for the transfer of a marketing authorization for a medicinal product falling within the scope of Council Regulation (EC) No 2309/93, http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000045.jsp&mid=WC0b01ac0580023e80 (Accessed Dec. 21, 2015)
7. "Transfer of marketing authorisation: questions and answers," *European Medicines Agency*, http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000045.jsp&mid=WC0b01ac0580023e80 (Accessed Dec. 7, 2015)
8. Carr, C., and Sudera, G. "Change of ownership applications - commercial opportunities and challenges" *Regulatory Rapporteur* 8, (2011) 12-15.
9. Gordon, G. "A critical review of the current marketing authorisation transfer procedure in Europe." Master's thesis, University of Bonn, 2013 http://dgra.de/media/pdf/studium/masterthesis/master_gordon_g.pdf (Accessed Dec. 7, 2015)

About the Author

Barbara Jentges, PhD, Senior Drug Regulatory Affairs Expert and Managing Director of PhACT GmH Switzerland, is a pharmacist with more than 22 years of experience in regulatory affairs.

Reports from the *2015 PDA/FDA Joint Regulatory Conference*

Day 1 Sees Regulators, Industry Members Converge

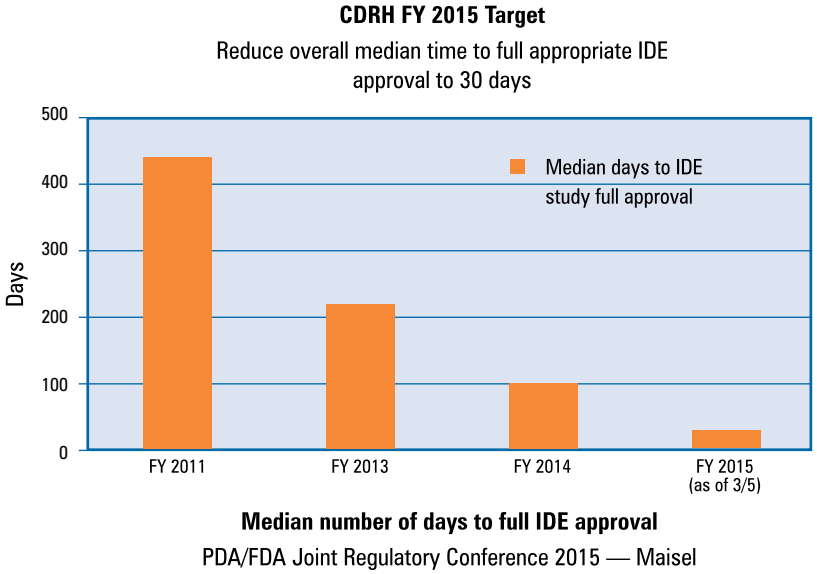
Leticia Quinones, Bristol-Myers Squibb

Once a year the morning commute into Washington, D.C. includes an uncommon number of vehicles filled with U.S. FDA scientists, headed to the annual *PDA/FDA Joint Regulatory Conference*, along with many members of the pharmaceutical and medical devices industries, converging in one single location to learn from each other and collaborate on potential solutions to common concerns. This year was no different, as government and industry gathered in one spot Sept. 28–30 to discuss shared patient-focused efforts in manufacturing, quality and regulatory science.

Attendees to the first plenary session learned how industry and government marshaled resources and extraordinary innovation in response to the Ebola health crisis in West Africa. **Joseph Woodring,** DO, Senior Medical Officer at the CDC, showcased the rapid response and risk management efforts that placed epidemiologists and medical personnel within the clusters of the Ebola epidemic. **Luciana Borio,** MD, Acting Chief Scientist, FDA, then explained the innovative study design and customization used to accelerate the start of clinical studies for an Ebola vaccine. These presentations not only illustrated the personal sacrifices made to assist patients, but also emphasized the importance of cooperation, planning and risk management for successful crisis management.

In the subsequent plenary session, **Laurie Norwood,** Deputy Director, DMPQ, CBER, led a panel discussion featuring panelists from CBER, CVM, CDER, CDRH and the Office of Regulatory Affairs, all of whom provided updates on PDUFA-related initiatives pertaining to their respective Centers. **Lawrence Yu,** PhD, Director, OPS, explained how FDA's team-based integrated quality assessment assisted in increasing first cycle approvals. **Dennis M. Bensley,** PhD, Division Director, CVM, presented drastic drops in review periods, including INAD study submissions that dropped from 180 to 60 days and original ANASAs that dropped from 270 to 180 days. Much of the improvement in review time has been facilitated by the funding of electronic submission processes and the Question-based Review (QbR) tool. **William Maisel,** MD, Deputy Director, CDRH, highlighted how approval times for medical devices have been reduced through guidances under PDUFA , including the addition of reviewers (**Figure 1**). **Christopher Joneckis,** PhD, Associate Director, CBER, described multiple gains from PDUFA V, centered on both the patient (e.g., meetings on patient perspective, benefit risk assessments, etc.) and electronic submissions and data standardization (e.g., data standards, eCTD BLA in 2017). All in all, the FDA presenters concluded that the reauthorization of PDUFA has led to considerable improvements for the industry.

Figure 1 Decrease in Investigation Device Exemption median number of days to approval 2011–2015



PDA/FDA Joint Regulatory Conference 2015 — Maisel

Quality Systems Draws Packed House

The afternoon brought three unique, parallel sessions on product quality, innovation and lifecycle management. The product quality session focused on change management as it relates to ICH Q12: *Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle* with talks from **Ashley Boam,** Acting Director, Office of Policy for Pharmaceutical Quality, OPQ, CDER, FDA, **Rick Friedman,** Deputy Director, CDER, and **Chris Watts,** PhD, Principal Consultant, VolPal. Boam stressed the diverse set of experts involved in the development of Q12; manufacturers of both small and large molecules are encouraged to practice continuous improvement at all stages of the product lifecycle. Friedman discussed how continuous improvement, change management and quality risk management, along with quality systems and culture are indispensable to ensuring product quality throughout the full product lifecycle. He emphasized using quality performance management to address performance risks and failures.

The other two sessions held concurrently were "Effective Corporate Auditing Programs" and "Supply Chain." In the corporate auditing session, **Jessica Walker,** Director, Quality Assurance, Afton Sci-

entific, presented a primer covering best practices on contract manufacturer auditing programs. For the "Supply Chain" session, **Steven Wolfgang,** PhD, CDER, offered a regulatory perspective on excipient standards. He reminded attendees that excipient manufacturers are not part of the FDA inspection inventory; compliance is voluntary, therefore, GMP oversight and governance falls to the finished dosage manufacturers.

In one of the last sessions of the first day, Rick Friedman moderated two presentations and a panel discussion on quality systems in a room filled to capacity. **Scott Macintire,** Director, Division of Enforcement, Office of Regulatory Affairs, FDA, stressed the importance of establishing a quality culture from management down that is supportive, leverages science and risk management, remains vigilant and rewards the right behaviors. He emphasized that the Agency's door is always open for discussion at the district and national level. **James Norris,** Executive Director, Pharma Biotech Consulting, NSF Health Sciences, presented on Human Reliability Improvement. Norris challenged the audience to consider human error not as a root cause but as a result. He showed strategies for process error elimination through facilitation, replacement and elimination.

The first day of the *2015 PDA/FDA Joint Regulatory Conference* concluded with further discussions in seven PDA interest group meetings specializing in a range of operational, scientific and regulatory topics. Some of these discussions have continued on PDA Connect℠ (community.pda.org). These interactive meetings capped a lively first day filled with discussion, debate and discourse. Whether from FDA or industry, attendees were not afraid to speak up during the sessions and all expressed the importance of keeping the patient first.

About the Author

Leticia Quinones, PhD, is a lead in quality systems initiatives in analytical and bioanalytical development at Bristol-Myers Squibb. She is also President of the PDA Metro Chapter.

Collaborative Spirit Continues Through Day 2

Cecilia Turoff, Baxter Healthcare

Quality metrics. Data integrity. Revisions to USP chapters. Quality Submissions. Innovation. These were only some of the intense sessions scheduled for the second day of the *2015 PDA/FDA Joint Regulatory Conference.* An atmosphere of collaboration permeated these sessions, fueled by the theme of the conference, "Mission Possible: Patient-Focused Manufacturing, Quality and Regulatory Solutions." The day began with a breakfast session covering quality metrics and ended with a breakout session on innovation in the industry.

Naturally, quality metrics received a lot of attention as the U.S. FDA had issued its draft guidance on metrics only two months before the conference. The draft guidance lists ten baseline metrics the Agency would request from companies "in advance or in lieu of" an inspection. **Alex Viehmann,** Operations Research Analyst, Office of Surveillance, CDER, FDA, reviewed some highlights from the Aug. 24 public meeting at FDA where representatives from industry shared their concerns about the draft. He discussed some common ones, such as the financial burden of implementing the metrics, the definitions used within the guidance and how the data will be used. Viehmann also discussed the Agency's short-term and long-term vision for the quality metrics program.

Ultimately, he explained that quality metrics is "a surveillance tool at its core" and should not to be used for enforcement or supply disruptions.

Next, **Russell Wesdyk,** Acting Director for the Office of Surveillance, Office of Pharmaceutical Quality, CDER, FDA stated that quality metrics should spur the following five questions for the industry:

- Who and what is out there?
- Do we understand our inventory?
- Can we sum up what we have with data and transfer that data into knowledge?
- How is industry performing?
- What should FDA do when they show up at the site?

Wesdyk also said that "more information is better than less information" and that submitting quality metrics should only decrease the risk of inspection and should never result in a 483.

Uber Offers Example for Pharma

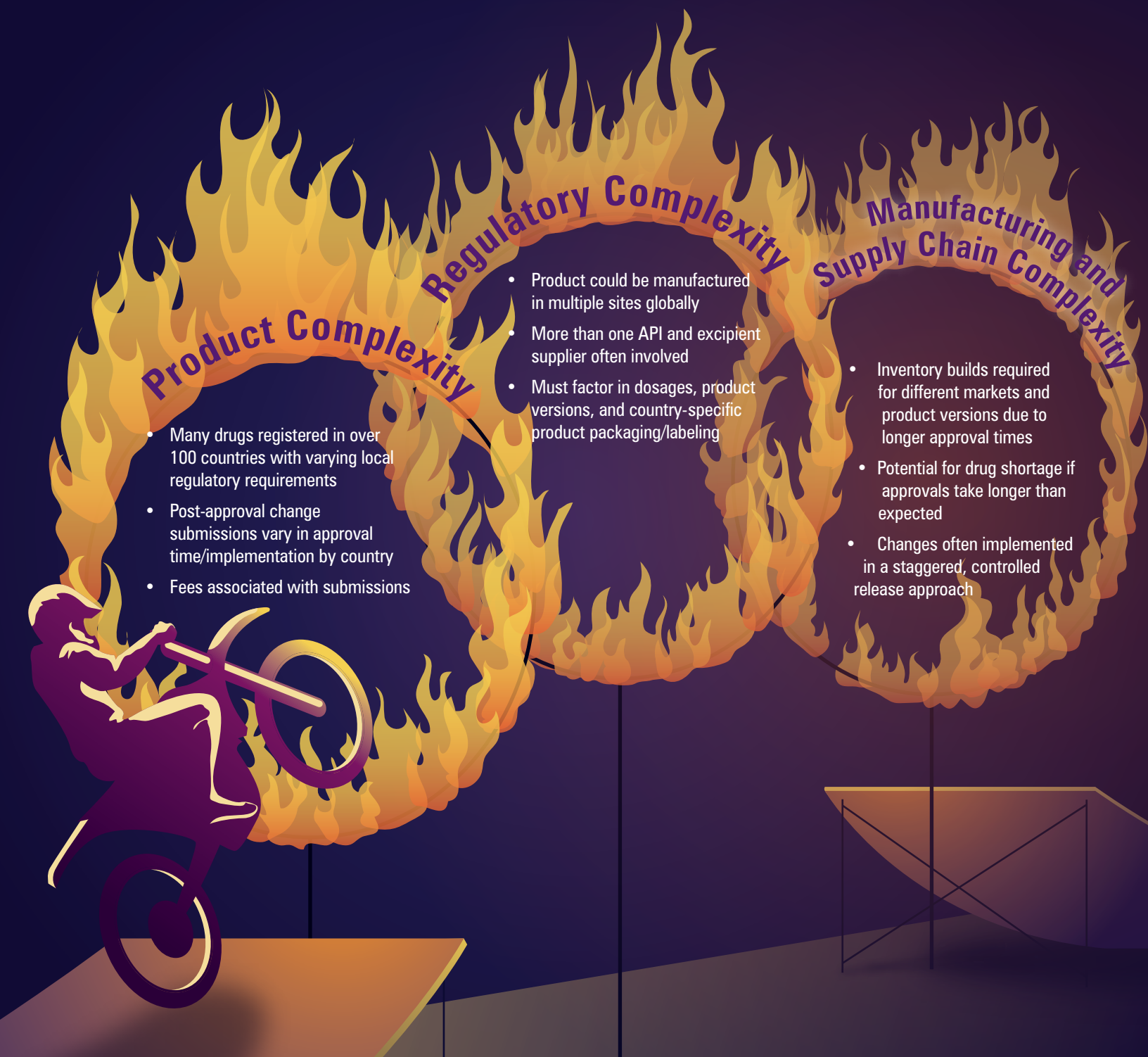
Following the breakfast session, the plenary talks delved into the crucial topic of data integrity. **Monica Cahilly,** from Green Mountain Quality Assurance, highlighted the impact of data integrity issues on the industry. She pointed out that the business model for pharma has shifted (notably due to increased outsourcing), and encouraged attendees to consider looking at how other industries have modernized, citing Uber as an example. Uber's model of one-to-one relationships based on scoring has changed how the taxi industry worldwide operates. For pharma to advance like Uber, companies will need to invest in quality. An outdated quality unit that only looks at paper cannot fully grasp all that is going on; it is not as simple as reviewing an audit trail.

Cahilly went on to urge that management needs to be completely engaged when setting up Quality Agreements. The foundational principles for a control strategy are in the feedback mechanisms; Good Documentation Practices for electronic data must be subject to

Continued at bottom of page 36

The Hoops of Post-Approval Change Complexity

When it comes to post-approval changes, it can seem like jumping through a series of challenging hoops, especially due to the globalization of the industry. Ultimately, all this can impact the reliable supply of product for the patient.



Reference

1. Skeens, L. "The Complexities Causing Challenges in Post Approval Changes." Presented at the 2015 PDA Manufacturing Science Workshop, Washington, DC, September 2015

SAMSUNG

SAMSUNG BIOLOGICS

Aseptic Fill & Finish at SAMSUNG

Engineered for Quality

CMO LEADERSHIP AWARDS 2015

CATEGORIES
- INNOVATION
- REGULATORY
- PRODUCTIVITY

www.samsungbiologics.com

Interest Group *Corner*

Interactive "Speed Dating" Leads to Intense Discussion on Key Inspection Topics

Zena Kaufman, ZGK Quality Consulting, Coleader, Inspection Trends Interest Group

PDA's Inspection Trends Interest Group reprised what has become the group's annual "483 Speed Dating" exercise at the *PDA/FDA Joint Regulatory Conference* this past September to a crowded room. In this session, seven eager facilitators, each passionate about a particular inspection-related topic, bravely put themselves and their topic "out there" during 15 minute speed dating rounds. The facilitators and topics were:

- **Jacqueline Veivia-Panter,** Consultant – Quality Metrics
- **Janeen Skutnik-Wilkinson,** Staff Associate Compliance & Standards, Biogen – Foundational GMP Observations
- **Wendy Zwolenski Lambert**, Global Validation Leader, Novartis – Validation
- **Shane Ernst,** Vice President, Quality, Pfizer – Data Integrity QC Lab
- **Stephan Rönninger,** PhD, Director, International Quality External Affairs, Amgen – Data Integrity (General)
- **Nicholas Markel,** Executive Director, NSF Health Sciences – Aging Facilities
- **Austin Caudle,** Senior Business Development Manager, NSF Health Sciences,and **Maxine Fritz,** Executive Vice President, NSF Health Sciences – Closeout and Response Writing

In addition, veteran U.S. FDA inspectors **Thomas Arista** and **Rebeca Rodriguez** along with fellow FDA colleagues **Rick Friedman, Carmelo Rosa** and **Christina Alemu-Cruickshank** floated throughout the speed dating groups.

Before the speed dating commenced, each facilitator shared why their topic was of the utmost importance and interest to participants and why they should secure a "date" at their table, from "50 Shades of Quality Metrics" to struggles with aging facilities and how one might end up in a situation trying to find engineering drawings from the year *E.T.* was the top movie.

During speed dating the energy level in the room was high, thanks to the lively discussions at each table. In fact, the validation group elected to be monogamous and continue the discussion rather than switch to other groups when it came time to rotate.

Quality Metrics, DI Prove "Hot" Dates

Data integrity proved to be a popular topic, with one group focused on general data integrity issues and one for data integrity issues specific to the QC lab. Regulators now routinely hold sites accountable for documentation violations and/or issues with computerized system requirements. FDA has been open in their request for firms to approach the agency proactively when data integrity issues are identified through a firm's quality system audits or quality indicators. This is much preferred over an inspector finding it during an inspection.

Audit trails served as the central theme of the discussions within the group focused on data integrity in the QC lab. While everyone agreed and understood the importance of having audit trails, the following questions remained unanswered:

- How often should a firm be checking their audit trails?
- Should it be batch-specific and part of the release process or a periodic system check?
- What about older instruments that either do not have an audit trail or have a first generation audit trail missing some of the common elements found today?

"50 Shades of Quality Metrics" offered a steamy discussion. There are many shades of gray surrounding the requirements and implementation of FDA's proposed quality metrics guidance, which has generated more questions than answers. Many expressed concern with how the metrics data will be utilized by FDA and the impact it may have on firms. Some firms do not have the capability to gather and report all the metrics required by the guidance. The current requirements could create a burden on firms to develop data reporting methods, and possibly even management systems not currently in place. The standardization of metrics will have to be transparent in order to be treated uniformly across the industry.

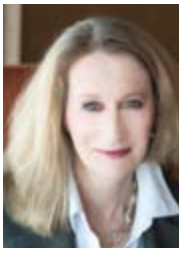
PDA will continue to participate in discussion relevant to the guidance and to the FDA's quality metrics initiative. And if discussions are any indication, it will be as stimulating as the second book of the *50 Shades of Grey* trilogy!

Participants enjoyed three lively "dating" sessions on aging facilities, exploring the challenges of modernizing facilities and processes in today's environment, and expressed a real need for clarity on expectations regarding facility improvements. Many felt they wanted to improve facilities but openly wondered about the incentives to replace/update aging facilities? For example, if the barriers to invest, improve and innovate are coming from within industry, are regulatory agencies really ready to embrace innovation? Finally, a lack of international harmonization was brought forth as another potential reason for some companies to avoid making improvements.

All in all, the speed dating discussions provided a fresh way to look at important topics within the industry. The interest group eagerly anticipates the next 483 speed dating session and looks forward to continued interest in this interactive and thought-provoking activity.

About the Author

Zena Kaufman is President of ZGK Quality Consulting.



Divergent Approaches to Stem Cell Regulation

James Akers, PhD, Akers Kennedy Consulting

*Published online first
letter.pda.org

Stem cells and other regenerative medicine products offer considerable benefits to patients as well as potential financial rewards for companies. At the same time, cell-based therapies present challenges to regulators because, in many cases, they involve withdrawing cells from a patient's bone marrow, blood or adipose tissue, growing cells in vitro with minimal to extensive manipulation, and then administering in some form the expanded (and possibly modified) cells population back into the patient.

To some, the ownership of these cells lies with the patient and these treatments are medical procedures that should require limited, or even no, specific regulatory oversight, particularly when there is little manipulation of the harvested cells other than expanding their numbers in a cell culture. In late 2014, a U.S. appeals court case on the issue of regulatory authority over regenerative medicines resulted in what may prove to be a landmark ruling in the United States. Yet Japanese regulators are moving in a different direction. The United States and Japan now appear to offer divergent approaches to regulating these novel therapies.

Within the past decade, stem cell clinics sprung up in many U.S. cities. One such company, Denver-based Regenerative Sciences, developed a procedure for treating orthopedic injuries using autologous (meaning a patient's own) stem cells. Regenerative Sciences licensed a number of clinics throughout the United States to provide their therapy, known commercially as Regenexx. The U.S. FDA sought to regulate the Regenexx process as a drug as the procedure is "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man" ***(1).*** Both the American Association of Orthopaedic Medicine and the Association of American Physicians and Surgeons formally supported Regenerative Sciences' contention that their process was a medical procedure rather than a drug or biologic falling under FDA's jurisdiction.

In 2009, Regenerative Sciences sued FDA over jurisdictional issues and this suit was dismissed. Then, in 2010, the U.S. government sued Regenerative Sciences after FDA conducted an inspection of the firm's Colorado facility. Ultimately, on Feb. 4, 2014, the U.S. Court of Appeals for the District of Columbia found that the stem cell procedure used in the Regenexx process fell under the jurisdiction of the Federal Food, Drug and Cosmetic Act as a compounded drug because mesenchymal stem cells and components used in the mixture had not been subject to FDA approval for use in compounded drugs ***(2).*** This ruling found that FDA has regulatory authority over the drug(s), and by extension, the biologic.

The impact of this ruling is unclear at this point in time but it may discourage clinics and startup companies from working with more-than-minimally manipulated stem cells in the United States.

Interestingly, as the Regenerative Sciences case moved through the courts, regulation of stem cell-derived products in Japan moved in the opposite direction. Japan has also targeted regenerative medicines as an area of economic development. In 2013, the Japanese parliament passed a law with the intention of liberalizing patient access to regenerative medicines. This new regulation, called the Act on the Safety of Regenerative Medicine, took effect on Nov. 25, 2014. The full impact of Japan's regulatory position on regenerative therapies remains unclear at this point but it may well attract business to Japan and make it easier for Japanese-based firms to use their products in clinics.

The regulation in question specifically gives provisional approval to products within a seven-year window, provided ➤

that the product has been demonstrated to have at least some efficacy and has been shown to be safe. So, in essence, Japan has focused on ensuring that products used in regenerative medical treatments are safe, placing a lesser emphasis on efficacy. It would seem that this is a mechanism to allow these treatments to be used clinically with limited information on efficacy, provided that patient safety can be asserted. Already, a council of the Japanese Ministry of Health, Labour and Welfare on Sept. 2, 2015 conditionally approved Tokyo-based Terumo Corporation's autologous skeletal myoblast sheets, which are used in the treatment of heart disease ***(3).***

Japan has chosen a safety-based approach which many would suggest is enlightened. It remains to be seen, however, whether this approach will prove the right one and whether other nations, including Japan's ICH partners will move in a similar direction. The ruling on regenerative medicine has triggered plan to expand insurance coverage to include these provisionally approved products.

The United States represents a more traditional "tough" approach to regulating stem cell therapies while Japan represents the "lightly regulated" approach. And the latter appears to be more in line with industry thinking. At the Tissue Engineering and Regenerative Medicine International Society global conference on Sept. 8, four international panelists, aligned on both sides of the discussion, debated the appropriateness of "tough" versus "light" regulation in this space. Following this debate, attendees voted on which "side" they preferred. The result? The majority of the roughly 1700 attendees supported the "light" approach to regulation rather than the "tough" approach.

In the end, national regulatory philosophy may dictate where and how these treatments are first made available to patients. These regulatory philosophies may, in the end, also dictate the nations in which the greatest treatment strides are first made.

References

1. "Regenerative Sciences, Inc," July 25, 2008. U.S. Food and Drug Administration. Accessed Nov. 16, 2015
2. United States of America v. Regenerative Sciences, LLC, 10-cv-01327 (C.A. DC 2014)
3. "Terumo's Autologous Skeletal Myoblast Sheets Are the First to Be Approved as a Cellular or Tissue-based Products in Japan by a Council of the Ministry of Health, Labour and Welfare," Terumo, Accessed Nov. 16, 2015

About the Author

James Akers has over 32 years of experience in pharma and has worked at various director level positions within the industry and for the last two decades as a consultant.

Reports from the 2015 PDA/FDA Joint Regulatory Conference continued from page 31

continuous review. The industry needs to determine how many data points are involved to support the release of one product, and learn to embrace imperfection in order to accept residual risk.

Douglas Stearn, Director of Enforcement and Import Operations, FDA, presented an interesting contrast to Cahilly's talk. He compared data integrity to the meaning of "wholeness."

"Does it [data] appear what it is meant to be," he said. "Data integrity is foundational—we have to rely on others to observe things for us."

The lack of data integrity in one area, Stearn emphasized, raises questions about the ability to assure safety and efficacy. Management, he said, should have a system for data accountability, with step one being remediation of a data integrity issue; FDA will expect details of the company's plan to address the people and systems involved. Step two of the remediation would be a risk assessment for potential impact on product quality, marketed product and the patient. And finally, step three of the remediation would be a management strategy that includes CAPAs. In closing, Stearn stated that data integrity issues are "not always easy to see," and difficult to remediate. It is better to be safe than sorry—proper controls can prevent and limit data integrity issues.

After the plenary talks, the remainder of the day consisted of breakout sessions. A session on USP updates covered packaging-focused revisions to USP chapters <1> *Injections*, <661> *Containers—Plastics* and <381> *Elastomeric Closures for Injections*, as well as the collaborative relationship between FDA and USP. For years, USP <1> has been the "catch-all" for all things related to injections, per **Desmond Hunt,** PhD, Senior Scientific Liaison, USP. The implementation for the revised USP <1> has been delayed. For the <661> revision, there will be an introduction to the subchapters where <661.1> would delineate what constitutes a well-characterized packaging system and <661.2> would delineate what constitutes a well-characterized material. The importance of the chemical analysis (extractables and leachables) would be defined in <1663> and <1664>. USP has been working on <381> for the past one-and-a-half years. As part of this rewrite, they are developing <1381> and working to align <87> and <88> more with ISO 10993.

After Hunt's talk, **Donald Klein,** PhD, Quality Assessment Lead, CDER, FDA, spoke about the FDA's contribution to the revision of USP <659> *Packaging and Storage Requirements* that addresses critical parenteral packaging issues. His efforts resulted in five definitions for containers: multidose, single-dose; single patient use, pharmacy bulk package and imaging bulk package. He is

now working internally to have finalized comments in late 2015.

Quality and Innovation are Linked

The topic of quality submissions fell under the "Innovation" heading in the afternoon breakout session. **Lisa Zboril,** Vice President, Regulatory Affairs, Pfizer, compared actions taken at the beginning of the product lifecycle to what occurs in manufacturing, and then how these actions can be applied to all submissions. She stated that the three key elements to delivering a quality submission are planning, control and continuous improvement.

Planning, especially early planning, is important for the Target Product Profile as well as labelling requirements. If these attributes are not defined well early, mistakes may end up being repeated. Therefore, it is key to regularly communicate uncertainties early on with regulatory agencies. Control involves governance, which means driving consistency within a company's processes, such as through development of global CTD templates, a comprehensive submission checklist for each market and technical reviews of the dossier.

After all, as Zboril stated, "the story is told through the dossier."

Lastly, she outlined methods for continuous improvement. This includes regulatory intelligence, which consists of deficiency tracking, lessons learned and communications with regulatory authorities to ensure that data is consistently generated with scientific rigor. In the generics world, the key to success is being efficient, timely and accurate.

Ted Sherwood, Acting Director, Office of Regulatory Operations, CDER, FDA, agreed with the concepts that Zboril presented. He encouraged attendees to carefully consider the contact information in a submission to make sure that the contact understands the application; the contact acts as a "tour guide" for the submission. If the contact person changes, submit a new 356h form. Deficiencies must be brought back to the team for review; FDA reviewers often see the same companies repeating the same mistakes time and time again. Sherwood also recommended ensuring that the cover letter is as clear-cut as possible since "stuff can get lost," i.e., don't make the reviewers have to hunt for data.

"Make the reviewer excited that they are getting an application from you," he said.

The next "Innovation" breakout session focused on breakthrough therapies. **Sarah Pope Miksinski,** PhD, Acting Director, New Drug Products, and **Mahesh Ramanadham,** PharmD, Branch Chief, Office of Pharmaceutical Quality, tagteamed to present the FDA perspective while **Susan Berlam,** Senior Director, Global CMC, Pfizer, offered the industry perspective.

Miksinski and Ramanadham posed the following question: What defines quality? ICH Q6A links the patient to the product and ICH Q9 links the product to the process. The major concern in expedited review is the lack of stability data to support a viable retest period for the drug substance and the expiration date for the drug product. Their take home message? Make sure that predictability for patient/product links is imparted.

Berlam presented an industry perspective based on a case study. Based on personal experience, her advice when it comes to breakthrough therapies is to "communicate, communicate, communicate." She emphasized that receiving meaningful feedback from the Agency requires submitting the appropriate information followed by additional communications.

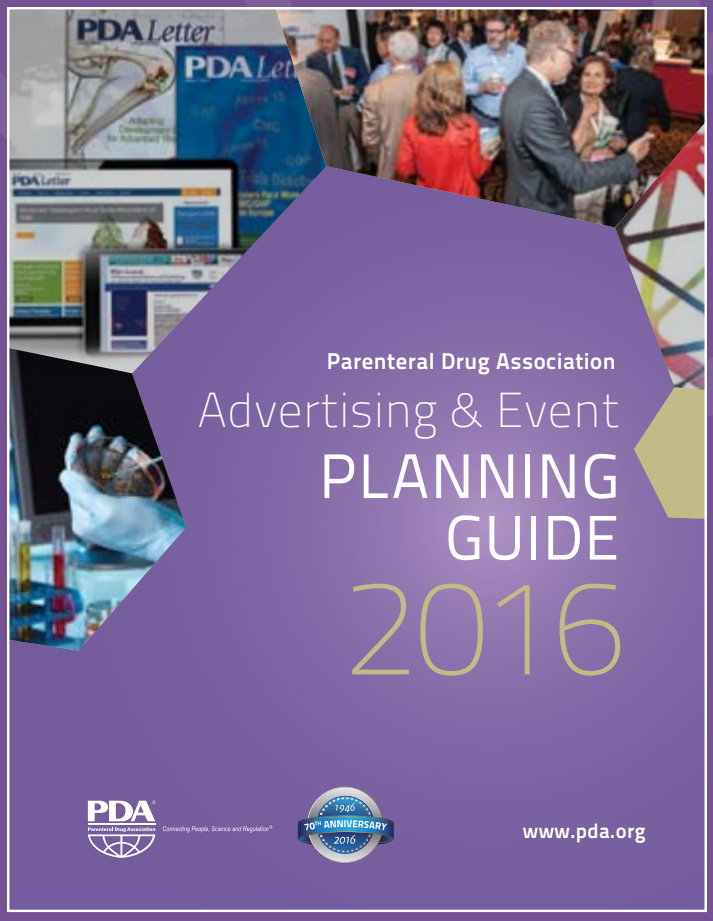
All in all, the presenters on the second day of the conference emphasized the importance of working together as well as continuing collaboration efforts between industry and regulatory authorities. From metrics to breakthrough therapies, meaningful change and innovative practices will require both sides to see each other as partners. Without this collaborative spirit, there can be no product and no benefit to the patient.

[Editor's Note: For an overview of a plenary talk on the third day of the conference, see "Change is Coming to FDA Inspections: Are You Prepared?" in the previous issue**.]**

About the Author

Cecilia Turoff is currently Global Regulatory Affairs CMC Manager with Baxter Healthcare, Inc. She has over 30 years in the pharmaceutical/medical device industry, holding various roles in sterilization technology, quality, validation and manufacturing.

The 2016 Advertising & Event Planning Guide is Now Available!



Download your copy of the *2016 Advertising & Event Planning Guide* and find a broad range of advertising, exhibit and sponsorship opportunities – both tried and true and brand new – to help you make the most of your investment with PDA.

Choose from print and electronic advertising – including our newest addition, electronic advertising on the updated *PDA Letter* website – meeting exhibition and sponsorship.

Make 2016 your best year yet, increase your brand recognition and promote products or services to the "Who's Who" in the biopharmaceutical manufacturing industry.

Please visit pda.org/mediakit to download your copy today!

QUESTIONS?

Contact David Hall:
Email: hall@pda.org | Tel: +1 (301) 760-7373 | Cell: +1 (240) 688-4405

Get Social with PDA!

Take advantage of several ways to "join the PDA conversation" on social media! Use these forums to get answers to your pressing questions and to discuss "hot topics" with your peers and leading industry experts.

And, find out what new tools and resources PDA has to offer to help you advance in your career!

Stay engaged, informed and ahead of the complex challenges of the pharmaceutical and biopharmaceutical manufacturing world by following PDA on:

PDA Connect at **community.pda.org** – Join PDA's members only online discussion forum @ PDA Connect SM

Twitter at **@PDAOnline**

LinkedIn at **linkedin.com/company/pda**

Join the conversation today!

GMP Oversight of Medicines Manufacturers in the EU

A System of Equivalent Member States, a Coordinating Agency and a Centralized Institution

Riccardo Luigetti, EMA, Emer Cooke, EMA, Brendan Cuddy, EMA, Sebastien Goux, European Commission, and Ian Rees, MHRA

[Editor's Note: This is Part II of an overview of the EU regulatory system for pharmaceuticals. It can be accessed in its entirety on the *PDA Letter* website. Part I was published in the last issue and Part III will be published in February.**]**

The EU System for GMP Supervision of Manufacturers and Inspection

Any manufacturer, no matter where it is located, must comply with GMP if they are to supply products to the EU. There is a single system for GMP supervision of manufacturers which is valid throughout all the EU Member States; this includes authorized medicinal products for human or veterinary use placed on the market and IMPs used in clinical trials. The system is based on two main pillars, the authorization/registration of operators in the supply chain and inspection of those operators to ensure compliance with legal requirements, including compliance with GMP and the requirements in the MA or CTA.

*Manufacturers and Importers of Medicinal Products**

Manufacturers and importers of medicinal products located in the EU need to be authorized to carry out their activities. This obligation also applies to manufacturers and importers of products only intended for export and IMPs. The competent authorities of each Member State are responsible for granting the authorizations for these activities occurring within their respective territory.

A condition for grant of a manufacturing or import authorization is that the manufacturers must comply with EU GMP. GMP principles and guidelines are set out in two Directives, one for medicines for human use and the other for medicines for veterinary use. More detailed guidelines have been developed through the work of the GMP and GDP Inspectors Working Group (GMDP IWG) and the European Commission and included in the EU GMP guide, published on the European Commission website.

Inspection of Manufacturers and Importers of Medicinal Products

Manufacturers and importers of medicinal products located in the European Union or manufacturers located in a

third country are regularly inspected by an EU competent authority for compliance with EU GMP. The outcome of these inspections must be accepted by all other EU authorities. After every inspection a GMP certificate (positive outcome) or noncompliance report (negative outcome) must be issued by the inspecting authority and entered in the EudraGMDP database, which is accessible by regulators in other countries. Most of this information is also available to the general public.

Inspections of manufacturers are typically requested in order to grant or maintain a manufacturing or import authorization (EU sites) or in the context of assessment, approval and maintenance of an MA (typically sites outside the EU) or CTA. For example, EMA may request that an EU competent authority undertake a preapproval GMP inspection of a site included in a MA application through the Centralised procedure or that an EU competent authority undertake periodic repeated postauthorization surveillance inspections of sites named in centralized MAs, in order to verify ongoing compliance with GMP and that the requirements of the MA are being met.

According to EU legislation, the interval for repeated GMP inspection should be based on risk. As a result, a procedure outlining a risk-based model to frequency of inspections is included in the Compilation of European Union Procedures on Inspections and Exchange of Information.

*Manufacturers and Importers of Active Substance***

Manufacturers, importers and distributors of active substance located in the European Union are required to comply with GMP and must be registered to the National Competent Authority of the Member State where they are located.

For active substances manufactured outside the EU and imported, each batch needs to be accompanied by a written confirmation issued by the competent authority of the country where it is produced, confirming, among other things, that GMP at least equivalent to that in place in the European Union has been applied to its manufacture. The competent authority of the exporting country also needs to confirm that any GMP noncompliance arising at the manufacturing site would be communicated to the European Union. The receipt of this noncompliance information is via the EMA.

Notes

* The term "Medicinal Product" in the European Union approximately corresponds to the term "Drug Product" in the United States. Sometimes the term "Finished Product" is used instead.

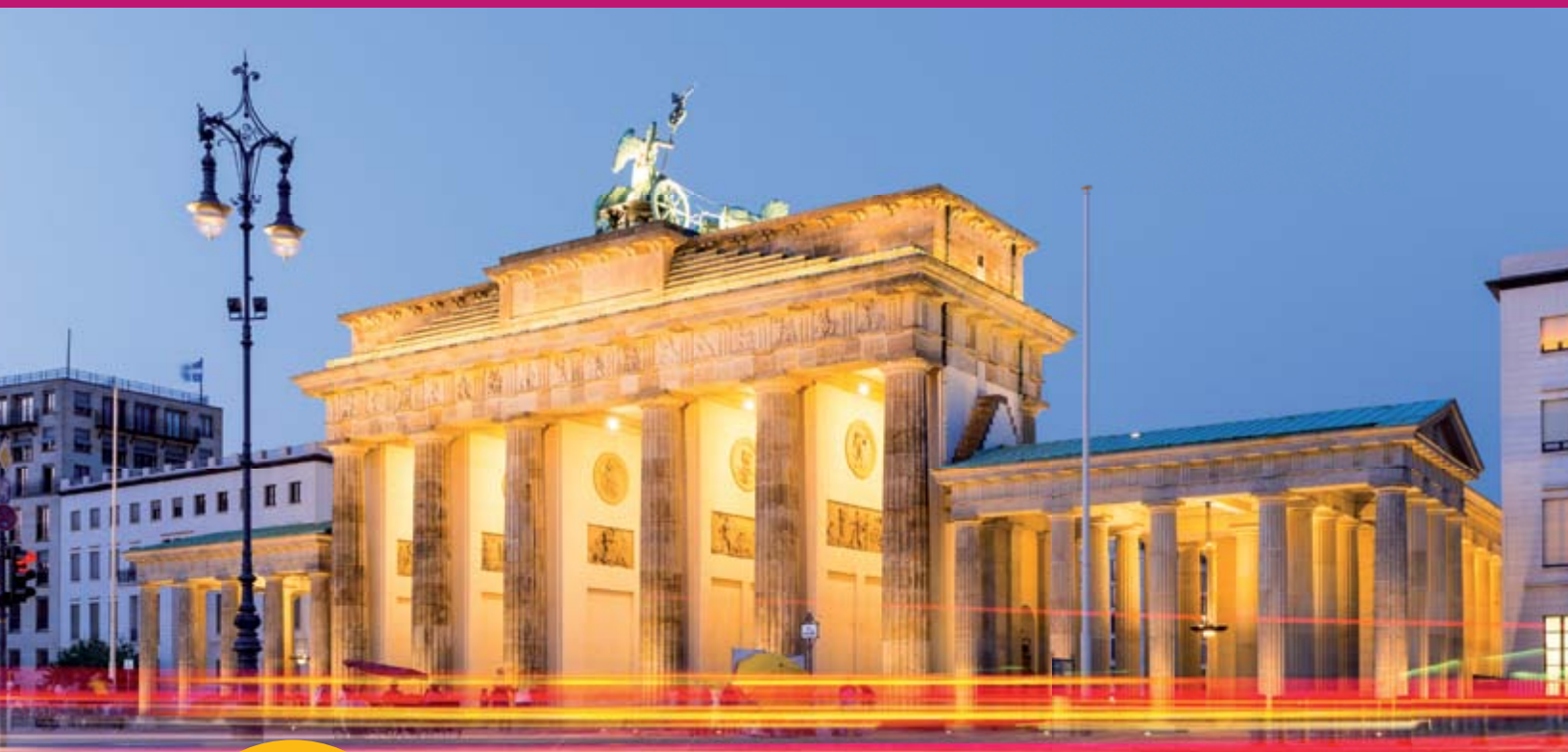
** The term "Active Substance" in the European Union corresponds to drug "Drug Substance" in the United States.

The Parenteral Drug Association presents:

2016 1st PDA Europe Annual Meeting

THE FUTURE IN INJECTABLES

28 June – 1 July | Conference, Exhibition, Education Program



Register by 25 March 2016 and SAVE!

28-29 June 2016

Estrel Hotel Berlin
Berlin | Germany

europe.pda.org/Event2016

Richard Johnson, PDA President

PDA Enters 2016 on High Note

2015 certainly was a busy year for PDA. We had more than 30 conferences and workshops in the United States, Europe and elsewhere around the world. We had joint events with PIC/S in South Korea, Brazil and India. Our *Universe of Pre-filled Syringes and Injection Devices* conference was the largest in our history. We delivered more than 100 courses worldwide in our PDA Education program, and saw the number of students rise to its highest level. We also produced 11 technical publications covering a wide range of topics including *Technical Report No. 69: Bioburden and Biofilm Management in Pharmaceutical Manufacturing Operations, Points to Consider for Aseptic Processing: Part 1, Technical Report No. 70: Fundamentals of Cleaning and Disinfection for Aseptic Manufacturing Facilities,* as well as the paper "Industry Perspectives on the Medical Risk of Visible Particulates" and a survey on quality culture metrics. We submitted more than 15 sets of comments to health authorities' draft documents around the world, including the WHO Good Pharmacopoeial Practices, the EDQM Chapter 5.1.2 on biological indicators, and the U.S. FDA draft guidances on combination products GMP and quality metrics. We also saw our membership grow to more than 10,000 members in more than 76 countries. And we had a high level of activities in our 24 global chapters.

We will continue these efforts in 2016, guided by our just published Strategic Plan, with a renewed focus on improving the manufacturing and quality of pharmaceuticals in order to meet the needs of patients. Our volunteers and staff are busy planning more than 30 events in 2016, including signature meetings such as our 65th Annual Meeting, our 25th *PDA/FDA Joint Regulatory Conference,* and our *Universe of Pre-filled Syringes and Injection Devices* meeting, as well as new events such as our first PDA Europe *Annual Meeting,* and a series of meetings on data integrity and aseptic processing issues in both the United States and Europe. We have boosted our capabilities to deliver education programs through our unique training facility, in lectures, and onsite at companies, as well as delivering training to regulators around the world. You, our volunteers, are engaged in more than 50 task forces that are leading to the development of technical publications that significantly contribute to the body of knowledge that has become a hallmark of PDA.

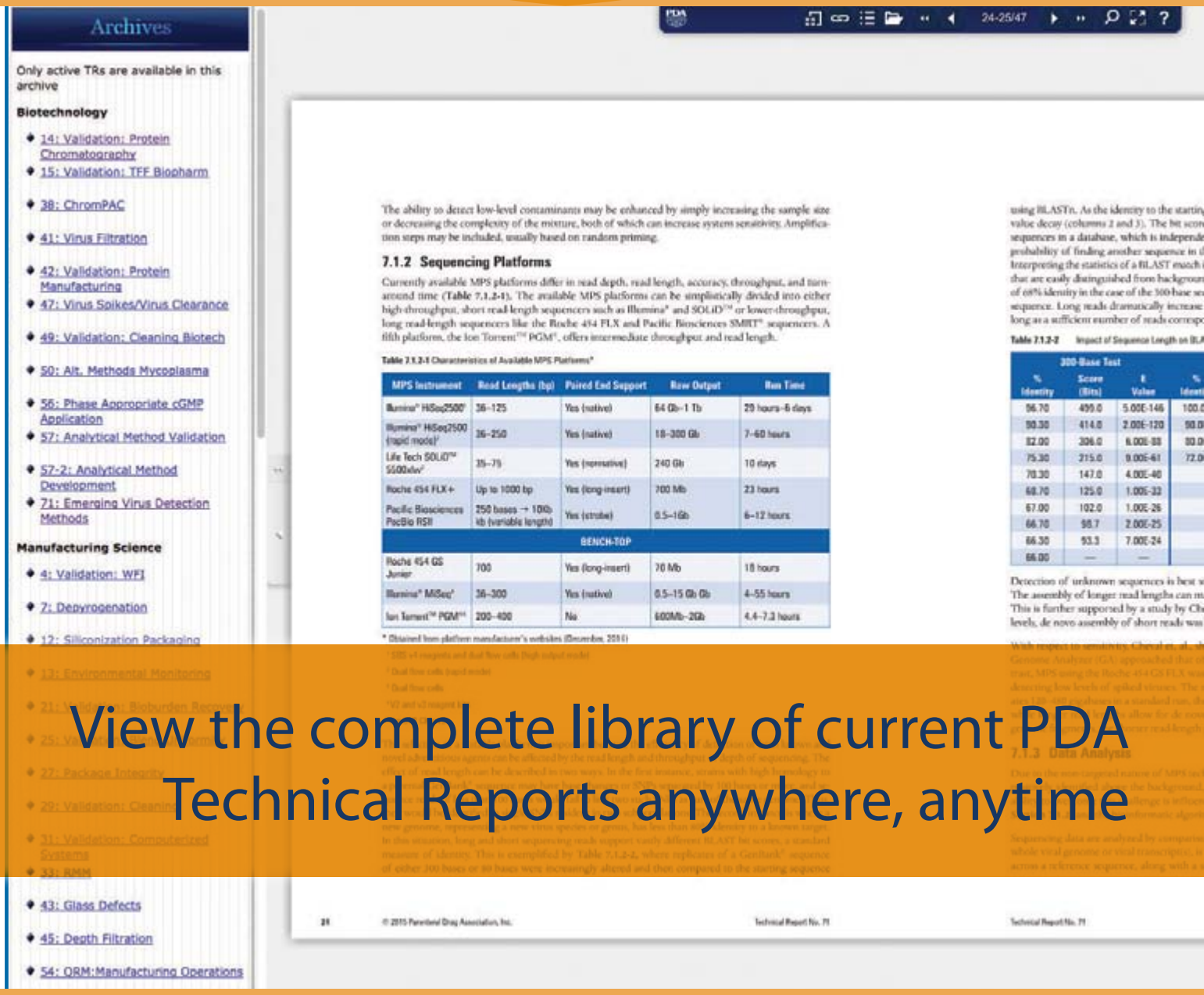
Through it all we remain dedicated to enhancing the value of your PDA membership, and in the coming months, I hope more of you will take advantage of these opportunities. PDA is an individual membership-based organization, and it is that diversity and independence that assures PDA's leadership in the industry and credibility with all stakeholders, including pharmaceutical and biopharmaceutical manufacturers, suppliers and regulators, will continue. Our focus has been, and will continue to be, on science-based solutions, rigorous commitment to the highest ethical standards, and collaboration and partnerships with professionals in academia, industry and regulatory bodies to better serve patients.

With your support, PDA will continue Connecting People, Science and Regulation®. Remember, this is your association. I look forward to hearing from you in the coming year. Happy New Year.

PDA's Technical Report Portal

1946 70TH ANNIVERSARY 2016

PDA Parenteral Drug Association



View the complete library of current PDA Technical Reports anywhere, anytime

For more information and to view PDA's Technical Report Portal please visit:

trarchive.pda.org/t/26426

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

PDA Chair Martin VanTrieste, Amgen

2020 Strategic Plan Offers Guidance in Changing Times

As Chair-Elect of the Board in 2015 I had the distinct pleasure of working on PDA's 2020 Strategic Plan. This plan outlines PDA's strategy for the next four years, focusing on people, science, and regulation along with leadership and management. Within each of these four areas are key objectives and goals which will be measured annually.

You may be asking yourself why PDA needs a 2020 Strategic Plan. Well, we're an industry currently in flux. Emerging markets have now become an important source of raw materials, APIs and even finished product. More countries now have their own regulatory requirements and enforcement bodies. Outsourcing is now a regular part of our business practices, furthering complexity in many areas. The utilization of biosimilars is growing. New therapies require new and different manufacturing operations. There remains continued pressure to refine our quality systems and even to model the systems used in other industries. The push for personalized healthcare is growing. And startups are shaking up the industry, particularly in the area of biologics.

Even our talent pool is changing. Millennials and members of Generation Z are entering the market as long-term personnel are leaving. What does this mean for retaining critical knowledge that has been gained by decades of experience? Who will pass on this information to the next generation?

There are many questions and few concrete answers. But by listing a set of shared goals we hope to generate discussion and debate so we can begin the journey of consensus.

How will we achieve the objectives of the 2020 Strategic Plan? Through the help of you, our members, of course. Our education courses, publications, conferences and networking opportunities will be the means of our success as we seek to facilitate global awareness of critical and important issues.

Since PDA's founding in 1946, we've been a leader in providing scientific, technical information to members worldwide involved in sterile manufacturing. The visionary objectives of the 2020 Strategic Plan will enable PDA to continue this leadership role and serve the needs of our many members.

And as your Chair for 2016–2017, I look forward to leading PDA and working for the benefit of not just our members but also the patients we serve.

1946 70TH ANNIVERSARY 2016

PDA® Parenteral Drug Association

The *PDA Letter* Podcast Series

Listen to leading experts on LAL, CMOs, the future of manufacturing, new manufacturing technologies and more!

In our Podcast Archive, you can listen to the following experts:

- Dr. Jack Levin, co-discoverer of the groundbreaking LAL test
- Lonza's Allen Burgenson
- Vetter's Joachim del Boca
- Amgen's Madhu Balachandran
- Pfizer's Michael O'Brien on modular manufacturing

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

www.pda.org/pdaletter

Success: The *PDA Letter's* New Online Home

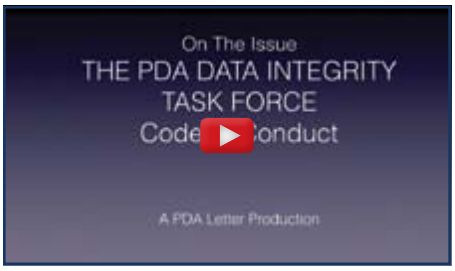
In September, the *PDA Letter* team, working hand-in-hand with PDA's webmaster, launched a new website for the publication. The results have been nothing but spectacular.

Previously, we placed three select articles online, which were unlocked for the entire industry, and placed a PDF of the entire issue in the archive for members only following publication of the print edition. Now, all articles are placed online in browser-friendly (and eye friendly) HTML. Some articles are still unlocked, but most are locked and exclusively available only for PDA members. The full issue remains available in PDF format for members, too.

This content is also easily accessible with most mobile devices as well.

The new website creates new opportunities. First, we have committed to publishing a new article online each week. These articles could be exclusive "online-only" content or they could be published ahead of print content. We are marking "online first" content with the following icon in the print edition:

The second opportunity is expanded multimedia. In October and November, we launched the *PDA Letter's* "On the Issue" video series with two videos covering the activities of PDA's Data Integrity Task Force. We are currently producing a third "On the Issue" series on IT in the pharmaceutical industry. Our goal is to produce six "On the Issue" videos a year. We will continue to produce audio podcasts, too.



Later this year, we will give readers the ability to voluntarily subscribe to email content updates. In addition, we are going to implement a "news" scroller on the homepage of the *PDA Letter* so our readers can more easily view the latest headlines from the global regulatory news that we continuously post to the *PDA Letter* website.

If you have any comments about the website or the Letter in general—good or bad—we want to hear from you. Let us know how we are doing so we can better serve you. After all, the *PDA Letter* is your magazine!

The *PDA Letter* video series is available at www.pda.org/pdaletter

PDA Letter

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

Subscriptions are not available.

PDA Global Headquarters — Bethesda Towers
4350 East West Hwy., Suite 200
Bethesda, MD 20814 USA
Tel: +1 (301) 656-5900 Fax: +1 (301) 986-0296
info@pda.org
www.pda.org

PDA Europe — Am Borsigturm 60
13507 Berlin, Germany
Tel: 49 30 4365508-0 Fax: +49 30 4365508-66
petzholdt@pda.org

PDA Training & Research Institute
4350 East West Hwy., Suite 150
Bethesda, MD 20814 USA
Tel: +1 (301) 656-5900 Fax: +1 (240) 482-1659
info-tri@pda.org

PDA ***Education*** *– Where Excellence Begins*

The Parenteral Drug Association Education Department presents...

GMP Week

February 29 – March 3, 2016 | Bethesda, MD

PDA Training and Research Institute

Identify issues involved with biological products under FDA CGMP compliance using a science/risk-based approach.

If you are involved with GMP manufacturing of clinical and commercial supplies of biopharmaceuticals or directly involved in quality systems activities, procedures and regulatory affairs, then this information-packed week is definitely for you!

Take one or both of the following courses to expand your knowledge and capabilities in meeting GMP requirements:

Biopharmaceutical Manufacturing under Regulatory Compliance: Process Strategies, CGMP Considerations and Facility Requirements (Feb. 29 – Mar. 1)
When you take this course, which uses a combination of lecture and interactive group discussions with case studies, you'll learn how to anticipate GMP compliance problems, develop effective approaches for establishing corrective and preventative action plans, discuss CGMP requirements at an advanced level and much more!

Application of a Quality Systems Approach to Pharmaceutical CGMPs (Mar. 2 – 3)
This course will help you define the concepts behind the application of quality systems and how to apply these systems to drug operations. It will also review specific elements discussed in the FDA Guidance for Industry: Quality Systems Approach to Pharmaceutical CGMP Regulation and the ICH Q10 guideline and compare these to PDA's guidance. Upon completion of this course, you will be able to conduct a gap analysis to determine your company's potential compliance risks, apply different levels of CAPA, and develop appropriate internal and supplier audit schedules corresponding to the risk being addressed.

Discounts apply when you register for both courses!

Register today at pda.org/2016GMPWeek!

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

The Parenteral Drug Association presents...

2016 PDA Annual Meeting

Achieving Manufacturing Excellence: Current Trends and Future Technologies in Bioprocessing

March 14-16, 2016 | San Antonio, TX

JW Marriott San Antonio Hill Country Resort and Spa

Exhibition: March 14-15 | Post-Workshop: March 16-17 | Courses: March 17-18

Register by Feb. 11, 2016 and save up to $200!

New Technology, New Facilities to Support Current and New Therapies and Drug Products

Join us in celebrating the 65th Anniversary of the *PDA Annual Meeting!* This is the most significant event covering the latest innovations in biopharmaceutical approaches, bioprocessing technologies and manufacturing sciences.

Industry and regulatory leaders will share their experience, address challenges and provide a platform for engagement and knowledge exchange with conference participants.

Hear from experts including:

- **David Allen, PhD,** Senior Director, Parenteral TS/MS, *Eli Lilly & Company*
- **George O'Sullivan,** Senior Director, Supply Chain, *Kite Pharma*
- **Veena Warikoo,** Director, Purification Development, *Genzyme – A Sanofi Company*
- **Greg Whitehead,** Senior Director, Quality Assurance, *blue bird bio*
- **George Wiker,** Executive Director, *AES Clean Technology, Inc.*
- And many more!

The *PDA Annual Meeting* continues to be the premier event providing a window into the future, equipping participants and their companies with the best information to overcome the rapidly evolving challenges of our industry.

You won't want to miss this important conference. **Save up to $200** when you register by Feb. 11, 2016!

Learn more and register at pda.org/2016Annual.
#2016Annual

Want to learn more? Expand your knowledge March 17-18 with six in-depth education courses:

- Recommended Practices for Manual Aseptic Processes (Mar. 17)
- Establishment of a Risk-Based Environmental Monitoring (EM) Program (Mar. 17)
- Quality Metrics: Performance Indicators (Mar. 17-18)
- Process Validation and Verification: A Lifecycle Approach (Mar. 17-18)
- Clean Room Design, Contamination Control and Environmental Monitoring for Controlled Environments (Mar. 18)
- Process Simulation Testing for Aseptically Filled Products (Mar. 18)

Learn more about these courses and register at pda.org/2016AnnualCourses