People • Science • Regulation

PDA Letter

Volume LI • Issue 7 www.pda.org/pdaletter July/August 2015

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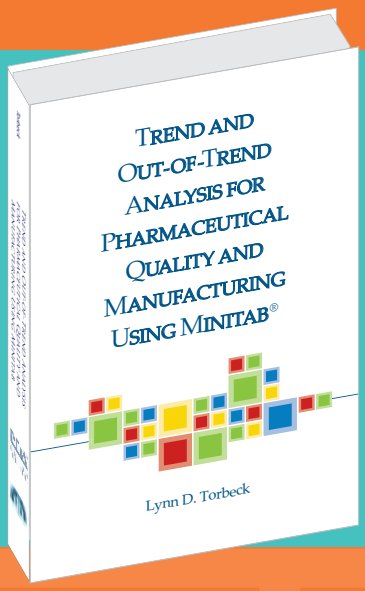
Three Years of Success

34

PDA/FDA Show Issue

Follow this logo to find articles on the *2015 PDA/FDA Joint Regulatory Conference*

PDA Bookstore New Release



Trend and Out-of-Trend Analysis for Pharmaceutical Quality and Manufacturing Using Minitab®

BY: LYNN D. TORBECK

PDA MEMBER PRICE: $210

ITEM NO. 17330

A trend is a series of events or data collected, generally over time, that has an established and expected pattern. The trend can be observed or it can be based on theoretical models. Any departure from the trend is then an unexpected out-of-trend event. It is atypical and begs for investigation.

Trend analysis is good business and good science. The need for a trend analysis book is justified by the continued interest in presentations and discussions, both public and private, and the lack of a widely accepted, clearly defined approach by the industry that lends itself to consistent interpretation and uniform application.

Trend and Out-of-Trend Analysis for Pharmaceutical Quality and Manufacturing Using Minitab®, a new publication by Lynn Torbeck, answers this call, contributing to an industry/regulatory dialogue and consensus that will serve and benefit all stakeholders, and patients in particular.

This book is for pharmaceutical professionals working in product discovery, development, manufacturing, quality assurance and quality control. It presents a basic introduction to data and Trend and Out-of-Trend definitions, and proposes terminology to clarify the use of the word "control" in several contexts. Outtakes from FDA warning letters, plant audits and investigations for trend and out of trend are presented to highlight the agency's viewpoint. Helpful graphs, charts and tables are also included throughout the book and in the appendices.

go.pda.org/TAPQ

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The Parenteral Drug Association presents the...

2015 PDA/FDA Joint Regulatory Conference

The Premier Forum Integrating Science, Technology & Regulation

September 28-30, 2015 | Washington, DC

Renaissance Washington, DC Downtown Hotel

Exhibition: September 28-29 | 2015 PDA Manufacturing Science Workshop: September 30-October 1 | Courses: October 1-2

2015 Theme: Mission Possible: Patient-Focused Manufacturing, Quality and Regulatory Solutions

Save up to $200 when you register by August 18, 2015

The *2015 PDA/FDA Joint Regulatory Conference* provides unprecedented access to information directly from the FDA and offers practical solutions and advice for the regulatory issues facing today's pharmaceutical industry.

Plenary sessions will focus on current challenges, including:

- Innovative Manufacturing and Regulatory Solutions for Patient Care in a Crisis
- Regulatory Submissions Update – FDA Panel Discussion
- Data Integrity
- Patient Perspective
- Compliance Update
- Program Alignment and Reorganization of ORA and CDER

Hear updates on current efforts impacting the development of global regulatory strategies directly from noted regulatory experts, including:

- **Robert Califf, MD,** Deputy Commissioner, Office of Medical Products and Tobacco, *FDA*
- **Dara Corrigan,** Associate Commissioner, Global Regulatory Policy, OGROP, *FDA*
- **Martine Hartogensis,** Deputy Director, CVM, *FDA*
- **William Maisel, MD,** Deputy Director for Science, CDRH, *FDA*
- **Anabela Marcal,** Head of the Compliance and Inspections Department, *EMA*
- **Robert McElwain,** Consumer Safety Office, OCBQ, CBER, *FDA*
- **Melinda Plaisier,** Associate Commissioner for Regulatory Affairs, ORA, *FDA*
- **Carmelo Rosa,** Division Director, CDER, *FDA*
- **Russell Wesdyk,** OPS, Scientific Coordinator, CDER, *FDA*
- **LCDR Joseph Woodring, DO, MPH, MTMH,** Senior Medical Officer, NCHS, *CDC*

Visit pda.org/pdafda2015 for more information.

Exceptional level of direct engagement with FDA officials – nowhere else can you ask questions of the experts and influence direction! To make this unique conference even more accessible and infinitely valuable to our Japanese-speaking attendees, for the first time, PDA will offer simultaneous translation of all plenary sessions and one concurrent track from Japanese to English and English to Japanese.

Want to learn more? On October 1-2, PDA will host five education courses designed to complement what you learned at the conference. ***Learn more at pda.org/pdacourses.***

PDA Letter

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

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Cover Art Illustrated by Katja Yount

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Features

PDA to Support 2016 Johnson & Johnson *Kilmer Conference*

PDA will serve as a supporting organization of the Johnson & Johnson *Kilmer Conference* on sterility assurance and sterilization in 2016.

Johnson & Johnson revived this conference following a series of high-profile superbug infections involving endoscopes. Previously, the company ran eight conferences on sterilization, validation and world health issues between 1976 and 2003.

PDA President and CEO **Richard Johnson** credited Johnson & Johnson for reviving this important event at a time when sterility assurance remains a critical issue.

"PDA is pleased that Johnson & Johnson is resuming the *Kilmer Conference* in 2016. PDA members across the globe are experts in the area of sterilization and sterility assurance for pharmaceutical products, and we are proud to support this effort," he said. "Like Johnson & Johnson, PDA has spearheaded efforts to bring the latest in sterilization technology and science to the pharma industry, and the focus of many of our publications, conferences and training courses is in this area."

PDA joins the Association for the Advancement of Medical Instrumentation (AAMI), another supporting organization of the May 2016 event.

Call for Volunteers

The *PDA Letter* Editorial Committee seeks active PDA members to help set the direction of the Letter, in addition to commenting on articles submitted for publication. For more information about this two-year volunteer commitment, please contact **Rebecca Stauffer** at stauffer@pda.org.

FDA's Robert Califf to Give Talk at *2015 PDA/FDA JRC*

Robert Califf, MD, U.S. FDA Deputy Commissioner of the Office of Medical Products and Tobacco, will deliver the keynote address at the *2015 PDA/FDA Joint Regulatory Conference*, 9 a.m. on September 28 in Washington, D.C.

Califf's remarks will occur during the opening plenary session, which also includes presentations on innovative manufacturing and regulatory solutions for patient care in a crisis. New tools have been given to the Agency to improve the quality of drugs through the Food and Drug Administration Safety and Innovation Act (FDASIA), the Drug Quality and Security Act (DQSA) and the Generic Drug User Fee Act (GDUFA). In addition to Califf, the Centers for Disease Control and Prevention's Sr. Medical Officer, **Joseph Woodring,** will speak in the same session on the CDC's response to the recent Ebola crisis.

"The *PDA/FDA Joint Regulatory Conference* is well known for the participation of high-level officials from the FDA and its sister agencies within the Department of Health and Human Services," said PDA President **Richard Johnson.** "Every year, PDA's efforts to connect people, science and regulation lead to the participation of over 50 officials from regulatory bodies in this conference, both as speakers and attendees. It is one of the best opportunities for PDA's members to get the latest updates on regulatory policy and compliance trends."

This conference also serves to draw interest across the globe. For this reason, the *2015 PDA/FDA Joint Regulatory Conference* will be simultaneously translated into Japanese for the benefit of PDA's more than 920 members in Japan.

BioPharm International

May 1, 2015

"Modular Manufacturing Platforms for Biologics"
—Randi Hernandez
tinyurl.com/pvu9yyt

"Quality Counts, Too"
—Rita C. Peters
tinyurl.com/q96d7zf

"An Update on the Quality Metrics Initiative"
—Susan Schniepp
tinyurl.com/qbeb8cc

BioProcess International

May 12, 2015

"Fundamental Strategies for Viral Clearance Part 2: Technical Approaches"
—Kathryn Martin Remington
tinyurl.com/nqvnfrd

"Reagent Clearance Capability of Protein A Chromatography: A Platform Strategy for Elimination of Process Reagent Clearance Testing"
—Xiaoyang Zhao, Henry Lin and **Jinshu Qui**
tinyurl.com/o2rmgx3

FDA Voice

March 18, 2015

"In India, With Our Sleeves Rolled Up"
—Howard Sklamberg and **Michael Taylor**
tinyurl.com/mhbf9ue

GMP LOGFILE

April 9, 2015

"Continuous Manufacturing: the FDA perspective on the future of medicinal product manufacturing"
—Sabine Paris
tinyurl.com/obvn73r

The Gold Sheet

March 27, 2015

"EMA, PIC/S to Revise Annex 1 Sterile Manufacturing Guidelines; PDA Offers Detailed Advice"
—Bowman Cox

Healthcare Packaging

March 18, 2015

"Is drug counterfeiting the perfect crime?"
—Michelle Maskaly
tinyurl.com/pg7xkvr

March 26, 2015

"Predicting the future of the pharma industry"
—Michelle Maskaly
tinyurl.com/ofg45m8

Infection Control Today

May 5, 2015

"Johnson & Johnson Donates Sterilization Conference Proceedings to AAMI"
tinyurl.com/omdwssb

IPQ Monthly Update

March 2015

"Novartis Exploring Boundaries of Biotech Manufacturing and Control to Make Cell and Gene Therapy Commercialization a Reality"

April/May 2015

"Pharma May be Missing 80% of the Power of Deming's Methods, Deming Institute Expert Maintains at PDA/FDA Q10 Workshop"

Laboratory Equipment

March 6, 2015

"New Technologies Empower Pure Water"
— Michelle Taylor
tinyurl.com/ocy9uzw

Life Science Leader

March 30, 2015

"Harmonized Post-Approval Changes: A Vaccine For Global Drug Shortages"
—Louis Garguilo

The Morning Call

April 18, 2015

"Local students are winners at Delaware Valley Science Fair"
tinyurl.com/np9wza9

PHARMABIZ.com

March 25, 2015

"Pharmexcil meets US FDA officials, discusses export related issues faced by industry"
—Suja Nair Shirodkar
tinyurl.com/ptsxrpo

Pharmaceutical Manufacturing

March 25, 2015

"PDA Annual Meeting Makes Magic"
— Karen Langhauser
tinyurl.com/odkgj2w

Pharmaceutical Technology

April 2, 2015

"Modern Manufacturing Systems Key to FDA Quality Initiative"
—Jill Wechsler
tinyurl.com/nt6omvn

Pharmaceutical Processing

April 15, 2015

"PBOA Hosts Workshop"
tinyurl.com/oqecya7

Renhets Teknik: The Nordic Journal of Contamination Control and Cleanroom Technology

Volume 1: 2015

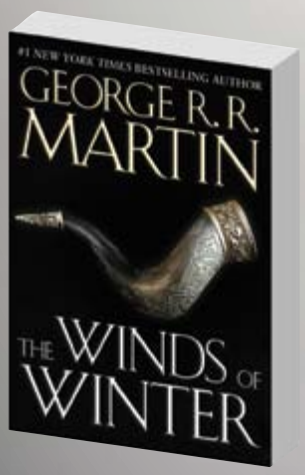
"International nyheter" ("International news")

PDA Volunteer Spotlight

Kelly Waldron

- Manager, Global Quality Risk Management
- *Genzyme Corporation*
- Member Since | **2014**
- Current City | **Gillette, New Jersey**
- Originally From | **Montville, New Jersey**

I love that in our industry we are proud of our work and eager to share it with others



Kelly impatiently awaits the release of George R.R. Martin's The Winds of Winter

How did you start volunteering for PDA?

I met some new people at the *2014 PDA/FDA Joint Regulatory Conference,* and we agreed to meet for a drink one evening. It turned out that we all have a passion for Quality Risk Management, which led to a lively dinner conversation, followed by an invitation for me to join the task force working on the forthcoming technical report on QRM. This just goes to show how important it is to network with your colleagues!

What is one thing that PDA does better than any other professional organization?

I find PDA to be the most forward-thinking professional organization in our industry. While other industry organizations do a good job at consolidating available knowledge and following trends by tapping into established experts, PDA creates experts by bringing innovators together and sets trends rather than following them.

What is something you learned/gained from PDA that you couldn't have gotten anywhere else?

The volunteer opportunities available at PDA are unlike any other. You're offered the opportunity to meet both like-minded and different-minded people within PDA. I have been able to learn and contribute by volunteering.

Looking back, what is one thing you wish you'd known when you started out in your career?

That business is more about people than tasks. I've always understood that science, engineering and technology are the underpinnings of our industry, but what I've learned over my career is that it's the people behind this—our colleagues and our patients—that allow us to realize our goals.

What on-the-job lessons have resonated with you?

The best lesson has been around the value of teamwork. A team focused on designing solutions will always have a better outcome than an individual working on that same problem. So, you could say I've learned that IQ is cumulative.

The Parenteral Drug Association presents the...

2015 PDA Manufacturing Science Workshop

Drive Efficiency and Quality through Continuous Manufacturing

September 30-October 1, 2015 | Washington, DC

Renaissance Washington, DC Downtown Hotel

2015 Theme: Advancing Pharmaceutical Manufacturing with Continuous Manufacturing and Efficient Implementation of Post Approval Change

Photo ©Sartorius AG

Are you prepared for the **future of manufacturing?** A progressive change from a batch production mode to **continuous manufacturing models** will lead to improved efficiency and higher quality, but updates to the regulatory filing through **post approval change submissions** will be required.

Explore the barriers for implementation, challenges to the adoption of these processes and regulatory changes that may be required at the *2015 PDA Manufacturing Science Workshop* through case studies and interactive participation.

Concurrent tracks on ***Continuous Manufacturing*** and ***Post Approval Changes*** will address such topics as Continuous Bioprocessing – Quality Challenges and Best Practices for Post Approval Changes – What's Being Done Now?

Additionally, you'll hear the most up-to-date experiences and recommendations directly from industry and regulatory experts, including:

- **Sau L Lee, PhD,** Associate Director, Office of Pharmaceutical Science, CDER, *FDA*
- **Salvatore Mascia,** CEO, *Continuous Pharmaceuticals (Formerly with MIT)*
- **Moheb Nasr,** Vice President, CMC Strategy, *GlaxoSmithKline*
- **Pierre - Alain Ruffieux, PhD,** Head of Quality, *Novartis Pharma*
- **Lawrence Yu, PhD,** Acting Director, Office of Pharmaceutical Science, CDER, *FDA*
- And many others!

Get ready for the future of pharmaceutical manufacturing!

Visit pda.org/manufacturing2015 for more information and to register.

chapter update

New England Chapter Learns from Process Validation Expert

Enith Morillo, Complya Consulting Group

The PDA New England Chapter's dinner meeting on process validation attracted over 100 industry professionals from across the New England region. Held at the spacious Rapid Micro Biosystems' cafeteria on May 13, the evening included a tour of the company's top-of-the-line facility.

PDA New England Chapter President **Jonathan Morse** officially opened the meeting. With a captive audience, he spoke briefly on the chapter's recent highlights, including its scholarship program for students in the Middlesex Community College biotechnology program, the opportunity to be coached by a veteran chapter volunteer to learn how to organize and plan future dinner meetings, the chapter's upcoming *Spirit of Boston* cruise event on August 19 and the unprecedented New England PDA/ISPE Boston meeting planned for the fall.

Speaker **James Agalloco** then took the stage and began with some background information predating the U.S. FDA 2010 process validation guidance. Drawing on "the cart before the horse" analogy, Agalloco challenged the audience to go backwards when implementing the guidance by starting with Stage 3.

The focus, he explained, must be on currently marketed products that are commercially distributed as these represent the greatest risk. The drive must be to ensure compliance of commercial products first, then build compliance for products under development. He commented on how the chances of getting a Warning Letter or Consent Decree are significantly higher for marketed product than they are for products in Stage 1 and 2. The FDA is unlikely to give out a Warning Letter for not following Design of Experiments (DOE) or Quality by Design (QbD) for early phase products, but will surely come down hard when commercial products are manufactured by a process that is not robust.

In going backwards, he continued, it is vital to understand the source of process variation, detect it, understand its impact on product attributes, and establish controls that are commensurate with the risk. Using an influence matrix to illustrate his point, Agalloco built on the parallel between the Proven Acceptable Range approach of the early '80s and risk mitigation measures defined during the process development phase that will be effective during commercialization.

Regarding statistics and the notion of how much is enough, he spoke about using expanded sampling to build confidence in the process performance, and reviewing batch data as it's been generated for a "live" approach to retrospective validation. He offered a word of caution on blindly following compendial limits that are not process-based, and encouraged industry professionals to look at their processes through the lens of their capabilities and variability.

Attendees listened intently as speaker James Agalloco encouraged them to implement process validation backwards by starting with Stage 3

As for commercial processes that do not measure up to the process validation guidance, he said the options are either to redevelop or discontinue. Agalloco also offered some insight as to how the guidance is not a one-size-fits-all document by noting how it does not work for validation associated with cleaning, computer systems, sterilization, manual processes and environmental controls, etc. It also does not favor smaller companies with financial and resource constraints, nor low volume products for which the number of batches a year can be counted on one hand.

To wrap up, Agalloco touched on the slight differences between the FDA and EMA expectations on process validation, and left the audience with encouraging progress being driven by the USP Microbiology Expert Committee on the FDA's misaligned expectations for non-sterile products and manufacturing sites.

The chapter thanks the following companies for sponsoring the event: Accuratus Lab Services, AAIPharma, Boston Analytical, Commissioning Agents, Complya Consulting Group, Lyophilization Technologies, Masy BioServices, Particle Measuring Services, Rapid Micro Biosystems, Solabs and WILCO. In addition, the chapter sends a special thank you to **Myron Dittmer** and **Aleshia Samson**, the hosts for the event.

PDA Who's Who

James Agalloco, President of Agalloco & Associates

Myron Dittmer, Principal Consultant, MFD & Associates

Jonathan Morse, President, Complya Consulting Group

Aleshia Samson, Validation Specialist, Rapid Micro Biosystems

2015 PDA Pharmaceutical Packaging Conference

May 18–19 | Baltimore, MD

During the opening keynote, the organizers of the meeting recognized long-time PDA volunteer Dana Guazzo

(l-r) Ronald Iacocca, PhD, Eli Lilly; Roger Asselta, Genesis Packaging Technologies; Dana Guazzo, PhD, RxPax; Diane Paskiet, West

PDA Visitors | PDA Headquarters

On May 26, PDA President Richard Johnson (third from the left) and Board Member Michael Sadowski (second from the left) welcomed a delegation of visitors from Baxter (China) Investment Co., the China Pharmaceutical Association of Plant & Engineering, and local branches of the China FDA.

P3: Stability/Container Closure Integrity
(l-r) Sherry Tamura, Biogen Idec; Olivia Henderson, PhD, Biogen Idec; Renato Ravanello, Genentech

P5: Adverse Event/Medical Device Reporting for Combination Products
(l-r) Maria Sanchez, Cordis; Alberto Velez, Johnson & Johnson; Joe Murphy, Janssen; Susan Neadle, Janssen

Opening Plenary: GMPs: Premarket System Requirements
(l-r) John Weiner, U.S. FDA; Kristi Kistner, Amgen; Mark Stielow, Johnson & Johnson

Expand Your Network at the *2015 PDA/FDA JRC*

Each year, the *PDA/FDA Joint Regulatory Conference* promotes discussion of significant regulatory trends in the industry in addition to encouraging greater dialogue between industry and regulators. Along with informative plenary and breakout sessions, this year's conference will again offer exciting networking events for attendees to get together to discuss and debate major topics.

Make it a plan to attend one, or all, of the following networking opportunities to share lessons learned from the conference and make connections with others in the industry.

Orientation Breakfast
(Monday, Sept. 28, 7–8 a.m.)
New PDA members can learn more about the Association from PDA's membership team as well as established members and volunteers. Attendees will also learn how they can volunteer for PDA. (*By invitation only*)

Networking Reception
(Monday, Sept. 28, 6:15–7:30 p.m.)
All conference attendees are invited to attend a networking reception in the Exhibit Area and chat with our exhibitors. Refreshments will be provided.

Gala Reception
(Tuesday, Sept. 29, 6:30–9:30 p.m.)
Music and refreshments will be provided at this year's Gala Reception. Bring your dancing shoes!

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

PDA Awards Trip to Berlin to Pharmtech Moscow Attendee

Last November, PDA—through its European office—participated in the Pharmtech Fair in Moscow by offering a session, "Trends in Manufacturing of Parenteral Pharmaceuticals," conducted by **Georg Roessling.** Over 100 visitors attended the session and were eligible to win a trip to Berlin with accommodations and flight expenses covered by PDA. The winner was **Iryna Lautsevich,** who made the trip this April, accompanied by her husband, and welcomed by staff from the PDA Europe office.

PDA thanks Lautsevich and the others who attended the session in addition to the seven speakers: **Dieter Bandtel, Dieter Rapp, Derek Duncan, Roman Loretts, Sergio Mauri, Alexander Schulgowski, Andrea Simonetti** and **Andrea Zambon.**

Iryna Funke, Registration Coordinator at PDA Europe (left) welcomes Iryna (center) and her husband to Berlin

PDA Who's Who

Dieter Bandtel, Product Manager, Vial Processing, Robert Bosch GmbH

Derek Duncan, PhD, Director, Operations, Lighthouse Instruments

Roman Loretts, Area Sales Manager, CEE/Russia/Turkey, Ellab

Iryna Lautsevich, Director, Filling Line, Syringes, NPO Petrovaks Pharm

Sergio Mauri, Manager, BU Integrated Projects, Fedegari

Dieter Rapp, Robert Bosch GmbH

Georg Roessling, PhD, Senior Vice President, PDA Europe

Alexander Schulgowski, Area Sales Director, Dividella

Andrea Simonetti, Senior Manager, Strategic Initiatives, Bonfiglioli

Andrea Zambon, EZ-fill Vials and Cartridges Product Manager, OMPI

So Much Still to Learn About Process Validation

Scott Bozzone, PhD, Pfizer, and Wendy Zwolenski-Lambert, Novartis

Process validation is not a new concept in our industry. While you may think you know the ins and outs of it, validation of pharmaceutical manufacturing processes continues to evolve globally due to changing regulatory expectations. Can you really say that you fully understand all the concepts?

Since the finalization of ICH Q8, Q9 and Q10, the industry has seen process validation move to a lifecycle concept. Beginning in 2011, with the finalization of the U.S. FDA process validation guidance, other regions of the world have also incorporated ICH principles into process validation guidelines. Process validation is now a lifecycle concept, reaching beyond the traditional three batches to ensure an ongoing state of control.

This holistic view of process validation makes sense, but raises a number of interesting questions in practice, such as:

- How are development data used to supplement validation of the commercial scale process?
- What approaches can be taken with established commercial products?
- How should protocols and reports be structured to reflect a lifecycle approach?

The PDA Education course, "Process Validation and Verification: A Lifecycle Approach," scheduled for Oct. 1–2 following the *2015 PDA/FDA Joint Regulatory Conference,* is designed to address these and other practical implementation questions. PDA *Technical Report No. 60: Process Validation: A Lifecycle Approach* serves as the foundation of the course. The authors of TR-60 expressed similar questions as above, and sought to craft a practical guide to lifecycle implementation. The task force behind TR-60 comprised experienced, multi-disciplinary industry professionals who consulted many references in addition to their own experiences to produce an authoritative technical report covering both theory and real-life case studies.

This course will provide participants with a better understanding of a lifecycle approach to process validation through examples, exercises and discussion. Practical application of ICH principles, such as Quality Risk Management, will be discussed, and examples of successful strategies for meaningful risk assessment and management will be shown. All stages of the process validation lifecycle will be covered, with emphasis on strategies and tools for maintaining ongoing state of control during manufacturing.

The case studies in TR-60 will be reviewed and participants will be encouraged to question and propose alternative approaches. Like all PDA Education courses, participants will be encouraged to share their ideas, perspectives and experiences. The entire group will benefit from the interactive sessions, gaining insight from veteran instructors as well as the experiences of other participants.

Finally, participants will receive an up-to-the minute look at the process validation landscape across the globe. The international landscape will be covered in depth by exploring similarities and differences between regional guidance documents and demystifying some of the terminology. For example, the content of the recently approved EC Annex 15: *Qualification and Validation* will be discussed and compared to the FDA guidance, as well as other draft guidances to gain a view of the process validation across the international arena. Recent inspectional observations and industry trends will be reviewed and evaluated.

Participants will emerge from the course with a comprehensive library of the most current industry and regulatory references, a number of which have been published or updated since the publication of TR-60 in 2013.

Other features to be included in the course:

- Importance of criticality assessments, quality attributes and process parameters
- Documentation such as validation master plans
- Bracketing and matrixing examples
- Validation approaches: concurrent, traditional, hybrid and continuous process verification
- Justifying the number of batches
- Sampling plans
- Statistical applications in process performance qualification (PPQ) and continued process verification (CPV
- ASTM standards—the most applicable standards
- New innovative processes
- Legacy products—what is industry doing? What are the trends?
- CPV monitoring plans
- Blend and content uniformity sampling
- Case studies, including an example used in a FDA training program

This course will provide the most current and practical aspects of process validation, while maintaining compliance and meeting recent regulatory expectations. With this level of information, it may pay to ask yourself, "what else can I learn about process validation to improve my day-to-day operations?"

[Editor's Note: For more information about this and other PDA Education courses following the *2015 PDA/FDA Joint Regulatory Conference*, visit www.pda.org/pdacourses.**]**

snapshot

Task Force Plans Survey on Particulate Matter in Oral Solids

Katrina Elia, SPI Pharma Inc.

Particulate matter-related recalls have continually increased for the fifth year in a row ***(1),*** and continue to be a major threat to uninterrupted product supply. Although extraneous particulate matter recalls are predominantly associated with parenteral products, several oral products have also been recalled for the presence of foreign particles. Currently, there is no global industry benchmark, standard or guidance on mitigation strategies, acceptable levels, clinical relevance, inspection, sampling, testing, and complaint handling for particulate matter in oral products. For this reason, PDA volunteers formed the Particulate Matter in Oral Solid Dosage Form Task Force to analyze and address this critical gap.

The task force consists of members with expertise in manufacturing, quality, safety and regulatory affairs, and will be responsible for conducting a blinded global survey. The survey has four tracks/paths with questions customized for manufacturers of APIs and excipients, drug products, primary packaging and regulators/consultants. The survey seeks to understand the current state of particulate matter in oral dosage forms (solids and liquids). The survey also seeks input on practices ranging from inspection and testing, mitigation technologies, compliant investigations, to safety/hazard assessments. The results from this survey will be used as the basis for a PDA technical report that will serve as a best practice guide to the pharmaceutical industry as well as aid regulators in understanding the industry's capabilities and challenges.

PDA looks forward to your participation in the survey and assistance in advancing science-based standards and best practices in a risk-based environment.

Reference

1. Cox, B. "2014 Drug Recalls: Contamination Surge Enters Fifth Year." *The Gold Sheet*, May 2015.

Journal *Preview*

July–August Issue Offers Case Studies on Rapid Methods, Reciprocal Translocation of Cells

The latest issue of the *PDA Journal of Pharmaceutical Science and Technology* features two case studies. One evaluates rapid microbial methods outlined in TR-33 using statistics. And the other looks at reciprocal translocation in end-of-production cells.

Letter to the Editor

Perceval Sondag, Raphael Joie, Harry Yang, "Comment and Completion: Implementation of Parallelism Testing for Four-Parameter Logistic Model in Bioassays"

Research

Christopher D. Mensch, Harrison B. Davis, Jeffrey T. Blue, "Characterization of Propylene Glycol–Mitigated Freeze/Thaw Agglomeration of a Frozen Liquid nOMV Vaccine Formulation by Static Light Scattering and Micro-Flow Imaging"

Case Studies

David Jones, et. al., "Evaluation of PDA Technical Report No 33. Statistical Testing Recommendations for a Rapid Microbiological Method Case Study"

Commentary

Maik Jornitz, "A Review of the Aging Process and Facilities Topic"

Sandra Cha Sifferlen, "Drug Shortages, Today and Tomorrow—An Industry Perspective"

Commentary

Dennis Jenke, "Moving Forward towards Standardized Analytical Methods for Extractables and Leachables Profiling Studies"

Aymen S.Yassin, et. al., "Quality Control Testing for Tracking Endotoxin-Producing Gram-Negative Bacteria during the Preparation of Polyvalent Snake Antivenom Immunoglobulin"

Y. John Wang, et. al., "Kinetic Modeling of Methionine Oxidation in Monoclonal Antibodies from Hydrogen Peroxide Spiking Studies"

Yolande Rouiller, et. al., "Reciprocal translocation observed in end-of-production cells of a commercial CHO-based process"

Juergen Knoebel, "Quality Culture vs. Cost of Quality—Quality Culture Is Understanding the Value, not Just the Price, of Quality"

Christopher J. Smalley, "Compounding Pharmacists, Skills and Knowledge, and the Role of Pharmacy Colleges"

Meeting *Preview*

Interest Group Meeting Schedule

As always, relevant interest groups will meet for the first two days of the *2015 PDA/FDA Joint Regulatory Conference.* Below is a schedule of interest group sessions falling under the PDA Science and Biotechnology Advisory Boards.

Monday, September 28	Tuesday, September 29
5 p.m. – 6:15 p.m.	**5 p.m. – 6:15 p.m.**
Applied Statistics Interest Group Biotechnology Interest Group Combination Products Interest Group	Process Validation Interest Group Facilities and Engineering Interest Group Microbiology/Environmental Monitoring Interest Group Filtration Interest Group

Patient Wants Should Drive Prefilled Syringe Design

Walter Morris, PDA

An unused drug is an ineffective drug, no matter how much it cost to develop, manufacture and administer. The late U.S. Surgeon General **C. Everett Koop** offered a simpler observation: "Drugs don't work in patients who don't take them."

Amgen's **Sheldon Moberg,** Vice President of Device Technologies, reminded attendees at the *2014 PDA Universe of Prefilled Syringes and Injection Devices* meeting of Dr. Coop's wise words during his talk, "Essential Parts of Innovation in Combination Products: Improving Patient Outcomes."

Moberg identified a variety of barriers that prevent patients from improving their overall health and healthcare outcomes. Among them were "patients unwilling to initiate treatment" and "lack of compliance/adherence."

Citing data from several sources, he showed that there is a disturbing lack of follow through on compliance/adherence to simple drug regimens following myocardial infarction. After 120 days, 17% of heart medication scripts and 65% of comorbidity scripts go unfulfilled. And these are relatively easy-to-take oral solids.

Moberg did not have any data on patient compliance with injectable drug products, but one can see where his line of reasoning was going. Oral solids are easy because they are painlessly swallowed, room-temperature stable, portable, discreet, simple (no special preparation) and lack disposal issues. Injections are painful, usually temperature-sensitive (necessitating refrigeration), sometimes complex and require special disposal.

Historically, however, injectable drug products were limited in therapeutic areas. But as PDA's prefilled syringe-oriented conference has shown over the years (and if you missed last year's, you can attend this year's meeting in Vienna; visit https://europe.pda.org/ups2015 for more information), injectable drugs are treating a wider range of therapeutic areas, both primary and specialty care, for an increasing number of less severe diseases with broad patient populations.

Injectable drug developers/manufacturers cannot prepare today's product users like they did in the old days when patients commonly had to visit their doctor for injections. Back then, it didn't matter if the patient knew how to use the product because typically the nurse performed the injection. Today, not only must patients be able to use autoinjectors and pen injectors, drug companies must make sure they *want* to use the products they are selling. In some respects, with the barrier between injectable administration and the patient dissolving, developers of such products now must consider the patient's motives as much as their medical needs. Drug companies, in a way, are now entering the realm of smartphone manufacturers.

Showing that patients *can use* a product through a variety of human factors testing and usability studies is the price of entry into the marketplace. Regulators will let companies sell a drug with such data. Yet today's prefilled syringe developers have to make sure the patient *wants to use* their product.

Moberg offered three considerations for manufacturers:

- Is the product minimally disruptive to lifestyle?
- What are the patient's perceptions of pain, discomfort, intimidation and anxiety?
- Can you assess the "total user experience?"

He showed a graph of sales for two insulin products administered in pen in-

jectors. One entered the market nearly a decade prior to the other, yet by 2012 the second product had eclipsed the first in total sales. He stated that differences in the pen injector (the second product's pen had 30% less force and better dosing accuracy than the other product) was one of the reasons for this discrepancy.

"We are delving into human psychology," said Moburg, and "all bets are off!"

Thus, gone are the days when manufacturers introduce any old autoinjector to the market. Consumers—many of whom demand the latest in technology and innovation when it comes to personal electronics such as smartphones and tablets—expect an injector that is highly innovative and meets their personal needs and preferences. The *Universe of Prefilled Syringes and Injection Devices* meeting is always replete with innovative technology that should appeal to increasingly tech-savvy consumers. The conference featured talks on a number of these products.

Consumer-friendly Drug Tech Growing

Jarne Elleholm, Business Development, INJECTOR, presented their "next gen" all-in-one dual chamber autoinjector.

Kevin Constable, Director, Technology Development, Terumo Medical Corporation, discussed his company's "innovative" tapered needle technology.

Drug companies considering partnerships with vendors like INJECTOR and Terumo Medical need to employ a solid risk-based approach to vendor evaluation, according to **Ivy Lin,** Device Development, Genentech/Roche. She noted that quality issues arising from the use of prefilled syringes/injection devices result from the drug manufacturer's "poor understanding of primary container interaction with the drug."

Lin outlined her company's supplier selection process, which includes multiple criteria with distinct workstreams. A figure accompanying this discussion outlined the various criteria and demonstrated how the workstreams overlap and the amount of time needed to prepare and actively engage suppliers (**Figure 1**).

One innovative approach adopted by Genentech as part of their supplier selection process was changing their "process and mindset on acceptable quality." The common method for controlling a process is to set an AQL and a sample size based on ISO 2859-1, she said. This method not only reduces the chances of finding defects, it "favors the supplier by reducing 'producer risk'" which is the risk of rejecting batches, lots and shipments in this case.

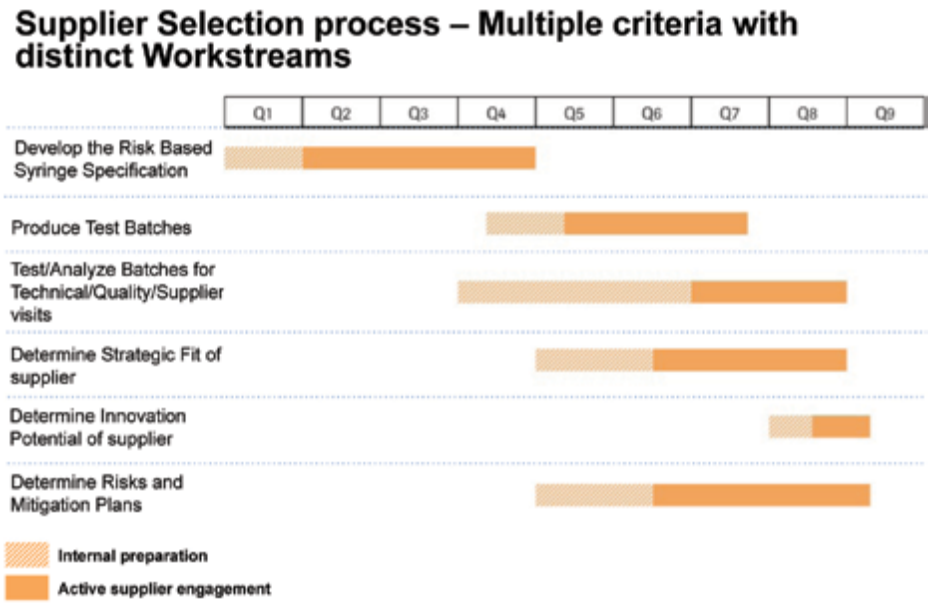
Genentech instead took the approach of understanding the suppliers process capabilities and defining the quality level by defective parts per million (DPPM) or parts per million (PPM). This requires an estimation of the percentage of nonconforming parts based on population mean and standard deviation. To make such estimates, test methods must be developed to generate variable data for statistical analysis.

The benefits, according to Lin, include:

- Aligned understanding of expected quality of product between supplier and customer
- Greater process knowledge
- Estimation of nonconformance possible with few or no defective observations
- Smaller sample sizes

She cautioned that the approach "does require some change in practice and understanding of statistics," and, as such, introduces "complexities" when implementing the approach at the supplier and internally in QC.

Figure 1 Supplier Selection Process*



* From Ivy Lin's presentation "Applying a Risk-Based Approach for Prefilled Syringe Vendor Evaluation," *2014 PDA Universe of Pre-filled Syringes and Injection Devices: Improving Patient Outcomes through Innovation*

Marketplace Growing for Inject Tech

The 2014 conference proved once again that prefilled syringes and other types of innovative injection devices are already an important segment of the overall injectable drug marketplace, and probably will become even more significant in a few short years.

Dena Flamm, Product Manager, Robert Bosch Packaging, noted the trend away from the traditional vial/syringe and towards pens and autoinjectors for new therapies and generic injectables. Therapeutic areas where these devices are already used are: anaphylaxis, cancer,

Continued at bottom of page 22

Driving PAC Efficiency and Embracing New Technology

Lisa Skeens, PhD, Hospira

For years, pharma manufacturers have been viewed as lagging behind other types of manufacturers when it came to the adoption of new technologies. This was attributed to the burden of regulatory oversight and the requirement to file any postapproval manufacturing changes with global regulators. While these challenges are real and must be overcome, the global pharmaceutical industry, as well as regulators, are now reevaluating the postapproval regulatory paradigm under a new ICH initiative. All parties understand the need to facilitate adoption of new technologies, such as continuous manufacturing, to allow pharmaceutical manufacturing and quality improvements to thrive in the pharma industry. The question is: how can manufacturers make this a reality?

The need to implement new technologies, such as continuous manufacturing, is a hot topic across the industry, all the way up to U.S. FDA, CDER Director **Janet Woodcock,** MD, who recently spoke of the advantages of continuous manufacturing to the U.S. Congress. Implementation of continuous manufacturing offers significant benefits including greater efficiency and higher quality, and is already standard in many industries. It can also facilitate faster development timelines, so why are pharmaceutical companies not embracing it?

These two hot topics will be discussed at the upcoming *2015 PDA Manufacturing Science Workshop* following the *2015 PDA/FDA Joint Regulatory Conference*. The workshop will include presentations from experts in continuous manufacturing and postapproval changes, as well as interactive breakout sessions promoting an exchange of ideas. This is an opportunity to interact directly with pharmaceutical/biopharmaceutical companies who have already successfully implemented continuous manufacturing, and learn how they overcame the challenges in adoption. Global postapproval changes experts will share best practices on managing the complexity of today's environment to support manufacturing innovation and drive efficiency, and will also discuss new FDA and global regulatory guidance along with the international work being done under new initiatives such as ICH Q12.

This is a unique opportunity to hear from regulators and industry experts on two very important and evolving hot topics, and interactively work together to move the pharmaceutical/biopharmaceutical industry forward in a meaningful way. For more information about the workshop, visit www.pda.org/manufacturing2015.

2015 PDA/FDA Joint Regulatory Conference

A Regulatory Perspective on Breakthrough Therapies

Rebecca Stauffer, PDA

The Food and Drug Administration Safety and Innovation Act (FDASIA) introduced the breakthrough therapy designation. This designation refers to a drug used to treat a serious or life-threatening condition that preliminary clinical evidence suggests may be a substantial improvement over existing therapies. If a drug receives the breakthrough therapy designation, the U.S. FDA will expedite development and review of the drug. The PDA Letter *spoke with* ***Mahesh Ramanadham*** *and* ***Sarah Pope Miksinski,*** *both with the FDA, who will speak on the topic in session B5 "Innovation" on Tuesday, Sept. 29 at the* 2015 PDA/FDA Joint Regulatory Conference.

PDA Letter: What are the top two takeaways you hope that members of industry will receive from your talk at the *2015 PDA/FDA Joint Regulatory Conference?*

Ramanadham and Miksinski: Our hope is that the audience will gain an understanding that there is a mutual incentive between industry and the Agency in promoting the development and introduction of medications to address unmet medical needs in the treatment of serious or life-threatening conditions. We also intend to convey FDA's strong commitment to working with sponsors of breakthrough therapies to find creative opportunities in streamlining the quality development program while meeting regulatory expectations for premarket review. The cornerstone of this effort is early, comprehensive, transparent, and risk-based communication that is framed within a patient-focused approach that ensures availability of the product to the American public.

PDA Letter: How does quality factor in to the Agency's evaluation of a "breakthrough therapy?" Does it impact the preapproval inspection at a facility? Is it the same as an inspection for a nonbreakthrough therapy, or do inspectors look at different things?

Ramanadham and Miksinski: Quality is the foundation for safety and efficacy. Building quality into any product, process and involved facility ensures that a patient will reliably receive a product that consistently delivers the performance it purports to. As such, the grave importance of ensuring a robust quality program has, by necessity, forged new approaches to quality review where integrated teams work collaboratively to ensure that comprehensive quality is built into the product. This involves all aspects of the program, including, but not limited to, analytical methods and stability data, manufacturing processes, and implementation in conformance with cGMP. Preapproval inspections benefit from intensive collaboration as investigators are also focused on assessing the most critical elements to ensure quality.

Finally, the rapid development needs that accompany breakthrough therapy timelines will sometimes result in challenges in the quality realm. Using an enhanced patient-focused approach, the entire quality team works proactively with sponsors and sites in addressing those challenges. Such intense commitment allows FDA to be effective in providing relevant support and feedback to industry in the quality development and commercialization of breakthrough products.

PDA Letter: How are meetings with review teams different for breakthrough drugs as opposed to other drug products?

Ramanadham and Miksinski: From a quality standpoint, meeting interactions target a patient-centric discussion of risks to quality relative to patient benefit. In the breakthrough realm, such discussions often include innovative approaches to risk identification, assessment and mitigation. Additionally, we encourage efficient and enhanced interactions for breakthrough products, especially during development and preceding application submission. Attachment 1 of FDA's MAPP "Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics" highlights essential topics for discussion during these meetings. **[Editor's Note:** This document can be accessed at tinyurl.com/p5xt4pz.**]**

PDA Letter: How different is the schedule for an approved breakthrough product different than one for other types of drug products?

Ramanadham and Miksinski: In alignment with FDA's commitment to breakthrough products, the quality review employs an "all hands on deck" approach to ensure availability of critically needed medications to the American public.

About the Experts

Mahesh Ramanadham is currently the Acting Branch Chief in the Division of Good Manufacturing Practice Assessment/New Drug Manufacturing Assessment Branch within the Office of Compliance/Office of Manufacturing and Product Quality .

Sarah Pope Miksinski, PhD, is the Acting Director of the FDA's Office of New Drug Products (ONDP), in the Office of Pharmaceutical Quality (OPQ).

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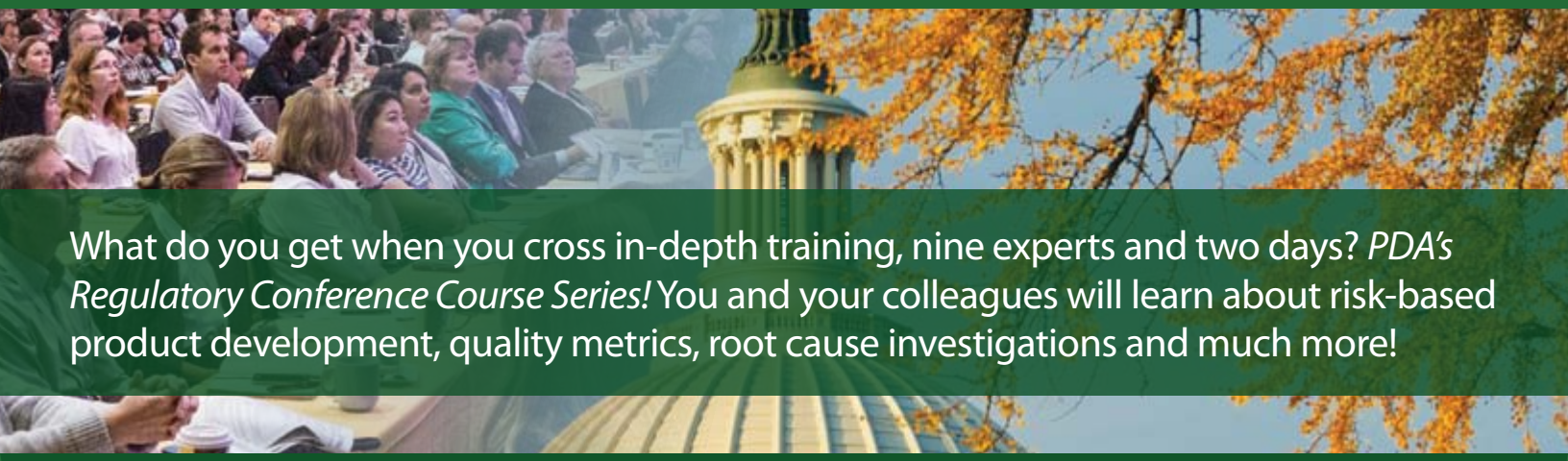

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Risk-Based Product Development Basics for Combination Products: Harmonizing Design Controls and Quality-by-Design in Product Development and Market Authorization Documents (October 1)
An overview of the challenges encountered in developing a combination product will be reviewed. This course will focus on drug-device or biologic-device products with an emphasis on how the controlled development process (design control and QbD) and the associated documentation of product and process development can support good regulatory submissions. The objective of the course is to introduce and harmonize the basic requirements of FDA's design controls (21 CFR 820.30) with Quality-by-Design expectations.

JUST ADDED **Risk Based Approach for Prevention and Management of Drug Shortages (October 1)**
This is a hands-on, interactive course based on *PDA's Technical Report No. 68, Risk-Based Approach for Prevention and Management of Drug Shortages*, that explores what controls can be established in the end-to-end product value chain to address drug shortage risks and proactively prevent them. Think creatively and in a risk-based manner about other practical solutions that can be leveraged beyond conventional solutions, such as collaboration with health authorities to expedite post-approval changes, short-term use of an alternate facility, activating short-term supply from an alternate source to address emergency needs and more. During this course, you will learn to develop a Drug Shortage Risk Register and a Drug Shortage Prevention and Response Plan using examples and standard templates.

Quality Metrics: Performance Indicators (October 1 – 2)
Learn how to select the appropriate quality metrics and determine how to best collect and utilize the data to improve the Quality System from this course. The types of processes to be discussed include the production process; supporting processes, such as change control, training and validation; supplier processes and materials management.

Root Cause Investigation for CAPA (October 1 – 2)
Participants will engage in learning a systematic, science-based methodology to identify the cause(s) for a decline in the performance of equipment, product (tangible or intangible) or work process (physical or virtual). Once identified, the methodology determines appropriate corrective actions to restore performance, preventive actions to assure similar issues do not occur and a control plan to assure the original problem does not return.

Process Validation and Verification: A Lifecycle Approach (October 1–2)
Designed to explain and facilitate the implementation of process validation and continued process verification from a practical perspective, this course will address the three stages of process validation activities from the design to the commercial production stage. Gain knowledge needed to ensure process validation strategies and approaches are consistent with current regulatory and quality system thinking. This course is based on a PDA Technical Report addressing the same subject.

CMC Regulatory Requirements in Drug Applications (October 2) GSA Schedule Contract GS-02F-113BA
Providing a basic understanding of CMC requirements in drug applications, this course will help prepare those in regulatory affairs to better address the key points required in the CMC sections of drug applications. Topics to be covered include: CMC in Investigational New Drug applications, New Drug Applications (NDAs), Abbreviated New Drug Applications, drug master files and post-approval change supplements. Compliance to cGMP will also be briefly discussed.

To learn more and register, visit pda.org/pdacourses

GSA Schedule Contract GS-02F-113BA **Denotes GSA Schedule Contract**

Vaccines: An Ages Old Industry Faces Modern Challenges

John Finkbohner, PhD, MedImmune-Astrazeneca

How can our industry effectively deliver new vaccines to the global patient population? What technical and regulatory challenges must vaccine manufacturers address at present?

These are some of the questions that vaccine manufacturers must ask themselves as the industry continues through changing times. While some view vaccines as a long-established, traditional class of biologics, the vaccinology space provides some of the more exciting opportunities to bring forward new treatments. Vaccine stakeholders face the challenge of creating an environment that can accelerate the development, licensure, and availability of novel vaccine candidates for emerging epidemics and chronic infectious diseases.

Answers may be found by attending the *2015 PDA/FDA Vaccines Conference.* The FDA and PDA are cosponsoring this conference in December in Bethesda, Md. This year's conference will be highly exceptional as some sessions will be simulcast between the conference in Bethesda and the PDA Europe *Vaccines* conference in Berlin, Germany, which will be held on the same days.

Plenary sessions will provide an overview of modern vaccine development, a case study in the approval of a vaccine formulated with a novel adjuvant, updates and lessons learned from current efforts to develop an Ebola vaccine, challenges in developing vaccines in developing countries, and an examination of recent disease outbreaks and implications for vaccine preventable disease. The more detailed parallel track sessions will focus on topics such as vaccine manufacturing strategies, potency assays, technology transfer for manufacturing and testing, virus detection using next generation technologies, novel vaccine delivery systems, FDA combination product review updates, development of new products using novel adjuvants, and updates on cutting edge vaccine priorities such as development of a vaccine for Ebola. This latter topic will set the stage for the plenary session looking at considerations when designing and conducting efficacy studies against emerging infectious diseases in developing countries.

This promises to be an exciting opportunity to focus on the current manufacturing and development challenges facing an industry with such a long and successful track record for contributing to the protection of the public health. For information about the U.S. conference, visit www.pda.org/vaccines2015 and for information about the parallel conference in Berlin, visit https://europe.pda.org/vaccines2015. Information about PDA Education courses following the Bethesda conference can be found at www.pda.org/vaccinescourses.

Patient Wants Should Drive Prefilled Syringe Design continued from page 18

hormone (including insulin), hepatitis, infertility, multiple sclerosis, Parkinson's disease, rheumatic diseases, etc. Citing 2012 data, she noted that there were over 30 million users of disposable (most) and reusable pens. Trends in the healthcare marketplace will drive the numbers ever higher. These include the shift to do-it-yourself healthcare, patient empowerment, and, sadly, the growth of insulin diabetics in the United States (the largest market for these devices already).

Manoj Pananchukunnath, Mylan, also spoke to the growing marketplace for prefilled syringes and injection devices. Currently, of the $243 billion (USD, 2013) marketplace for injectable drugs, prefilled syringes, pens, autoinjectors and implants accounted for just 7%. Still, the market for these products can only continue to grow.

With innovative devices, increasing demand, and the need to deliver drugs in devices that technology-minded patients "want to use," it is clear that the universe of prefilled syringes, autoinjectors and pens will continue to expand for years to come.

[Editor's Note: This is the second report from the *2014 PDA Prefilled Syringes and Injection Devices* conference. "Exciting Technological and Scientific Advances Drive Prefilled Syringe Market" appeared in the November/December 2014 issue.**]**

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Visible Particulate Detection Finally Emerging from the Fog

Roy Cherris, Bridge Associates International

Within this industry, 100% visual inspection for visible particles has been a parenteral requirement for more than 70 years; however, there has been a lack of clear guidance and harmonized scientific approach for much of this time, resulting in many U.S. FDA 483s and warning letters, along with particulate-related recalls. In fact, the last five years have featured the most contamination-related regulatory actions of all time. In 2014, there were 82 contamination-related recalls, of which 43 were rated as Class 1. Without defined FDA or industry guidance, there has been significant variance in the individual expectations of inspectors, CDER, CBER and companies' particle control practices.

Much of the problem can be attributed to little written guidance and the nebulous terminology of "essentially free," or "practically free," from visible foreign particles. Both terms have been standard—with variable meaning—until August of last year when USP <790> became official.

At the turn of this century, PDA chartered the Visual Inspection Task Force and started the annual Visual Inspection Forum meetings which focused on periodic benchmarking surveys and in-depth study of inspection practices and particulate control. In 2009, USP established an expert panel including FDA representation which took this information and developed a definition of the minimum requirements necessary to declare a batch of product "essentially free" from visible foreign particles. Then, in January of this year came comprehensive guidance in the form of the draft USP chapter <1790>, which is currently available for comment in the *Pharmacopeial Forum*. A second draft of <1790> will be reissued soon.

It is clear from this recent activity that the industry can harmonize its approach for the fundamentals of inspections and subvisible-to-visible particle control. Indeed, we are finally emerging from the fog to adopt common practices to inspect for, and control, particulates, however, this harmonization in the industry will not happen overnight.

The *2015 PDA Visual Inspection Forum* returns to the United States this year. It will be followed by a PDA Education visual inspection training course. For information about the Forum, visit www.pda.org/visualinspection2015. To learn more about the PDA Education course, visit www.pda.org/visualcourse.

What is the Future of Contamination Control?

The following blinded, unedited remarks are taken from PDA Connect℠, PDA's online forum that allows members to discuss and 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 PDA Letter *will periodically publish selected dialogue from PDA Connect℠. If you're not already part of PDA Connect℠, you can join at community.pda.org to continue the conversation!*

The following dialogue is from the Sterile Processing Interest Group forum.

Questioner

Today I read an observation from an inspector noting (within a terminal steilizing LVP manufacturing facility) zero microbiological testing of IPA…it made me think of this question:

How clearly do we see and are we moving to the future of contamination control? A better question is WHAT is the [future] paradigm?

Please let me know your thoughts…

Respondent 1

Well, one would think that IDEAL paradigm is when there are no contamination and we know EXACTLY how everything is operates. The question: will it ever be possible? One can probably say that out of space in the vacuum is the place with no contamination. Another will ask: and what about viable but not recoverable organisms? How can we be sure that we are in control?

Going back to the observation that was mentioned in the original quote - testing IPA for bioburden provide more information about control. If you buy sterile IPA, then you don't have to test it for bioburden, regardless of what type of the facility it is being used as long as you audited your supplied and can assure the quality of that IPA. However if 70% IPA preparation is done in-house and used in the clean rooms (regardless of the sterilization process), than one might want to show awareness of what is in the solution that used to sanitize surfaces. Testing IPA is one way of showing that manufacturing knows what is going on and can remediate if needed. The question might be how much of a control we really need when were are talking about terminally sterilized LVP? I think if we make a claim that this LVP is manufactured in the classified rooms and we want to sell this product in US and EU or Japan, than we might want to follow regulatory suggestions and requirements, which often very strict. If we want to break free from the regulation guidelines and still make all the claims on the product that we are trying to sell, than the world of RISK ASSESSMENT must come into play. It often requires more than just one attempt to convince agencies that with risk assessment testing of the IPA for terminally sterilized LVP is not needed. And in order to do so a lot of data and justification should be put in the document. We have to realize

though that Risk Assessment should not be an aftermath. It should be a very thoughtful process before we stop doing something (like not testing IPA).

The most logical future for contamination control in my opinion is by detailed risk assessment. We can test everything to death, but I think it is more logical to assess the risk of contamination and then implement some limited testing program for IPA, Environment APIs, etc…

What's your opinion? Do you [prefer] testing? Do you believe in risk assessment? Other?

Questioner

I agree and disagree with [redacted]. Fundamentally the rigour of activity is dictated by the context. For a terminally sterilized LVP the rigour should be different from aseptically manufactured product in isolators, in open cleanrooms ..so forth. Rigour of risk assessment might be considered part of that. An observation made without consideration of context does not assist patient safety, and often confuses firms resulting in a simple capitulation to the request. A better observation would address why (in this case) IPA was not considered (fundamentally assessment of risk) in the context…

In other words the firm failed to state the logic (documented) nor perhaps possessed sufficient systems to ensure that this was captured. In other words 'systems-based microbial control' (covered in PDAs Annual Micro Conference October 2015). Risk assessment is fine but is only one lelement of a system that needs to self-detect and self-address - systems-based microbial control.

The future? FDA's Janet Woodock has made it clear that the agency expects firms to be the expert in what they do and the FDA should not and aspires not to tell firms how to do things…this is the best way of looking after the patient. But it does mean firms have to understand, design, control using the likes of ICHQ8, Q9, Q10, augmented with the likes of industry best practices (eg PDA Technical Reports). I sense that other guidances (Annex 1 in revision for example) will adopt an approach where firms have to use risk-based approaches and not necessarily be provided strict items to adhere to.

As for testing — this is a part of systems-based microbial control, however certain things need to happen in the future to retire or manage measurement uncertainty (remember CoV of compendil bioburden test is likely ~35% compared to HPLC assay of ~1%). New technology, retirement of the cfu (per Dr Akers of USP) and adoption of genuine quantitative risk assessment…

Respondent 1

I would agree and disagree. I agree that observation without consideration does not assist patient safety.

However, if we will continue talking about citation for not testing IPA one other thing comes to mind - company had no idea they had to state the logic as to why they are not testing IPA and that failure to do so (not provide the logic) might lead to the observation by an auditor. I have countless examples from the clients I work with that they are not aware about all details that could lead to an observation or delay in the submission approval (action letters or un-approvable letter). It is not because they failed to do so intentionally but because they did not know they should be doing it. So rigorous risk assessment is great, but how much do you assess? Is there a limit how far we need to go with assessments? Can any process be assessed so perfectly that will have safest drug on the market and no observations from the agency? or is it all going to be based on trial and error? Yes there are guidance that telling us what we should be doing as part of risk assessment, but there is no itemized list, simply because it is not possible to have one.

I don't think we can ever compare bioburden CoV of 35% due to living cells and human manipulation and CoV of chemical method performed by machine. Using RMM might reduce CoV, but by how much? And then there is an ROI comes into play - do we really have to qualify that expensive machine that does not have standardize methods, then get agency involved to approve the method and all that to walk away from cfu. You might say I don't see the big picture. I think I do it just I am rather skeptical about it. One of the examples are from the meeting I had today. We were discussing LER (Low Endotoxin Recovery phenomena) and one thing comes very clear — agency requires companies to generate very large amount of data so it can make decision whether LER is an issue or not. Some of the companies don't have enough resources to do so. Those companies that do have data don't want that data to be available to everyone because they spent a lot of effort and money to generate it. So CoV of 1% from HPLC analyses is great, it is standardized and you can buy reference standard (though expensive) from USP website. Bioburden tests are far from being standardized in the same manner. I also think that operating under "genuine quantitative risk assessment" will create complete detachment from the physical production world and with time people might completely forget what colony is. I don't think that should happen.

Just my two cents.

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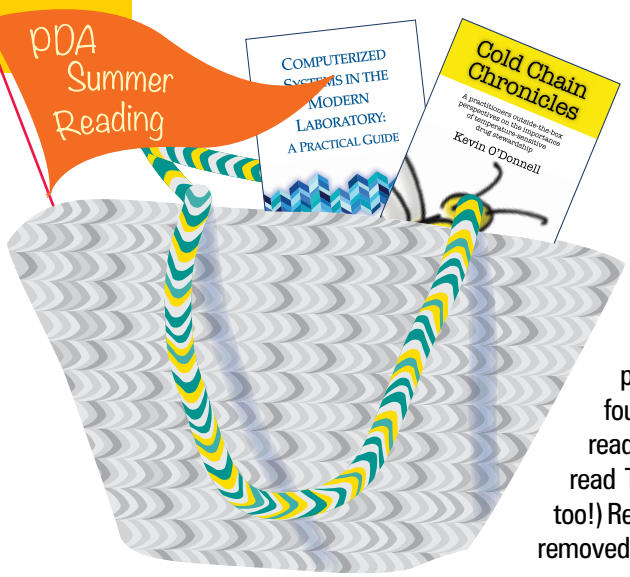


Ah, summer! The perfect time to crack open a good book. In honor of this tradition, the Editorial Team with the *PDA Letter* chose to include an expanded "In Print" of PDA literature published recently, and also found out what some PDAers are reading for fun. (But if you want to read TR-69 on the beach, that's fine too!) References and graphics have been removed from the excerpts.

excerpted from

Laboratory Systems: Current State, Paperless, Integration, and Technology Planning

by **Joseph G. Liscouski**

from *Computerized Systems in the Modern Laboratory: A Practical Guide*

The Need for Technology Planning, The Need for a Science Technology Specialist

In the past laboratory technology planning has focused on scientific tools: instruments and equipment that are used by scientists in the conduct of work on the laboratory bench. The need for new microplate handling equipment, columns for chromatography, new detector technologies, basically the stuff of laboratory work, the stuff you were trained to handle as part of your education, both formal and on-the-job.

When we look at laboratory tools in the digital realm, our comfort levels drop. Compare your reaction to the apps that you use on smart phones and tablets with laboratory software. First, you don't think of "apps" as software, even though the term is short for applications — software applications. Second, they are easy to use and there is an immediate benefit with little risk (aside from having to possibly pay for something). The ease of use and risk are the result of your having little control over how they function — they do what they do, you have some options over cosmetic points, and some control over how features behave (for example, turning background sound on or off), but in reality it is very limited. Those limitations are intentional to ensure that things work and to minimize or eliminate support costs. Sometimes apps break when the operating system is upgraded, and then you either delete them or wait for the vendor to fix them.

Laboratory software is more complex. It could be easier to use, but that would be at the sacrifice of your ability to get the results you need and to be able to adjust parameters to meet experimental requirements. You can use the vendor default settings ("they made it so they must know what they are doing"), but those are only intended as starting points, not universal settings to meet all needs. The more choices you have for software applications to address your needs, the more complex life becomes. Sometimes the answer is "it's software, let IT handle it". IT, unless educated for it, (see Chapter 2 and Appendix 4), probably isn't up to the task.

This raises a conflict: people who have been hired to do scientific work and/or manage the laboratory's operations are faced with the prospect of becoming mired in laboratory information technology. One important point: *laboratory personnel do have to be competent users of laboratory software systems, and, to be able to articulate informed user requirements for systems to solve laboratory problems.* They don't have to be system de-

PDA's Personal Reading List

Das Jahr, in dem die Mauer fiel: 20 Jahre Mauerfall – Zeitzeugen erinnern sich (The Year the Wall Came Down – 20 Years after Reunification, Contemporary Witnesses Remember), Johann-Friedrich Huffmann
— PDA Manager of Programs & Events at the Berlin headquarters **Sylvia Becker**

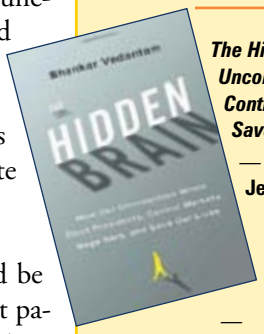
The Samson Syndrome, Mark Atteberry
— PDA Sr. VP and CFO **Craig Elliott**

One Summer: America, 1927, Bill Bryson
— Visual Inspection of Parenterals Interest Group Coleader John Shabushnig, PhD, Insight Pharma Consulting

First, Break All The Rules: What The World's Greatest Managers Do Differently, Marcus Buckingham and Curt Coffman
— *PDA Letter* contributor and Annual Meeting Speaker, **Ira Mann,** FPC of Atlanta

The Traitor Spy Trilogy, Trudi Canavan
— Technology Transfer Task Force Leader **Mirko Gabriele,** Patheon

The Book Thief, Markus Zusak
— Israel Chapter Liaison **Karen Ginsbury,** PCI



The Hidden Brain: How Our Unconscious Minds Elect Presidents, Control Markets, Wage Wars, and Save Our Lives, Shankar Vedantam
— Missouri Valley Chapter Volunteer **Jeff Kisslinger,** Steris

The Malazan Book of the Fallen, Steven Erikson
— Sr. Manager, Membership and Chapters, **Trevor Swan,** PDA

Mort(e), Robert Repino
— Writer/Editor, **Rebecca Stauffer,** PDA

Agent to the Stars, John Scalzi
— *PDA Letter* Graphic Designer, **Katja Yount,** PDA

velopers. The conflict can be relieved by the creation of a position of a scientific technology specialist/manager, someone to help laboratory professionals understand the technological options available to them, and to work with them and LAB-IT specialists to help describe and implement laboratory systems. They would also be able to get away from the day-to-day activities and be able to look at things from a higher-level perspective. The primary function of this position is to advise people on technology choices and to manage technology planning.

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excerpted from

ENVIRONMENTAL MONITORING OF COMPRESSED GASES

by **Tim Cser and Anne Connors, EMD Millipore**

from *Environmental Monitoring*

edited by **Jeanne Moldenhauer**

Uses of Compressed Gas

Compressed gas is used in a wide variety of industries including, but not limited to, pharmaceutical and biologics manufacturing, microelectronics manufacturing, food and beverage production, cell cultures, reagent manufacturing, etc.

It has a wide variety of uses in production environments. Biologics manufacturers may use nitrogen or argon as an overlay to create an inert environment within their vials. Pharmaceutical manufacturers will use compressed air or CO_2 to evacuate vials or containers that are to be filled as well as keeping the filling needle area clear of any contaminants. Microelectronics manufacturers require the strictest level of purity as even the smallest impurities can ruin a microelectronic circuit.

More recently, food manufacturers are being encouraged by Safe Quality Food Institute, British Retail Consortium, United States Department of Agriculture, etc., to test their compressed air that comes into contact with food. Food manufacturers use compressed gas to expand packaging prior to inserting the food product, while beverage manufacturers use compressed gas to evacuate bottles and cans prior to filling.

Compressed Gas Testing

Compressed gas is tested for a variety of contaminants including oil, water, particulates and microbes. For the purposes of this chapter, the focus will be on particulates and microbes.

Manufacturers who use compressed gas should be as concerned about microbial and particulate contamination in their compressed gas as they are for their ambient air. Small compressors can produce more than 10,000 liters of water per year depending on the environmental conditions (Bowers et al., 2011). Ambient air can have 4,000 colony forming units (CFU) or more per cubic meter of air. Combine this heavy bioburden with the warm, moist conditions within a compressed gas and one has the perfect breeding ground for bacteria, yeast and mold.

Bacteria Yeast and Mold

ISO 8573-4 and ISO 8573-7 are the two documents that give guidance on how to test for total particulates and total microbial contamination, respectively.

Due to these preferable growth conditions, quality control (QC) laboratories and manufacturers should be testing for a variety of different microbes. Since the air going into the compressor will contain a wide variety of organisms, most companies should use a general, all-purpose medium to detect contamination. Tryptic Soy Agar (TSA) is the most commonly used but a medium for detection of yeast and molds might also be useful as it will select for those types of organisms. In the latter case, Potato Dextrose Agar, Malt Extract Agar (MEA), or Sabouraud Dextrose Agar (SDA) may be preferable. TSA will grow the viable organisms present in the gas whereas Potato Dextrose Agar, MEA and SDA will mostly grow yeast and mold. The plates should be incubated at the temperatures normally used in the environmental monitoring risk-based study. In general, 30–35°C is the most commonly used temperature range, followed by 20–25°C.

If anaerobes are a concern, pre-reduced TSA could be incubated in an anaerobic incubator or chamber. There is no specific requirement to test for anaerobes, but it may be worthwhile if there is a risk of anaerobic contamination or the gas being tested is oxygen-free.

ISO 8573-4 also gives the method on how to test compressed gases for total particulates. Total particulate enumeration will help determine whether or not there has been a contamination event.

Coupled with the viable sample, particulate samples can be correlated with the viable CFU count to gain valuable environmental monitoring data for the compressed gas component.

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excerpted from

Section 4, Chapter 14: Facts And Myths About Expanded Polystyrene

by **Kevin O'Donnell**

from *Cold Chain Chronicles*

Polystyrene: It's Like the Baking Soda of Plastic

Polystyrene is extremely versatile and durable. Expanded polystyrene is more remarkable still. The structure of EPS bead is 98% air and its initial thermal properties are maintained throughout its entire working life. It can be molded, cut, and tinted into virtually any shape, size, or color; it is inert, non-toxic, moisture resistant, and rot proof. It is also totally absent of any nutritional value so no fungi or micro organisms can grow within EPS. Pound for pound, it offers greater advantages at less cost than any other packaging material. Because of its light weight, transporting it where it needs to go requires relatively low fuel consumption.

One of the more remarkable attributes of EPS is that it can be engineered for opti-

2015 PDA Upcoming Events

SAVE THE DATE for PDA's 2015 Events

JULY

21 – 23
Moist Heat Sterilization Week
Bethesda, MD
pda.org/moistheat

27 – 29
Risk-based Qualification of Sterile Drug Product Manufacturing Systems
Bethesda, MD
pda.org/risk

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AUGUST

3 – 7
SOLD OUT GSA Schedule Contract GS-02F-113BA
2015 Aseptic Processing Training Program – Session 4, Week 1
(Week 2: August 24-28)
Bethesda, MD
pda.org/2015aseptic4

10 – 11
NEW COURSE
Airflow Visualization Techniques and Practices
Bethesda, MD
pda.org/air

12 – 14
GSA Schedule Contract GS-02F-113BA
Validation of Dry Heat Processes Used for Depyrogenation and Sterilization
Bethesda, MD
pda.org/depyro

17 – 19
GMP Week
Bethesda, MD
pda.org/GMP

SEPTEMBER

8-9
Introduction to Visual Inspection
Berlin, Germany
europe.pda.org/IntroVI2015

9-10
Fundamentals of an Environmental Monitoring Program
Bethesda, MD
pda.org/enviro

10-11
Particles of Injectables
Berlin, Germany
europe.pda.org/Particles2015

11
NEW COURSE
Establishment of a Risk Based Environmental Monitoring (EM) Program
Bethesda, MD
pda.org/EMP

PDA
Parenteral Drug Association

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

14-18
2015 Glass Quality, Visual Inspection and Foreign Material Identification Week
Bethesda, MD
pda.org/glassqual

14-15
2015 PIC/S-PDA API ICH Q7 Training Course
Hyderabad, India
pda.org/picshyderabad

15-16
2015 PDA Europe Pharmaceutical Freeze Drying Technology
Munich, Germany
europe.pda.org/FreezeDrying2015

17-18
Development of a Freeze Drying Process
Munich, Germany
europe.pda.org/TCFreezeDrying2015

17-18
2015 PIC/S-PDA API ICH Q7 Training Course
Ahmedabad, Gujarat
pda.org/picsahmedabad

22
Utilization of Statistical Methods for Production Monitoring
Bethesda, MD
pda.org/statistics

24-25
CMC Regulatory Compliance for Biopharmaceuticals
Berlin, Germany
europe.pda.org/TC_Compliance2015

28-30
2015 PDA/FDA Joint Regulatory Conference
Washington, DC
pda.org/pdafda2015

30 – OCTOBER 1
2015 PDA Manufacturing Science Workshop
Washington, DC
pda.org/manufacturing2015

OCTOBER

1-2
2015 PDA/FDA Joint Regulatory Course Series
Washington, DC
pda.org/pdacourse

5-9
SOLD OUT
2015 Aseptic Processing Training Program – Session 5, Week 1
(Week 2: November 2-6)
Bethesda, MD
pda.org/2015aseptic5

6-7
2015 PDA Europe Pharmaceutical Cold & Supply Chain Logistics
Amsterdam, The Netherlands
europe.pda.org/ColdChain2015

8-9
Good Cold Chain Practices
Amsterdam, The Netherlands
europe.pda.org/TCColdChain2015

12-16
GSA Schedule Contract GS-02F-113BA
Filtration Week
Bethesda, MD
pda.org/filtration

mal performance depending on its application — of which there are many. The mechanical properties of EPS foam can be varied depending on the material density. Generally, strength and insulation properties increase with density. This unique characteristic allows a packaging engineer to fine-tune performance by implementing simple processing changes without the need to redesign or retool.

EPS has excellent thermal insulation properties. Depending on its density, its thermal conductivity (k factor) is about 0.24 per inch (BTU-In./Ft.2Hr °F).

For shock cushioning, the EPS packaging industry has developed typical cushioning curves for applications in transport packaging which are not significantly affected by changes in temperature.

Dimensional stability is another important characteristic of EPS foam; it will retain its original shape and size under widely varying environmental conditions. Optimizing thermal properties, shock cushioning, and dimensional stability can help to minimize raw material content.

excerpted from

4.1 Overview of Microbial Control Strategy

from *Technical Report No. 69: Bioburden and Biofilm Management in Pharmaceutical Manufacturing Operations*

To ensure product quality, the microbial-control strategy should be designed to prevent or minimize ingress, proliferation, and persistence of microorganisms in the facility, process, and equipment. The type of product is a key consideration for this strategy because inherent product properties may facilitate or inhibit microbial growth, and specific manufacturing process designs may promote or prevent microbial ingress. In addition, the strategy cannot be successful without a supporting, well-integrated quality system and significant management support. The quality system provides the support and processes required to design and establish the microbial-control strategy, with a focus on product impact.

A science-based risk assessment is the starting point of the control strategy, which should be performed at the early stages of process and product development. This initial assessment is needed to identify potential points of microbial ingress, proliferation, and persistence in the facility, equipment, and process unit operations. Once the risks are assessed, control points can be identified and control measures implemented to mitigate the risks.

4.1.1 Quality System

Quality oversight is an essential component of a microbial-control strategy and ensures compliance with regulatory requirements and cGMPs. The quality unit should develop measurable objectives for product quality, should participate in the development and approval of the microbial-control strategy, and ensure that critical control points are monitored and maintained in a state of control. Internal and external audits, trending reports, and reviews and approvals of relevant records can be used to implement appropriate quality oversight.

4.1.2 Risk Assessment

The risk-management process guides the pharmaceutical manufacturer in establishing a multidisciplinary team to identify, assess, and mitigate risks to product quality. Information on establishing a risk-management program can be found in ICH Q9: *Quality Risk Management* and PDA *Technical Report No. 54: Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations.*

Microorganisms are ubiquitous throughout most environments and challenging to detect and enumerate, even when present in large numbers. As explained above, they are particularly difficult to control when present in the form of a biofilm. Effective prevention of bioburden and biofilm relies on tools such as risk assessment to identify and evaluate the risk factors for microbial ingress, proliferation, and persistence within the manufacturing facility, equipment, and processes.

There are multiple ways to perform a risk assessment and evaluate the potential for product contamination. The methods selected to assess the risks should be suitable for the process/product being evaluated. Detailed information on risk assessment and the failure modes and effects analysis (FMEA) method can be found in PDA *Technical Report No. 44: Quality Risk Management for Aseptic Processes*. An effective risk assessment should distinguish between low-, medium-, and high-risk areas for product contamination. Controls to manage and mitigate the identified risks, should be implemented based on risk severity to manage and mitigate the identified risks.

4.1.2.1 Ingress of Microorganisms

Microbial ingress into the facility and equipment is the first step in the establishment of bioburden and development of biofilm in the process stream. Microbial contamination is associated with raw materials and clean utilities (inputs), facilities (environments), equipment, processes (unit operations), and personnel.

Incoming raw materials, if they are not sterile, are a potential source of microbial ingress. The raw material itself may harbor microorganisms, the outside surface of its storage container, and personnel handling of the materials may also contribute to contamination. In addition to raw materials, attention must be given to facility design and maintenance, and to equipment setup, storage, and return from calibration (e.g., parts such as probes and gauges).

4.1.2.2 Proliferation of Microorganisms

Processing conditions, such as high or low temperature or humidity, and the presence of water are critical for enabling microorganism proliferation. Most processing occurs at ambient temperatures and provides near-optimal conditions for the growth of most microorganisms found in the manufactur-

ing environment. In general, temperatures below 8°C or above 60°C, low humidity (dry conditions), extreme pH, and low water activity inhibit microbial growth. High humidity is frequently associated with mold growth.

Environmental factors, process interventions, manipulations by personnel, and transfers should be evaluated for their potential to introduce additional nutrients or microorganisms into the process or product. The type of operational step should also be considered. Steps with the highest risk are those that are associated with nutrient-rich process streams; have extended hold times; are open to the environment; or are difficult to drain, clean, and sanitize.

4.1.2.3 Persistence of Microorganisms

An acceptable level of bioburden should be set for all product contact equipment/systems, and the risk related to the use of the equipment should be assessed. For certain processes, it may be necessary to sterilize equipment. Components that can contribute to microorganism persistence include transfer lines, equipment piping, ports, and seals because these can be difficult to access for cleaning and sanitization. Infrequent replacement of soft equipment parts can significantly contribute to product contamination. Some processing equipment, such as chromatography resins and columns, ultrafiltration/diafiltration (UF/DF) membranes, and other filtration membranes are incompatible with high temperatures and certain sanitization chemistries and, therefore, are prone to microbial colonization and persistence. For this reason, additional diligence should be applied to the cleaning, sanitization, and monitoring of these pieces of equipment.

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excerpted from

Topic J: Growth-Promotion Testing of Environmental Monitoring Media

from Points to Consider for Aseptic Processing: Part 1

Problem Statement

What constitutes a scientifically appropriate program for routinely growth promotion testing of environmental monitoring media?

Recommendation

A quality management program for all incoming or in-house prepared media should be in place for evaluating media for its intended use and for its acceptance. Lots of media should be tested for their ability to reliably recover microorganisms. The growth-promotion test is one of the tests conducted by the microbiology laboratory that is used to achieve this. For growth-promotion testing of media used for environmental monitoring, there should be a predefined list of test organisms. This list should include compendial organisms and may include environmental isolates if those isolates differ materially from compendial microorganisms. This list should represent a range of "representative" microorganisms that could be encountered in manufacturing environments (e.g., Gram positive rod; Gram positive coccus; filamentous mold and yeast; Gram negative rod).

Growth-promotion testing may also demonstrate that the transportation route and different processing methods do not adversely impact the ability of the media to recover microorganisms.

Skip-lot testing, in which not all of the lots are tested, might be justified based on consideration of risk elements, including but not limited to a robust supplier quality system, audit program, communication/notification policy, and experience with the vendor.

Rationale for Recommendation

Environmental monitoring media should have demonstrated capability to recover a range of potential microbial contaminants.

FDASIA: Three Years of Success

Rensi Sutaria, Banner Life Sciences

It has been three years since the Food and Drug Administration Safety and Innovation Act (FDASIA) was enacted. This Act expands the U.S. FDA's authorities and strengthens its ability to safeguard and advance public health by giving it the power to collect user fees from industry to fund reviews of innovator drugs, medical devices, generic drugs and biosimilar biological products; promote innovation to speed patient access to safe and effective products; increase stakeholder involvement in FDA processes; and more. FDA has established a three-year implementation plan to help the public track the progress of these, and other provisions, established under FDASIA. As the three-year anniversary approaches, it presents a critical milestone to evaluating the success of this multifaceted law. It is difficult to cover the law's entirety, however, some highlights are provided herein to summarize progress of some of its provisions.

New User Fees for Generics, Biosimilars

FDASIA authorized continued enactment of the fifth Prescription Drug User Fee Act (PDUFA V), which provides FDA with resources to maintain a predictable and efficient review process for human drug and biological products. The third authorization of the Medical Device User Fee Act (MDUFA III)—also part of FDASIA—represents a similar commitment between FDA and the medical device industry to increase efficiency of regulatory processes for devices. The Act also introduced two additional user fees: the Generic Drug User Fee Act (GDUFA) and the Biosimilar User Fee Act (BsUFA). Both GDUFA and BsUFA promote access to generics and biosimilars as part of an effort to generate cost savings for patients ***(1).***

Article at a Glance

- Biosimilars and generics now have own user fee laws
- "Breakthrough therapies" and other tools encourage innovation
- Law also entices development of new antibiotics, pediatric drugs

Development of biosimilars is challenging as they can be difficult to characterize since they are composed of highly complex molecules; hence, there are currently few therapeutic alternatives to biologics available. As of this date, only one biosimilar has been approved; however, approximately 17 products are at the IND stage and approximately 51 products are under the biosimilar development program ***(2).***

Encouraging Innovation

New user fees are not the only provisions encouraging innovation in FDASIA. The Act also introduced the "breakthrough therapy" designation. This serves as a powerful expedited drug development tool designed to assist the development and review of new drugs with preliminary clinical evidence that indicates that the drug may offer a substantial improvement over available therapies for patients with serious or life-threatening diseases. Simultaneously, FDASIA amended other expedited programs such as fast track and accelerated approval to ensure availability of medications to prevent life-threatening diseases.

Figure 1 Number of breakthrough therapy designation applications received (a), granted (b), denied (c) and approved (d) by CDER after implementation of the FDASIA ***(3)***

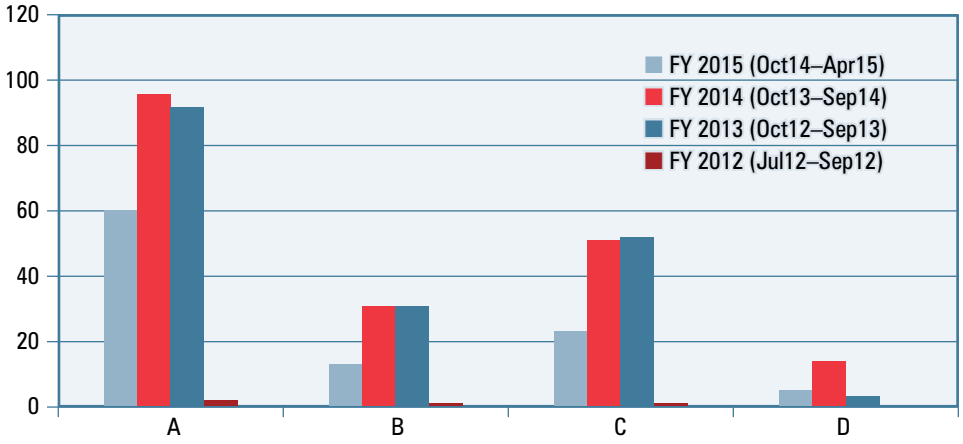


Figure 2 Number of breakthrough therapy designation applications received (a), granted (b), denied (c) and approved (d) by CBER after implementation of the FDASIA ***(3)***

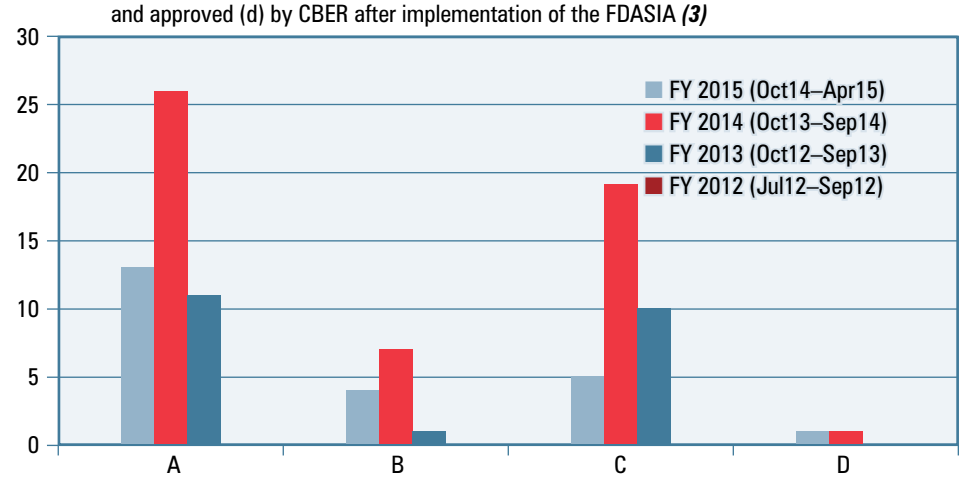
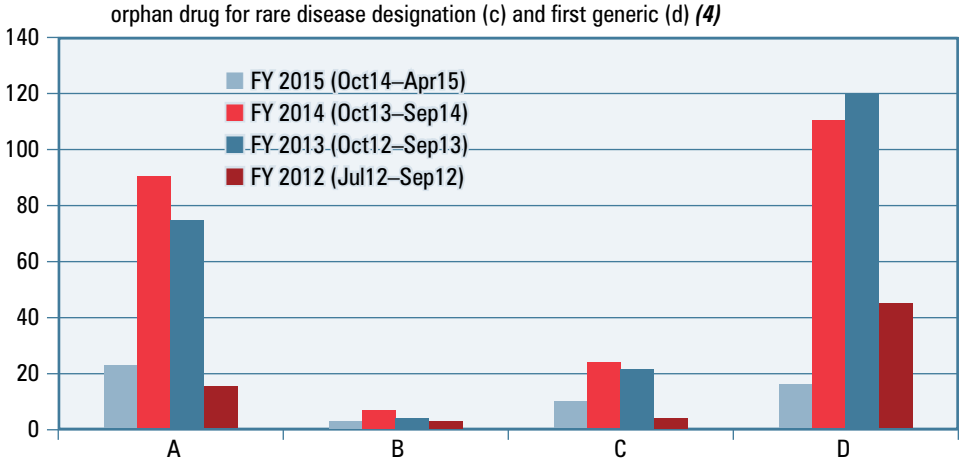


Figure 3 Number of applications granted for fast track designation (a), accelerated approval (b), orphan drug for rare disease designation (c) and first generic (d) ***(4)***



For some insight into the impact of the breakthrough therapy designation, **Figures 1** and **2** represent the number of breakthrough therapy designation application received, granted, denied and approved by CDER and CBER respectively after implementation of FDASIA. Similarly, **Figure 3** signifies the number of applications granted fast track designation, accelerated approval, orphan drug designation and status of first generic. **[Editor's Note:** See story on p. 20 for two FDA regulators' perspectives on breakthrough therapies.**]**

FDASIA also features provisions for initiatives supporting drug products for rare pediatric diseases, such as the rare pediatric disease priority review voucher program. In November 2014, FDA published a draft guidance which describes criteria for the process of requesting the designation. To date, three companies have received the voucher.

GAIN Act Plus Pediatrics Provisions

The Generating Antibiotic Incentives Now (GAIN) Act was included in FDASIA as an attempt to entice the development of new antibiotics, particularly treatments for "serious or life-threatening infections." Antibiotic drugs for these conditions are designated as Qualified Infectious Disease Products (QIDPs) under the GAIN Act, and eligible for priority review under the expedited review program for fast track products. Upon approval, the designated products are qualified for five years of marketing exclusivity. To date, FDA has granted the QIDP designation to approximately 50 antibiotics under development and approved three products.

Disparities in Clinical Trials

David Cummings, U.S. FDA

PDA and the U.S. FDA share an interest in public health and ensuring global access to quality, safe and efficacious medical products. For over 24 years, PDA and FDA have joined forces in an effort to advance the thinking, practices and application of sound regulatory science among manufacturers through the *PDA/FDA Joint Regulatory Conference.* For the last two years, the conference has highlighted sections of the Food and Drug Administration Safety and Innovation Act (FDASIA). The mandates established by FDASIA are far reaching, impacting a number of areas.

In particular, the law directs FDA to investigate how well demographic subgroups (sex, age, race and ethnicity) are included in clinical trials for medical products. The Affordable Care Act (ACA), passed in 2010, included a provision also reinforcing the need for collecting statistics on subgroup representation to prevent disparities.

Collectively, FDASIA and ACA aim to expand our understanding of medical product needs in the context of addressing health disparities among minority and ethnic groups, especially since medical genomics continue to grow, the treatment population is becoming more and more genetically and geographically diverse, and medical product access is expanding. It is important that developers ensure those participating in clinical trials are representative of the intended treatment group. In turn, this data must be factored into the target product profile.

This year we will hear from **Jonca Bull,** MD, Director, of the FDA's Office of Minority Health, who will offer a FDA perspective on this topic. Bull will give a unique overview of the data collection and reporting activities to date, and share FDA's outlook on opportunities to narrow the gap in public health disparities. Plan to attend this important conference and participate in this important discussion and the many other opportunities to listen, learn, and share with FDA staff and your colleagues.

For more information, visit www.pda.org/pdafda2015. To learn about PDA Education courses, visit www.pda.org/pdacourses.

These numbers are encouraging; however, there is still a long way to go in terms of qualifying pathogens, streamlining clinical trial requirements, prescribing information upon approval and more.

Recognizing public support and interest for products specifically targeted for pediatric patients, FDASIA renews and strengthens three essential laws to improve the safety and effectiveness of pediatric drugs, biological products and medical devices used in children. These are the Best Pharmaceuticals for Children Act (BPCA), the Pediatric Research Equity Act (PREA) and the Pediatric Medical Device Safety and Improvement Act. Under FDASIA, PREA was amended to require the submission of a pediatric study plan, typically at the end of phase 2. FDA implemented this provision in early 2013. As of May 2015, FDA has granted pediatric exclusivity for pediatric studies for 211 total approved drugs ***(5).***

Abuse-deterrent Formulation

Opioids can be abused in a number of ways. Abuse-deterrent formulations target the known or expected routes of abuse for the specific opioid drug substance in that formulation. The science of abuse deterrence is relatively new but methods for evaluating those technologies are rapidly progressing. The final guidance, published in April 2015, explains FDA's current thinking about the studies that should be conducted to demonstrate that a given formulation has abuse-deterrent properties, how those studies will be evaluated by the agency, and what labeling claims may be approved based on study results.

Stakeholder Involvement

FDASIA initiated a patient-focused drug development program with the goal of obtaining a patient perspective on certain disease areas during the five-year period of PDUFA V. Patient-focused drug development assessment of a product's benefits and risks involves an analysis of the severity of the condition and the current treatment options available for the given disease. More than 15 public meetings have been held on various disease areas from various cancers, central nervous system disorders, gastrointestinal diseases, human immunodeficiency virus (HIV), and more.

Conclusion

FDASIA is a commitment between the FDA, industry and patients; thus, success its success is not only an achievement of the FDA, but a combined effort among all three. On the third anniversary of the passing of this law, it is clear that progress has been made to achieve this success and will continue to be made.

(The information presented here is the personal view of the author and does not reflect that of Banner Life Sciences. The data provided in the figures are approximate numbers with the sole purpose of summarizing the progress of FDASIA and are taken from the publicly available sources listed under reference.)

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About the Author

Rensi Sutaria has expertise on preapproval and postapproval regulatory submission for U.S. and global markets for IND, NDAs and ANDAs.

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Following the conference, on November 11, PDA will be hosting a course on *The Quality Culture and its Measurement*. This course will help participants select appropriate metrics to measure quality and determine how best to collect and use the data to improve the Quality System.

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Check out the preliminary agenda for a complete list of topics that will be discussed at pda.org/visual2015.

Benefit from lessons learned and best practices shared by noted industry and regulatory experts, including:

- **Scott Aldrich,** Principal Consultant, *Ultramikro LLC*
- **Andreas Brutsche,** Head of Global Quality Assurance, *Sandoz International GmbH*
- **Kevin Kerls,** Senior Manager, Inspection MSAT, *Genentech, Inc.*
- **Stephen Langille, PhD,** Acting Branch Chief, Division of Microbiology Assessment, Branch 3, CDER, *FDA*
- **Ewa Marszal, PhD,** Chemist, CBER, *FDA*
- **Heino Prinz,** Director, Inspection Devices, *Rommelag*
- **Roy McLean,** Manager, Sterile Manufacturing, *Hospira*

Success is the desired outcome of consistently applying basic fundamentals, and PDA's Education course, *An Introduction to Visual Inspection* (Oct. 28-29), is *the* course to attend to learn the fundamentals of visual inspection and their application to injectable products. This laboratory course provides the unique opportunity to practice inspection skills under close guidance of experienced faculty.

Learn more and register at pda.org/visualcourse. Register before September 15, 2015 and save up to $250.

FDASIA and Its Impact on Global Drug Supply

Dipti Gulati, PhD, PJI Biotech

How is the Food and Drug Administration Safety and Innovation Act (FDASIA) affecting the global drug supply chain?

This is a key question currently on the mind of many in the pharmaceutical industry. With more changes to come, the law has already impacted all of the players involved in the supply chain: raw material suppliers, manufacturers, repackagers, wholesalers, secondary wholesalers, distributors, pharmacies/hospitals and, ultimately, patients themselves.

All the titles of FDASIA impact drug supply management and patient access to drug supply at varying levels but two in particular carry significant impact: Title VII and Title X. Title VII addresses the management and protection of the global drug supply by requiring increased risk information about domestic and foreign manufacturers. Title X allows FDA to impose drug shortage reporting requirements on manufacturers so that appropriate actions can be taken to prevent potential shortages.

Title VII: Protecting the Drug Supply Chain

With nearly 40 percent of finished drugs imported, and nearly 80 percent of active ingredients coming from overseas sources ***(1),*** protecting the supply chain is a priority for FDA. Title VII provides FDA mechanisms to manage the challenges posed by importation of drugs produced at subpar foreign manufacturing facilities, adulterated drugs and counterfeit drugs ***(2).*** Title VII will advance the FDA's transformation into a global public health agency, primarily by enabling it to better oversee the safety and integrity of drug ingredients and finished drugs in the supply chain. It also provides new enforcement tools and facilitates cooperation with foreign regulators—essentials for the global marketplace.

There are 18 Sections in Title VII ***(2).*** According to **Ilisa Bernstein,** Director, Office of Compliance, CDER, the 18 Sections of Title VII can be divided into three main categories: increased risk information, global supply chain and enhanced tools ***(3).***

The first category requires manufacturers to provide new risk-based information about existing facilities, associated products and manufacturers of excipients for drug products. This also allows FDA to exchange information with foreign regulators about commercial importers and requires manufacturers to provide notification in case of product theft or counterfeiting. FDASIA's provisions include the creation of a facility registration system with unique facility identifiers that applies for both foreign and domestic manufacturers, and a requirement for drug manufacturer facilities to register annually with FDA. For a long time, importers have come in and out of the marketplace without appearing on FDA's radar screen. By requiring this annual registration, the Agency will be aware of the location and whereabouts of all manufacturers involved in the process.

The second category of Title VII covers the global supply chain and includes risk-based inspection and preinspection record availability, granting FDA authority to obtain certain records from a drug manufacturer in lieu of, or in advance of, an inspection. This information allows FDA to target its resources to higher risk facilities, enabling the Agency to be more efficient in further ensuring the quality and safety of drug ingredients and finished drugs. This category also allows FDA to recognize foreign government inspections based on their inspection capabilities to meet FD&C Act requirements and to support FDA's risk-based inspection schedule.

And the third category of Title VII involves enhanced tools for ensuring products that are marketed or offered for import into the United States are compliant, safe and effective. It gives FDA the ability to detain or destroy adulterated and counterfeit products at the border and to deny import if an inspection is delayed, limited or refused. This category also gives FDA increased authority to prosecute and impose penalties in cases involving adulterated, misbranded and counterfeit drugs.

In the past two years, the FDA has made many parts of Title VII a reality. Successful accomplishments include one annual report ***(4–5),*** two final guidances ***(6–7),*** one final ***(8)*** and one proposed rule ***(9).***

Title X: Prevention of Drug Shortages

Between the years of 2005 and 2011, the number of new drug shortages quadrupled. **Figure 1** illustrates the number of new drug shortages by year from 2005 to 2013. In fact, drug shortages were one of the major factors resulting in the enactment of FDASIA.

Title X addresses the issue of drug shortages and provides FDA mechanisms to better manage and track drug shortages. Specifically, the drug shortage provision of Title X expands drug supply disruption reporting requirements, provides specific actions for FDA to take for mitigating or preventing shortages, creates a mechanism for tracking data and sharing that information with key stakeholders and designates a task force to analyze the causes of shortages and devise a plan that addresses them.

FDASIA requires manufacturers to provide advance notice to the FDA when they make a decision to stop manufacturing a product, regardless of whether they intend to discontinue the product permanently or only expect a temporary

In the past two years, the FDA has made many parts of Title VII a reality

interruption of supply. Manufacturers also must provide notification of changes in production quantities of drugs, which may result in a drug shortage.

According to CDER Drug Shortages Team Leader **Emily Thakur,** FDASIA's greatest impact has been "the requirement that manufacturers must report shortages to us. This has resulted in additional early notifications to the FDA about potential shortages, and we have used that information to prevent shortages" ***(10).***

In 2011, the number of reported (new) shortages was 251, compared to 117 in 2012 and just 44 in 2013. From Jan. 1 to Sept. 30, 2014, CDER tracked 33 new shortages. For the same period in 2013, that number was 38. **Figure 1** shows the new and prevented U.S. drug shortage data from 2005 to 2013 ***(11–12).*** The number of ongoing shortages has fallen as well. At the end of 2014, there were 74 ongoing shortages, down from 100 at the end of 2013.

Conclusion

FDASIA provides FDA new tools to manage the global drug supply chain. Full implementation will be challenging not only for the FDA, but also for life science companies. Not only FDA will have to deliver new regulations, guidances and significant operational changes, but companies will have to develop new systems, policies and procedures as well to ensure compliance with newly developed regulations of FDASIA, ultimately, impacting global supply of drug product.

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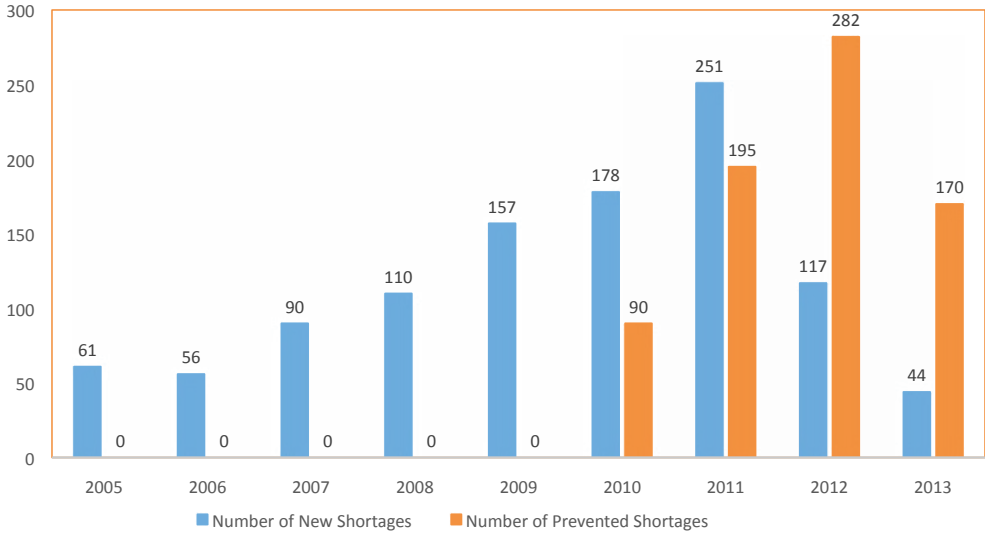
Figure 1 Drug Shortage Data 2005–2013



About the Author

Dipti Gulati, PhD, is currently President of PJI Biotech, a consulting organization. Previously, she held various management positions in large biopharma and medical device companies

Analyzing FDASIA's Progress Since 2012

Jeffrey Broadfoot, Emergent BioSolutions

July 2015 marks the three year anniversary of the Food and Drug Safety and Innovation Act (FDASIA). This law—specifically Title VII of it—gives the U.S. FDA new tools and authorities to address the challenges of an increasingly complex and globalized drug supply chain. So, what has FDA been able to accomplish in these past three years, and what is yet to come?

The provisions of Title VII generally fall into one of the following categories: data collection for risk management, risk-based facility oversight, partnering with foreign agencies, and strengthened enforcement tools.

The authorization to collect data, covered in sections 701–704 and 713–715 (**Table 1**), is intended to improve FDA's ability to make risk-based decisions, and put foreign and domestic firms on par by requiring all to register with FDA annually. Included in these sections is the authority to require drug excipient manufacturers to register with FDA, meaning that all establishments used in their manufacture will be required to have a Unique Facility Identifier (UFI) and be listed. While FDA has specified the UFI format to be used for registration, the registration database is not required to be operational until November 2016—two years after finalization of the UFI system. In addition, the Agency still needs to write regulations to implement these new requirements. The law also requires FDA to publish regulations establishing good importer practices, but it has yet to do so. FDA has previously published guidance in this area, although not specifically focused on drugs. Final regulations are due within 36 months of FDASIA being signed into law, which is July 9, 2015. While some progress has been made in this area, there appears to be more for FDA to do to realize the full benefit of these measures.

Table 1 Current Status of FDASIA Title VII Provisions

Section	Description	Progress
701/702	Facility registration	Final guidance issued November 2014
703	Excipient information	Pending
704	Registration system	Electronic database for registered facilities due November 2016
705	Risk-based inspection schedule	Full implementation still pending; annual reports for FY13 and FY14 published as required
706	Records for inspection	Procedures in development; no specific due dates
707	Inspection Guidance	Delaying, denying, limiting or refusing inspection guidance issued October 2014
708	Administrative Destruction	Proposed rule published May 2014; final rule was due July 9, 2014
709	Administrative Detention	Final rule issued May 2014
710	Exchange of information	FDA exploring how to use; no due date specified
711	Safety/Quality	FDA revising existing GMPs; no due date specified
712	Foreign government inspections	FDA exploring how to use; no due date specified
713	Admission of imports	Final rule was due January 9, 2014; not yet issued
714	Good Importer Practices	Guidance due July 9, 2015
715	Notifications	Draft guidance in development; no due date specified.
716/717	Penalties	716 – no due dates; 717 – self-executing
718	Extraterritorial jurisdiction	Self-executing

Arguably, Section 705 of the Act is the one that industry has been asking for, if not the loudest, then perhaps the longest. It allows FDA to leverage inspections conducted by foreign National Competent Authorities, and to consider the compliance history of the establishment as part of a risk-based facility oversight strategy, allowing them to determine how frequently to inspect. Almost three years in, FDA's website indicates the Agency is still working on full implementation of the risk-based inspection scheduling approach. Apart from implementing the risk-based schedule itself, FDA was required to provide annual reports on inspections of establishments starting in 2014, which it has done. While the two reports published to date meet the specific requirements laid out by Congress, based on reviews of the current reports, it's difficult to see how much insight they will provide on whether the intent of the risk-based inspection provision is being met once it is fully implemented.

On the other hand, Section 706, which provides FDA with the authority to request records in advance of, or in lieu of, an inspection, has created significant activity and discussion both within industry and between industry and the Agency. PDA, through the Quality Metrics Task Force, has been very active in this discussion, having hosted or cohosted

Continued at bottom of page 46

Continuous Manufacturing Success Lies in New Technologies, Integration and Education

Rebecca Stauffer, PDA

On Sept. 30, ***Salvatore Mascia,*** *CEO, CONTINUUS Pharmaceuticals, will present his talk on continuous manufacturing at the* 2015 PDA Manufacturing Science Workshop *in Washington, D.C. following the* 2015 PDA/FDA Joint Regulatory Conference. *Previously, he worked for MIT on the Novartis-MIT Center for Continuous Manufacturing, a collaborative research project to develop a fully continuous integrated manufacturing system for oral solid dosages. Mascia spoke with the* PDA Letter *about his upcoming talk. The interview was recorded and will be available online as a forthcoming podcast at www.pda.org/pdaletter. Below are selected questions and answers from the interview.*

PDA Letter: You've identified "industry inertia" as one of the top organizational mindsets that present a barrier to the adoption of continuous manufacturing. Why is that? Especially considering the inefficiencies in traditional batch manufacturing?

Mascia: If we go in a manufacturing plant right now for pharmaceuticals and look at the technologies that are implemented, we realize that these haven't changed for many, many decades. So, we've been using the standard technologies, only the people using this, either in process development or manufacturing, are basically [educated] in the same way to develop processes for drugs…so with the introduction of new methods, it's very challenging. In addition to that, obviously, this infrastructure is in place, as you can imagine, because of so many years of doing batch manufacturing. And so the investment into a completely new infrastructure to make this transition is a big, big barrier in the pharmaceutical industry right now.

PDA Letter: Tell us more about the challenges you encountered in your involvement with the Novartis/MIT project. What lessons do they offer industry?

Mascia: One of the key objectives of the Center was to look at continuous manufacturing in a different way than was done previously. Instead of trying to retrofit existing process technology or batch processes running for longer, the Center is really based on developing new process technologies specifically designed for continuous manufacturing. So, we came out with a completely new technical solution for doing continuous manufacturing with the idea that all the steps in the pharmaceutical manufacturing chain, from chemistry, separation, purification and final drug product formation, can be integrated in one single production line that runs automated 24/7. So this was a big challenge, really, to try to develop the novel technology to enable this integration and to run these processes continuously and under fully automated control And we realized even when we need to develop a specific step at a very low throughput there was no equipment available. This led us to come out with new technical solutions, so that was really one of the key challenges.

And the second one was integrating all this new technology—all these new steps—into one seamless process and controlling it because now you have several unit operations connecting into one single process and you need to be able to control that and make sure the process is under control to produce a product with high quality specification.

These are also challenges that companies implementing this manufacturing technology need to take into consideration. When implementing new equipment, make sure this equipment is reliable… it's very, very important and this is why, when we refer to our vision of continuous manufacturing, we call it "integrated continuous manufacturing" to try and distinguish ourselves from many other approaches of continuous manufacturing, because it's really through the integration of this multiple set of unit operations that you can gain the full benefit of continuous manufacturing.

PDA Letter: And this certainly also fits with the move toward more modular forms of manufacturing.

Mascia: Our platform is absolutely modular. It has to be modular, otherwise it becomes like a single rigid line that can be applied for a specific compound but does not work for others. You can imagine this technology platform with multiple flow steps, different types of reactor designs, different types of purification systems, different platforms to produce dosage forms, and you can basically interchange the unit operations one with another through some sort of plug-and-play concept to make it modular, and so be able then to produce many different compounds.

PDA Letter: The system at MIT produces oral solids. Can it be configured to produce fill finish product?

Mascia: Again, the system is modular. We started with solid dosages—with tablets—because it is still the most acceptable dosage form and it's still the most challenging to produce in flow because when you think about solid, you can have issues with clogging.

When you think about liquid finish or liquid formulation, it is actually easy to handle in flow. Our concept of integrated continuous manufacturing is that the entire process is fully contained. The

process material remains in the system all time so it's less prone to contamination. And regarding the sterilization, you can use continuous microfiltration, and the use of heat as needed.

PDA Letter: You've cited statements from CDER's **Janet Woodcock** and former U.S. FDA Commissioner **Margaret Hamburg** in support of continuous manufacturing. Why do you think these regulatory leaders have expressed support for continuous manufacturing?

Mascia: The FDA is looking for more modular, agile and flexible manufacturing plants. And the reason being is because the pharmaceutical industry is changing. We're going through the advent of personalized medicines. In the future, we will need to produce many different pharmaceuticals, with different physical and chemical characteristics. And those existing large scale, batch processes do not have the flexibility to accommodate that. Same when you think about the advent of breakthrough therapy designations. So we have therapies that will have an accelerated regulatory path.

PDA Letter: Yet in other presentations you've mentioned that one barrier to adoption of continuous manufacturing in the industry is "perceived risk" among regulatory reviewers. Doesn't this contradict the views of regulators like Woodcock and Hamburg?

Mascia: I don't think it contradicts actually. That's why I mention it as a "perceived risk" among the [individual] regulatory reviewers who actually look at applications, and need to assess the new specific technology. If the knowledge of this specific technology might be lacking, then there could be some perceived risk about whether or not this would be an effective way to produce those pharmaceuticals. This goes back to the question about education, and the FDA is actually setting up numerous educational programs to actually make sure that all the people working at the Agency are actually [familiar with] implementing those technologies coming out. There is a lot of effort going into this direction, and as you can imagine in a big organization, the vision has to come from the top.

PDA Letter: For those attending your talk at the *Manufacturing Science Workshop* in September, what are some takeaways you hope attendees leave with?

Mascia: The first one is that companies should move on from being worried about the regulatory agencies being a block for this technology, because I don't think this is the case as there has been a strong statement from the regulators, especially from Janet Woodcock at the conference that we organized last year at MIT, where she said that the major regulatory hurdle comes from the company, from the actual manufacturer being worried that the regulator will balk at these processes.

And the second point is that continuous manufacturing, the way we see it with this fully integrated concept, it will enable the vision of "on-demand" manufacturing. The future will be based on this concept of "on-demand" manufacturing—producing pharmaceuticals immediately when you need it. So, we should really start looking at continuous manufacturing in an integrated fashion as we are proposing it, rather than a unit op or piecemeal approach because the huge benefit will come when you have lines that will be modular, flexible and able to produce pharmaceuticals end-to-end. This is an important concept which I believe will bring [about] change in the way we develop and manufacture drugs in the next ten years.

About the Expert

Salvatore Mascia is the Founder & CEO of CONTINUUS Pharmaceuticals. He was the former Strategic Project Manager for the Novartis-MIT Center for Continuous Manufacturing, where he led the integration of the first end-to-end continuous manufacturing process for pharmaceuticals.

The ABCs of the *PDA/FDA Joint Regulatory Conference*

FDASIA, GDUFA, QbD, GMPs...the annual *PDA/FDA Joint Regulatory Conference* can be a veritable alphabet soup of issues and ideas. Some may be discussed for years, and others contribute to the alphabet soup. Check out some of the ABCs of this signature PDA event over the years.

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europe.pda.org/FreezeDrying2015

15-16 September 2015

Sheraton Hotel Munich
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snapshot

Meeting *Preview*

Interest Group Meeting Schedule

As always, relevant interest groups will meet for the first two days of the *2015 PDA/FDA Joint Regulatory Conference.* Below is a schedule of interest group meetings that fall under the Regulatory Affairs and Quality Advisory Board (RAQAB).

Monday, September 28	Tuesday, September 29
5 p.m. – 6:15 p.m.	5 p.m. – 6:15 p.m.
Inspection Trends Interest Group	Pharmacopeial Interest Group
Quality Risk Management Interest Group	Quality Systems Interest Group
GMP Links to Pharmacovigilance Interest Group	Regulatory Affairs Interest Group
Management of Outsourced Operations Interest Group	

Analyzing FDASIA's Progress Since 2012 continued from page 41

conferences, workshops and individual sessions on the topic, as well as authoring documents recommending specific metrics and definitions that could be used across different product types and manufacturing sites. From the start, the collective understanding has been that metrics drive behaviors; therefore, the metrics should be carefully chosen to avoid unintended consequences. The discussion has since broadened from a focus on product quality metrics to a focus on quality culture. Many in industry, along with regulators, believe a positive quality culture drives production of high-quality products, so agreeing on a set of metrics that reliably predicts a strong quality culture would allow FDA to identify at-risk manufacturers. That is both the prize and the challenge. Despite this challenge, the conversation itself has been very worthwhile, and is sure to continue even after the metrics are chosen and implemented.

Sections 710 and 712 allow the FDA to exchange information with foreign regulatory partners and to recognize inspections conducted by them as evidence of compliance with the Act. The implications of these sections are: more timely and comprehensive information from FDA's regulatory partners when dealing with troubled manufacturers abroad who import to the United States, the ability to share such information relating to domestic manufacturers exporting internationally, and flexibility for FDA to focus their inspectional resources on sites of concern. It is clear that international agencies are collaborating more now than ever and have been for some time. FDA is still studying these new authorities, however, to determine how best to use them; Congress gave FDA the latitude to determine when to implement these sections. It is likely that FDA will prioritize implementation of elements that have the most direct and immediate impact on public health, such as the sharing of information during an international crisis, e.g., contamination events like the heparin contamination or counterfeit drug investigations.

In the remaining sections, Congress provided FDA with stronger enforcement tools to enable it to ensure the safety and quality of products entering the US supply chain. This category includes provisions for administrative detention and destruction of adulterated or counterfeit products to prevent reimportation, harsher penalties for those found to be counterfeiting pharmaceuticals, and the ability to declare products adulterated if a firm delays, denies, limits or refuses an inspection. Many of these elements have already been implemented through recent guidance and regulation. The elephant in this room is Section 711. Section 711 clarifies that cGMPs extend beyond the walls of the manufacturing site and that each firm should consider its suppliers within the scope of its quality management system. This aligns expectations for drug manufacturers more closely with the purchasing controls required of medical device manufacturers. As a result, drug manufacturers can expect closer FDA scrutiny of their supplier management programs. While this will likely start with discussions about incoming material quality, ultimately, they will try to determine how well manufacturers know and control their raw material supply chain. FDA has indicated plans to revise existing GMP regulations to reflect these new requirements, but there's no due date specified for their completion. This situation creates the potential in the interim for inconsistent application of the requirement, or application not consistent with the intent of the law itself.

In some ways, FDASIA is simply a legislative reflection of the things FDA has already been doing. In others, FDASIA represents quite a step forward in terms of the tools and authorities FDA now has to protect public health. Three years after approval, there is still much work to be done to realize its full potential. The question is, will potential translate into change that is a step in the right direction, or change that is transformational?

About the Author

Jeffrey Broadfoot is currently the Head of Quality Assurance for the Biosciences Division of Emergent BioSolutions. He also serves as Vice-Chair of PDA's Regulatory Affairs and Quality Advisory Board.

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- **Alan Dobson, PhD,** Director, Environmental Research Institute and Professor, Environmental Microbiology, *University College Cork Ireland*
- **Dennis Guilfoyle, PhD,** Senior Director, Microbiology and Analytical Regulatory Compliance, *Johnson & Johnson*
- **Patricia Hughes, PhD,** Team Leader, Biotech Manufacturing, CDER, *FDA*
- **David Hussong, PhD,** Senior Consultant, Microbiology and Regulatory, *ValSource* and Chair, *USP Microbiology Expert Committee*
- **Michael Kurilla, MD, PhD,** Director, Office of BioDefense Research Affairs, NIAID, *NIH*
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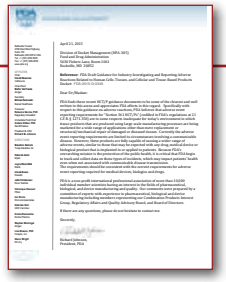
Limitations of Adverse Event Reporting for HCT/P Products

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



April 21, 2015

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

Reference: FDA Draft Guidance for Industry Investigating and Reporting Adverse Reactions Related to Human Cells, Tissues, and Cellular and Tissue-Based Products Docket: FDA-2015-D-0349

Dear Sir/Madam:

PDA finds these recent HCT/P guidance documents to be some of the clearest and well written in this arena and appreciates FDA efforts in this regard. Specifically with respect to this guidance on adverse reactions, PDA believes that adverse event reporting requirements for "Section 361 HCT/Ps" (codified in FDA's regulations at 21 C.F.R. § 1271.350) are in some respects inadequate for today's environment in which tissue products that are produced using large-scale manufacturing processes are being marketed for a wide range of applications other than mere replacement or structural/mechanical repair of damaged or diseased tissues. Currently the adverse event reporting requirements are limited to circumstances involving a communicable disease. However, these products are fully capable of causing a wider range of adverse events, similar to those that may be expected with any drug, medical device or biological product that is implanted in or applied to patients. Because FDA's overarching mission is the protection of the public health, it is critical that FDA begin to track and collect data on these types of incidents, which may impact patients' health even when not associated with communicable disease transmission.

The requirements should be consistent with the current requirements for adverse event reporting required for medical devices, biologics and drugs.

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by a committee of experts with experience in pharmaceutical, biological and device manufacturing including members representing our Combination Products Interest Group, Regulatory Affairs and Quality Advisory Board, and Board of Directors.

If there are any questions, please do not hesitate to contact me.
Sincerely,
Richard Johnson,
President, PDA

PDA Commenting Task Force

Michael VanDerWerf (Lead)
Patrick Bilbo
Allen Burgenson, Lonza
Zorina Pitkin, PhD, Organogenesis

Report From Outsourcing/Contract Manufacturing Conference

Maintain Your Client/CMO Relationship in Sickness and Health

Karen Ginsbury, PCI Consulting

Maintaining a relationship, be it friendship, marriage or otherwise, requires hard work and open communication between two individuals to be successful. Personal relationships also face numerous challenges, and, at times, can be severed by both parties for a myriad of reasons.

The relationship between a client and a contract manufacturing organization (CMO) can be compared to a personal relationship, as expressed by numerous presenters at the PDA *Outsourcing/Contract Manufacturing* conference held in Berlin last December.

The comparisons to human relationships began immediately on the first day. **Firelli Alonso-Caplen**, PhD, Senior Director, Pfizer, opened the conference with her keynote presentation, "Outsourcing in the 21st Century: 'Partnersourcing' and Beyond," reminding participants that you never really know a CMO until you have done at least one project with them, similar in a way to dating. **Morten Munk,** Senior Technology Partner, NNE Pharmaplan, then compared it to a marriage and pointed out that like a marriage, it could end in divorce or could have many anniversaries and celebrations. During the keynote, attendees learned about Pfizer's multimillion dollar experiment where the company selected two CMOs and invested in both by giving each the same project to complete within 15 months of receiving cell bank vials; ultimately, Pfizer's senior management selected the CMO that met the most important of their selection criteria (several dozen weighted metrics).

Table 1 Hard and Soft Outsourcing Facts

Hard facts: Critical success factors for CMO for biopharm
Regulatory compliance and high quality standards
Reliability of supply and high customer service level
State-of-the-art process and production technologies
Flexibility in capacities including economy of scale
Competitive: cost and timelines
Project manager – ability to create and manage a team – useless without it
Soft facts: Listen to expectations
Establish a good working relationship
Comply with company's quality standards
Protect intellectual property
Effectively handle cross contamination issues
Stick to a schedule
Have regulatory compliance expertise – smaller companies don't have it and need ours

Following this fascinating talk, **Siegfried Schmitt,** PhD, Principal Consultant, PAREXEL, provided some different CMO/client business models while **William Downey,** President, High-Tech Business Decisions, offered some interesting examples of pricing options. Next, **Philine Dobberthien,** Senior Project Manager, Customer Business, Boehringer Ingelheim, shared some hard and soft facts (**Table 1**). The hard facts she listed can be considered elements important to achieving a successful relationship between a biopharma company and a CMO; the soft facts are characteristics inherent in a CMO/client relationship that lead to a higher probability of success in the endeavor, not dissimilar to the concept of "soft skills."

Other speakers discussed the advantages and disadvantages of micro- and macromanagement. These speakers also recommended paying attention to organizational resilience—the ability to survive adverse situations, understand the brutal reality of a situation, maintain cherished values or set new ones and be resourceful and adaptable in shaping the future.

There was also some captivating discussion about the Person in Plant (PIP). Apparently, at some sites these individuals have been referred to as "spies" who report back to their company's headquarters without first discussing concerns with the CMO. This led to attendees discussing the nature of the PIP—a discourse still ongoing in the Management of Outsourced Operations Interest Group discussion forum of PDA Connect℠.

Some include the PIP in the Master Services Agreement. The person has to know the process, i.e., all aspects of the project, and has to be empowered to make decisions on the spot. English is often not the primary language, so the PIP sometimes needs to give correct translations. Not every CMO allows a PIP.

Other presentations focused on specific areas of concern for external service providers, such as transitioning from phase I/II to commercial manufacturing, single-use systems, customized packaging solutions for speeding projects through CMOs with less concerns for highly potent drugs and faster access to clinical sites and refurbishing ageing equipment and cleanroom pods.

PDA will hold another *Outsourcing/Contract Manufacturing* conference in Copenhagen for Nov. 17–18. For more information, please visit https://europe.pda.org/outsourcing2015.

About the Author

Karen Ginsbury is President and CEO of PCI, Pharmaceutical Consulting Israel Ltd., a company which provides services to the pharmaceutical, biotech and allied industries.

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Quality Metrics: Drive Results with a Valuable Program

Steven Mendivil, Amgen, and Russell Wesdyk, U.S. FDA

Quality metrics continues to be an evolving topic in pharmaceutical manufacturing as regulators and industry strive to find metrics that drive real continuous improvement in product quality and create a strong quality culture of doing the right thing for patients.

PDA's first conference on quality metrics in 2013 focused on which metrics should be submitted to the U.S. FDA to help assess quality and compliance risk. The breakout sessions from this conference became the basis for PDA's Points to Consider on Quality Metrics paper published in September 2014.

In 2014, PDA's second conference on quality metrics shifted the focus to the importance of quality culture and whether a set of culture metrics could be developed to augment the quality metrics recommendations in PDA's Points to Consider document.

Regardless of what metrics need to be submitted to FDA, a company should create and use metrics within their organization that make a difference and add unique value to its products and culture.

This year's quality metrics conference looks at current thinking and best practices for quality metrics that drive continuous improvement within a firm. Presenters will discuss how to establish and build an efficient and effective quality metrics program with limited resources and how such a program can drive not only product quality improvements but also foster a strong quality culture to prevent unintended consequences that can result from too much focus on metrics and foster bad behavior. FDA will also provide an update on their quality metrics program and industry leaders will provide their vision on the value of FDA's metrics program.

For more information about this year's conference, please visit www.pda.org/metrics2015. Attendees can also submit questions about quality metrics using this site in advance of the meeting. To learn about the PDA Education course following the meeting, visit www.pda.org/metricscourse.

[Editor's Note: The breakfast session, "Quality Metrics/Quality Culture," will be open to all attendees at the *2015 PDA/FDA Joint Regulatory Conference* on September 29 at 7 a.m.**]**

Regulatory Briefs

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

North America

21st Century Cures Act Moves Closer to a Full Vote

In late May, the U.S. House Energy and Commerce Committee unanimously passed the 21st Century Cures Act. This legislation accelerates the approval process for certain device and drug products. The Act also requires the U.S. FDA to award grants to entities studying processes for continuous manufacturing of pharmaceuticals. The proposed law now heads to the floor of the House of Representatives for a full vote.

FDA Releases Biosimilars Guidances

In late April, the U.S. FDA released three finalized guidance documents concerning biosimilars. One document specifies how sponsors should demonstrate biosimilarity to the reference product. Another addresses quality considerations as well as CMC information used for a biosimilar application. And the third is a Q&A document looking at implementation of the Biologics Price Competition and Innovation Act of 2009.

Reporting Requirements for CMC Changes

On June 1, the FDA released the draft guidance, *Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products.* This document outlines the Agency's current thinking on what CMC information needs to be reported to the FDA in the event it is changed. In addition, the document provides recommendations for managing CMC changes over the lifecycle.

Comments are due July 31.

Key Regulatory Dates

Comments Due

July 31 — Reporting Requirements for CMC Changes

PDA
Parenteral Drug Association

The Parenteral Drug Association presents:

2015 PDA Europe Training Course

An Introduction to Visual Inspection

The training course covers the fundamentals of visual inspection methods and their application to injectable products. It will be a combination of lecture/discussion and hands-on laboratory exercises used to develop and practice practical inspection skills. The skills developed through this course may be applied to both manual human inspection and automated machine inspection.

8-9 September 2015

Berlin | Germany

europe.pda.org/IntroVI2015

Are All Employees Rewarded for Good Quality?

Jennifer Magnani, Sanofi Pasteur, and Anders Vinther, PhD, Sanofi Pasteur

In this final article of our three part series covering Quality's role as a Financial Officer (see articles in the May and June issues of the *PDA Letter*), we look at incentives. This is part of driving the conversation from *cost* to *value*. Here, the Quality organization has a huge opportunity to show the value of good quality processes and systems.

Let's provide an example of poor incentivizing. Ben just started a job in Procurement. He identifies an opportunity to save money on the glass barrels used for Product X. With the volume of barrels the company buys, if he can save 10 cents per glass barrel, the cumulative savings to the company would be $2 million per year. So, Ben negotiates with the supplier to lower the cost. But Ben did not know that to lower the cost, the supplier began producing the glass barrels on an older manufacturing line with a history of producing lower quality glass barrels with higher defects. As a result, incoming inspection rejects 40% of all batches and now the company doesn't have enough barrels to fill Product X. The end result? A drug shortage at the patient level and the company ultimately loses 25% of its market share, equal to $85 million per year. It's quite obvious to conclude that the savings Ben made in Procurement ($2 million per year) did not result in an overall savings to the company; in fact, it resulted in a severe loss.

How was Ben incentivized? For the discounts he could generate, or for high-quality raw materials delivered to the operations group? Your guess is as good as ours. Rewards-based compensation for *all* employees should be linked to delivering high-quality product, in particular, every department or group with potential to impact the quality of a product. Manufacturing shouldn't be incentivized on production output only; they need to be measured on output of product that can be sold. Finance shouldn't be incentivized on keeping costs down, but rather for increasing value. The reward structure of a company drives behaviors.

How are rewards structured in your company? Quality's role as a Financial Officer is to call these things out and support the establishment of value-based reward systems. Interestingly, in cases like Ben's, even when companies face similar situations, rarely are they corrected at a systematic level; instead they are resolved on a case-by-case basis.

So, in our three-part article series we have described the importance of Quality professionals being able to speak and articulate topics in financial terms. It starts with bringing visibility to where the money goes through a good Cost of Quality Model. The next steps entail moving from a reactive approach to a preventive one by showing the cost of deviations versus what it would have cost to prevent these deviations, and by including the financial element into Quality Risk Management. These activities, combined with a reward system based on quality performance, can lead a company on the path from merely meeting minimum cGMP compliance standards to fully embracing a quality culture that leads to strong quality performance and employee engagement.

About the Authors

Jennifer Magnani is Senior Director of Pasteur Quality Academy. Her experience includes establishing and continually improving quality systems across varying countries and cultures, portfolio management, communication, and employee development.

Anders Vinther, PhD, is Chief Quality Officer at Sanofi Pasteur. His experience includes QC, QA, executive and strategic management in a variety of cultures and a number of companies ranging from start-ups to large biologics companies.

Ursula Busse, PhD, Novartis

PDA: A Connecting Force

Is change beautiful or a source of trouble?

Whether you like change or not, it is here to stay as our industry is undergoing a profound metamorphosis. Groundbreaking innovations in science and technology have prompted paradigm-changing ICH guidelines which impact the way we develop and manufacture pharmaceuticals. Informed patients request faster access to better medicines. And, last but not least, globalization not only entails a worldwide marketplace but also increased complexity of supply chains, global customers and stakeholders, and issues spreading to a global scale. Of the latter, counterfeit drugs, shortages of critical medicines and data integrity breaches continue to make headlines and put patients at risk. Responses we've witnessed include a number of legislative changes (FDASIA, DQSA, etc.), increased regulatory scrutiny and renewed focus on manufacturing quality. In this day and age, it is more and more important to foster dialogue between the various stakeholders involved in our industry for the ultimate benefit of patients. As part of its mission of connecting people, science and regulation®, PDA has been doing just this for the past couple of decades.

Many PDA initiatives involve active participation by regulators from major regulatory authorities. Two examples of recent topics taken up jointly by industry and regulators through facilitation by PDA are drug shortages and quality metrics. PDA fostered intense dialogue between industry, the U.S. FDA and EMA to promote solutions to the drug shortages issue. A series of meetings and workshops resulted in *Technical Report No. 68: Risk-Based Approach for Prevention and Management of Drug Shortages*—which might well become an industry standard for managing drug shortages. On FDA's proposed quality metrics initiative, PDA similarly spurred intense dialogue with regulators in various public forums. Discussions have now expanded to include quality culture attributes, and PDA, like the rest of us, awaits FDA's new guideline on quality metrics.

But PDA is not only promoting dialogue to address issues. In many circumstances, PDA proactively engaged regulators and industry in discussions around emerging scientific topics. Notable examples include advanced therapy medicinal products (ATMPs), monoclonal antibodies and drug device combination products. PDA has been organizing ATMP and monoclonal antibodies workshops for several years in Europe. Prepared jointly by volunteers from industry and European regulatory agencies, these meetings drive effective dialogue and progress in emerging regulatory and technical topics. Early dialogue also translates into broken barriers to improvements and the building of trust.

PDA has succeeded in building relationships based on trust with regulators across the globe over the last couple of decades. PIC/S chose to partner with PDA to provide a series of joint training sessions on ICH Q7 in countries around the world, notably Brazil, India and China. PIC/S, likewise, closely collaborated with PDA on the recent PDA Europe *Quality and Regulation Conference* in Brussels. In Europe, PDA also teamed up with EMA for several joint meetings on multiple relevant regulatory topics. And, last but not least, PDA has a long history of dialogue and collaboration with FDA. The annual *PDA/FDA Joint Regulatory Conference* is one of the highlights of this professional collaboration, now entering its third decade. It's a unique opportunity to interact with industry and regulators face-to-face and become actively involved in shaping the global regulatory environment and our industry's future in order to better serve patients. The *PDA/FDA Joint Regulatory Conference* was my first experience as a newcomer to PDA. It is still one of my favorites, and I will make sure I do not miss this year's event.

I look forward to meeting you at the *2015 PDA/FDA Joint Regulatory Conference* in Washington, D.C.!

PDA
Parenteral Drug Association

The Parenteral Drug Association presents:

2015 PDA Europe Conference

Particles in Injectables

europe.pda.org/Particles2015

8-9 Sept
Training Course
An Introduction to Visual Inspection

10-11 September 2015

Berlin | Germany

Connecting with Regulators Around the World

The July/August issue has become the standard issue for highlighting the *PDA/FDA Joint Regulatory Conference,* and there are many good reasons for doing so. You can read all the articles related to the meeting to understand quickly why it has become PDA's best attended event year after year. But this is not the only PDA meeting that does a great job of connecting members with regulators.

I just attended PDA Europe's *Quality and Regulations Conference* in Brussels, June 23–24. The conference drew over 30 regulators from EMA, MHRA, and even an inspector from South Africa. What a truly unique opportunity to hear voices from these agencies on important topics like drug shortages, quality metrics, data integrity and inspection trends! PDA's Board of Directors met in Brussels prior to the event, signalling its significance. Hopefully, the momentum of the event will result in a repeat meeting next year.

As to PDA/FDA, this year's event once again is overloading the *PDA Letter* staff with information. Choosing which sessions to cover, whom to interview and what articles to publish requires a lot of hard decisions, as every session seems to have high impact. I'm sure those attending face similar hard choices in determining which concurrent sessions to attend. I hope our coverage helps attendees get the whole picture.

In the meantime, check out the second installment of the PDA Summer Reading in this issue. Excerpts of recently published PDA books will give you another hard choice: Which ones should I buy? Of course, we recommend buying them all and also the ones not listed in this issue! The summer is always a good time to relax with a good book, particularly for leisure reading, so once again, we list what some PDA staff and members are reading along with the excerpts.

If you are tired of all this reading, take some time to listen to the latest PDA Podcast. This time, **Rebecca Stauffer** and I interview **Sumant Ramachandra,** Hospira and **Joerg Windisch,** Sandoz, at the *2015 PDA Annual Meeting.* Our discussion covered technical and scientific aspects of developing and marketing biosimilars. This interview will serve as the basis of a full article we are working on for the October issue.

To all our readers, on behalf of the *PDA Letter* staff and PDA, I hope you enjoy your summer!

PDA Letter

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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 — Adalbertstr. 9

16548 Glienicke/Berlin Germany
Tel: +49 33056 23 770 Fax: +49 33056 23 7777
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

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

CALL FOR POSTERS/CASE STUDIES

The Program Planning Committee encourages you to submit an abstract for a one-day poster presentation at the *2016 PDA Annual Meeting*, which will be held on March 14-16, 2016 in San Antonio, TX. Abstracts must be non-commercial, describe industry developments, strategies or practical implementation and contribute to the current body of knowledge for biopharmaceutical manufacturing, quality management and technology. Abstracts related to novel manufacturing and analytical technology are preferable, but those addressing other bioprocessing topics are welcome. Case studies are particularly desired. All abstracts will be reviewed by the Program Planning Committee for consideration.

Suggested topics include, but are not limited to:

ADVANCES IN BIOPROCESS DEVELOPMENT

- Manufacturing: Human Error Prevention
- Process Capability Improvements
- Process Validation/Lifecycle Approach
- Managing Supply Chain Complexity
- Technology and Knowledge Transfer
- Microbial Control Program
- Quality by Design Application
- Process Analytical Technology

LIFECYCLE MANAGEMENT AND CONTINUOUS IMPROVEMENT

- Quality Metrics
- Drug Shortages and Regulatory Submissions
- Supply Chain Security (Serialization, Track and Trace, Counterfeiting)
- ICH Q12
- Post-approval Change Management
- Breakthrough Therapies
- Combination Products
- Managing Data Integrity Risks

INNOVATION IN MANUFACTURING SCIENCES

- Aging Facilities
- Challenges in Manufacturing
- Single Use Systems Technology
- Emerging Methods for Adventitious Agents and Removal
- Microbial Contamination in Biomanufacturing: Risk Mitigation, Preparedness and Response
- Pharmaceutical Package Integrity Testing: Industry Challenges, Technology and Advancement
- Bioprocess/Downstream Purification Technology
- Continuous Manufacturing

ABSTRACTS MUST BE RECEIVED BY AUGUST 24, 2015 FOR CONSIDERATION.

The committee may also consider abstracts for an oral presentation. Visit **pda.org/annual2016cfp** to submit your abstract.

By submitting an abstract you confirm that you have received your company's approval to present if selected. You will be advised in writing of the status of your abstract **by October 8, 2015**. **To confirm your participation as a** Poster presenter and be listed in the final program, you are required to register as a *paid full conference* attendee at the rate of $1,895 member/$2,144 nonmember no later than **January 11, 2016**. After January 11th, poster presenters are required to pay the prevailing registration rate and will be listed in the online program agenda.

Attention Exhibitors: Registrations included with exhibitor packages are not eligible; exhibitors who wish to present a poster will be required to register as a paid full conference attendee.

For more information, please contact **Wanda Neal** via email at neal@pda.org or phone at (301) 656-5900 ext. 111.

pdaannualmeeting.org

The Parenteral Drug Association Presents...

2015 PDA/FDA Vaccines Conference

The New Vaccinology: Global Trends in Development, Manufacturing & Regulation

December 1-2, 2015 | Bethesda, MD

Bethesda North Marriott Hotel and Conference Center

Exhibition: December 1-2 | Courses: December 3-4

2015 Theme: *Focusing on Today's Challenges to Deliver Tomorrow's Vaccines*

The *2015 PDA/FDA Vaccines Conference* will showcase innovative manufacturing approaches and how they are being applied using an exciting new format that will give attendees a truly global perspective on the evolution of the vaccine industry. Co-sponsored by the U.S. FDA, this unique conference will simulcast six presentations between two locations, the U.S. and Europe. Experts will address global technical and regulatory challenges and how to effectively deliver new vaccines to the global patient population. There will be interactive Q&A allowing participants in both locations to ask their most pressing questions.

Hear from regulatory and industry experts about the latest "hot topics" in vaccinology, including:

- **The Future of Vaccines and the Impact, Rino Rappuoli, PhD,** Global Head, Vaccines Research, *Novartis Vaccines*
- **Development of Vaccines from a Government Perspective, Kathryn Zoon, PhD,** Director, Intramural Research, NIAID, *NIH*
- **Ebola Vaccinations – Where Are We Now, Cliff Lane, MD,** Deputy Director, Clinical Research and Special Projects, NIAID, *NIH*
- **Clinical Trials and IRBs in Developing Countries, Penny Heaton,** Director, Vaccine Development, Global Health Program, *Bill and Melinda Gates Foundation*
- And many more!

Be part of the global solution — prepare for emerging trends in vaccine development and manufacturing.
Learn more and register at pda.org/vaccines2015

PDA Europe will host the *2015 Europe Vaccines Conference* concurrently, December 1-2 in Berlin, Germany, which will take an in-depth look at other emerging topics in vaccines.

Are you looking for an individualized learning experience? PDA Education brings you the *2015 Vaccines Course Series* on December 3-4 at the Bethesda North Marriott Hotel and Conference Center.

Choose from the following offerings:

Current Challenges in Vaccines (Dec. 3)
Learn the complexities and unique challenges of the vaccine field and gain a basis for assessing and proposing resolutions to manufacturing and quality issues. Case studies will underline topics of particular interest to the field today.

Modern Manufacturing and Trend Monitoring Techniques for Vaccines (Dec. 4)
Obtain an overall understanding of effective methods for vaccine manufacturing processes and how to maximize controls to meet and exceed current international regulatory expectations.

For more information and to register for the *2015 Vaccines Course Series,* visit pda.org/vaccinescourses