People • Science • Regulation

PDA Letter

Volume LIV • Issue 7 www.pda.org/pdaletter July/August 2018

The Growing Supply Chain Web

2018 PDA/FDA Joint Regulatory Conference

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

Engage with experts from industry and the U.S. FDA and EU regulatory authorities at the *2018 PDA/FDA Joint Regulatory Conference*, the premier Conference addressing the development, manufacture, quality, and safety of necessary medicines to serve patients.

Over two and a half days, explore topics that ensure innovation, quality, and compliance; address issues affecting the reliability of your supply chain; and gain insight into the evolving regulatory landscape.

Choose the area of most interest to you with breakout sessions divided into three parallel tracks covering:

- Lifecycle Management and Innovation
- Quality and Compliance
- Supply Chain

Don't miss the Center and Compliance Update sessions, back by popular demand! Also be sure to attend the FDA Q&A breakfast session with FDA Center and ORA experts.

Join us for this unique forum for discussion of current standards that assure the availability and delivery of high-quality medicinal products.

Learn more and register at pda.org/2018PDAFDA

FDA

PDA Parenteral Drug Association

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

CONNECTING PEOPLE SCIENCE AND REGULATION®

July/August 2018 PDA Letter

2018 PDA/FDA Joint Regulatory Conference

Show Issue

The *2018 PDA/FDA Joint Regulatory Conference* will feature numerous sessions and panels that bring together regulators and industry representatives. Much of the discussion will focus on the state of the supply chain in recognition of the ten-year anniversary of the heparin incident. Look for this banner at the top of the page for articles previewing this meeting.

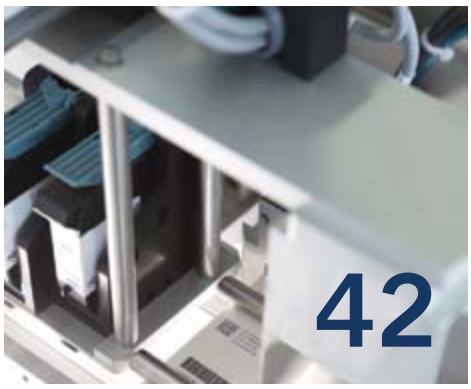
Blockchain

Will it Transform the Pharmaceutical Supply Chain?

Mark Crawford

The pharmaceutical supply chain is becoming an increasingly complex system, making it harder for drug manufacturers and their partners to ensure safe and timely delivery. Keeping track of products is not always a transparent process.

Cover Art Illustrated by Creative Edge Design Studio



New Serialization Regs Impact Global Pharma

Darryl Peterson, Antares Vision

Pharmaceutical companies must contend with challenges stemming from supply chain security lapses (resulting in theft, diversion and product recalls), counterfeiting and stringent regulations. These challenges also impair the health of the industry by adversely impacting profits, brand credibility and research initiatives.

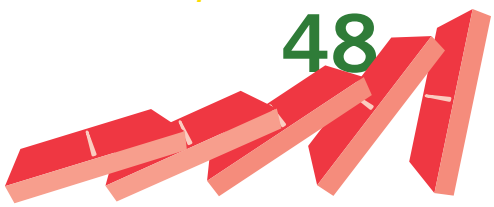
A Risk-Based Approach to Supplier Management

Roche/Genentech's Ralph Quadflieg Discusses the Company's Supplier Oversight

Rebecca Stauffer and Aneeta Mathur-Ashton, PDA

As the supply chain grows ever more complex, firms must closely monitor suppliers of raw materials, APIs and excipients. **Ralph Quadflieg,** PhD, Global Head of Lean Production System for Global Supplier Quality and External Quality, Roche/Genentech, discusses his company's approach to supplier management.

InfoGraphic



The Dominoes of Natural Disasters

Learn how a natural disasters can impact drug supply.

PDA Letter

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

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Subscriptions are not available.

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

Departments

Digital Exclusives

> **On the Issue** | Japanese Regulatory Considerations: Continuous Manufacturing
PDA board member **Masahiro Akimoto** interviews the Japan PMDA's **Issei Takayama** on Japanese regulations for continuous manufacturing at the *2018 PDA Annual Meeting*.

> **Editor's HotSeat** | Cell Viability After Cryopreservation
BioLife Solutions' **Brian Hawkins** discusses his *2018 PDA Annual Meeting* poster presentation.

> 3 Questions for Biogen's Amy Wilson
Biogen's **Amy Wilson** answers three questions about how the company's resilience approach has impacted manufacturing operations.

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2018 Universe of Pre-Filled Syringes and Injection Devices

Transforming Pre-Filled Systems through Innovation

The *2018 PDA Universe of Pre-Filled Syringes and Injection Devices* will focus on a core facet of the delivery device business – ***innovation!***

Industry and regulatory experts will share the very latest advances in:

- New methods for using new materials for syringes, their components, and new power sources
- Flexible manufacturing and assembly methods that promote lower costs and higher quality
- Improved packaging to both protect the product and enable communication with the patient
- "Patient Centricity" to ensure patients can safely and effectively deliver their medications

Business case studies to support connected health will be covered, and updates on changing requirements and their impact on the industry will also be addressed.

Plan to spend time in the packed Exhibit Hall, where suppliers will showcase novel products and solutions, and take advantage of numerous opportunities to network with colleagues and peers.

This is ***the*** must-attend Conference for anyone involved in the pre-filled syringes and injection device industry!

Don't miss out – register now to be sure *you* have a spot!

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

PDA® Parenteral Drug Association

October 8-9, 2018 | Orlando, FL
Exhibition: October 8-9
PDA Combination Products Workshop: October 10
Courses: October 11-12
#PDAPFS

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On the Issue Videos by the *PDA Letter*

Interviews with leading industry experts on the issues important to you

Watch the following experts:

Vetter's Ute Schleyer — RABS/Isolator combination

PDA Education Instructor Elaine Lehecka Pratt — Reducing Human Error

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

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

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

www.pda.org/pdaletter

What Have We Learned Ten Years After the Heparin Crisis?

Ten years ago, contaminated heparin sourced from China entered the U.S. market, leading to 81 deaths ***(1).*** Naturally, this spurred considerable attention to the pharmaceutical supply chain, particularly as the products were supposed to pass through several screenings before entering the market ***(1).***

Rebecca Stauffer

The pharmaceutical supply chain has become increasingly complex due to its global nature. While the heparin incident highlights the dangers inherent to a global supply chain, there are still several benefits, most notably greater access to critical medicines for patients worldwide. With that in mind, this means protecting drug product is more critical than ever. As we have seen even within the past year, a natural disaster in one region can result in shortages of critical drugs in another. And do not forget there are bad actors out there, too. I have seen the *60 Minutes* segment about the Eli Lilly warehouse theft in 2010 multiple times and the brazenness of that theft never ceases to amaze me. While writing this, I even received a news alert from the U.S. FDA regarding a theft of 16,000 packages of injectable fertility drug products in Italy ***(2).***

In light of the anniversary of the heparin contamination incident, this year's *PDA/FDA Joint Regulatory Conference* will focus on supply chain-related issues. Various sessions will cover a range of supply chain topics, including supplier quality audits, disaster recovery, the Food and Drug Administration Safety and Innovation Act (FDASIA), distribution challenges for cell and gene therapy products, raw material oversight and more.

I look forward to attending these sessions and learning how industry and global regulators are responding to the challenges of the growing supply chain. There will certainly be extensive Q&A and panel discussions featuring FDA representatives. It all sounds exciting and I hope you can come to D.C. this September to participate.

You may also see me and my team about, possibly carrying equipment to film another "On the Issue" video. On that note, we have been expanding our library of "On the Issue" videos, including one conducted entirely in Japanese featuring PDA board member **Masahiro Akimoto** and Japan PMDA representative **Issei Takayama.** Do not worry! We worked with both of them to subtitle the video in English. It can be found on the *PDA Letter* videos page (https://www.pda.org/pda-letter-portal/multimedia/videos) and on the PDA YouTube channel.

References

1. Greenemeier, L. "Heparin Scare: Deaths from Tainted Blood-Thinner Spur Race for Safe Replacement." *Scientific American* (Nov. 4, 2008) https://www.scientificamerican.com/article/heparin-scare-deaths/ (accessed June 19, 2018)
2. "More Than 16000 Packages of Fertility Drugs Stolen in Italy." *Maas & Peither Publishing* (June 18, 2018) http://www.pda.myindustrytracker.com/en/article/96708/more-than-16000-packages-of-fertility-drugs (accessed June 19, 2018)

PDA In the News

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

American Pharmaceutical Review
April 20, 2018
"Limitations of Microbial Environmental Monitoring Methods in Cleanrooms"
— Angel L. Salaman-Byron
tinyurl.com/y8jerlo2

Packaging Digest
March 9, 2018
"Corning prepares for demand for Valor Glass"
— Daphne Allen

Pharmaceutical Online
May 28, 2018
"Quality Risk Management 101: A Review of Required Reading for QRM Practitioners"
— Kelly Waldron
tinyurl.com/yc6s3hpo

May 23, 2018
"Best Practices In Environmental Monitoring Sampling — Transportation & Analysis"
— Allan Marinelli
tinyurl.com/yc4gvohb

March 5, 2018
"Industry 4.0: Improving Performance of Pharma Manufacturing & Aseptic Processing"
— Rich Levy
tinyurl.com/yaef8x5v

Pharmaceutical Technology
June 2, 2018
"Industry Perspectives and Practices on PUPSIT"
— Josh Eaton
tinyurl.com/y97gu64b

May 2, 2018
"Best Practices for Shipping Single-Use Systems"
— Agnes Shanley
tinyurl.com/y7avbaex

"Improving Visual Inspection"
— Hallie Forcinio
tinyurl.com/y9k9mb57

2018 PDA/FDA Joint Regulatory Conference

PDA/FDA JRC Sessions to Include Irish, UK Regulators

Two international regulators have been confirmed to speak at the *2018 PDA/FDA Joint Regulatory Conference* in September.

John Lynch, Director of Compliance, Irish Health Products Regulatory Authority (HPRA), will deliver a presentation in the second plenary, "The Evolving Regulatory Landscape," on the first day of the conference, Sept. 24, at 11:15 a.m. The session will cover major U.S. and European regulatory initiatives including the U.S. FDA program alignment, organizational changes, key inspectional priorities, the impact of BREXIT, the Mutual Recognition Agreement (MRA) and PIC/S collaboration.

Lynch will also serve as a panelist in the breakout session, "A2: Aging Facilities and Quality Risk Management," that same day at 5 p.m.

Tracy Moore, GMDP Operations Manager and Senior Inspector, Inspection Enforcement and Standards Division, UK MHRA, will speak in the session "B1: Aseptic Processing/Annex 1." Her presentation, "EU Regulatory Perspective on Aseptic Processing/Annex 1," is scheduled for 1:45 p.m. on Sept. 24.

In addition, 25 FDA speakers have been confirmed, with more to come. Continue to check the conference website at www.pda.org/2018pdafda for updates as new speakers are added to the agenda.

John Lynch

Tracy Moore

PDA Volunteer Spotlight

Declan Quinlan

- **Operations Director**
- ***MSD (Carlow) Ireland (Merck)***
- Member Since | **2007**
- Current City | **Waterford, Ireland**
- Originally From | **Cork, Ireland**

Simplicity is the key to sustained success

How did you get involved with the Ireland Chapter?
I became aware of PDA through the Association's technical reports and by attending some conferences. When a former colleague informed me they had recently established an Irish chapter, I was very interested in getting involved. It has been a great opportunity to expand my network, connect with peers in the industry and collaborate on best practices. I took up the role of chapter president in November 2017.

What has been your most memorable PDA experience to date?
The Ireland Chapter hosted an isolator event in October 2017. We had people from several companies and functions (engineering, validation, operations and quality), a presenter from the Irish Health Products Regulatory Authority and a few vendors. The willingness to share and discuss challenges and solutions in a transparent way was fantastic, highlighting the benefit of such events. It also showed the need to facilitate these very tactical discussions. The chapter is now in the process of starting a focus group to further explore isolator technology.

What significant changes have you seen take place in your profession/area of expertise through the years?
Two of the most significant changes for me have been the adoption of operational excellence principles in the pharma/biotech industry, and the move to electronic systems for operations and control. When operational excellence started being introduced within the industry, I was initially concerned it would weaken compliance. But I was soon converted and now believe it is the only way to succeed—simplicity is the key to sustained success.

What is your morning routine for success?
It starts the night before by getting to bed at a reasonable hour. Then, exercise first thing (gets my head right for the day), followed by oatmeal!

What is something not many people know about you?
I have a potential alternative career as an Irish dancer, having danced twice in Riverdance (local charity fundraising events not to be repeated!).

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

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

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

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Authors wanted

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

Chapter Grows Opportunities Across Industry

Elizabeth Hunt, Pharmalex, Ireland Chapter Event and Media Administrator

PDA's Ireland Chapter sprang into spring with a busy slate of events geared toward both seasoned professionals and those just beginning their careers.

The season kicked off with the chapter's first-ever event for young professionals on March 22 in Dublin. This provided an opportunity for students and recent graduates to network with PDA members, learn more about the pharma industry in Ireland and discover how PDA and the chapter can help those entering the field. Students from each of the third-level colleges in the Dublin area attended, as did recent graduates currently working for Amgen, Pfizer, BMS and Allergan. **Shane Costigan,** who received an award to attend the *2nd PDA Europe Annual Meeting* last year in Berlin, talked about his journey with PDA over the past year. Attendees gave the event high marks and chapter leaders plan to arrange similar events in other parts of the country later in the year.

In another professional development event, the annual *Careers in BioPharma,* the chapter exhibited and met with students and jobseekers. Over 500 attendees learned about the rapidly expanding Irish biopharma industry, which has added 20 biologics manufacturing sites and $10 billion in capital investment within the last decade. The sector forecasts an increase in 8,400 new jobs

Siegfried Schmitt speaks at the Ireland Chapter's cleaning validation event

by 2020. This event, held April 14 at the National Institute for Bioprocessing Research and Training (NIBRT) facility in Dublin, offered individuals interested in working in the biopharma sphere an opportunity to talk to employers and others who work for some of the major biopharma companies.

Later in April, the chapter hosted an event focused on cleaning validation. Over 100 people came to NIBRT to hear about the latest developments related to cleaning validation in pharmaceutical production. Experts on the topic provided case studies containing practical information on risk- and science-based approaches. The event also included a demonstration of techniques for effectively cleaning equipment.

The Ireland Chapter thanks everyone who participated in these events and looks forward to providing more useful resources to the Irish pharmaceutical community in the future.

PDA Who's Who

Shane Costigan, Student, University College Dublin

Siegfried Schmitt, PhD, Principal Consultant, PAREXEL

2018 PDA/FDA Joint Regulatory Conference

Opportunities to Build and Grow Your Network

Looking to expand your network of colleagues in the industry? Consider attending the *2018 PDA/FDA Joint Regulatory Conference* in September. There will be several opportunities to network throughout the conference.

Monday, Sept. 24

Orientation Breakfast (invitation only)
New to PDA? Learn all about the benefits of being a PDA member and available volunteer opportunities. 7–8 a.m. *Supported in part by Amgen.*

Networking Reception
Close out the first day of the conference with a masquerade-themed networking reception. Masks will be provided along with food, music and a photo booth. 6:45–10 p.m.

There will also be opportunities to network during continental breakfasts before the conference and during morning and afternoon breaks.

Manual Aseptic Small-Scale Runs and Validation

Are We Making Mountains Out of Molehills?

Cheryl Custard, Custard Consulting Group

When most of us think about manufacturing or aseptic processing, we envision large-scale bulk formulation or fills that take longer than 24 hours. But is this what a product looks like for everyone? After all, not every company focuses on large-scale bulk products, some specialize in small-scale products. Does this mean the regulations change if we go from large-scale to small-scale? In other words, are we scaling mountains to meet requirements that do not pertain to molehills?

The goal of an aseptic operation is to prevent the contamination of materials intended to be sterile. This is where process verification testing becomes important. For large-scale automated operations with infrequent operator interventions, determining if the process can produce sterile products requires analyzing large-scale automated media fills that resemble normal production. Small-scale processes using all or partial manual procedures must also be evaluated by process verification testing.

Manual operations present unique operational and evaluation challenges not generally encountered with automated operations. Manual aseptic processes rely heavily on the proficiency of the individual operator. Operations personnel and their activities are generally recognized as the greatest source of microbial contamination during any given process.

Humans present the greatest source of contamination

We can be qualified and tested, but we humans cannot provide the reproducibility of an automated system

Reproducible human performance cannot be assumed over time. In other words, unlike automated processes, humans cannot be "validated." We can be qualified and tested, but we humans cannot provide the reproducibility of an automated system.

In effect, what does this mean and how can we state that our drug products are safe, pure and effective if we cannot validate the manual or human aspect of our process? To achieve these key regulatory criteria, special attention to operator training and qualifications, as well as length of time away from/or absence from the process must be considered. Operator training should be extensive and include multiple challenges of all critical steps to a point of proficiency. Training must include qualifications not limited to gowning procedures, technique and media challenges. Documentation must include a list of all critical steps trained on, how many times an operator showed proficiency prior to final evaluation and length of time away from the process.

This process takes into account a number of questions:

- Is this product manufactured or processed daily, monthly or as needed by demand?
- What if an operator is away from the manual process for any length of time?
- What steps are needed to ensure the operators retained all critical steps during their time away from the process?
- How is this process documented?

The PDA Education course, "Recommended Practices for Manual Aseptic Processes," addresses these and other challenges facing operators during small-scale runs. It not only covers the requirements of how to perform a manual aseptic process but also provides students with a hands-on laboratory media challenge. This course is designed for operations personnel who design, perform and evaluate manual aseptic processes—including personnel involved with compounding, filling, packaging and quality assurance operations, and is suitable for supervisors and managers as well as personnel engaged in manual processing operations.

About the Author

Cheryl Custard is an independent pharmaceutical consultant and PDA Education instructor. She will teach the course, "Recommended Practices for Manual Aseptic Processes."

Recommended Practices for Manual Aseptic Processes

Bethesda, Md.
Sept. 26–28
www.pda.org/2018rpap

PDA Photostream www.flickr.com/parenteral-drug

(l-r) James Klein, PhD, Merck; Marla Stevens-Riley, PhD, U.S. FDA; Gabriele Gori, GSK Vaccines; Andrew Hopkins, UK MHRA

2018 PDA Sterile Medicinal Products Manufacturing Conference
May 14–15 |Bethesda, Md.

(l-r) Frederic Ayers, Eli Lilly; David Hussong, PhD, Eagle Analytical Services; Marsha Steed (Hardiman), ValSource

(l-r) Andrew Hopkins, UK MHRA; Ghada Haddad, Merck; Mitchell Garber, GSK

(l-r) Hal Baseman, ValSource; Brian Joseph, Pall Life Sciences; Sangeetha Nair, Baxter Healthcare

(l-r) Sarah Mollo, U.S. FDA; Olivia Henderson, PhD, Amgen; Jon Bell, Fulcrum PDC

CAPT Alan M. Stevens, U.S. FDA

(l-r) Corinne Lengsfeld, PhD, University of Denver; Paul Harber, Modality Solutions; Pooja Sane, PhD, Biomarin

(l-r) Lei Li, PhD, Eli Lilly; Brandon Zurawlow; Containsure Solutions; Allison Dill, PhD, Eli Lilly

2018 PDA Container Closure Performance and Integrity Conference

June 13–14 | Bethesda, Md.

(l-r) John Metcalfe, PhD, FDA; M. Isabel Tejero del Rio, MD, PhD, FDA; Steven Badelt, PhD, Suttons Creek; Carolyn Dorgan, FDA

(l-r) Anja Fritsch, PhD, Confarma SAS; Marc Hogreve, Sartorius; Carole Langlois, Sartorius

(l-r) Philippe Bunod, Pfeiffer Vacuum SAS; Coralie Richard, PhD, Eli Lilly; Qingyu Zeng, PhD, West Pharma; Dominick DeGrazio, Janssen R&D; Oliver Stauffer, PTI

SNAPShot

IG Corner

2018 PDA/FDA Joint Regulatory Conference

Meeting Preview

Interest Group Schedule

In addition to evening interest group meetings, some interest groups will convene during the lunch break at this year's *2018 PDA/FDA Joint Regulatory Conference.* Below is a schedule of meetings for interest groups focused on science and biotech topics.

Monday, Sept. 24	Tuesday, Sept. 25
5:45 p.m. – 6:45 p.m.	**12:30 p.m. – 1:30 p.m.**
Environmental Monitoring/Microbiology Interest Group *(joint meeting with Quality Risk Management Interest Group)* Facilities and Engineering Interest Group Packaging Science and Visual Inspection Interest Groups *(joint meeting)*	Vaccines Interest Group
	5:45 p.m. – 6:45 p.m.
	Cell and Gene Therapy Interest Group

A schedule of regulatory-focused interest group meetings can be found on p. 51.

Journal TOC

Check Out the Latest in New Technology Advancements in the PDA Journal

The July/August issue of the *PDA Journal of Pharmaceutical Science and Technology* features two articles spotlighting new technologies and applications. One looks at ozone generation during high-voltage leak detection and the other explores human factors for Ranibizumab 0.5 mg prefilled syringes. Learn more at journal.pda.org.

Research

Yuh-Fun Maa, et al., "Vapor Phase Hydrogen Peroxide Decontamination or Sanitization of an Isolator for Aseptic Filling of Monoclonal Antibody Drug Product—Hydrogen Peroxide Uptake and Impact on Protein Quality"

Alejandra Nieto, Holger Roehl, "Sealing Behaviour of Container Closure Systems under Frozen Storage Conditions: Nonlinear Finite Element Simulation of Serum Rubber Stoppers"

Alberto Chillon, et al., "Introducing the Alba® Primary Packaging Platform. Part 1: Particle Release Evaluation"

Alavattam Sreedhara, et al., "Determination of the Acceptable Ambient Light Exposure during Drug Product Manufacturing for Long-Term Stability of Monoclonal Antibodies"

Technology/Application

Martin Becker, et al., "Ozone Generation during High-Voltage Leak Detection: Fiction or Reality?"

Andrew Antoszyk, et al., "Usability of the Ranibizumab 0.5 mg Prefilled Syringe: Human Factors Studies To Evaluate Critical Task Completion by Healthcare Professionals"

Case Study

Yushi Uetera, et al., "The Role of Heat-Tolerant Endotoxin-Retentive Ultrafilters (UFs) for the Remediation of Reverse Osmosis (RO) Plants Employed for Surgical Hand Antisepsis Using Periodic Thermal Disinfection—A Ten Year Longitudinal Experience Study in the Operating Theater"

Commentary

Kyle Zingaro, David Shaw, et al., "Implementation of Plate Imaging for Demonstration of Monoclonality in Biologics Manufacturing Development"

Erratum

John Mattila, et al., "ERRATUM: Retrospective Evaluation of Low-pH Viral Inactivation and Viral Filtration Data from a Multiple Company Collaboration"

Viscous Product No Match for New CCI Tech

MicroCurrent HVLD Might Ensure Better Container Closure Integrity for New Product Formulations

Oliver Stauffer, PTI

New product types and packaging configurations, such as highly viscous formulations, pose a significant threat to traditional leak-testing methods, challenging current practices for container closure integrity testing (CCI). In light of this, a series of feasibility studies was conducted to challenge traditional leak-testing methods. Using real-world positive control methods conducted to detect defects occurring in the manufacturing process, MicroCurrent High Voltage Leak Detection (HVLD) proved a significantly better test for highly viscous low conductivity products. The studies showed that MicroCurrent HVLD can achieve a reliable leak detection limit even all the way down to critical leak sizes.

Liquid properties are critical in testing for CCI. For HVLD test methods, liquid conductivity can impact test method performance. MicroCurrent HVLD has been recognized as a technology that can leak-test a wide range of product conductivities and chemical characteristics. This is practical for leveraging test method development on products with different liquid conductivities. If a manufacturer is producing 1mL syringes, they may be filling the syringes with different types of parenteral product. MicroCurrent HVLD can also be used to develop test methods for such a broad range of liquid conductivities **(Figure 1).** Once a method is validated on a range of product conductivities, the resulting broad range of method development can be leveraged as a bracket to validate the test method for other parenteral products within that conductivity range.

Test method development for CCI requires challenging the test method with known good samples and positive controls (leakers). Positive controls can be made using laser-drilled defects; these can then be accurately measured to test specifications. Typical defects from the manufacturing process generally do not manifest as a fine pinhole in the glass—cracks are the more common defect. Traditional vision methods may not detect crack defects in complex geometries or hidden portions of the container. Crack defects that better reflect real world circumstances can be created using a process involving rapid thermal fluctuation. To challenge MicroCurrent HVLD technology, researchers scratched the glass surface, heated the glass and applied a droplet of cool water to the scratch site to create cracks.

Continued at bottom of page 51

2018 PDA/FDA Joint Regulatory Conference

How to Best Tackle Biosimilar Challenges

Stephan Krause, PhD, AstraZeneca Biologics, and Jens Schletter, PhD, Novartis

Regulatory approval of biosimilars remains a challenge, forcing sponsors of biosimilar products to face regulatory complexity during development.

Demonstrating analytical similarity and inclusion of appropriate information in market authorization submissions are just two of the recurring challenges manufacturers face.

Following the conclusion of the *2018 PDA/FDA Joint Regulatory Conference,* the *2018 PDA Biosimilars Workshop* will focus on the most common challenges identified in biosimilar applications by the U.S. FDA and other regulatory agencies, including EMA and Health Canada. **Stephan Krause**, PhD, Director, QA Technology, AstraZeneca Biologics, and **Emanuela Lacana,** PhD, Associate Director for Biosimilar and Biologics Policy, FDA, will co-chair the workshop. The workshop will offer an opportunity to gain consensus among regulators and industry on what are appropriate compliance standards on analytical similarity data along with regulatory expectations for data quality, preapproval inspections and method validation studies. The use of appropriate statistical tools for analytical similarity study design will be evaluated in great depth.

With a combination of presentations and breakout sessions and a primary focus on learning from experience, the workshop will encourage active discussion among regulators and industry with the intent to increase successful registration submissions. Starting with a session moderated by Krause on regulatory perspectives on biosimilar marketing applications, presentations in this first session will feature **Steven Kozlowski,** MD, Supervisory Medical Officer, CDER, FDA, **R. Martijn van der Plas,** PhD, Senior Assessor Biologicals, Medicines Evaluation Board (MEB), The Netherlands, and **Chantal Depatie,** PhD, Biologist Evaluator, Health Canada. Speakers will provide an overview of challenges encountered during the assessment of biosimilar marketing applications, with a focus on development, control strategy and commercial production. Each of the agencies will provide their expectations of the CMC information needed for a successful submission.

Joel T. Welch, PhD, Acting Review Chief, CDER, FDA, will moderate the session titled, "The Trapeze and The Trap Door: Navigating High-Level Technical Challenges in Biosimilar Development." This session will describe approaches to addressing high-level technical challenges and avoiding pitfalls frequently encountered during biosimilar candidate development, including data quality expectations, the creation of the final control strategy, and strategic choices necessary for candidate selection and development. Both regulators and industry representatives will share their perspectives and experiences. Presentations will

Continued at bottom of page 21

Five Critical Endotoxin Testing Concerns

Jennifer Farrington, PhD, Associates of Cape Cod, and Friedrich von Wintzingerode, PhD, Roche Diagnostics GmbH

As pharmaceutical manufacturing processes continue to become more streamlined and therapy delivery continues to evolve, so has endotoxin control. Five topics in particular have dominated recent discussions around endotoxin control: low endotoxin recovery, non-LAL detection methods, modulating impurities, data integrity and depyrogenation.

These five topics are integral to the future of endotoxin testing, and the industry recognizes the need to discuss the role they will play in this future.

In a continued effort to keep the community updated, PDA will host the *2018 PDA Endotoxins Workshop,* with specific sessions focused on each of these five areas. This meeting follows up on last year's successful endotoxin workshop. Below is an overview of how the workshop will address these topics:

Low Endotoxin Recovery (LER)

PDA's LER task force plans to publish a technical report in September. The task force, composed of subject matter experts from academia, U.S. FDA, biopharmaceutical industry, and reagent-supplier/testing companies, will address critical LER concerns such as:

(i) The root cause of LER
(ii) Standardization of the experimental protocols for spike/hold recovery studies
(iii) Potential safety impact of LER and mitigation strategies

Key technical report authors will speak on each of these topics, giving the audience the unique opportunity to get firsthand information on LER.

Non-LAL Endotoxin Detection Methods

For years, compendial endotoxin testing has been dominated by the Limulus Amoebocyte Lysate (LAL) assay. But interest in non-LAL endotoxin detection methods is growing. Non-LAL methods, such as the Monocyte Activation Test (MAT) and Recombinant Factor C Testing (rFC), have been shown to overcome some of the limitations presented by LAL testing. At this session, key experts from academia and industry will look at method development and applications for these solutions.

Endotoxins and Other Microbial Immune-Modulating Impurities

Endotoxins and other microbial impurities can cause varying levels of immune responses when introduced to the blood system. Therefore, the rapidly growing area of innate and adaptive immunity needs to be explored. This session will explain innate immune response-modulating impurities and discuss strategies for control.

Data Integrity

Recent years have seen a strong focus from regulators on data integrity topics. This session will allow attendees to discuss data integrity strategies for manual (gel clot), kinetic and automated endotoxin LAL testing with experts from industry.

Depyrogenation

In previous years, sterility and depyrogenation have often been combined as a single topic. USP, however, has recently created a dichotomy between the two, expanding understanding about the use of depyrogenation in manufacturing processes. In this session, compendial representatives will discuss the USP chapters <1228> Depyrogenation, <1228.1> Dry Heat Depyrogenation, <1228.3> Depyrogenation by Filtration and<1228.5> Endotoxin Indicators.

Anyone interested in delving more deeply into these five topics is encouraged to attend the *2018 PDA Endotoxins Workshop*.

2018 PDA Endotoxins Workshop

Bethesda, Md.
Oct. 17–18
www.pda.org/2018endotoxins

How to Best Tackle Biosimilar Challenges continued from page 20

cover "fit-for-purpose" analytical methods, inspectional expectations, the intersection of the analytical similarity assessment with the proposal for a final control strategy and critical strategic decisions necessary for a biosimilar development program.

Another session, moderated by **Bev Ingram**, PhD, Senior Director, Portfolio Lead Biosimilars Regulatory Affairs, Pfizer, will address the role of statistical tools in the demonstration of analytical similarity. Presentations in this session will explore the use of statistical tools to provide meaningful contributions to the demonstration of analytical similarity, highlighting common issues that arise when applying statistical tools. Solutions that could be used to address the known challenges will be discussed, including practical alternative solutions to current approaches. Experiences from regulatory agencies outside the United States will be shared, complementing details presented in the FDA draft guideline on statistical approaches to analytical similarity.

The workshop has been structured to allow attendees to learn from presenters and each other by combining full-group presentations and small-group breakout sessions. By sharing perspectives and clarifying concerns, regulators and industry may ultimately increase the success of registration submissions.

2018 PDA Biosimilars Workshop

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

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Pharma Must Work "Smarter" in New Era

Some Thoughts on the Impact of Cloud Computing on Parenteral Manufacturing

Toni Manzano, bigfinite

Parenteral manufacturers are just now testing the waters of Industry 4.0. The factories of the future will operate in a state of continual monitoring as manufacturers increasingly rely on analytics to ensure effective processing. Yet the goal of producing quality product remains the same.

In 2011, the term "Industry 4.0" was used for the first time to describe the beginning of the fourth industrial revolution, referring to manufacturing processes powered by interconnected cyber systems. Fast forward to 2018, and we are well into this fourth revolution and so-called "smart manufacturing" is on the rise.

While many sites manage their critical information with electronic systems (e.g., manufacturing executing systems, laboratory information management systems or warehouse management systems), not all can be characterized as smart manufacturing. That standing can only be earned when a factory uses artificial intelligence (AI), machine learning (ML) and deep learning (DL) to make decisions using reliable knowledge based on generated data. Those factories that already manage significant parts of regulated tasks with electronic data and IT systems are ready to transition into smart manufacturing.

What is the difference between an electronic factory and a smart factory? The difference lies in the ability to apply existing siloed data into advanced algorithms and then transforming this information into knowledge.

Smart manufacturing requires two key components for implementation:

- Physical elements designed under Industrial Internet of Things (IIoT) principles that acquire and process raw data on-site and export it via the internet
- Cloud systems where information is transformed into knowledge by applying massive indexing and powered analytics

Discussions about smart manufacturing must take into account a fully connected layout, where each individual manufacturing component emits all the available information in real time. This same action is then repeated top-down across the different production levels. Physical elements, such as the IIoT or edge computing, require being combined with intangible objects like digital twins or cloud computing. But among all these components, the most revolutionary are those related to the predictive analytics and artificial intelligence. And managing the large quantity of data

Continued on page 45

A Not-So-Sweet Smell: Part II

Strategies for Preventing Contamination of Wooden Pallets

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

[Editor's Note: Part I appeared in the June issue**.]**

Part I of this article reviewed the available literature on wooden pallets. How can companies use this information to address concerns around wooden pallets?

For one, it is important that pallet manufacturers identify the source of their wood materials. In addition, pallet manufacturers should avoid using any chemical treatment that can induce "anisole taint" or have the potential to contaminate products stored in the warehouse. Drug products, components or packaging materials should not be stored near wood or wood-derived storage materials unless there is assurance that the wood material has not been treated with a halogenated phenolic preservative. Manufacturers should be vigilant for the characteristic odor of offending compounds, so they can intervene before product is potentially contaminated or further distributed.

Table 1 Wooden Pallets: A Simple Warehouse Audit Checklist*

	Audit Criteria
Control	Are wooden pallets entering the goods receipt area visually checked and replaced, if needed, before entering the warehouse? Are remanufactured pallets** permitted? Are pallets stored in a location with adequate ventilation? Is there adequate monitoring/temperature and humidity control in the warehouse? Are storage periods on wood pallets minimized using a first-in, first-out method for components?
Certification	Are drug products, components or packaging materials near wooden or wood-derived storage materials? If so, are supplier agreements in place, including specifications for residual moisture? Do pallets include the necessary markings (see **Table 2**)?
Condition	Is there evidence of broken, split, damaged, stained, wet or soiled pallets in the warehouse? Pallets should be "household" clean, meaning if they look clean (and are structurally sound), they are generally acceptable. Are any wooden splinters evident on packaged production materials or on the floor directly below damaged pallets? Are any pallets stored close to warehouse doors and visibly wet or damp?
Containment	Do procedures prevent wooden pallets from entering the production facility? Are wooden pallets with packaged production materials located in nonclassified zones close to air locks used for materials' transfer into classified areas?

* The suggested checklist has been developed by the authors and is not based on specific regulatory requirements or GDP associated with the use of wooden pallets.

** Remanufactured pallets are considered wooden pallets that have had approximately one third of components replaced. Remanufactured wood packaging material must have any previous applications of the mark permanently removed and remarked. ***(1)***

Pallet treatments are not intended to provide ongoing protection from contaminating pests or fungi ***(1).*** Management of wooden pallets should be considered as part of a supplier audit program, particularly if drug products, packaging or critical materials entering production areas are transferred into the warehouse and stored on the pallets received directly from the supplier ***(2).*** Although methods to detect such contaminating compounds exist (e.g., gas chromatography and mass spectrometry, GC-MS), analytical methods may be impractical for periodic screening; regulators generally expect that manufacturers prevent contamination from wooden pallets through adherence to CGMPs ***(1).*** Audit agenda items associated with pallet management are presented in **Table 1.** It may also be worthwhile to include elements of wooden pallet management as part of an internal audit program ***(3).*** **Table 2** provides a guide of certain international ➤

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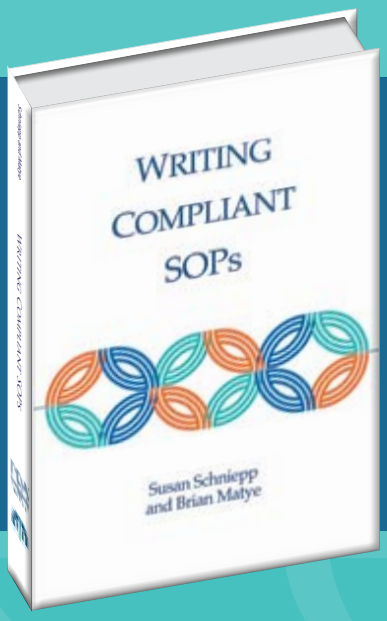

Writing Compliant SOPs

By: Susan Schniepp and Brian Matye

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Table 2 Pallet Markings

International Pallets	Pallet Marking
The IPPC logo should be present on pallets that are used and shipped internationally (orange or red markings should be avoided as these colors are typically used for labelling of dangerous goods) ***(1)***	An International Plant Protection Convention (IPPC) logo should be visible and contain the information specified in Annex II of ISPM 15. This mark consists of a dedicated symbol used in conjunction with codes identifying the specific country, the responsible producer or treatment provider and the treatment applied. Pallets must be made of a material that will not carry invasive insect species or plant diseases through different countries. To meet IPPC standards, a pallet cannot be made of raw wood that has not been treated
Pallet treatment code	Treatment codes: [HT] = Heat treatment / (MB) = Methyl Bromide / (DB) = Debarked / (KD) = Kiln Dried / DH = dielectric heating (e.g., Heat treatment by microwave). The purpose of kiln-dried lumber is to reduce the moisture content of the wood to 19% or less; newer pallets no longer require a debarking (DB) stamp by the IPPC, as most modern wooden treatment procedures require debarking as part of the standard process. Small pieces of remaining bark are considered acceptable by the IPCC if they are less than 3 cm in width (regardless of length), or greater than 3 cm in width, with the total surface area of an individual piece of bark less than 50 square cm ***(1).***
EUROPEAN PALLETS	
European stamp (EPAL)	Pallets may be marked with a single EPAL stamp. Pallets are debarked and heat-treated
European stamp (EUR)	Pallets may be marked with a single EUR. This marking represents an older European Pallet Association logo, pallets should generally be avoided unless also EPAL approved
No stamps visible	Pallets generally used for domestic transport, or are considered single use (for example, those used for building materials). Although unmarked pallets are generally not treated with chemicals, use of unmarked pallets should be avoided

pallet markings. A comprehensive risk identification matrix associated with wooden pallets can be found in *PDA Technical Report No. 55: Detection and Mitigation of 2,4,6-Tribromoanisole and 2,4,6-Tribromoanisole Taints and Odors in the Pharmaceutical and Consumer Healthcare Industries.*

Wooden pallet management in the warehouse begins with good housekeeping, i.e., storing pallets to control the moisture content of wood so it is not conducive to fungal growth. This means storing pallets dry with adequate airflow. Pallets should be odor-free, structurally sound and lack debris and foreign substances. Pallet suppliers should be part of a site supplier management program with agreed and documented pallet specifications ***(4).*** With appropriate controls in place, the use of heat-treated wooden pallets obtained from a certified supplier may generally be considered low risk. Wooden pallets remain a source of microbial growth with potential risk of contamination on the surfaces of outer packaging of materials transferred into classified production areas.

The risk of product and facility contamination from wooden pallets is often considered low as outer packaging and cardboard is usually removed, quantities of production chemicals and raw materials are usually dispensed into new containers and many items are repackaged and sterilized before entering production areas. In addition, other GMP systems and controls in place minimize the risk of contamination from the warehouse, such as environmental and personnel monitoring, facility cleaning, HVAC systems controlling airflows and pressure differentials, but there is still a regulatory expectation that manufacturers prevent contamination through adherence to cGMPs and the management of wooden pallets should be included as part of a pharmaceutical manufacturers' GMP/GDP quality system ***(5).*** With appropriate controls in place, a manufacturer can minimize the risk to products and avoid the not-so-sweet smell of wooden pallets within the pharmaceutical warehouse.

References

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2. Whitfield, F.B., Hill, J.L., and Shaw, K.J. "2,4,6-Tribromoanisole: A Potential Cause of Mustiness in Packaged Food." *Journal of Agricultural and Food Chemistry* 25 (1997): 889–893.
3. Montalvo, M. *Effective Implementation of Audit Programs.* Bethesda, MD: PDA/DHI, 2017.
4. Stumpff, J. "FDA Expectations for Supplier Management." *Pharmaceutical Technology* 37 (2013)
5. "Questions and Answers on Current Good Manufacturing Practices—Buildings and Facilities." *FDA.gov.* Dec. 21, 2015 https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm192869.htm#5 (accessed June 7, 2018)

About the Authors

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PDA Europe Conference, Exhibition, Education

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PDA Summer Reading

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

PDA Technical Series: Pharmaceutical Glass

Excerpt from the chapter, "Historical Review of Glasses Used for Parenteral Packaging" by Robert A. Schaut and W. Porter Weeks

Why Is Glass an Ideal Material for Packaging Pharmaceutical Products?

Glass has been used for millennia to package various precious materials. In Egyptian times, "sacred liquids" such as fragrances, cosmetics, and oils were contained in glass vessels for preservation and transport. In Greek and Roman times, glass vessels served wine or displayed cremated remains and other funerary materials. In the 12th century, glass ampoules were used to transport anointing oils and the blood of martyrs for the Catholic Church. Wines have been frequently stored in glass since the 17th century when new forming equipment allowed for mass production of bottles. Glass has been used to transport and store dry and liquid pharmaceutical products since the 1700s, and now in the 21st century new drug and biologic formulations rely upon glass to provide a safe barrier from the environment (light, moisture, and contamination), enabling a long shelf life.

In each of these examples, glass is chosen to store precious liquids because it uniquely combines several properties that other materials do not. For example, glass is non-porous unlike pottery and other ceramics where inherent porosity increases the risk of evaporation losses or contamination from material trapped in pores. Glass is transparent, allowing the user to inspect the contents for degradation or contamination prior to use, and it can be colored for easy identification or added functionality such as preventing light degradation of the contents. Unlike crystalline materials, glass can be reshaped by heating into complex shapes with thin walls, and glass is gas impermeable, keeping water, oxygen, and other gases that might cause oxidation or degradation away from the liquid. The high elastic modulus of glasses prevents deformation under applied loads. Finally, glasses are more chemically durable than metals or other crystalline materials against a wide range of aqueous solution chemistries—reducing the impact of the container upon its contents.

In the 21st century, the most valuable liquids are no longer perfumes or wines but delicate pharmaceutical drug products. These delicate active ingredients increasingly require aggressive and complex excipient solutions to prevent their degradation due to changes in pH, oxidation, and other processes. Glass remains the optimal material for their storage, and it has evolved substantially over the past two centuries. Even with the advent of materials such as plastics, no new materials have been developed that are as well-suited for storing these precious materials as glass. Here, we review the use of glass as a primary packaging material for parenteral drugs and evolutions in its composition, forming, durability, and regulatory requirements.

Contamination Prevention for Nonsterile Pharmaceutical Manufacturing — Andrew Dick

Excerpt from the chapter, "Hygienic Manufacturing Practices"

Filling

- Cover the filling line equipment with Plexiglas® to minimize airborne contamination.
- Clean and sanitize all equipment (hoppers, hopper lids, hoses, pumps, pistons, nozzles, rollers, cutters, blades, conveyor belts, etc.) no more than six hours before filling. If a prior batch was filled with the same formula, only a purge of new product into the line is required rather than cleaning and sanitization. If the site provides documentation stating the maximum time filling can be done without cleaning and sanitization, review the document and provide validation data.
- At filling start-up, purge the initial product from the line. If the site has a procedure that states the volume to purge, review how it is purged, the quantity to be purged, and how the purged product should be disposed.
- All operators handling packaging components (bottles, caps) must wear clean, single-use gloves sanitized with 70% IPA, and change gloves frequently before they become soiled.
- Clean and sanitize the hopper containing the packaging bottles, caps, and pumps with 70% IPA or EtOH prior to filling with new components, or when a long period of time (more than three days) has elapsed without cleaning and sanitization. In addition, cover the hopper and all opened containers to minimize airborne contaminants.
- Keep any hoses used to connect a drum or tote to the filling pump off of the ground.
- During filling, ensure that product does not splash or spray from nozzles which may cause airborne contamination.
- Use a 0.2 µm filter at the point-of-use on any compressed air used at the filling line to reduce the risk of compressed air contamination. Keep the compressed air dry and free of oil.
- Place caps, bottle inserts, and pumps inserts onto and into bottles using machines rather than manual operators; manually inserting components into bottles increases the risk for microbiological contamination.
- If manual insertion of pumps and caps is necessary for packaging, have operators wear clean, single-use gloves sanitized with 70% IPA or EtOH and change gloves frequently before they become soiled.
- If the filling line is down for a long period of time, e.g., due to troubleshooting, increase sampling of finished goods for the duration of the shift. An SOP should be in place indicating the maximum amount of time a line can remain stagnant before requiring action.
- Once filling is complete, if a different formula will be filled next, clean and sanitize the filler equipment. Fill within six hours of cleaning and sanitization; if time exceeds six hours, resanitize the equipment.

Aseptic Sampling Procedures

- To prevent contamination through handling, sample any microbiologically sensitive raw materials, bulk samples, and finished goods using aseptic techniques, as follows:
  - — Use clean, dry, and sterile utensils for all sampling.
  - — Use clean, dry, sterile sample containers of appropriate size.
  - — Wear clean, single-use gloves while sampling materials.
  - — Sanitize the sampling area with 70% IPA prior to taking the sample.
  - — Check all material containers for cleanliness and integrity.
  - — Mark clearly all material containers with the supplier name, material name, lot number, and approved status.
  - — Label the sample containers with the material name, supplier name, lot number, and sampling date.
  - — Close the lid of the sample container immediately after sampling, being careful not to touch the inside of the lid or the container.
- Collect bulk samples during the beginning, middle, and end of process.
- If sampling from a large tank, use an instrument, if needed, that has been cleaned and sanitized no more than six hours prior to use to retrieve the sample.
- If sampling from a tote, collect the sample from the top opening using a sterile pipette, spatula, or scoop and place it in a sterile container.

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2018 PDA Upcoming Events

SAVE THE DATE for PDA's 2018 Events

JULY

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

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

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

AUGUST

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

20-22
PDA Biotechnology Course Series
Bethesda, MD
pda.org/2018Biotech

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

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

SEPTEMBER

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

5-7
■ **Validation of Moist Heat Sterilization Processes – September**
Bethesda, MD
pda.org/2018SeptVMH

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

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

17-21
■ **PDA Aseptic Processing – Option 5**
Week 2: Oct. 15-19
Bethesda, MD
pda.org/2018Aseptic5

18-19
All About Virus Filtration – A Practical Approach
Cologne, Germany
pda.org/EU/VirusFiltration2018

24-26
2018 PDA/FDA Joint Regulatory Conference
Washington, DC
pda.org/2018pdafda

26-27
2018 PDA Biosimilars Workshop
Washington, DC
pda.org/2018Biosimilars

26-28
■ **Recommended Practices for Manual Aseptic Processes**
Bethesda, MD
pda.org/2018RPAP

27-28
PDA Regulatory Conference Course Series
Washington, DC
pda.org/2018RegCourses

27-28
PDA Quality Culture Assessment Tool and Training
Washington, DC
pda.org/2018SeptQCP

OCTOBER

1-3
PDA Sterilization Course Series
Bethesda, MD
pda.org/2018SCS

1-4
■ **Fundamentals of Aseptic Processing – Option 4**
Bethesda, MD
pda.org/2018OctFundAP

8-9
2018 PDA Universe of Pre-Filled Syringes and Injection Devices
Orlando, FL
pda.org/2018PFS

8-9
■ **Isolator Technology – Option 2**
Bethesda, MD
pda.org/2018OctIT

10
2018 PDA Combination Products Workshop
Orlando, FL
pda.org/2018Combo

11-12
PDA Universe of Pre-Filled Syringes and Injection Devices Course Series
Orlando, FL
pda.org/2018PFSCourses

14
Prozesschromatographie
Clausthal-Zellerfeld, Germany
pda.org/EU/PC18

15-16
PDA Europe Pharmaceutical Microbiology Conference
Berlin, Germany
pda.org/EU/PharmaMicro

15-17
13th Annual PDA Global Conference on Pharmaceutical Microbiology
Bethesda, MD
pda.org/2018Micro

Denotes laboratory courses taught in Europe. | ■ This course is taught in PDA's U.S. manufacturing training facility.

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

17-18
2018 PDA Endotoxins Workshop
Bethesda, MD
pda.org/2018Endotoxins

17-18
Best Practices and Points to Consider in Aseptic Processing
Berlin, Germany
pda.org/EU/BP-Aseptic2018

17-18
Mastering Challenges of Data Integrity and Computer System Validation
Berlin, Germany
pda.org/EU/MasteringDI

17-18
Rapid Microbiological Methods
Berlin, Germany
pda.org/EU/RMM2018

18-19
13th Annual PDA Conference on Pharmaceutical Microbiology Course Series
Bethesda, MD
pda.org/2018MicroCourses

22-25
■ **Filtration Processes in the Pharmaceutical and Biopharmaceutical Industry**
Bethesda, MD
pda.org/2018Filtration

23-24
2018 PDA Cell and Gene Therapy Conference
Bethesda, MD
pda.org/2018CGT

23-24
Visual Inspection Forum
Berlin, Germany
pda.org/EU/VIF2018

23-25
SOLD OUT
■ **Airflow Visualization Techniques and Practices – Option 2**
Bethesda, MD
pda.org/2018OctAir

25-26
An Introduction to Visual Inspection: A hands-on course
Berlin, Germany
pda.org/EU/VIF2018

25-26
Einfache und Prozessorientierte Qualifizierung
Berlin, Germany
pda.org//EU/EPQ2018

25-26
Mastering Automated Visual Inspection
Berlin, Germany
pda.org/EU/IntroVisual2

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

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

NOVEMBER

5-8
Quality Risk Management Certificate Program
Bethesda, MD
pda.org/2018QRM

6-7
2018 PDA Taiwan Conference
Taipei, Taiwan
pda.org/2018Taiwan

6-7
Outsourcing and Supply Chain – A 360° View
Seville, Spain
pda.org/EU/2018Outsourcing

6-8
■ **Validation of Moist Heat Sterilization Processes – November**
Bethesda, MD
pda.org/2018NovVMH

8-9
Pharma Supply Chain Qualification
Seville, Spain
pda.org/EU/PharmaSC

13-15
■ **PDA Environmental Monitoring Course Series**
Bethesda, MD
pda.org/2018NovEMCS

15-16
■ **Single Use Systems for the Manufacturing of Parenteral Products**
Bethesda, MD
pda.org/2018SUS

22
Project Management in the Pharmaceutical Industry – Challenges and Possibilities
Berlin, Germany
pda.rog/EU/PM2018

27-28
Pharmaceutical Freeze Drying Technology
Seville, Spain
pda.org/EU/FreezeDrying2018

27-28
11th Workshop on Monoclonal Antibodies
Seville, Spain
pda.org/EU/MABS2018

29
Application of a Risk-based Approach to Freeze-Drying Processes
Seville, Spain
pda.org/EU/RBP2018

29-30
Development of a Freeze Drying Process
Seville, Spain
pda.org/EU/FDProcess2018

29-30
Extractables & Leachables
Seville, Spain
pda.org/EU/E-and-L2018

29-30
CMC Regulatory Compliance for Biopharmaceuticals
Seville, Spain
pda.org/EU/cmc-regulatory2018

DECEMBER

3-6
Fundamentals of Aseptic Processing – Option 5
Bethesda, MD
pda.org/2018DECFundAP

7
NEW COURSE
Assay Validation by Design
Bethesda, MD
pda.org/2018Assay

2017 PDA PUPSIT Survey

11. Have you had a regulatory inspection within the past 18 months where there was a discussion on PUPSIT?

Answer Options	Response Percent	Response Count
Yes	25%	2
No	75%	6

Please document any expectations communicated concerning the physical distance between the sterilizing filter and the downstream operation (e.g., filler):

- Indicated preference that PUPSIT performed "in-situ" and that filters not be moved further away from downstream filling step as a result of PUPSIT implementation.
- The sterilizing filter should be located as close as possible to the filling line.

Please document any expectations communicated concerning the HVAC classification of the sterilizing filter during filtration:

- Not clear. Inspectors didn't like moving filtration step further from the filler as a result of performing PUPSIT (this also involved changing HVAC classification). Clear that they did not like increased distance. Not sure if HVAC was also a concern.
- None

Please document any expectations communicated concerning whether or not it is acceptable to perform PUPSIT in one area and then move the PUPSIT tested filter to another area to perform the filtration operation:

- Inspectors made it clear that they expected PUPSIT to be performed "in-situ" – meaning that PUPSIT performed in same physical location where sterile filtration occurs.
- None

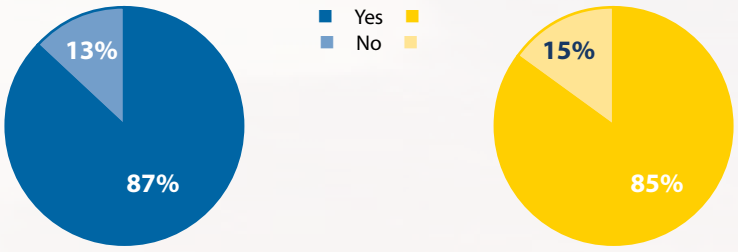
Please document any expectations communicated concerning the fluid used to wet the filter to perform PUPSIT (e.g., any preference to use product or water as the wetting fluid):

- Although it was not stated as a firm requirement, inspectors indicated preference to perform PUPSIT by wetting with product instead of water if possible as a potential means to keep sterile filter close to downstream step during PUPSIT.
- Water or product.

2017 PDA Glass Quality Survey

7. Do you apply acceptance sampling according to ANSI/ASQ Z1.4 or ISO 2859-1?

Answer Options	2013		2017	
	Response Percent	Response Count	Response Percent	Response Count
Yes	86.8%	59	85.4%	35
No	13.2%	9	14.6%	6
	Answered	68		41
	Skipped	13		3



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8. Do you apply the 1+√n rule for representative sampling?

Answer Options	2013		2017	
	Response Percent	Response Count	Response Percent	Response Count
Yes	55.2%	37	67.5%	27
No	44.8%	30	32.5%	13
	Answered	68		41
	Skipped	13		3

PDA Technical Report No. 79: Particulate Matter Control in Difficult to Inspect Parenterals

4.3 Nondestructive Acceptance Sampling and Testing

After 100% inspection of each batch, a sample of the accepted portion is sampled and inspected again. This statistical acceptance sampling is often referred to as an "AQL inspection" based on the percent parameter (e.g. 0.65%) used to set the sensitivity of the inspection. This requirement is explicitly stated in USP <790>, but is also generally expected by regulatory authorities in other regions. Acceptance sampling is required for all product types; it is not unique to DIP inspection. It provides a verification of inspection performance and batch quality prior to release of the batch.

The general sampling plans found in ANSI/ASQ Z1.4 and the equivalent standards ISO 2859-1 and JIS Z9015 are most often used to set the size of the sample and the criteria for batch acceptance. This nondestructive inspection is generally performed manually using the reference conditions specified in the relevant pharmacopoeias: diffuse illumination of 2,000–3,750 lux, viewed for five seconds per sample against a white and black background, with swirling or inversion (for liquid products). According to the PDA *2014 Visual Inspection* survey, the Quality Unit inspectors (71%) most often perform this inspection; however, it can be delegated to the Production Unit with proper control and oversight by the Quality Unit staff.

Before selecting and using any sampling plan, its performance characteristics must be understood. These are described by the plan's operating characteristic curve, a plot of the probability of batch acceptance (y-axis) versus the lot percent defective or defect rate in the batch (x-axis).

The AQL mentioned previously and the unacceptable quality limit, or lot total percent defective, are two points on this curve. The AQL is the defect rate for which there is a 95% probability of acceptance (or a 5% probability of rejection). This is a measure of the producer's risk of falsely rejecting good batches. An alternate approach is to evaluate the unacceptable quality limit (UQL) or other equivalent terms such as lot total percent defective (LTPD) or rejectable quality limit (RQL) which represents the defect rate for which there is a 10% probability of acceptance (or a 90% probability of rejection), and a measure of the customer's or patient's risk of receiving a batch with an unacceptably high number of defects. This is more like the traditional quality limits associated with test methods.

PDA's Personal Reading List

Personal History, Katharine Graham
— **Tina Morris,** PhD, PDA Vice President, Scientific and Regulatory Affairs

Blue Ocean Strategy, W. Chan Kim and Renee Mauborgne
— **Mirko Gabriele,** Patheon, *PDA Letter* Editorial Committee member

Just Mercy, Bryan Stevenson
— **Aneeta Mathur-Ashton, PDA Publications intern**

The referenced statistical standards provide tables to guide the selection of sample size (with a reference letter code), which is based on the size of the batch. The acceptance criteria or accept numbers are then determined for each defect category (critical, major, and minor, or other, if used). Often a sampling plan is selected such that no critical defects are permitted in the sample and the accept number is zero. The acceptance table is used to find an accept value of zero (reject on 1) and to check the associated AQL% value. This value should be no more than 0.10%; the use of lower values provides increased protection. When testing all attributes in one examination the sample size is based on the most critical defect AQL value in the product defect list. All other AQL acceptance limits are listed on the same line in the table.

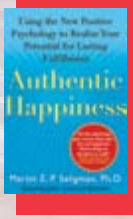
Using the ANSI/ASQ Z1.4 tables an example of how the sampling plan is applied begins with selecting an AQL% sensitivity. A critical defect such as cracked containers which could breach sterility typically carries an AQL value of 0.025% or less. Based on a batch size of <35,000 units the letter code is a "M" using a Normal, Level II, sampling plan (315 units). However, the up or down arrow in the table should be followed to an accept number of zero. In this example following the arrow brings you to a plan code of "N" with a sample size of 500 units. This indicates the new sampling plan and this new sample size specified for this plan. Once a plan is chosen with an accept number of zero for critical defects, the accept numbers for major and minor defects in the sample is found by following the same row across to the right and locating the value under the AQL appropriate for that defect type.

Another example is applied to DIP products for destructive sampling for the presence of visible particulate matter using the S-levels of ANSI/ASQ Z1.4 tables. Using an S-4 sampling plan and applying an AQL value of 0.65% as stated in USP<790> with a batch size up to 10,000 units would require a sample size of 20 units with an accept on zero. For larger batches up to 500,000 units would require a sample size of 80 units with an accept on one unit with evidence of a visible particle.

When considering the appropriate classification and AQL for particles, USP <790> uses a maximum AQL of 0.65%, generally associated with major defects as noted in the example and table above. This is appropriate for single particles, in most cases, based on an assessment of patient risk. When considering the risk from extrinsic particles, especially those of biological origin (e.g., hair, insects), the use of a critical classification and associated AQL (0.065%) may be more appropriate. This is based on the increased risk of microbiological contamination and reduced sterility assurances as well as a general failure to maintain GMP conditions. High risk routes of administration (e.g., intraocular, intrathecal) or high-risk patient populations may also require a critical classification for particles to assure patient safety. Representative rather than random samples are typically collected for practical reasons. These samples are usually collected as a fixed number per bulk container (e.g., tray or tote) or interval of time and represent an even distribution across the entire batch. The number collected per container is based on the sample size required by the sampling plan and the number of bulk containers in the batch.

In routine use, a batch meets the acceptance criteria if the number of defects in each category does not exceed the stated accept numbers. If an accept number is exceeded, a deviation should be recorded and the cause investigated. If, after investigation, there is a reasonable expectation that re-inspection can effectively further remove the defect from the batch, it should be undertaken with pre-approval from the Quality Unit and following appropriate procedures. Repeated re-inspections of a batch are not recommended.

PDA's Personal Reading List



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— **Stephanie Gaulding,** DPS, *PDA Letter* Editorial Committee member

JFK and the Unspeakable: Why He Died and Why It Matters, James W. Douglass
— **Valeria Frigerio Regazzoni,** Merck, *PDA Letter* Editorial Committee member

Inferno, Dan Brown
— **Cheryl Custard,** PDA Education instructor

PDA Technical Report No. 78: Particulate Matter in Oral Dosage Forms

5.0 Sources and Mitigation

Particulate matter in oral dosage forms can come from many sources including raw materials, packaging components, manufacturing and packaging equipment, facility utilities, abrasive materials, and facility hygiene. Therefore, manufacturers and packagers of oral dosage forms must minimize particulates and particulate generation through proper equipment design and handling; selection of construction materials; procedures for operations, cleaning, gowning, and maintenance of infrastructure; in-process inspections at the appropriate frequency; allocation of resources to perform required tasks; and preventive maintenance to minimize potential for introduction of particles into product. Suppliers of raw materials and packaging components should also have measures in place to minimize particles.

Since particulates can never be totally excluded from the manufacturing and packaging processes of oral dosage forms, manufacturers and packagers should determine the level and type of particles that are considered intrinsic (i.e., due to normal wear and tear) as opposed to those that are extrinsic (i.e., from foreign contamination or a catastrophic equipment failure). In order to make this determination, manufacturers and packagers should establish a baseline of particulates resulting from normal equipment use, raw materials, and component performance. The baseline should include an assessment of particulates found:

- In raw materials through screening evaluations and from supplier-provided TUPs
- On in-process screens during visual inspection for screen integrity
- During visual inspections of incoming packaging components
- During finished product visual inspections.

The baseline data should be assembled in a particulate library that can be used in the future to assist in determining the source of particles that are found. If particulates are found that have not been previously characterized and/or at levels beyond what was seen in the baseline, an investigation should be considered.

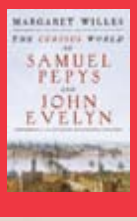
To minimize the presence of particles in oral dosage forms, manufacturers and packagers should consider establishing preventive measures as well as removal and inspection methods. The first line of defense for mitigation of particulates involves prevention—removing particles prior to the manufacturing process (e.g., raw material inspections, filtration/screening, packaging component blowers, effective cleaning methods, proper equipment maintenance) and selecting inert equipment and materials compatible with process streams based on their safety characteristics. The second line of defense for mitigation of particles is removal of particulates during the manufacturing and packaging processes (e.g., filters/screens, magnetic devices, bottle blowers). The last line of defense for mitigation of particles is detection in the finished product (e.g., visual inspection, metal detectors, in-line detectors); particles detected in finished product must be identified and assessed for impact on product quality and patient safety.

Regarding sources of particulate matter in oral dosage forms, the *2015 PDA Survey* revealed that APIs and excipients were ranked as the largest contributor of particulates in oral dosage forms, followed by the primary packaging and manufacturing process. The lowest-ranking contributors of particulates were the packaging process, equipment, and human error. Two-thirds of respondents representing drug product manufacturers or packagers reported testing incoming raw materials for particulate matter, and about 40% of those have a library of known particulate matter found in the products and primary packaging components.

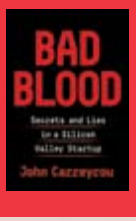
As to mitigation of particulate matter in oral dosage forms, the *2015 PDA Survey* showed that approximately 70% of respondents representing drug product manufacturers and packagers use in-line metal detectors for inspection of tablets/caplets/capsules, and 25% of manufacturers perform 100% visual inspection for particulate matter in oral dosage forms. About 70% of the manufacturers that do not perform 100% visual inspection for particulate matter perform another type of visual inspection, such as acceptable quality limit sampling and testing, periodic in-process checks, and statistically based sampling and testing. Other mitigation actions to remove particulates from the processes practiced by the *2015 PDA Survey* respondents include sieving (70%), preventive maintenance of product contact surface (77%), and personnel training and gowning (both at 82%). Other practices to remove particulates included use of filtration, environmental controls, in-line magnets, and mechanical screening.

PDA's Personal Reading List

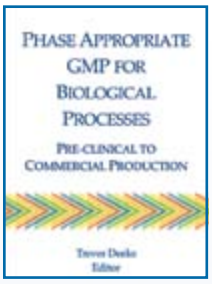
Proxima Dying, Brandon Q. Morris
— **Kerstin Wilken,** PhD, PDA Europe, Director Programs and Education



The Curious World of Samuel Pepys and John Evelyn, Margaret Willes
— **Rebecca Stauffer,** *PDA Letter* Managing Editor



Bad Blood: Secrets and Lies in a Silicon Valley Startup, John Carreyrou
— **Claire Briglia,** MilliporeSigma, *PDA Letter* Editorial Committee member



Phase Appropriate GMP for Biological Processes — Trevor Deeks, editor

Excerpt from the chapter, "Microbiological Control and Testing for Phase Appropriate GMP" by Tim Sandle

CLEANING VALIDATION

An important microbiological (as well as chemical) concept is cleaning validation. This is undertaken to ensure there is no crosscontamination in a multi-product manufacturing plant. Microbiological assessment is typically performed by taking and testing surface swabs and through the analysis of rinse samples (such as final rinse water), to assess bioburden and endotoxin levels. The results of cleaning validation should lead to the development of a suitable cleaning Standard Operating Procedure (SOP) that can be used in product scale-up. In addition to cleaning validation, cleaned equipment must be stored in such a way as so not to be at risk from recontamination.

RAW MATERIALS

The raw materials used in the manufacture of pharmaceutical products should be shown to be below an acceptable level of contamination of microorganisms: both in terms of overall bioburden and free from any objectionable microorganisms of concern. These are controlled foremost by purchasing materials from an approved supplier who produces materials of pharmacopeial grade. The status of the supplier can be verified by auditing and the microbial levels in the product can be verified by testing. Testing does not need to be with every batch, for skip lot testing can be undertaken depending upon the nature of the material and the likelihood that it contains microbial contamination. Typically materials of natural origin, especially those containing animal ingredients, present the greatest risk.

A Certificate of Analysis indicating all tests performed, with results, and including data on the purity and identity of the material, should also be obtained.

INTERMEDIATE PRODUCT TESTING

Bioburden testing

With bioburden testing this provides a measure of process control. Ideally the bioburden levels from early processing, through intermediate processing and to final formulation, should decrease (or, from a low starting point, not increase) as the process advances.

With bioburden testing a number of decisions are required. These relate to:

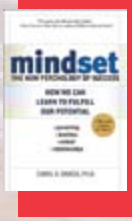
- Where will samples be taken?
- What limits are appropriate?
- Is there a concern with the presence of any specified microorganisms?
- What methods will be used for testing?

In answering these questions, with the appropriate points for sampling these should be identified through risk assessment and be based on the evaluation of risk factors. Points in the process where ingredients are added, especially where this involves open processing, are stages that are appropriate for bioburden testing.

The time of sampling also needs to be considered. A common regulatory issue relates to process hold times, where a hold stage in the process presents an opportunity for microbial growth. For hold stages that run into several hours, consideration should be given as to whether a bioburden and/or endotoxin test is appropriate. This is because pharmaceutical preparations, especially biologic products include the types of carbon sources and other growth factors that favor microbial growth.

When assessing hold times, product, process, time, and temperature should not be viewed as discrete factors. These factors often need to be combined since one factor in conjunction with another may lead to a different risk outcome. For example, one type of growth promoting product held at 2–8°C would be at a lower risk due to this temperature inhibiting the growth of most microorganisms than the same product held for the same time period at 30–35°C. Hold times are typically assessed by taking bioburden samples, with the sample taken immediately at the end of the hold time (that is just before the next processing phase).

PDA's Personal Reading List



Mindset: The New Psychology of Success, Carol Dweck
— **Tamer Helmy,** *PDA Letter* Editorial Committee member

Gunpowder Moon, David Pedreira
— **Christine Bui,** Dark Horse Consulting, *PDA Letter* Editorial Committee member

Poor Economics: A Radical Rethinking of the Way to Fight Global Poverty, Abhijit Banerjee and Esther Duflo
— **Walid El Azab,** STERIS, *PDA Letter* Editorial Committee member

Blockchain

Will it Transform the Pharmaceutical Supply Chain?

Mark Crawford

> **The initial focus of blockchain efforts for pharma has been rooted in the secure sharing of data, creating a universal truth of secure, immutable product information**

The pharmaceutical supply chain is becoming an increasingly complex system, making it harder for drug manufacturers and their partners to ensure safe and timely delivery. Keeping track of products is not always a transparent process.

Thousands of people and companies interact with supplies and products being shipped, including those that require special care because they are perishable, fragile or very expensive. Trading partners in the supply chain typically exchange contracts, agreements and transactions using individual administrative systems (some still paper-based), often duplicating work and wasting time. Supply chain partners also use legacy systems of varying sophistication with different levels of speed, functionality and security, creating further inconsistency and slowdowns.

One solution to these challenges may lie in blockchain, an electronic transaction ledger that contains a continuously growing list of records, called blocks. Each block is a cryptographically secured, time-stamped transaction record. The blocks are linked and recorded as a chronological "chain." Blockchain can be used to secure both internal and multiparty supply chains.

This network, typically peer-to-peer managed, follows a set of established rules. Distributed across a network of computers, the database has no centralized entry point that could attract hackers. Heavy-duty encryption ensures security so that each time-stamped record cannot be hacked or modified. Data transaction is conducted for a minor fee. After blocks are recorded, data and/or program modification is virtually impossible, which assures transparency and builds consistency and trust across all users of the blockchain.

Even the U.S. FDA is looking into blockchain. A top challenge for pharma is complying with the U.S. Drug Supply Chain Safety Act (DSCSA) by the November 2023 deadline; this law requires all prescription drugs, including returned drugs, to be tracked and traced through the supply chain using an interoperable system—essential for fighting counterfeit medicines, which are not only dangerous to patients but cost the global pharmaceutical market hundreds of billions of dollars annually.

"FDA is actively exploring the potential of blockchain technology to identify appropriate technological solutions that will help trace drugs as they move from manufacturer to pharmacy, enhancing the agency's ability to protect consumers from exposure to drugs that may be counterfeit, stolen, contaminated, or otherwise harmful," said **Jeremy Kahn,** Trade Press Officer for CDER. "This is part of an FDA effort to help develop the enhanced drug distribution security tools needed to comply with DSCSA."

FDA held a public meeting on this topic in December 2017 that included a presentation on blockchain. "We are currently reviewing the information gathered from the meeting and comments submitted to the docket to better determine the advantages and limitations of this technology for tracing the movement of prescription drugs," Kahn added.

Advantages of Blockchain

Blockchain has the potential to make the supply chain more secure, transparent and streamlined. Every checkpoint or hand-off is recorded and traced via biometric measures, multiple barcode scans or sensor technologies (including radio frequency identification). This ongoing, real-time record can be viewed at any time by authorized parties, even patients, at the end of the supply chain. The technology also provides an audit trail that satisfies regulatory requirements and makes it easier to manage smart contracts across the entire value chain. All of these safeguards and controls make it much more difficult for criminal networks to penetrate the pharmaceutical marketplace and sell counterfeit drugs.

Blockchain can also protect the quality of products. Sensors can track location and also measure and record external environmental factors that are especially crucial for pharmaceutical supplies. For example, shock or temperature can be monitored to detect (and hopefully correct in real time) any unacceptable variances that could result in degradation during shipping.

"The blockchain promise is that many databases will behave as one, driving efficiencies and effectiveness across supply chains of companies operating together," stated **Michele D'Alessandro,** Vice President and Chief Information Officer, Manufacturing IT, Merck & Company.

This, however, is easier said than done.

Article at a Glance

- Blockchain technology could offer a solution for securing complex supply chains
- U.S. FDA is looking into it
- Pharma and device manufacturers are conducting pilots around blockchain

One of the biggest obstacles to implementing blockchain is the huge variety of legacy platforms used within the pharmaceutical supply chain, often running different operating systems with varying levels of security. The pharmaceutical industry is highly IP-sensitive, and companies are already reluctant to share data, being wary of autonomous systems that claim to be secure and foolproof. In essence, blockchain is an emerging technology that has yet to be fully scaled up and tested for the pharma supply chain, so many companies are taking a "wait-and-see" approach to blockchain before investing in its implementation.

Blockchain can also help smaller vendors within the supply chain run their businesses more smoothly and improve their flow of capital. This is especially true for supply chain partners in developing countries, where hundreds of companies crowd the market. Trading records made transparent through blockchain help build trust in these small and medium-sized companies and their business practices, making it easier for them to access credit and reduce turnover time for payments from weeks to days.

Ultimately, building trust is perhaps the biggest benefit of blockchain. "The initial focus of blockchain efforts for pharma has been rooted in the secure sharing of data, creating a universal truth of secure, immutable product information," said D'Alessandro.

"The real potential lies in the data and process models and how far companies are willing to explore new ways of doing business in a highly connected, process- and data-shared environment," added **Bob Celeste,** founder of the Center for Supply Chain Studies. "Blockchain creates added trust between trading partners by using a shared, auditable environment that can lead to new business practices that add value to the relationship."

Pilots, Prototypes and Case Studies

Forward-thinking companies are moving ahead with blockchain initiatives, often in collaboration with like-minded partners. For example, Merck partnered with SAP, AmerisourceBergen and Cryptowerk to build a proof-of-concept (POC) blockchain system to comply with regulations and help fight counterfeit drugs ***(1).*** The SAP Pharma Blockchain POC app runs on a mobile Android or iOS device. It uses simple barcode scanning to provide real-time visibility for the location of drugs at any point in the supply chain, whether it is the manufacturer, brand owner, wholesaler or delivery system. This allows for verification of drugs by serial number, batch and expiration date, ensuring drug products can be tracked any point in the supply chain.

Another solution addresses prevention of counterfeiting. Blockchain company TBSx3 stands for "To Be Sure, To Be Sure, To Be Sure." Although serialization is a useful traceability tool, counterfeiters can still copy a product's serial code. TBSx3 provides three layers of protection. Each TBSx3-protected product has a unique encrypted code that identifies the individual product. The product is tracked as it moves through the supply chain. Machine-learning analysis of the movement pattern can detect and report any suspicious anomalies. The third layer is the "no double spend" feature that crosses off an ID/code after it has been used, assuring that any attempt to use a counterfeit copy of the ID/code will be rejected ***(2).***

In another pilot, DHL and Accenture have released initial findings on a jointly-developed working prototype that tracks pharmaceuticals from point of origin to the consumer, preventing tampering and errors ***(3).*** This blockchain-based serialization prototype uses nodes in six geographies to track pharmaceuticals across the supply chain. The ledger may be shared with stakeholders, including manufacturers, warehouses, distributors, pharmacies, hospitals and doctors. Lab simulations show that blockchain could handle more than seven billion unique serial numbers and 1,500 transactions per second.

The MediLedger Project, launched in 2017 by Chronicled, assembled a working group of leading pharmaceutical manufacturers and distributors to explore blockchain technology for meeting track-and-trace regulations and improving overall performance and safety of the supply chain ***(4).*** In 2018 the group plans to rigorously test data/product ownership transfer and verification among its members using a blockchain prototype.

Moving Forward

Blockchain is a relatively new technology that many pharma companies do not fully understand (or trust), causing them to move slowly in terms of adoption. Some drawbacks include having already invested in other technologies that would ensure traceability and satisfy DSCSA, the uncertainty and risk that is always part of investing in new technology and costly implementation with limited short-term benefits until large-scale adoption occurs.

Blockchain platforms are quickly evolving to meet industry needs. "The blockchain of today and tomorrow is not the blockchain of three years ago," said Celeste. "Advancement is being aided by the projects undertaken between trading partners or small groups of trading partners. The benefits from these experiments will lead the way on how this technology matures from its current state to production-ready platforms."

There are also plenty of policy, standards and governance decisions that remain to be made before industry-wide adoption takes place. Celeste predicts the exploration and adoption of blockchain will proceed in measured steps, starting with low-risk processes or processes that have few alternatives (e.g., DSCSA). These processes need to be carefully mapped, tested, validated and examined from a regulatory perspective. "The regulators and certification bodies may need to reassess their understanding of process and data, given the unique features of a shared, immutable programmable environment," he said.

What will accelerate the development of blockchain the most is cooperation, communication and experimentation among the regulatory, industry and academic partners who are working to advance this technology. As trust grows, research partnerships and projects will continue to find (and share) new and better ways to use blockchain to secure pharma supply chains.

"It is most beneficial to experiment through targeted-use cases, like we would

Continued at bottom of page 55

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New Serialization Regs Impact Global Pharma

Darryl Peterson, Antares Vision

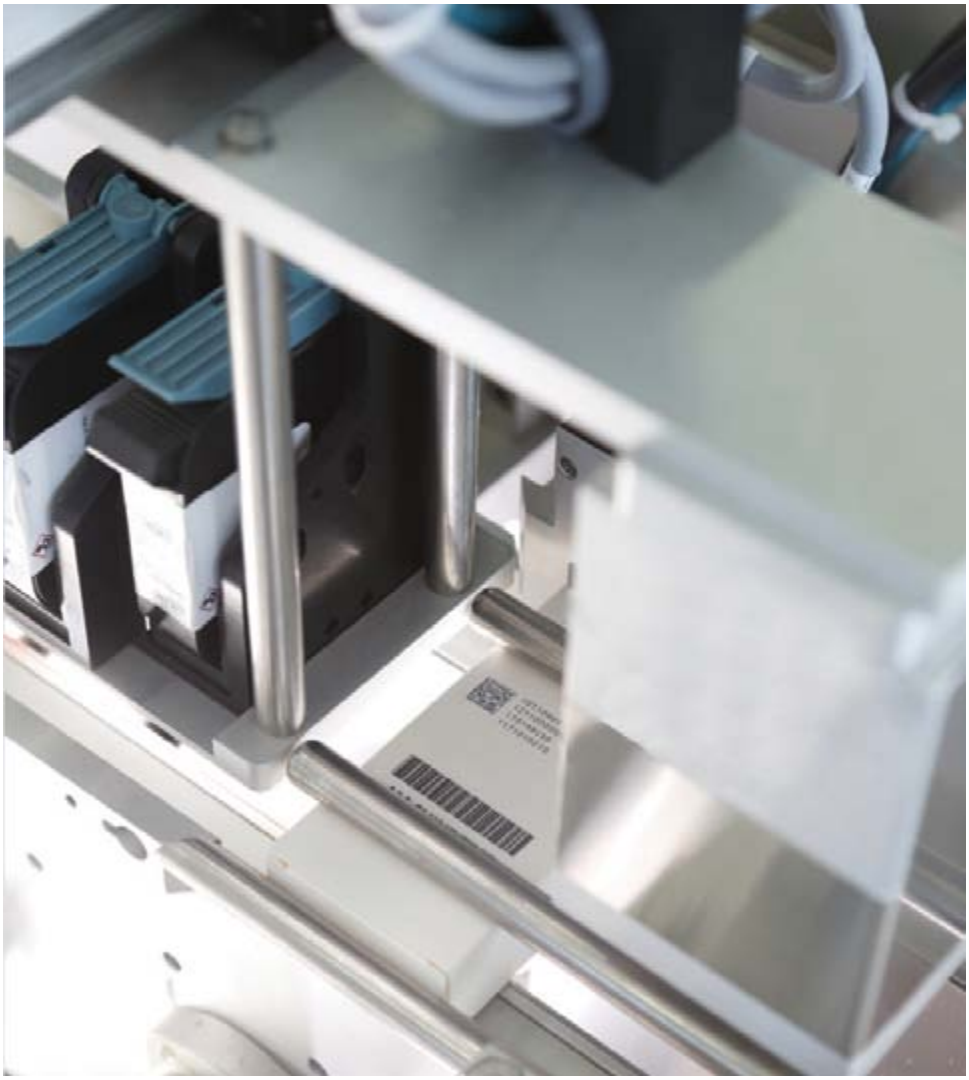


Photo courtesy of Antares Vision

Pharmaceutical companies must deal with challenges stemming from supply chain security lapses (resulting in theft, diversion and product recalls), counterfeiting and stringent regulations. These challenges also impair the health of the industry by adversely impacting profits, brand credibility and research initiatives.

With industries and governments around the world realizing the complexity of implementing product serialization programs, pharmaceutical manufacturers in the United States are already busy attempting to comply with our own federal track-and-trace legislation, part of the Drug Supply Chain Security Act (DSCSA). This law took effect in 2015 and not only applies to U.S. drug manufacturers, but also to wholesalers and pharmacies that buy, distribute and dispense medications in the United States. The DSCSA includes certain milestones for phasing in compliance across the drug supply chain over a ten-year period; full traceability is intended to be implemented by 2023.

GS1, a non-profit organization, has emerged as a unifying force within the drug industry as it seeks to establish standards around serialization. This organization develops and maintains global standards for business communication. The best known of these standards is the barcode, similar to the one a cashier scans at the checkout counter. GS1 has actively participated in the worldwide adoption of standards around barcodes for DSCSA-compliance. They do this by defining protocols around linear bar codes, such as Serialized Shipping Container Codes (SSCC) and 2-D data matrix codes that can encode required information. A serialized barcode **(Figure 1)** contains, at a minimum, a Global Trade identification Number (GTIN)—unique to individual drug products and companies, serial number, lot number and expiration dates.

Figure 1 shows the application identifiers (two-digit prefixes with parentheses around them). The application identifier that begins with (01) stands for the 14-digit GTIN that includes the embedded NDC number with a check digit at the end. The (21) identifier serves as the serial number; this can go up to 20 digits. The (17) 190519 is the expiration date in YYMMDD format, i.e., May 19, 2019. And (10) LN001 is the batch number.

Serialization Dominates the Globe

The United States is not alone in expanding serialization requirements. U.S. drug companies planning to export their products overseas for sale need to carefully navigate changing serialization requirements in other markets. Coun-

(01)00301234567896
(21)000000000017
(17)190519
(10)LN001

Figure 1 Example of a GS1 Compliant Serialized Label for the USA with encoded 2-D Data matrix code on left

tries have adopted different standards around unique identifiers (serial numbers) and regulatory reporting which must be strictly adhered to. Some countries require aggregation: the reporting of the parent-child association between packaged items (lowest saleable unit) and the next box or packing unit it goes into (case or bundle) all the way to the pallet. Aggregation helps subsequent buyers of serialized product scan the outer-most barcode and know all the individual items and groups packed within it. Although aggregation is not a requirement in the European Union or United States, many major drug distributors (e.g., Amerisource Bergen, Cardinal and McKesson) have requested their customers ship aggregated products to aid in efficiently identifying serial numbers within pallets and cases of received shipments and inventory.

Serialization is having a ripple effect throughout companies by changing the way pharma companies manufacture along with their product labeling and packaging operations. Regulatory compliance is now more complex, as is IT integration with other systems and trading partners for exchanging serialized data about transported goods. Companies should take care to analyze the commercial markets where they exchange their products to make sure they are up to date and compliant. **Table 1** covers some of the major pharmaceutical markets in the world and the serialized laws that have been passed.

“Serialization is having a ripple effect throughout companies by changing the way pharma companies manufacture”

Over the next decade, there will be a seismic shift in how pharmaceuticals are manufactured, packaged and distributed throughout the world. Ultimately, the regulatory laws governing each country will have a ripple effect within companies, affecting everything from the redesign of labels to accommodate required serial numbers and barcodes to the exchange of transactional information between trading partners like wholesalers and pharmacies. Care should be taken to understand, leverage and adopt standards (such as GS1 standards) to meet these challenges and provide a framework for future compliance. Aggregation has the potential to add more complexity and cost to the serialization process, and companies should plan accordingly as this is increasingly becoming a requirement. Finally, although the

countries mentioned in **Table 1** are proactive in their measures to secure the drug supply, one should consider serialization an evolving compliance issue in which change is inevitable.

But do not make the mistake of sitting on the sidelines to see the eventual outcome. The laws and penalties for not complying with serialization today are severe and costly, consequently, they should be followed as stringently as possible.

About the Author

Darryl Peterson is a Key Account Manager for Antares Vision of North America, which develops hardware and software solutions for visual inspection, track and trace, and data management for life science companies. Previously, he was Vice President of Business Development at another serialization company known as rfxcel corporation.

Table 1 Sampling of Global Serialization Regulations

Country/ Region	China	Brazil	United States	India	European Union (Falsified Medicines Directive)
Local Regulatory Body	CFDA	ANVISA	U.S. FDA	DGFT	EU Commission, Each EU Country member has a national database where serial numbers are stored
Status	Law enacted, under review	Issued	Law enacted	Law enacted	Issued
Scope	Serialization aggregation to bundle/case. Required reporting.	Serialization, aggregation and reporting	Serialization, product tracking and reporting	Serialization, reporting	Serialization, product tracking and reporting
Products	All pharmaceuticals	Selected list of pharmaceuticals	Most prescription pharmaceuticals	All pharmaceuticals	Selected list of pharmaceuticals
Supply Chain Effects	Manufacturers, wholesalers, distributors and pharmacies	Manufacturers, importers, distributors, pharmacies	Manufacturers, wholesalers, repackagers, Dispensers	Manufacturers, wholesalers, distributors, dispensers	Primarily manufacturers, dispensers
Serial No. Format	20-digit drug supervision code issued by CFDA (e-Code). Items, bundle and cases all require e-code. Pallet level can have SSCC code	GS1 standard up to 20-digit serial number	GS1 standard	GS1 standard	GS1 standard with random serial numbers generated
Notification Standard	Manual uploads to Chinese system	All supply chain members report to ANVISA	Transaction information, history and statement (TI, TH, TS) for each change of ownership currently required. Each supply chain stake holder to maintain records of transactions	Manufacturers reporting to DAVA	Manufacturer reports to EU hub
Key Milestone Deadlines	Dec. 31, 2015 for all pharmaceutical products	De. 28, 12/16 New law 13.410 signed. April 2017 ANVISA releases first technical specification. April 28, 2018 end of piloting phase for selected manufacturers. Dec. 28, 2018 ANVISA expected to release final technical specification. Dec.28, 2021 full compliance requested.	Nov. 27, 2018- Serialized codes on all products by manufacturers and repackers. Nov. 2019 Wholesalers can only receive serialized products, Nov. 2020 Dispensers can only receive serialized products. Nov. 2023 "Interoperable system" for complete traceability	Oct. 2013- Serialized codes on all products by manufacturers April 1, 2016 reporting from large manufacturers. April 1, 2017 reporting from small-scale manufacturers	Feb. 9, 2019 serialization and reporting
Notes	China has opted to generate serial numbers at the government level directly to companies. Dedicated animal product healthcare has also been enacted. QR codes are used for baby food.	This is the second attempt to clarify previous legislation around serialization in Brazil.	Aggregation not mandatory, but commonly implemented for wholesaler convenience	Law only pertains to products exported out of India. Ministry of Health is considering adding aggregation. Regulation for domestic market is under development	Tamper evident features mandatory on packaging; aggregation not mandatory

Pharma Must Work "Smarter" in New Era continued from page 23

generation by a smart factory is no easy task when using traditional systems. This has led to reliance on big data systems, which requires significant resources to data and AI ecosystem, including specialized staff and expensive technology.

The smart alternative is to delegate heavy data processing to already-existing cloud services. Using cloud technologies produces better, high-quality products through efficient processes that are not complex and do not require powerful computation centers. When cloud computing is used, previously hard-to-understand variables within the manufacturing process transform into calculable solutions that define the future state of the processes. Cloud computing encompasses pattern recognition, automatic outlier identification, anomaly detection, neural networks and clustering and classifier algorithms. Other common analytic tools are Golden Batch Fitting, root cause identification for CAPA, cleaning process optimization or continuous manufacturing support. The common denominators in all use cases, however, are complexity, large numbers of involved variables, a huge amount of data that must be managed, and regulated requirements.

Elephant in the Room: Regulators

Whether a company invests in big data architecture or relies on cloud computing, the rules of GxP still apply. Some regulatory agencies and pharmacopoeias have already started to address this area. For example, the European Pharmacopoeia has included two frequently used ML and DL algorithms as valid chemometric techniques for processing analytical datasets.

Additionally, when information is processed under a regulated framework, the data, metadata, and the operation to transform it into knowledge must obey data integrity rules. With this in mind, the UK MHRA published the "GxP Data Integrity Guidance and Definitions" this past March. These guidelines introduced cloud systems consumed as services as valid computerized systems to manage the regulated information under the principles and recommendations included in the document.

To be fully accepted in the contexts of biotechnology and pharmaceuticals, the IIoT devices, the ecosystem of infrastructure, platforms and required computing to perform analytics, must be qualified and validated using the same criteria that has been applied for years. The digital transformation also applies to the quality system that wraps the entire process. The new players involved in the big data and cloud computing must understand the regulatory requirements when they work on GxP environments. Factories are evolving toward a state where everything is monitored and measured. Yet the end goals remain efficient, accurate, secure and traceable data and product/process quality.

[Editor's Note: A follow-up article from the author will address the impact of data integrity on big data**.]**

About the Author

Toni Manzano is Chief Scientist Officer for bigfinite, a company that provides cloud, big data and AI services for biotech and pharma companies.

A Risk-Based Approach to Supplier Management

Roche/Genentech's Ralph Quadflieg Discusses the Company's Supplier Oversight

Rebecca Stauffer and Aneeta Mathur-Ashton, PDA

As the supply chain grows ever more complex, firms must closely monitor suppliers of raw materials, APIs and excipients. ***Ralph Quadflieg,*** *PhD, Global LPS Lead for External Quality, Roche/Genentech, will present his company's risk-based approach for managing APIs, excipients and primary packaging materials, providing best practices for managing a large portfolio of materials and suppliers, in the session, "C5: Ingredient Supplier Oversight," Sept. 25, 4 p.m., at the* 2018 PDA/FDA Joint Regulatory Conference *in Washington, D.C.*

Recently, he provided some information from his talk to the PDA Letter.

PDA Letter: How does Roche/Genentech conduct supplier risk assessments?

Quadflieg: Our Roche/Genentech supplier risk assessment truly focuses on the capabilities of our suppliers to deliver according to what we need. We carefully assess our suppliers' capabilities—the better these are, the lesser the risk. A key part of this risk/capability assessment is identifying discrepancies with materials coming from our suppliers, either in incoming control or during production.

Market complaints, whether from suppliers or about the materials, are also considered in this assessment. Take safety needle syringes; if we get a market complaint that the needle is blunt, and it is due to a supplier, the market complaint will be included in the risk assessment.

Another aspect is that we conduct onsite audits with at all or most of our suppliers, examining their controls, manufacturing processes and quality systems. If we find observations, we write them up. Open major observation representing gaps in the production and control systems are also part of this supplier risk assessment/capability assessment.

In general, the more discrepancies we find, the more market complaints we receive, and the more open audit observations we see, we increase the risk of those suppliers.

However, supplier risk is only one element; we also pair that with our material risk. For example, when we receive sterile primary packaging materials like ready-to-fill syringes, there is a higher risk than for primary packaging materials we sterilize ourselves. The combination of the material risk and the supplier risk determines our risk-based approach for global supplier quality management.

PDA Letter: How do you audit the suppliers' suppliers?

Quadflieg: As a matter of fact, our team discusses this a lot. I would like to give you an example: needles are mostly delivered sterile into our facility, so we deem the sterilization process as one of the very critical process steps. Sometimes, however, this sterilization process is not performed by our suppliers because they outsource it to service providers. In this example, when we initially qualify a new supplier, we do one initial audit at the sterilization service provider, mostly together with our supplier jointly, and we look into the sterilization process, including control steps, validation, etc., of the service provider which is an onsite audit of this subsupplier.

PDA Letter: Do you use a specific tool to review supplier qualifications?

Quadflieg: We have several databases that we use. One key element is our Trackwise Audit Tool; we use it to manage our audits as well as the annual audit plan. We use our risk management tool to determine the frequency of supplier audits. One key aspect of supplier management is that for all our suppliers and materials we have a holistic overview of which supplier is supplying what for which product. We use this information to assign the material risk and together with the supplier risk that I've described earlier, we derive the audit frequency for our annual audit plan.

PDA Letter: How does this take into account the recent EU requirement to include completed risk assessments for each excipient?

Quadflieg: The EU excipient risk assessment really fits well into our own Roche/Genentech direct material risk assessment. [This meant] there were only few elements we had to add to our existing material risk assessment process to fully comply with the excipient risk assessment as described by the European Union.

Factoring in a Lean Mindset

PDA Letter: How do lean methods come into play with this approach?

Quadflieg: There are two dimensions of lean that we have applied in supplier quality management. One dimension is purely internal: how can we at Roche/Genentech be lean? How can we reduce waste? How can we continuously improve our own processes? How we plan audits, how we qualify API, excipient, and primary packaging material suppliers, how we do supplier risk assessments? This is one very important element for ourselves for deploying lean elements. Traditionally, because we are working with our suppliers to continuously improve their quality, we have built significant experience with lean six sigma in our quality department. And, of course, we are taking advantage of these skills and expertise when working with our suppliers and internally when we improve our processes.

And very important for us, is the other dimension, the external view with regard to our suppliers where we strive to continuously improve the material quality our suppliers deliver to us, meaning reduced material defects, reduced material deviations and reduced market complaints. We are also working on a zero-defects mentality with selected strategic suppliers and have started to implement quality-by-design elements and development processes for raw materials at our suppliers.

> **When we audit our suppliers, it is more than just looking into the quality systems**

These are the two dimensions that we look at when it comes to lean. One is internal, how to continuously improve our processes, how to identify waste in our processes and reduce that, and the other element, working with our suppliers to continuously improve the direct material quality they deliver to us.

PDA Letter: What part of the audit process does Roche/Genentech place the most value on?

Quadflieg: A while ago we were discussing at Roche/Genentech how to do audits and we all quickly agreed that when we audit our suppliers, it is more than just looking into the quality systems and it is more than just looking into documentation, it is truly an assessment of whether or not our suppliers are capable to manufacture and control the materials they deliver to us.

We are training our auditors to focus on the manufacturing and control processes at our suppliers…this is where we place the most value: understanding the critical process steps at our suppliers and understanding how well they are controlled. This helps us to assess how much risk we have of receiving materials that do not meet to our needs.

Program Success Built on Trust

PDA Letter: How challenging is it to implement this approach across a global organization?

Quadflieg: I think this only works when people are working with each other, not only the leaders, but everyone across the entire global organization. This way all the people in an organization have the chance to build up trust and build up relationships to work with each other and rely on one another's expertise.

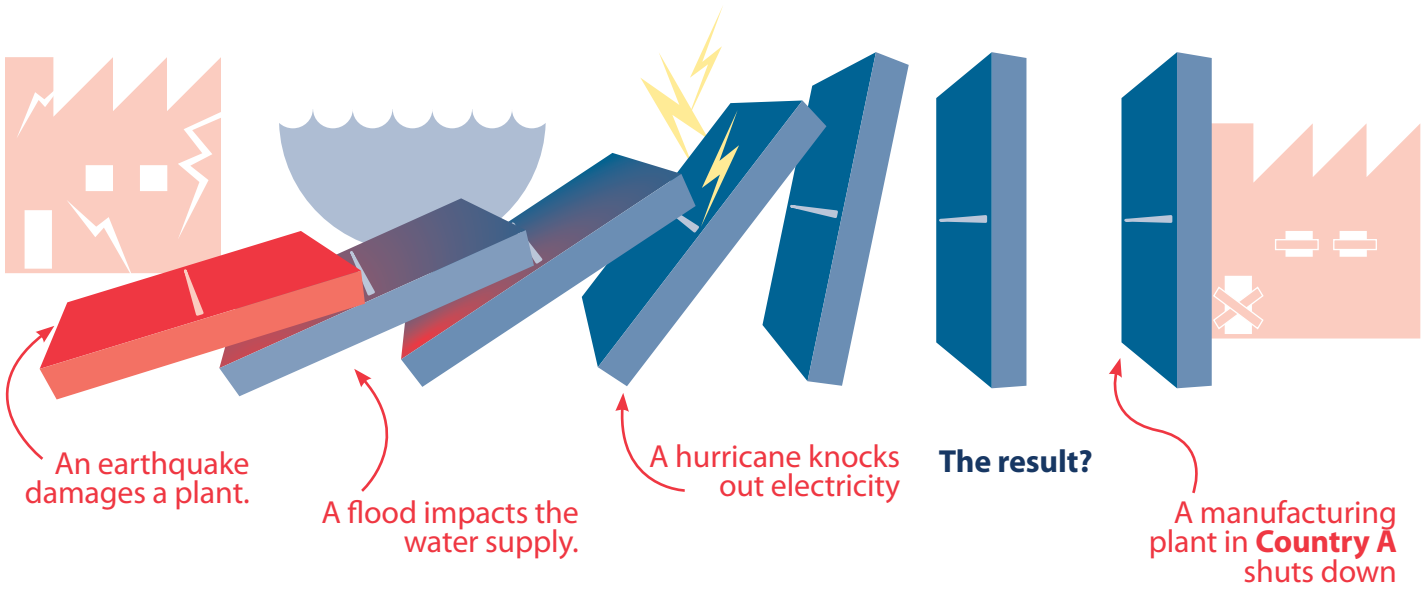
We are organized in regions, which means, for example, our Genentech colleagues conduct all the audits in the Americas for suppliers in that region. And here, in Europe, we perform all the audits for the European-based suppliers disregarding to where they deliver.

We constantly exchange on all levels in our team, e.g., our auditors have an audit calibration workshop at least twice a year where all auditors from all regions, including our Asia/Pacific hub, discuss the audit process and audit observations, such as how they rate them. Not only do they calibrate themselves, but they also identify continuous improvement opportunities for the audit process. This is how we foster collaboration across all regions. To us, this is one element, building that trust to work in that global environment.

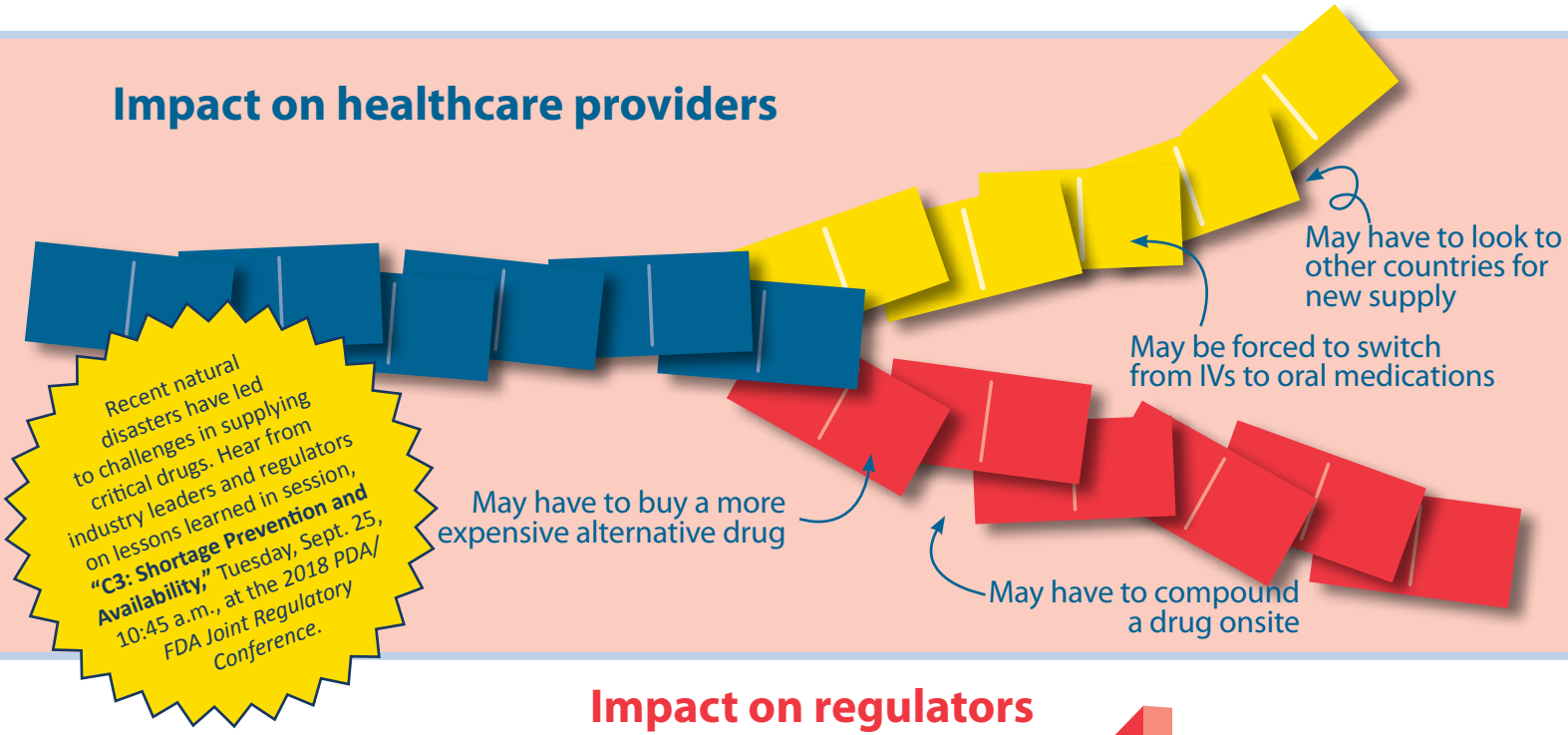
About the Expert

Ralph Quadflieg, PhD, is currently Global LPS Lead for External Quality at Roche/Genentech. Previously, he oversaw different areas of responsibility at Roche/Genentech's supplier quality, including primary and secondary packaging materials, medical devices, chemicals and biologics.

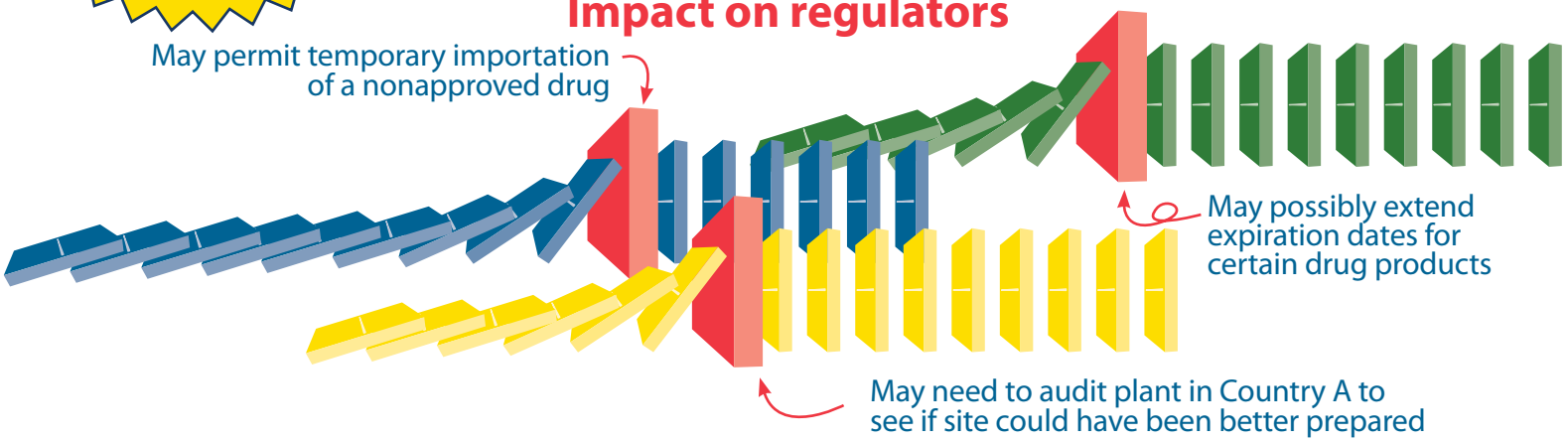
The Dominoes of Natural Disasters



Impact on healthcare providers



Impact on regulators



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2018 PDA FALL COURSE SERIES

Find out about our 2018 Fall Course Series!

This October and November, PDA is offering six Course Series that provide industry-leading education, specially designed to equip you with both theoretical and practical knowledge.

Explore the options below to find the Course Series that best suits your need for further training and professional development:

Sterilization Course Series | **Oct. 1-3** | Bethesda, MD | ***pda.org/2018SCS***

Universe of Pre-Filled Syringes and Injection Devices Course Series | **Oct. 11-12** | Orlando, FL | ***pda.org/2018PFSCourses***

13th Annual PDA Conference on Pharmaceutical Microbiology Course Series | **Oct. 18-19** | Bethesda, MD | ***pda.org/2018MicroCourses***

Validation Course Series | **Oct. 29 – Nov. 2** | Bethesda, MD | ***pda.org/VCS***

Quality Risk Management Certificate Program | **Nov. 5-8** | Bethesda, MD | ***pda.org/2018QRM***

Environmental Monitoring Course Series | **Nov. 13-15** | Bethesda, MD | ***pda.org/2018NovEMCS***

To learn more and register, visit PDAtraining.org

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PDA is an accredited provider of continuing education, offering high-quality, relevant training for both new and experienced professionals working in industry, government (health authority), and academia. Visit ***pda.org/courses*** for more information.

CONNECTING PEOPLE **SCIENCE** AND REGULATION®

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Medical and technological advances are revolutionizing patient treatment options, creating new challenges and opportunities for the parenteral packaging market.

PDA is a recognized leader with longstanding expertise and focus in packaging science. In light of new developments and the dramatic impact of primary packaging on the safety and efficacy of drug product, PDA is intensifying its efforts to provide the most up-to-date tools and resources to the industry.

A snapshot of PDA's extensive offerings includes:

- **Global Conferences and Workshops** on topics such as glass quality, parenteral packaging, container closure integrity testing, and pre-filled syringes
- A broad array of **Topic-specific Training Courses**
- **Technical Reports and Resources,** both already published and under development
- **Interest Groups** dedicated to addressing pharmaceutical packaging issues
- **The Ed Smith Packaging Science Award,** granted annually to recognize outstanding contributions to PDA and Pharmaceutical Packaging Science

To find out more about how PDA is leading the way to improved patient safety through better pharmaceutical packaging processes and practices, please visit www.pda.org.

PDA – *Connecting People, Science and Regulation®*

SNAPShot

2018 PDA/FDA Joint Regulatory Conference

IG Corner
Meeting Preview

Interest Group Schedule

In addition to afternoon sessions, interest group meetings are scheduled for lunch breaks during this year's *PDA/FDA Joint Regulatory Conference.* Below is a schedule of meetings for regulatory-focused interest groups.

Monday, Sept. 24	Tuesday, Sept. 25
12:30 p.m. – 1:30 p.m.	**12:30 p.m. – 1:30 p.m.**
Pharmacopoeial Interest Group Regulatory Affairs Interest Group Supply Chain Interest Group	GMP Links to Pharmacovigilance Interest Group Inspection Trends Interest Group
5:45 p.m. – 6:45 p.m.	**5:45 p.m. – 6:45 p.m.**
Quality Risk Management Interest Group *(joint meeting with Environmental Monitoring/Microbiology Interest Group)* Management of Outsourced Operations Interest Group	Data Integrity Interest Group Quality Systems Interest Group Technology Transfer Interest Group

The schedule for science- and biotech-oriented interest group meetings can be found on p. 18.

Viscous Product No Match for New CCI Tech continued from page 19

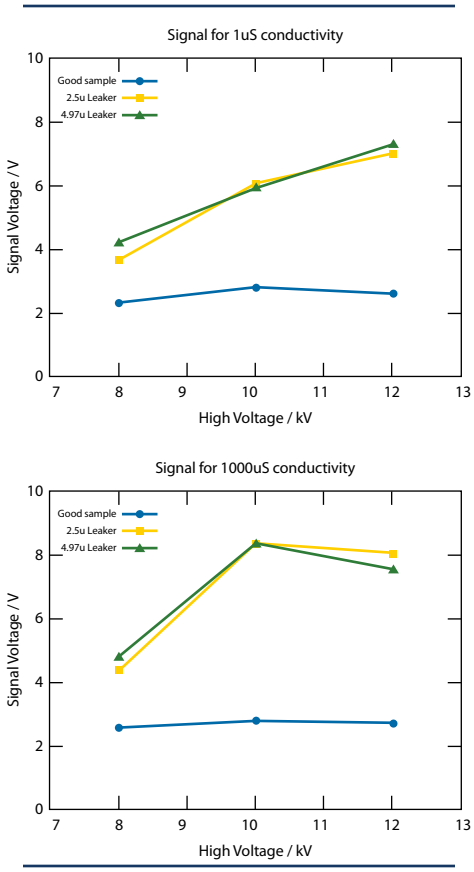


Figure 1 Samples with 1µS and 1000µS Inspected for CCI Using MicroCurrent HVLD

The culmination of the studies established the sensitivity and range of product conductivity that can be tested with MicroCurrent HVLD. Crack style positive control samples were created in both vials and syringes. The cracks were certified using the helium leak test method and showed defect flow rates to below the one micrometer diameter defect size. The results produced reliable detection of micro leaks down to helium leak rates of 0.25 10-5 mbar·l/sec (equivalent to a 0.15 micrometer pinhole) placing the MicroCurrent HVLD test method at the forefront of CCI test sensitivity.

Sensitivity of a test method is crucial to providing greater assurance against the risk of microbial ingress. The results using a range of products and defect types accurately determined CCI across the full range of sample sets. While the sensitivity of a method is crucial, the reliability of a test method is at the very foundation of the container closure integrity testing.

These studies suggest that MicroCurrent HVLD technology could help ensure container closure integrity of new types of drug products with viscous formulations. No matter how innovative the drug product or packaging, container closure integrity will remain a critical part of ensuring the sterile barrier.

[Editor's Note: Additional figures and images can be found in the online version of this article**.]**

About the Author

Oliver Stauffer joined PTI in 2005 as a member of the research and development team working on nondestructive testing of high-risk pharmaceutical packaging. During his time with PTI, he has developed several technology platforms, measurement methodologies, and technology patents. In 2016, he was appointed as CEO.

Visual Inspection Remains Critical

John Shabushnig, PhD, Insight Pharma Consulting, and Markus Lankers, PhD

Visual inspection and the detection of particles remain at the forefront of product manufacturing control, quality assurance and regulatory compliance. From 2010 to 2017, 48% of all injectable product recalls in the United States were associated with visible particulate matter. Particle-related recalls reached a high of 25 in 2014. Since then, the number of recalls and FDA 483 observations has continuously decreased. This may be due, in part, to the introduction of improved regulatory guidance as found in USP <790> Visible Particulates in Injections and <1790> Visual Inspection of Injections, in addition to better understanding and greater emphasis by the pharmaceutical industry.

The long-awaited draft revision to the EU GMP Annex 1 guideline was published in December. New expectations for visual inspection have been included in its brief chapters on the topic. Further discussion, however, is needed to better understand and implement these changes to Annex 1.

Since 2000, PDA has organized the *Visual Inspection Forum* to discuss new technical and regulatory developments in this field. This annual meeting alternates between the United States and Europe. This year it returns to Berlin. At this meeting, experts will discuss new developments in the field of visual inspection, including a basic understanding of the inspection process, special requirements for difficult-to-inspect products, practical aspects of manual and automated methods, and regulatory and compendial requirements like those found in the update of Annex 1. Discussion of recently published PDA technical reports on particle control in difficult-to-inspect products and nonconformities in elastomeric closures are also on the agenda.

This is an excellent opportunity to learn more about visual inspection and to discuss inspection challenges with the experts. The meeting will conclude with a roundtable discussion on topics of specific interest to those in attendance. As in past years, the meeting will feature an exhibition where attendees can see the latest in commercial inspection hardware and discuss production needs with key suppliers of inspection systems and services.

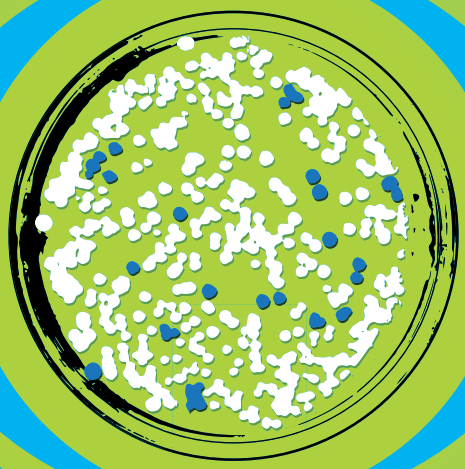
2018 PDA Visual Inspection Forum

Berlin
Oct. 23–26
www.pda.org/EU/VIF2018

PDA Europe Conference, Exhibition, Education

Pharmaceutical Microbiology

17-18 October Berlin, Germany	Training Course **Rapid Microbiological Methods**
17-18 October Berlin, Germany	Training Course **Best Practices and Points to Consider in Aseptic Processing**



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15-16 October | Berlin | Germany

15-17 October | Bethesda | USA

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pda.org/EU/PharmaMicro

2018 PDA/FDA Joint Regulatory Conference

Quality/Compliance Management for Virtual Companies

David Chesney, DL Chesney Consulting

Today, many companies operate on an outsourcing model. This is very common for companies with plans to have a product ready for market approval in the coming months. Most of these companies are small and may not have deep expertise in QA and GMP compliance, instead, relying on their partners to cover those areas.

In spite of the advantages of outsourcing, companies still remain responsible for the quality and compliance status of the products that enter the marketplace.

Quality and Compliance Management for Virtual Companies

Washington, D.C.
Sept. 27–28
www.pda.org/2018regcourses

How can companies learn how to address the GMP needs of outsourced operations? In the new PDA Education course, "Quality and Compliance Management for Virtual Companies," following the *2018 PDA/FDA Joint Regulatory Conference,* attendees will learn about U.S. FDA and other global regulatory expectations for these "virtual" companies. These expectations include diagnosing a company's needs based on which GMP-governed operations are retained and which are outsourced, identifying best industry practices for selecting, qualifying and monitoring contractors to ensure they meet requirements and designing a quality system framework that has the structure and integration to "grow with the company" as the scope of operations changes over time.

Participants in this course will:

- Recognize the GMP requirements all virtual companies must meet regardless of the extent of their outsourcing operations
- Learn which elements to include in a quality agreement (also known as a technical agreement)
- Determine which GMP requirements apply to the contract giver
- Understand the legal obligations for products released to the marketplace
- Appreciate the importance of maintaining data integrity
- Learn what to expect from an FDA or other health regulatory inspection, including the usual scope of virtual company inspections and why they occur, effective responses to document requests and inspectors' questions, the inspection exit discussion, effective responses to observations and applicable FDA, EMA and Health Canada inspection references/procedures.

Virtual companies may outsource

responsibilities to others but still retain legal *Responsibility* for the outcomes. Compliance requires an understanding of which requirements apply to the company and which apply to vendors. Understanding those requirements assures that the company remains compliant and can better successfully manage the vendor relationship to assure product launch.

About the Author

David Chesney is the Principal and General Manager of DL Chesney Consulting, LLC. His career includes 23 years with the FDA and over 21 years in GMP and GCP consulting worldwide. His career includes 23 years with the FDA and over 21 years in GMP and GCP consulting worldwide.

Interested in learning how to get out from under a consent decree?

The author will present his talk, "Anatomy of a Consent Decree," in session "B2: A Successful Journey under Consent Decree," 4 p.m., Sept. 24 at the *2018 PDA/FDA Joint Regulatory Conference*

Blockchain continued from page 40

with any other emerging capability," said D'Alessandro. "It is also important to partner with out-of-industry experts who have technical know-how to share. The more our ecosystem of companies, partners and practitioners learns and works together, the faster the innovation, growth and adoption curve for blockchain will be."

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About the Author

Mark Crawford is a professional business and technology writer in Madison, Wis. He is also the author of five books on science and American history.

Are You Ready for the eCTD Mandate?

Mckenzie Orchowski, Biologics Consulting

Regulatory submissions to the U.S. FDA for NDAs, BLAs, and ANDAs must be submitted in electronic Common Technical Document (eCTD) format. This requirement has been in place since May 5, 2017, per the timeline set forth in the "umbrella" guidance ***(1)***.

Large pharmaceutical firms have made great progress toward the successful adoption of the appropriate processes, standards and technology needed to meet this deadline. But small, early-stage biotech companies struggled with the transition. To accommodate them, the Agency allowed commercial INDs and Master Files to be submitted in paper format until May 5, 2018. Less than two weeks before this date, FDA announced an extension of the eCTD deadline to May 5, 2019 for Type III DMFs. With this new extension, what insight can late adopters learn from the companies that paved the way?

First, the most crucial element that should be taken into consideration prior to submitting in eCTD format is the selection of the publishing software. Does the company want to purchase an in-house system or use Software-as-a-Service (SaaS)? For many years, smaller firms watched as early adopters (primarily large pharma companies) invested hundreds of thousands of dollars on the purchase, implementation and ongoing maintenance of on-premise solutions. This requires significant upfront spending to cover the costs associated with project management, as well as the procurement of additional IT resources dedicated to managing the server, applying patches/fixes and overseeing major upgrades. Unfortunately, such costs were hard for smaller firms to justify. Luckily, the rise of SaaS and cloud-based computing has caused a fundamental shift in the industry. SaaS allows users to connect to and use internet-based publishing software hosted by a third-party provider, usually via a remote desktop connection or Web browser. High overhead costs are shifted to the provider, and the pharmaceutical firm simply pays a monthly or annual subscription fee per user. Late adopters of eCTD with limited resources can benefit from this cost-effective alternative, and a growing number of software vendors now exist to meet the increasing demand.

The next step is to search for possible software vendors. You may choose to send them an informal Request for Information (RFI) to help narrow your options to a "short list" of three to five potential candidates who will receive a formal Request for Proposal (RFP). Keep in mind that several approaches to RFPs are available. Traditionally, an RFP outlines very specific rules regarding content procurement and provides a strict deadline by which all vendors must respond. On the other hand, some companies are opting for software demonstrations, either onsite or via a webinar, in lieu of an RFP.

Final steps involve selecting the winning vendor and negotiating a contract. Once the software is purchased, implementation can take anywhere from a year or more (for an in-house installation) to a matter of weeks (for a SaaS solution). This timeframe is highly dependent on how you choose to interpret 21 CFR Part 11.

21 CFR Part 11 Compliance is Key

There is considerable ambiguity surrounding 21 CFR Part 11, especially as it relates to publishing software. For those unfamiliar with Part 11, it is the 1997 regulation that defines the requirements for the control of electronic records and electronic signatures, as well as the computer systems used by pharmaceutical and medical device companies ***(2)***. As companies started making the transition from paper to PDF, FDA sought to ensure patient safety to prevent electronic documents from being compromised through Part 11.

The industry seems to unanimously agree that Part 11 applies to document management systems. It is unclear, however, if the regulation also applies to publishing software. Every eCTD tool is different, but many do not create or store documents—they merely point to a file and reference its location via the xlink:href leaf attribute. In this case, a company could perform an internal GxP criticality assessment of

Complete outsourcing helps to circumvent the high costs associated with software and talent acquisition

the publishing system and deem it low-risk. Such a classification would provide justification for an abbreviated approach to validation (e.g., a brief "approved vendor" statement and some informal User Acceptance Testing). The key to overall Part 11 compliance is defining realistic expectations for your organization.

Once the new system has been implemented, existing employees will need to be trained on your new publishing software. Proper compilation of an eCTD submission requires a unique skillset, one which may not be found in an individual who is only familiar with paper dossiers. An outside hire may be necessary.

A unique challenge faced by small companies employing one full-time publisher is the lack of additional regulatory operations personnel to QC their work. Even the best publisher is bound to make a mistake in an eCTD submission with hundreds (or thousands) of bookmarks and hyperlinks. In this case, cross-training involving regulatory affairs or administrative staff is recommended.

Content contributors within your organization, such as CMC experts and medical writers, will also need training on basic eCTD concepts, and should be taught how to author eCTD-appropriate cross-references.

3 Ways to Review eCTD Submissions

Internal review of an original application or large lifecycle submission in eCTD format always takes much longer than anticipated. Content changes to approved documents (after they have been added to the eCTD XML backbone) can have wide-sweeping consequences, especially when the page count shifts. One additional sentence can potentially affect hundreds of bookmark and link destinations.

There are three ways to review an eCTD submission: (a) navigating through the folder structure in Windows Explorer, (b) opening the index XML in Internet Explorer or (c) with eCTD viewing software. The first method is not ideal because document metadata and lifecycle information are only stored within the XML. The second method is an improvement, but you can only view one sequence at a time, and the current version of eCTD (v3.2.2) does not always display regional XML and study tagging files correctly, depending on your version of Internet Explorer and/or Adobe Acrobat. Furthermore, the next major update to eCTD (v4.0) does not provide a stylesheet and will render the second method obsolete in the coming years.

The third method offers more benefits. The main advantage to the third method is that an eCTD viewer can display the entire application at once (i.e., all documents from all sequences), enabling you to quickly determine which documents are no longer relevant to your review. Any employee who will be expected to review eCTD submissions on a regular basis should have access to an eCTD viewer. Standalone viewers are available, but most publishing software is now built with viewer licensing in mind.

Considerations for Outsourcing

Some of the early adopters now supplement their internal publishing efforts by outsourcing certain types of documents and/or entire submissions. Complete outsourcing helps to circumvent the high costs associated with software and talent acquisition and is an attractive option for small companies expecting a low output of eCTD submissions each year.

If you decide to outsource all publishing activities, certain employees at your firm will still benefit from training on the fundamentals of eCTD. These individuals include all document authors and anyone who will interact with your assigned project manager. Effective communication with your project manager regarding upcoming submissions, the content of those submissions and any timeline expectations you may have is key for an effective working relationship.

The last piece of the puzzle is submitting your final eCTD output through the Electronic Submissions Gateway (ESG). Before you can access the ESG website, you must obtain a WebTrader production account. This involves purchasing a personal digital certificate, which will be used to encrypt each submission before it is transmitted to FDA. Navigating this setup process can be challenging, even for the most tech-savvy users. Some companies with an in-house publishing team choose to outsource ESG submission, while others take the reverse approach. If you are considering outsourcing in any form, keep in mind the top consulting groups are often the busiest and will need to be booked early, well before the final May 5, 2019 deadline.

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About the Author

Mckenzie Orchowski is an Electronic Publishing Specialist at Biologics Consulting, a full-service regulatory and product development consulting firm for biologics, pharmaceuticals, and medical devices. She has over six years of experience in regulatory operations and is proficient in assembling complex clinical trial authorizations and marketing applications in eCTD format.

Dual Background Shapes RAQAB Experience

Steve Lynn

I am very humbled and honored to serve my fellow PDA members on the Board of Directors and Regulatory and Quality Advisory Board (RAQAB).

A little over four years ago, I left the U.S. FDA to pursue endeavors in the private sector. This decision did not come lightly. I was leaving a great team at the FDA—one dedicated to quality pharmaceuticals and protecting patient health. Once I joined the industry ranks, however, I quickly realized that I went from one great team to another. This new team was also dedicated to the same patient-centric objectives but from a slightly different angle. Quality and patient health/safety were still of paramount importance, but instead of overseeing the pharmaceutical industry as a regulator, I was now on a regulated team dedicated to developing, manufacturing and delivering innovative pharmaceuticals to patients around the globe.

As I adjusted to this new role, I was invited to join RAQAB. I jumped at the opportunity because I wanted to collaborate with other quality and regulatory professionals and help influence issues affecting our entire industry. RAQAB's mission is to serve the PDA membership by influencing scientific-based regulations and providing interpretation on quality and regulatory issues affecting development, manufacturing and control of healthcare products. This means working with global regulatory bodies, including FDA, EMA, etc.

My experiences as a regulator, coupled with my experiences on the regulated side, serve me well on RAQAB because I can oftentimes see both sides of the equation. For example, I can understand why a regulatory agency may write something a certain way in a guidance versus the way it could be interpreted by industry. This dual-empathetic perspective can help how we in industry comment on a regulatory document or drive an internal PDA initiative on the issue at hand. Additionally, having other professionals and ex-regulators on RAQAB to discuss, debate and determine the best PDA viewpoint on an issue helps me to become a more well-rounded professional and better assist the companies with which I am associated. It is a wonderful symbiotic relationship.

If you are interested in someday joining the ranks of RAQAB, I encourage you to volunteer. RAQAB is always looking for volunteers to help with regulatory comments and key documents such as technical reports, Points to Consider papers, etc. For those of you new to volunteering, contact PDA's Volunteer Coordinator (volunteer@pda.org).

I am proud to share by dual experience with RAQAB. Volunteering with PDA has truly opened doors for me. I encourage you to follow in my footsteps.

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