People • Science • Regulation

PDA Letter

Volume LV • Issue 7 www.pda.org/pdaletter July/August 2019

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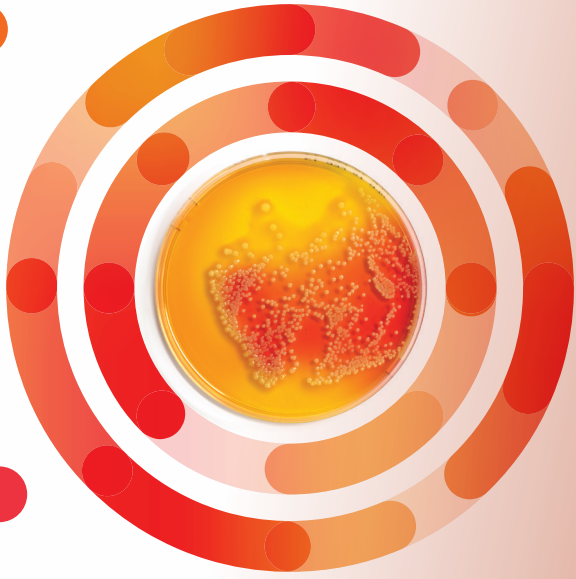

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July/August 2019 PDA Letter

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Learn what to expect at the *2019 PDA/FDA Joint Regulatory Conference* in our special section.

DATA INTEGRITY

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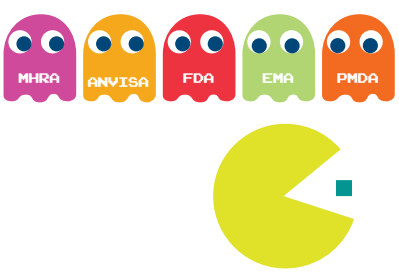

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Departments

Digital Exclusives

> **On the Issue** | Here They Come: Pharma Young Professionals
West Pharma's **Amy Kim** and Biogen's **Maria Bednar** discuss their Young Professionals presentations at the *2019 PDA Annual Meeting.*

> Excipients' Attributes Crucial for Parenteral Preparations
Learn why quality attributes are important for the excipients used in our industry.

> SoCal Student Chapter Keeps Busy
Find out what the PDA Southern California's student chapter has been up to!

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Data Integrity: A Hot Button Issue

Rebecca Stauffer @RebeccaStauPDA

Data integrity is always a popular topic with our readers, so I was excited to put together an issue around the topic, although perhaps "excited" is not the best word to use when it comes to data integrity. After all, it is a focus of concern for many regulatory agencies, including the U.S. FDA, who issued a Q&A guidance in December ***(1).***

To keep readers informed, I have attended many PDA conferences featuring talks on the topic, including a 2016 workshop in London ***(2).*** From these presentations and also from talking with members of PDA's Data Integrity Task Force, it has become clear to me that data integrity must be supported by all levels of an organization.

Data has always been important, even in the days of paper-based recordkeeping. As labs become increasingly paperless and automated manufacturing systems more prevalent, data and analytics are taking center stage. Throw in cell and gene therapy manufacturing, personalized medicines and other types of small batch manufacturing and data integrity is now more critical than ever.

Fortunately, this issue's cover story on page 26 features a good overview on the current state of data integrity. The second feature from **Ann Milliman** at Baxter (p. 32) offers some strategies for handling audit trail reviews. The third feature, from members of the planning committee behind this year's *PDA Data Integrity Workshop,* looks at the impact of big data technologies on data integrity strategies (p. 36).

Speaking of the latter article, consider attending the *2019 PDA Data Integrity Workshop* in September. Data integrity will also be addressed at the *2019 PDA/FDA Joint Regulatory Conference.* I will be at both events, so if you see me, feel free to let me know what you think about the Letter.

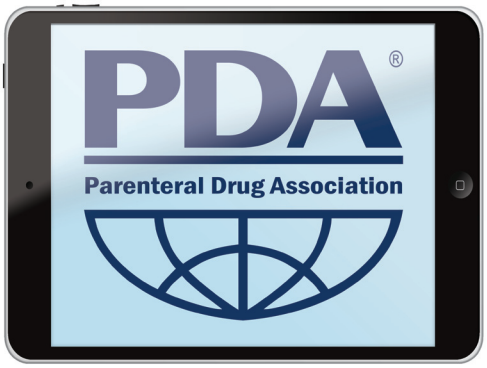
Before I close out this message, I want to introduce **Madeline Cusick,** our summer intern. Currently, she is a junior at Georgetown University majoring in English and interested in journalism. She hopes to learn as much as possible about the intersection between science and communications in the upcoming months. Madeline has been fully involved in editing this issue and she is enthusiastic about continuing to help out with the *PDA Letter!*

Reference

1. U.S. FDA, Data Integrity and Compliance With Drug CGMP Questions and Answers Guidance for Industry, Dec. 2018 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/data-integrity-and-compliance-drug-cgmp-questions-and-answers-guidance-industry
2. Stauffer, R. "Workshop Offers DI Insights from Regulator, Industry." *PDA Letter* 52 (July/August 2016) 54.

PDA In the News

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



American Pharmaceutical Review
June 14, 2019
"Environmental Monitoring Program for Aseptic Vaccine Products"
— Randy Hutt
tinyurl.com/yxphhat7

April 23, 2019
"Focusing on the Operator: Reducing Facility Environmental Contamination"
— Tim Sandle
tinyurl.com/y3fox95h

March 21, 2019
"Applying Data Integrity Principles to the Cleanroom"
— Tim Sandle
tinyurl.com/y3e3gwv6

BioProcess International
May 15, 2019
"Integrity Redefined: Consistent Robustness and Integrity Testing Lead to Enhanced Process Integrity and Patient Safety"
— Marc Hogreve, Carole Langlois, Katell Mignot and Jean-Marc Cappia
tinyurl.com/y5s4bttv

Global Manufacturing
March 15, 2019
"Expert comment: Beyond the production line"
tinyurl.com/yxv3mgan

Healthcare Packaging
March 26, 2019
"Nonprofit Targets Drug Shortages with a New Approach"
— Keren Sookne
tinyurl.com/y5oy69m6

Pharmaceutical Manufacturing
May 6, 2019
"Learning from pharma's failures"
— Meagan Parrish
tinyurl.com/y6cwb75x

Pink Sheet
May 8, 2019
"Gene Therapy: Industry Seeks Greater Clarity In Final FDA CMC Guidance On INDs"

April 25, 2019
"FDA: Despite Improvement, Particulate-Related Injectables Recalls Remain A Concern"
— Joanne S. Eglovitch

Shore News Network
April 29, 2019
"Toms River Students Earn Rewards at Delaware Valley Science Fair"
tinyurl.com/yynya4hh

PDA TRI Wall Acknowledges Suppliers' Support

Madeline Cusick, PDA

Many PDA Education courses depend on the immense generosity of suppliers, who donate or loan both equipment and services to make these educational offerings possible. To demonstrate PDA's appreciation, PDA unveiled a special wall with plaques recognizing these contributions in June.

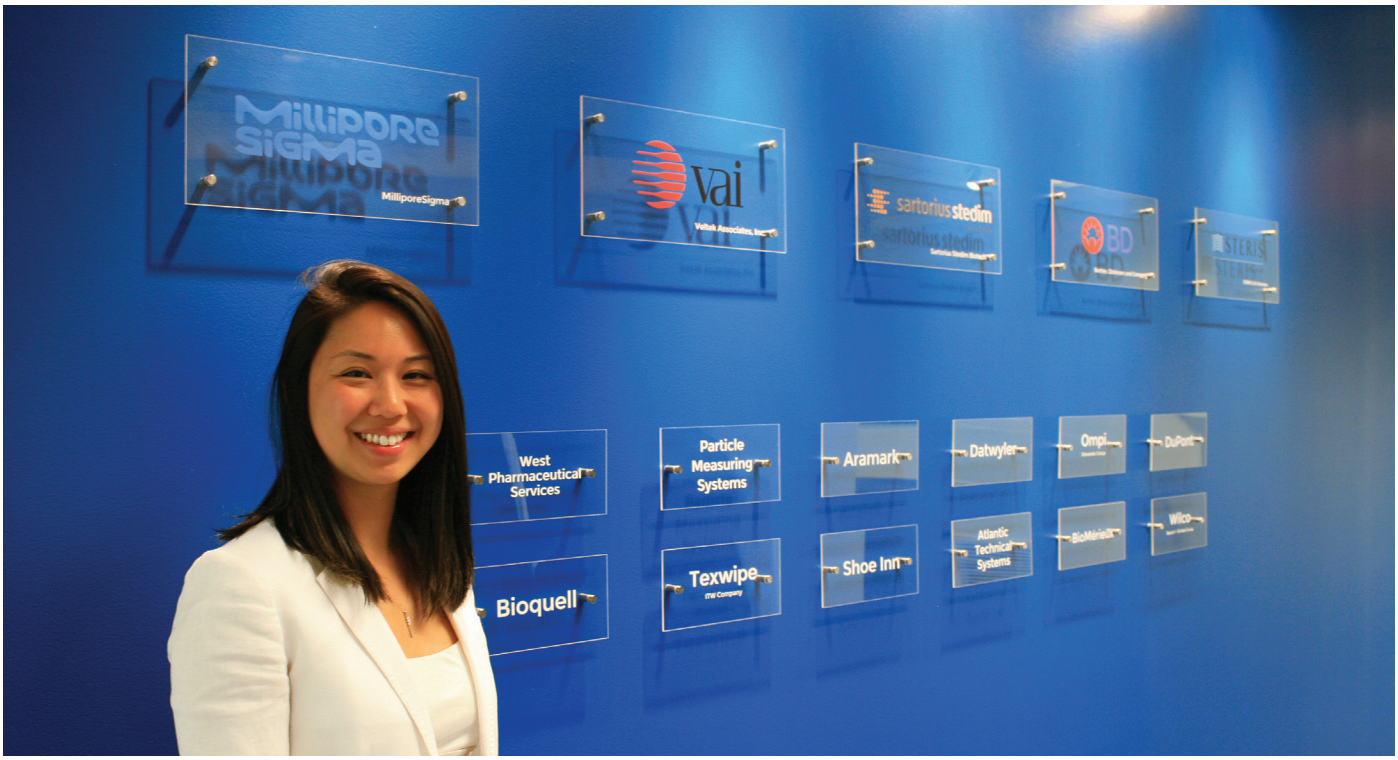
Work on the wall began last year. **Kimberly McIntire,** Manager of Education, took the lead in executing the project, and **David Talmage,** Vice President of Education, contributed significantly as well. The wall features large plaques with company logos for the five biggest suppliers. The names of the remaining suppliers are displayed below.

Recognition involves a variety of factors, such as need for the products supplied, value of the donation or loan, commitment to the task and reliability.

The wall can be seen inside the main entrance of PDA's Training and Research Institute (TRI) in Bethesda, Md.

If you are planning to attend a PDA Education course at TRI in the future, take a moment to check out this recognition for the following suppliers:

- MilliporeSigma
- Veltek Associates, Inc.
- Sartorius Stedim Biotech
- Becton, Dickinson and Company
- STERIS Life Sciences
- West Pharmaceutical Services
- Particle Measuring Systems
- Aramark
- Datwyler
- Stevanato Group
- DuPont
- Bioquell
- Texwipe, ITW Company
- Shoe Inn
- Atlantic Technical Systems
- BioMérieux
- Wilco
- Bausch + Ströbel Group



PDA's Manager of Education Kimberly McIntire poses in front of the supplier recognition wall

PDA Volunteer Spotlight

Laurie Masiello

- President
- *Masy BioServices*
- Member Since | **2010**
- Current City | **Pepperell, Massachusetts**
- Originally From | **Lynn, Massachusetts**

Mountains were meant for me to move

Why did you join PDA?
My husband and business partner, **John Masiello,** joined PDA in 1991. When we incorporated our business in 1995, I started attending meetings of the New England Chapter as a sponsor. Eventually, I became an official member of the chapter.

As chapter president, what have been some of the accomplishments that you are most proud of?
I developed the sponsorship program which gave sponsors advance notice of events and made the meetings profitable. I also created the "metallic sponsor" program for sponsors to make contributions to the scholarship fund. As a member of the chapter's Scholarship Committee, I am proud to say the chapter has awarded deserving students $18,000 in scholarships the last two years.

How can volunteers be successful with PDA?
Get involved and share your talents! You will meet new friends, learn more about your industry and develop a sense of accomplishment as part of a team that produces valuable information and creates opportunities for fellow members at different stages of their careers.

What are some of your hidden talents?
I am not sure how "hidden" my talents are, but persistence and tenacity are my strong traits. I remember my brother learning to read and I was sure I could do anything he could, so at age four I learned to read. I learned to ride a bike as he was learning. And I changed a flat tire on our family car because I watched a video in driver education class.

I am sure mountains were meant for me to move.

Tell us something surprising about you.
I stopped drinking soda in 2006 and I stopped eating chocolate in 2007.

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PDA Chapters

Your Local PDA Connection

Are you curious about the issues unique to your region?

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

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

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More than Volcanoes or Solar System Models

Delaware Valley Chapter Supports Local Science Fair

Leo Posner, PhD, Johnson & Johnson, and Chapter President, PDA Delaware Valley Chapter

Each year, 900 to 1,000 students representing grades six through 12 from schools in the Pennsylvania, Delaware and southern New Jersey area participate in the Delaware Valley Science Fair. On April 4, five volunteer judges from the Delaware Valley Chapter, **Michele Laudenslager, Nicole Shulde, Margit Olson, Traute Ryan** and **Kristi Ballard,** evaluated all of the outstanding entries, awarding over $5,000 in prize money to ten projects related to the pharmaceutical and healthcare industries.

In addition to this recognition, the chapter takes the top high school winners to the Intel International Science and Engineering Fair (ISEF) competition in May to compete for more than $4 million in scholarships and awards. Top middle school winners compete in the Broadcom MASTERS national competition.

As always, the chapter's judges enjoyed reviewing each of the science fair posters and talking with the students about their research, quickly forgetting that these presenters are in middle/high school not master's programs!

The chapter congratulates all the students who participated and especially the ten PDA Delaware Valley Chapter's Special Award Winners.

The 10 Winning Projects

An In-Silico Approach to Immuno-Oncology: Novel Small Molecule Inhibitors of the PD-1 Immune Checkpoint
Sindhura Siddapureddy — Central Bucks High School- West

Urine as an Alternative to Blood for Cancer Liquid Biopsy and Precision Medicine
Adam Zhang — Methacton High School

Programmed Apoptotic Hepatocellular Death Induced by SMAC Mimetic on SHB Producing Cells
Alec Maraska — Central Bucks High School- West

Exosomal Haptoglobin Potential as Protein Biomarker for Hepatocellular Carcinoma
Madison Charnigo — Central Bucks High School- West

The Effect of a Vegan Diet on an Omnivorous Gut Microbiome
Sarah Rojas — Germantown Academy

Effacious And Effectual Antifungal Natural Remedies?
Rachel Li — Parkland High School

Synergistic Effects of Essential Oils and Olfactory Lures as Attractive Toxic Sugar Baits (ATSBs) on Culex and Aedes Species
Gwen Ericson — Marine Academy of Technology & Environmental Science

The Effects of Mangifera indica and Cinnamomum zeylanicum Evergreen Tree Bark Extracts on Oral Bacteria Causing Caries and Periodontal Disease
Julietta Onofrietti — Toms River High School North

A Novel Approach to Combating Cancer Using Chelation Therapy (EDTA)
Vishruth Hanumaihgari — Springhouse Middle School

Monthly Toxocara Contamination Levels in Montgomery County, PA
Devyn Stek — St. Teresa of Calcutta

PDA Who's Who

Kristi Ballard, Associate Director, Technical Operations, Merck

Michele Laudenslager, Validation Specialist, Strategic Maintenance Solutions

Margit Olson, President, MonarchBioscience

Traute Ryan, Science Fair Coordinator, PDA Delaware Valley Chapter

Nicole Shulde, Manager, Strategic Program Lead, Johnson & Johnson

Chapter Offers Coffee with PDA President

Dinesh Khokal, PhD, Amgen, PDA Singapore Chapter President

It is not every day that pharmaceutical leaders have the opportunity to speak directly to PDA President **Richard Johnson** about the direction of the industry over coffee. Yet the PDA Singapore Chapter offered just such an opportunity on April 26.

This successful invitation-only event featured strong representation by local leaders within Singapore's pharma community along with members of the Indonesia International Institute for Life Sciences (i3L). During this two-hour meeting, Richard briefed attendees on PDA's long-term plans for expansion in the Asia-Pacific region. He also shared the Association's various initiatives with global regulatory and standards-setting organizations. These projects cover a number of areas in sterile manufacturing, supply chain management, biotechnology and manufacturing science.

(l-r) Ming Chua, Trevor Swan, Marcel Ewals, Tony Chan, Andiyanto Sutandar, Leonny Hartiadi, Richard Johnson, Dinesh Khokal, Wallace Torres

He concluded his talk by emphasizing PDA's role in shaping the industry.

"CGMP is more than just following the regulations or directives," he said. "Interaction with industry peers and regulators is critical to keeping up. Either you are actively participating in developing 'standards,' or you run the risk of being a victim of 'standards'… PDA can be your best vehicle to global impact."

PDA Photostream www.flickr.com/parenteral-drug

2019 PDA Cell and Gene Therapy Conference

May 6–7 | Long Beach, Calif.

Conference Planning Committee: (l-r back) Josh Eaton, PDA; Brian Hawkins, PhD, Pluristyx; David Smith, Hitachi Chemical Advanced Therapeutics Solutions; Richard Johnson, PDA; Marsha Steed, bluebird bio; Michael Blackton, Adaptimmune; Tom Whitehead, Emily Whitehead Foundation; Irving Ford, Celgene (l-r front) Brooke Schneider, PDA; Kimberly Carnes, Director, Quality Systems, REGENXBIO; Michael Kuczewski, bluebird bio; Lori Daane, bioMérieux

Capital Area Chapter Meet & Greet Networking Event

May 22, 2019 | PDA Headquarters, Bethesda, Md

In May, PDA's Capital Area Chapter hosted a networking reception with refreshments at PDA's Training and Research institute (TRI). Attendees had opportunities to tour the facility, network and learn more about volunteer opportunities with PDA and the chapter.

David Talmage, PDA's Vice President of Education (right), shows off some the latest equipment in TRI to Laurie Masiello, President of the New England Chapter (left)

PDA volunteer and former staff member Denyse Baker (left) chats with President-Elect Tita Tavares (right)

PDA Aseptic Processing Course Instructors Go Global

Popular Aseptic Processing Course Gains Enthusiastic New Students in India

In March, three PDA instructors provided PDA's popular "Aseptic Processing Training Program" course to students in India. Longtime instructors **Hal Baseman, Marc Glogovsky** and **Cheryl Custard** enjoyed the opportunity to expand the course within the country as part of PDA's expanded offerings in the Asia-Pacific region. Hal even returned in May to teach a course on aseptic process simulations!

Below are their thoughts about the experience.

Hal Baseman

During the first week of May, I had the pleasure of giving back-to-back, two-day "Aseptic Process Simulation" courses in Bangalore, India. The courses were a collaborative effort organized through PDA Education, our Indian training partner, EduOriens Skill Development LLP, and the PDA India Chapter. The classes were attended by approximately 60 senior team members from about a dozen Indian pharmaceutical firms. The course was designed to be interactive, combining lecture with practical group exercises, emphasizing an understanding of why we perform aseptic process simulations, including the objective, benefits and limitations of such studies.

The first day was devoted to providing students with a background in critical thinking and risk-based decision making. It included segments on critical thinking, quality risk management principles and techniques, aseptic process validation and industry and regulatory trends. The second day took the techniques discussed the previous day and used them to define and debate the best practices for aseptic process simulation, media fill study design, implementation and investigation. An advanced course further exploring the use of risk-based techniques and principles to design, perform and address issues resulting from an aseptic process simulation is planned for October.

Marc Glogovsky

Teaching and training on behalf of the India Chapter was a tremendous experience! I had the opportunity to work with wonderful folks from varying backgrounds and representing many companies located in India. We had lively debates/discussions, active participation and lots of communication surrounding microbiology, contamination control and environmental monitoring. I quickly discovered that many of the students had similar regulatory concerns, misconceptions surrounding the contamination control system and questions about implementing new technologies.

I am looking forward to offering the advanced portion of our course in September.

Cheryl Custard

I felt very welcomed during our training in India. I quickly realized that the biggest gap between India's pharmaceutical expectations and those of the United States was that great big ocean between us. The students came with thoughtful insights which led to many side conversations similar to those I have experienced when teaching our training courses in the United States. Despite some cultural differences, I learned that if you put good people with good ideas together under one roof, great things can happen. I am honored to be part of this new PDA Education experience.

PDA Summer Reading

With summer here, what better way to pass the time than soaking in the sun 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, enjoy some recommendations from PDA staff and volunteers' summer reading lists. References and graphics have been removed.

PDA Technical Series: Endotoxin Analysis and Risk Management

Excerpt from the chapter, "Risk Analysis of Sterile Production Plants: A New and Simple, Workable Approach," by Guenther Gapp and Peter Holzknecht

Regulatory agencies and company management require the quality assurance (QA) microbiologist to perform a successful investigation with a clear and rapid identification of the problem, to define CAPAs (corrective and preventative actions), and, subsequently, to make or propose the correct batch disposition decision both for the sake of the patient and, ideally, for the lowest loss by the company as well. As a result he or she has to write a scientifically sound investigation report that has to fully satisfy all auditors. Therefore, the position of a QA microbiologist is often very challenging. It is therefore no surprise that in worldwide conferences many presentations with topics like "Training in Handling of Microbiological Deviations" are offered to give advice and assistance in reaching the right conclusion.

Imagine this scenario: you are a microbiological laboratory supervisor sitting in your office, the door opens, and your lab technician informs you that "non-sterility" has been detected in your company's most important sterile product that is expected to be launched in the next week. This presents a serious problem. The question is (a) does the microbial contamination originate from your microlab and is thus not correlated with the product (false positive result); (b) does it originate from the production plant, thus actually contaminating the product; or (c) is it a non-product/process-related sampling problem. There are no quick answers available, and while the identification of the contaminant may help to identify the root cause of the contamination, even with the species name the origin is mostly unknown.

You are immediately aware that your final decision has a dramatic impact on the patient as well as on your company, and the investigation must be performed immediately and in the best way. Your decision must be correct and defensible. Additional difficulties would arise if you are not familiar at this time with what goes on in your lab and in production, or you have no knowledge about the sampling procedure.In order to prevent such a scenario or at least be better prepared, it would be a good idea to walk through your laboratory to experience what is going on and also to walk through the production plant including the cleanroom operations, at least from the outside, to become familiar with common practice. In combination with the activities mentioned above, it is nowadays required (e.g., in the updated EU GMP Guide) to perform a "risk analysis of the process and product."

This was also the main reason why the authors decided to set up "Risk Analysis for Sterile Products/Processes" in mid-2006 and combine all their technical expertise, knowledge, and past experience within a questionnaire. Many of the questions are based on personal experience and come from daily practice in sterile production and aseptic processing. The last 3 years have shown that this risk analysis approach does indeed work, is practicable, and, in conclusion, provides the required information while also serving as a good tool to go directly into the CAPAs.

Audit and Control for Healthcare Manufacturers — Tim Sandle and Jennifer Sandle

Excerpt from the chapter, "Microbial Data Deviations"

CORRECTIVE AND PREVENTIVE ACTIONS

Following assignment of the root cause, it may be appropriate to propose corrective and preventive actions. A corrective action is an action designed to eliminate the cause of a detected non-conformity or other undesirable situation. The corrective action is taken to prevent recurrence. A preventive action is an action to eliminate the cause of a potential non-conformity or other undesirable situation. The preventive action is taken to prevent occurrence. A related term, "correction", refers to an action undertaken to eliminate a detected nonconformity.

In the microbiological context, areas for consideration of corrective action are:

- Re-testing of the sample (if the sample has not time expired).
- Re-sampling.
- Holding the product at a defined storage temperature.
- Cleaning and disinfection.
- Additional testing (for example, conducting an endotoxin test on held product).
- Product filtration.
- Increase sampling to determine the extent of the problem.
- Consideration of quarantine of area/equipment/outlet/sample/batch.
- Any necessary engineering work, e.g., HVAC maintenance.

Examples of preventative actions are:

- Re-training of the sampler or the tester.
- Awareness training for personnel involved.
- Re-assessment of procedures.
- Re-assessment of cleaning/sanitization/sterilization/depyrogenation techniques, frequencies and procedures.
- Re-assessment of calibration/service frequencies.
- Re-assessment of sampling procedures and equipment.
- Re-assessment of test method and equipment.
- Re-assessment of sampling/testing environment.
- Preventative maintenance.
- Consideration of workflows.
- Need for additional supervision.

Such actions should be agreed with the owner of the process or system. Where CAPAs are set, part of closing the CAPA will involve an assessment of the CAPA's effectivity, which is based on a review of whether the event has reoccurred (the "effectivity check"). When an incident happens, and the review of previous history indicates a reoccurrence.

ACTION MEMORANDA

In addition to the investigation forms and the system of contacting responsible managers, for samples which exceed alert and action levels, or where significant changes to trend are detected, it may be necessary to issue an Action Memorandum to the appropriate manager. The purpose of this would be to bring to the attention of the manager that a potential problem is emerging or that the processing is drifting from the norm. The activity should require a response from the manager and proposed remediation solution.

Contamination Control in Healthcare Product Manufacturing: Volume 5 — Russell E. Madsen and Jeanne Moldenhauer (editors)

Excerpt from the chapter, "Practical Approaches to Leveraging Environmental Monitoring Trend Data to Improve Performance," by Michael Hodgkinson

ENVIRONMENTAL TREND ANALYSIS

Once the program has had the proper foundations established, the generation of data begins. To get the most out of the environmental monitoring trending program the appropriate types of analysis to perform must be selected. This depends on a number of factors including the size of the facility, how well the facility performs from an environmental perspective and if the program is fully automated or paper based. There are certainly many acceptable approaches to performing trend analysis and this chapter does not provide an exhaustive list of types. In this section some of the expected and useful tools will be briefly explored along with other important considerations.

Frequency

A schedule for performing trend analysis and review must be established. For manufacturing sites that have fully automated trending systems, the availability of data becomes near real time and even more frequent reviews can be performed. For those on a more manual or semi-automated system, it is important to differentiate a formal trend analysis report from an informal review. It is an expectation that formal trend reports are generated on a periodic basis. However, to get the most out of an environmental monitoring trending program, utilizing informal reviews with area owners will be far more useful in leveraging the data to improve performance. This will allow for timely attention to adverse trends. The team review concept will be discussed later on in the chapter.

To be clear, to get the absolute most out of an environmental monitoring trending program, the review of the data with users must be as close to real time as possible. In order to do this well, an automated system of trending is required. In a manual trending system, users

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can experience a minimum of a one-month delay in getting trends to the manufacturing group with the time needed to read the results, upload the data and produce the trends. Where microbial identifications are needed, the timelines can be much longer.

Contamination recovery rate

One suggested type analysis of data from controlled environments is the calculation of contamination recovery rates as described in USP general chapter <1116> (USP, 2017). CRR can be a valuable trend analysis tool in detection of adverse trends (mainly in higher classification areas due to increased recovery levels). CRR determines the incidence rate of a given room, sample type or sample location. A CRR of 2% means that 2% of samples taken had some level of contamination recovered while 98% recovered no microorganisms. From this, one can see the limitations of CRR, in that it measures the frequency of contamination on a given sample but does not speak to how severe the contamination is. It also has limitations in Grade A and B areas where nearly all samples result in a zero count.

PDA Technical Report No. 81: Cell-Based Therapy Control Strategy

4.1 Criticality Assessment

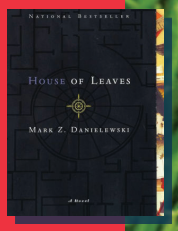
Identification of CQAs follows the principles outlined in ICH Q9, which defines their risk analysis as "the qualitative or quantitative process of linking the likelihood of occurrence and ***severity of harms***" [emphasis added]. Various risk assessment tools referred to in ICH Q9, the Failure Mode and Effects Analysis (FMEA), for example, are available to evaluate the criticality of individual quality attributes. PDA Technical Reports Nos. 44, 54, 54-4, and 60, which discuss quality risk management and product lifecycle management, also offer examples of suitable risk assessment tools and explain their use. Tools used in previous exercises for the A-Mab or A-VAX studies are also applicable for use with CGTP.

For this discussion, and in keeping with the scope of this report, a criticality assessment was selected to illustrate a risk-based approach. This is a simple method to both organize data and facilitate decision-making that is commonly used to prioritize quality attributes based on risks or the criticality of their impact on a product's safety or efficacy. In this manner, the criticality of each quality attribute is assessed for the severity and uncertainty related to product impact; the results provide a continuum of criticality based on risk. The risk can be characterized as critical, potentially critical, or noncritical. Noncritical attributes, ranking the lowest in criticality, are those for which current manufacturing controls and testing are adequate to mitigate the risk related to the product. Potential CQAs are quality attributes that cannot be excluded as critical and will require further evaluation as product development progresses.

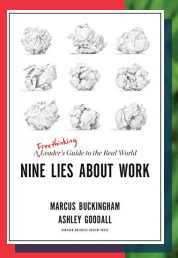
In the early stages of development, a criticality assessment is more likely to be performed using qualitative or semiquantitative measurements. To generate a quantitative output of the risk assessment, the risk is not only described, but also ranked. Several scoring scales are available that can be used to assess the criticality of a particular attribute. Severity is defined as how significantly the attribute could or would impact product safety and/or efficacy. As CGTP are a novel class of therapy, and the literature and in-house experience of the sponsors are consequently small when compared to the huge body of knowledge available for pharmaceutical proteins, uncertainty levels are expected to trend higher. Early in development, severity may be scored as low, medium, or high; the uncertainty score provides the level of confidence in assessing the criticality of the attribute. Uncertainty may be scored as low, medium, or high; those attributes for which there is limited knowledge (i.e., high uncertainty) should be the subject of characterization studies and/or a relevant clinical study. The two scores are multiplied to assign an overall attribute criticality, or risk score, as shown. **Note:** There is no one way to assign an attribute as critical versus potentially critical based on matrixes such as those found in the table. These risks are determined by the organization, depending on the level of risk it is willing to accept.

PDA's Personal Reading List

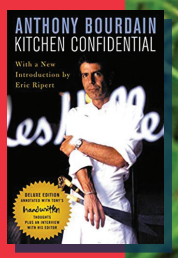
House of Leaves, Mark Z. Danielewski
—**Rebecca Stauffer,** Managing Editor, *PDA Letter*



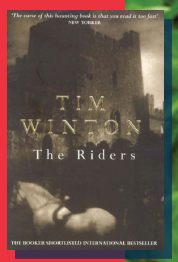
Nine Lies About Work, Marcus Buckingham and Ashley Goodall
—**Stephanie Gaulding,** Pharmatech Associates, *PDA Letter* Editorial Committee member



Kitchen Confidential, Anthony Bourdain
—**Rich Levy,** Editor, *PDA Journal of Pharmaceutical Science and Technology*

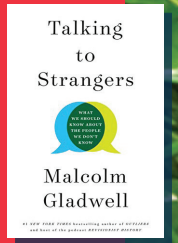


The Riders, Tim Winton —**Zena Kaufman,** ZGK Quality Consulting, *PDA Letter* Editorial Committee member



Good Omens, Neil Gaiman and Terry Pratchett
—**Maria Bednar,** Biogen (appeared in an "On the Issue" video)

Talking to Strangers, Malcolm Gladwell
—**Tamer Helmy,** Alcon Laboratories, *PDA Letter* Editorial Committee member



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The resulting list of attributes classified as CQAs, pCQAs, and non-CQAs should be available during early development and reviewed and revised as data from clinical and product characterization studies become available.

PDA Technical Report No. 82: Low Endotoxin Recovery

4.2 Investigation of LER Causes

LER has been reported in biopharmaceutical drug products, some of which contain high protein concentrations (e.g., monoclonal antibodies). Some are formulated with chelators and/or phosphate buffer systems and polysorbates**.** As discussed in **Section 3.0,** LER hold-time studies are performed to identify if a product causes LER. If LER is observed in a specific product, hold-time studies on the drug alone and placebo (formulation without drug) may provide elucidation of which components cause LER.

LER may be caused by the formulation components alone or in combination with the protein drug substance**.** It can also be caused by the drug substance itself, e.g., monoclonal antibody**.** Identification of the root-cause is helpful in understanding the underlying mechanism of LER and the subsequent development of mitigation strategies. If, for example, formulation excipients causing LER are identified, one approach would be to avoid them by improving or modifying the formulation of a given drug product. This is often not possible, however, if the product is already in clinical development or requires these components for stability. If avoidance of LER-causing components is not possible, additional mitigation strategies are recommended**.**

4.3 Proposed Two-Step Reaction Model of LER

LER can be caused by the formulation components of a drug product and/or by the drug substance itself. To study the impact of formulation, any model developed should be based on the components whose chemical and physical attributes are known.

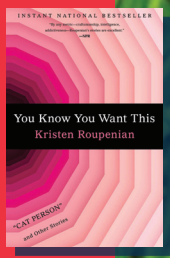
Although the properties of proteins may be known, their interactions with LPS are less well understood, depending on 3D structure, hydrophobic/charged patches, etc. Typical formulation components causing LER, such as buffers and surfactants, have been used to investigate the LER mechanism. For example, a combination of chelator and nonionic surfactant has been shown to commonly induce LER; whereas, the presence of only one of the components, chelator or surfactant, has been less likely to induce LER**.**

Chelators, citrate for example, are known to form a complex with divalent cations. And surfactants like polysorbate, e.g., Tween 20R and Tween 80R, are also commonly used to stabilize protein drugs. Therefore, in case studies examining the LER phenomenon, a system containing citrate and polysorbate 20 was used**.** Based on these findings, a model is presented to describe LER in molecular terms. By using various concentrations of the chelator, research has shown that LER is a kinetically controlled process that follows a two-step mechanism**.**

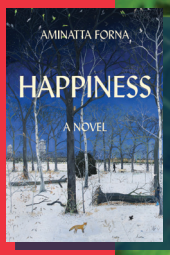
In the first step, during mixing of the sample with the chelator, the salt bridges between LPS and divalent cations (e.g., Mg2+, Ca2+) may be destabilized, leading to reduced rigidity of the LPS aggregate. In the second step, the surfactant may intercalate among LPS molecules and change the initial supramolecular structure by formation of mixed aggregates, e.g., micelles, lamellar, or hexagonal structures. The equilibrium state of the LPS is shifted, in some cases, to become non-detectable; in other words, the endotoxin is masked (P-LPS).

Origin, Dan Brown —**Cecilia Turoff,** Pfizer, *PDA Letter* Editorial Committee member

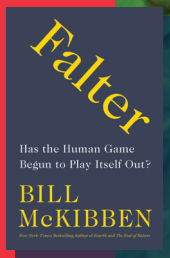
You Know You Want This, Kristen Roupenian —**Walid El Azab,** Steris, *PDA Letter* Editorial Committee member



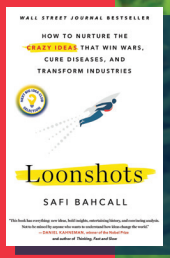
Happiness: A Novel, Aminatta Forna —**Madeline Cusick,** PDA Publications intern



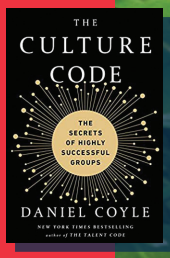
Falter, Bill McKibben —**Frank Matos,** SOFIE, *PDA Letter* Editorial Committee member



Loonshots, Safi Bahcall —**Marcia Baroni,** Eli Lilly, *PDA Letter* Editorial Committee member



The Culture Code, Daniel Coyle — **Ajay Pazhayattil,** Eurofins, *PDA Letter* Editorial Committee member



SNAPShot

Journal *TOC*

Study Looks at Endotoxin Testing for Snake Bite Antivenoms Produced Using Horse Plasma

Find out how the *limulus* amebocyte lysate test can serve as an end-product endotoxin test for snake antivenom in the July/August issue of the *PDA Journal of Pharmaceutical Science and Technology* (journal.pda.org).

Research

"Factors Affecting Measurement of Equilibration Time of Dry Goods Loads in Autoclaves," Soham Shah, et al.

"A Validation study of the Limulus Amebocyte Lysate test as an end-product endotoxin test for Polyvalent Horse Snake Antivenom," Norhan Saif Sheraba, et al.

Technology/Application

"Comparative Leachable Study for Glass Vials to Demonstrate the Impact of Low Fill Volume," Bernhard Hladik, et al.

"Enabling Robust and Rapid Raw Material Identification and Release by Handheld Raman Spectroscopy," Thomas Earl Matthews, et al.

Commentary

"What Does It Really Look Like to Properly Address a 'Human Error Problem' in Biopharma? The Human Performance Blue-Sky Description That Will Help Improve Industry Performance," Cliff Berry, et al.

"A Mechanistic Understanding of Polysorbate 80 Oxidation in Histidine and Citrate Buffer Systems-Part 2," Anant Navanithan Sharma, et al.

"Quality Risk Management Competency Model - Case for the need for QRM Competencies," Ghada Haddad and Anne Greene

"Provable Data Integrity in the Pharmaceutical Industry based on Version Control Systems and the Blockchain," Valentin Steinwandter and Christoph Herwig

Conference Proceeding

"PDA Biosimilars Workshop Report (27-28 September 2018) - Getting It Right the First Time for Biosimilar Marketing Applications," Stephan Krause, et al.

Future of Packaging on Display at Stevanato Tour

Gabriele Peron, Stevanato Group

Each year, packaging supplier Stevanato Group hosts an Innovation Day, allowing members of the biopharma industry to share their expertise and expand their connections within the industry.

This year, Innovation Day took place immediately following the PDA *Parenteral Packaging Conference* on March 21 in Venice, Italy with over 400 global biopharmaceutical professionals in attendance. Some of PDA's top leaders attended this exciting forum which focused on patients' needs and offered live discussion about concrete solutions to some of today's challenges. Participants also took the opportunity to celebrate Stevanato Group's 70th birthday.

Georg Roessling, the former Senior Vice President of PDA Europe, chaired the conference and introduced the first topics of the day and their speakers: megatrends and implications for the global pharmaceutical ecosystem (**Daniel Cohen,** RBC Capital), the future of drug delivery devices in the biotech era (**Dr. Robert Langer,** Massachusetts Institute of Technology) and a patient perspective (**Jette Christensen,** Novo Nordisk and PDA Chair-Elect).

Next, a panel discussion moderated by ISO/Haselmeier's **Paul Jansen** focused on the latest innovations in drug delivery devices. Panelists **Jim Collins** (Sanofi), **Bill Rich** (Amgen), **Marc Rohrschneider** (Novartis) and **Steven Kaufman** (Stevanato Group) discussed regulatory hurdles, patient adherence by design and biosimilar challenges.

The last panel discussion, moderated by **John Cox** of Torque Therapeutics, looked at manufacturing trends. **Jerry Cacia** (Roche), **Luigi Nava** (Diasorin), **Paolo Patri** and **Alessandro Zannini** (both from Stevanato Group) covered:

- The facility of the future
- Industry 4.0 and flexible manufacturing frontiers
- Diagnostics and pharma's outlook

Attendees view the manufacturing of ready-to-fill containers for prefilled syringes, cartridges and vials at the Stevanato Group's headquarters

The day closed with a memorable boat ride at sunset in the lagoon to attend a dinner held at the historical site of Arsenale. During the Middle Ages, this location was renowned for producing the bulk of the Venetian Republic's naval power. It is also symbolically recognized as one of history's first massive industrial enterprises—a fitting site to close out Innovation Day.

The day after Innovation Day, attendees had the option of touring Stevanato Group's headquarters in Piombino Dese. Here, they could view manufacturing of the company's EZ-fill® ready-to-fill glass primary containers for prefilled syringes, cartridges and vials. Through a dedicated area in the new building, participants could also experience the capabilities offered by Stevanato Group under the SG 4D approach for drug delivery systems: analytical services for drug delivery systems, inspection solutions, assembly and packaging machines, serialization equipment for glass containers and secondary packaging.

"Stevanato Group is about a history of passion, commitment, trust, and partnership, led by one important mission: to provide products, processes, and services to guarantee the integrity of drugs," said **Franco Stevanato,** CEO of Stevanato Group. "Today, through our new global organization and thanks to the combination of our capabilities, we are ready to provide integrated solutions for drug delivery systems."

Stevanato Group appreciates those PDA leaders and staff who participated in Innovation Day and the plant tour and looks forward to new technologies able to respond to current and future patient needs for a better and safer life. To learn more about the Innovation Day celebration, visit https://innovationday.stevanatogroup.com.

[Editor's Note: More photos from the Innovation Day celebration can be found in the online version of the article**.]**

Published online first
PDA letter.pda.org

Air Bubbles versus Transparent Particles

How to Differentiate Between the Two During Automated Visual Inspection

John MacEwen, Körber Medipak Systems NA Inc.

The demand for faster multicontainer inspection machines has pushed the development of sophisticated new technologies. After all, one single technology is no longer sufficient to inspect all drug products at the highest standards.

Yet new visual inspection technologies also present challenges. Fortunately, there are ways that the industry can address these challenges while using these innovative solutions to ensure product quality and patient safety.

The key to higher product quality/patient safety lies in combining these new technologies with vision tools, lighting techniques and inspection approaches. Achieving this is an essential part of improving the quality of parenteral drugs around the world.

One of the challenges faced by pharmaceutical manufacturers is air bubbles created in the product as part of the process, whether that be in the filling process, material handling or just naturally occurring. Air bubbles create an issue for vision systems in inspection machines.

Visual inspection teams continue to struggle with fully automated inspection machines as these machines require artfully balancing higher detection rates with false reject rates. The challenge they face is how to differentiate between transparent particles and air bubbles. Earlier ways to address air bubbles involved placing the product in cold storage after filling and capping for at least 24 hours to allow for degassing of air bubbles. In addition, traditional inspection approaches place a prespin turret or stations before inspection to dissipate air bubbles. Here, machine manufacturers focused on material handling to reduce the formation of air bubbles in the process.

Still, those involved in visual inspection struggle with gravity as air bubbles rise in liquids, while some particles sink. With high speed inspection there is often not enough time for this determination to be made. Some equipment focuses on shape as the key to detection, assuming all air bubbles are round, and that light will create a doughnut effect for the camera to see. Vision tuning of fully automated machines has become an art form that has to consider the container being inspected, product characteristics, limitations of the system in use and the target particle size.

The solution lies in the physical principle of light refraction, i.e., rays of light usually travel in straight lines until they hit something **(Figure 1).** Since each medium has clearly characteristic refractive properties, this can differentiate air bubbles from transparent particles.

With spectral coded illumination, a method has been developed to increase detection rates during particle inspections

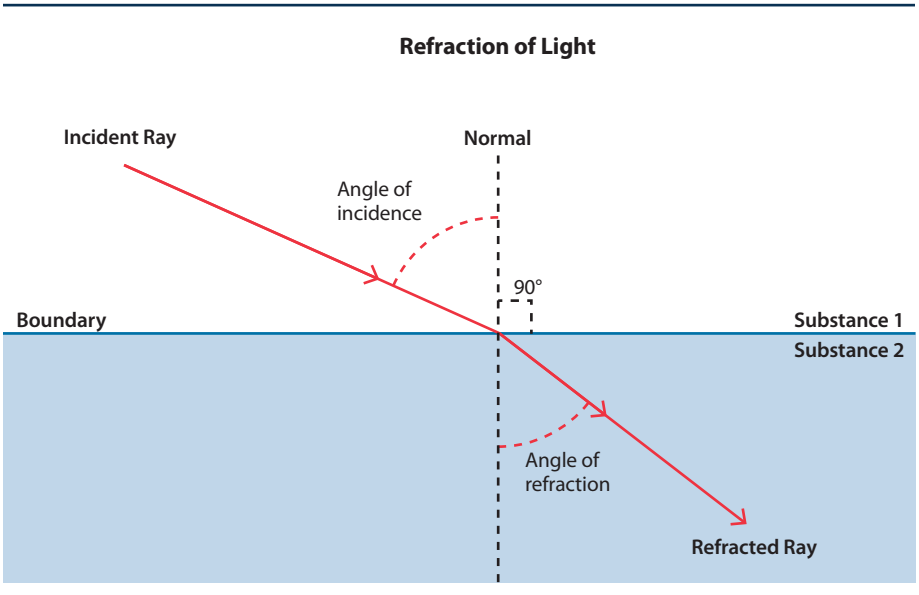


Figure 1 Light Refraction

It is important not only to focus on the image processing tool, but to improve the image itself

and to reduce false reject rates when air bubbles occur in liquid products.

A standard industrial camera with color recording function detects light from three line lights of different light colors (red, green and blue), which is manipulated by diffusers and a lens system before it passes the liquid to be inspected. The lights are arranged in such a way that the middle beam (green) provides bright field illumination and the two outer beams (red and blue) provide dark field illumination. **[Editor's Note:** see the online version of the article for a figure showing this spectral coded illumination**.]**

When the light from all three sources can pass through the sample without interference and only the middle light source is detected, no defect or air bubble is detected.

A nontransparent particle in the liquid shades the light (the green light beam), creating a dark area in the camera image—as with standard transmitted light illumination **(Figure 2).**

When a transparent particle is in the liquid, the light is refracted at the structures of the particle and passes completely or partially past the detector of the camera. Due to the spectrally coded light and the characteristic refraction properties of the material of the particle, a typical color pattern on the sensor is obtained.

The particle can be detected in the camera image. When a light beam passes an air bubble in the liquid, the relatively central incident light of the middle (bright field) illumination can pass through the air bubble almost unhindered and hits the detector of the camera.

Due to the transition into an optically thinner medium, the incident light of the dark field illumination is refracted and deflected in such a way that it also hits the detector.

Figure 2 Nontransparent Particle in a Liquid

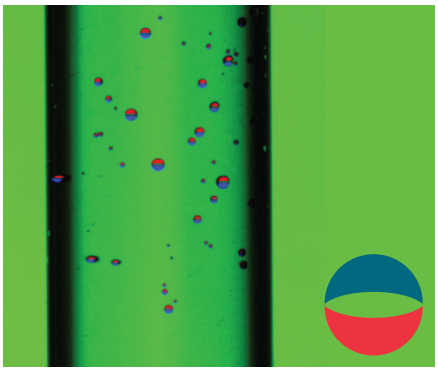


Figure 3 Real Image From a Visual Inspection System

*Picture on the left is a real image from a vision system

Air is a thinner medium than, e.g., glass, so there is a different color pattern compared to a glass particle **(Figure 3).** It is important not only to focus on the image processing tool, but to improve the image itself by taking a new approach.

By combining spectral coding illumination, lens systems and color cameras, an air bubble can be reliably distinguished from a transparent particle. This approach significantly reduces the false reject rate compared to conventional camera inspection. Visual inspection teams using this approach can successfully address the challenges of new inspection technologies, ensuring the quality of the product.

About the Author

John MacEwen has five years of experience in the pharmaceutical industry working on inspection and packaging projects in North America. Currently, he focuses on supporting inspection applications.

2019 PDA/FDA Joint Regulatory Conference (September 16-18)

Renaissance Washington, DC Downtown Hotel | Washington, DC

A Supplement to the PDA *Letter*

Manufacturing Innovation, Quality, and Compliance: Achieving 20/20 Vision

PDA and the U.S. FDA are once again co-sponsoring the *PDA/FDA Joint Regulatory Conference*, now in its 28th year. This flagship conference consistently provides a unique opportunity to hear from and engage with numerous regulatory and industry leaders concerning the latest manufacturing, quality, supply and compliance issues in an ever-evolving landscape.

This year's theme is "Manufacturing Innovation, Quality, and Compliance: Achieving 20/20 Vision," and the conference will explore the continuing development of innovative manufacturing capabilities and the potential effect on quality, compliance, and regulatory lifecycle paradigms. Plenary and concurrent sessions will delve into the details through the assessment of the latest innovative technologies, regulatory expectations, and forward-looking perspectives, including:

- CGMP challenges associated with cell and gene therapies
- Combination products and connected care applications
- Compliance updates and case studies
- Data integrity remediation and an update on the associated PDA technical report
- Designing aseptic processes to reduce quality risk
- Effective internal and external audits
- Evolving approaches to quality management systems
- Improving deviation and failure investigations
- Strategies for continuous improvement of facilities and equipment
- Use of augmented reality and artificial intelligence in manufacturing

This year's conference will focus on how advances in manufacturing, quality, and compliance are advancing the continued supply of innovative drugs, biologics, and combination products. Collaborative efforts between industry and regulators are necessary to assure uninterrupted supplies of safe and high-quality products while advancing the use of new capabilities.

Attendees will also learn about hot topics, such as inspection updates, laboratory controls, rapid microbiological methods, optimizing regulatory submissions, conducting effective smoke studies, and quality trending. Multiple interest groups will meet to discuss in-depth regulatory and compliance issues.

Center Updates, the traditional FDA presentations from each of the medical product Centers, will return this year. Here, senior officials from FDA will discuss Center-specific initiatives and provide compliance updates. The new "Lunch with the Regulators" (formerly "Breakfast with the Regulators") session will provide an opportunity for attendees to ask their most pressing regulatory and compliance issues.

The lineup of speakers also includes regulators from agencies around the world and industry leaders who will explore the global regulatory issues facing industry.

2019 PDA/FDA Joint Regulatory Conference

Washington, D.C.
Sept. 16–18
www.pda.org/2019pdafda

Networking Opportunities

Monday, September 16

PDA Orientation Breakfast
(invitation only)

7–8 a.m.

New members can learn about volunteer opportunities with PDA.

Evening Reception

7–10 p.m.

Unwind from a busy first day during the Monday Evening Reception! Use this time to catch up or make new connections with colleagues, peers and suppliers over food and drinks.

Lunch with the Regulators

Back by popular demand and at a new time! Grab your boxed lunch and bring questions for FDA investigators, reviewers and compliance officers to this Q&A session that will allow for direct input and will provide you with insights regarding inspection trends and center initiatives.

PDA
Parenteral Drug Association

history@pda.org

Share Your PDA History!

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Do you have photos from PDA events? Holding on to some special PDA memorabilia? Have an interesting story to tell about a PDA connection?

PDA is publishing an interactive history for our upcoming 75th anniversary. If you want to share your PDA history, contact history@pda.org.

Get the Latest on Specialized Topics

PDA Interest Group Sessions

Monday, September 16

12:30 – 1:30 p.m.

Pharmacopeial Interest Group

Quality Systems Interest Group

Technology Transfer Interest Group

Vaccines Interest Group

Boxed lunches will be provided for those that are participating in interest group sessions during lunch.

5:45 – 6:45 p.m.

Combination Products Interest Group

Facilities and Engineering and Quality Risk Management Interest Groups (*joint interest group meeting*)

Filtration Interest Group

GMP Links to Pharmacovigilance Interest Group

Process Validation Interest Group

Visual Inspection of Parenteral Interest Group

Tuesday, September 17

5:45 – 6:45 p.m.

Inspection Trends Interest Group

Lyophilization and Packaging Science Interest Groups (*joint interest group meeting*)

Regulatory Affairs Interest Group

Prefilled Syringes Interest Group

Supply Chain Management Interest Group

Sterile Processing Interest Group

JOIN THE REVOLUTION

100%
of companies said employee misunderstanding placed the public at risk

94%
of pharma executives said current training content does not enable learners to evaluate new occurrences and apply concepts learned to a new event

93%
of pharma executives felt available educational content was not consistently accurate, up to date and of superior quality

89%
of pharma executives reported risk of reduced productivity due to employee misunderstanding

86%
of pharma executives believe training down to the shop floor level is routinely not the best, nor provided by relevent experts

82%
of pharma executives do not feel current training methods adequately educate employees to understand "Why" requirements are in place

79%
of companies said lack of frontline manager training and development negatively impacts their company's performance

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2019 PDA Upcoming Events

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JULY

22-26 2019 PDA Aseptic Processing – Option 4 ■
Week 1
Bethesda, MD | *pda.org/2019Aseptic4*

AUGUST

6-9 Glass Training Course Series
Bethesda, MD | *pda.org/2019GlassTCS*

- **6** Polymer Primary Packaging
- **6-7** Glass Breakage Analysis and Fractography *(This training course will be held in Indianapolis, IN)*
- **7** Identification and Classification of Nonconformities in Molded and Tubular Glass Containers for Pharmaceutical Manufacturing
- **8-9** Extractables and Leachables for Parenteral Applications

12-16 QA/QC Training Course Series – Option 2
Bethesda, MD | *pda.org/2019QualityCourses2*

- **12** The Common Sense of Quality Auditing
- **13-14** Application of a Quality Systems Approach to Pharmaceutical CGMPs – Option 2
- **13-14** Fundamentals of an Environmental Monitoring Program – Option 2 ■
- **15** Drug Delivery Device and Combination Product Risk Management and Safety Assurance Cases
- **15** Regulatory Aspects of Microbiology in a Non-Sterile Environment
- **15-16** Mold Identification for Quality Control ■

19-23 2019 PDA Aseptic Processing – Option 4 ■
Week 2
Bethesda, MD | *pda.org/2019Aseptic4*

SEPTEMBER

2 Freeze Drying Interest Group Meeting
Munich, Germany | *pda.org/EU/IGFD19*

2 Technology Transfer Interest Group Meeting
Munich, Germany | *pda.org/EU/IGTT19*

2 Building the Foundations for Single-Use Manufacturing Workshop
Munich, Germany | *pda.org/EU/Pre-WSSUS19*

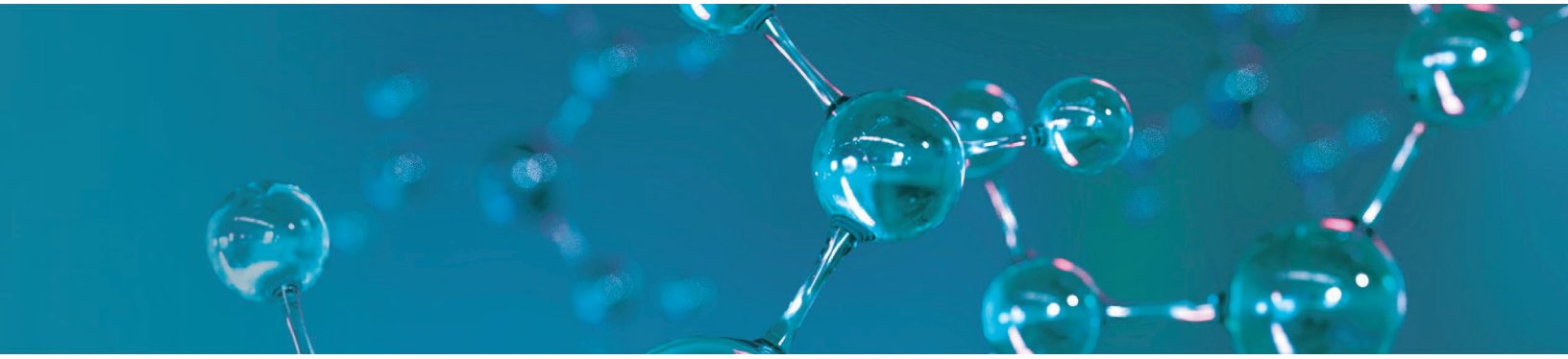
3-4 2019 PDA Europe BioManufacturing Conference
Munich, Germany | *pda.org/EU/BIO2019*

3-4 Managing Technology Transfer Projects in Pharma
Munich, Germany | *pda.org/EU/TTPP19*

5 Project Management in the Pharmaceutical Industry Conference
Munich, Germany | *pda.org/EU/PM2019*

5 Vaccines Interest Group Meeting
Munich, Germany | *pda.org/EU/IGVac*

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



5-6 Environmental Monitoring and Contamination Control
Munich, Germany | *pda.org/EU/EMCC19*

5-6 Mastering Challenges of Data Integrity and Computer System Validation
Munich, Germany | *pda.org/EU/MasteringDI19*

5-6 Quality Training Course Series
Munich, Germany | *pda.org/EU/CMC-Regulatory2019*
- **5-6** CMC Regulatory Compliance for Biopharmaceuticals
- **5-6** Best Practices and Points to Consider in Aseptic Processing

5-6 Classical or Rapid Microbiological Methods?
Munich, Germany | *pda.org/EU/TC-CRMM19*

9-13 Biopharmaceuticals Training Course Series
Bethesda, MD | *pda.org/2019BioTCS*
- **9-10** Biotechnology: Overview of Principles, Tools, Processes and Products
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U.S. FDA CONTINUES DATA INTEGRITY FOCUS

A Review of U.S. Regulations on cGMP and Data Integrity

Lina Genovesi

The consent decree required Ranbaxy to comply with data integrity requirements before FDA would resume reviewing drug applications

The U.S. FDA continues to inspect pharmaceutical facilities for compliance with cGMP regulations, and as a result of these inspections, has issued numerous warning letters citing several significant violations involving data integrity.

During 2018 alone, FDA issued 56 warning letters, and as of the end of May 2019, the Agency has issued 13. Of these 13 letters, the majority (six) were issued to pharmaceutical facilities located in India, two issued to facilities in China, and the remainder issued to facilities in Taiwan, Canada, France, Spain and Singapore.

If after several inspections, cGMP violations are not corrected, and there is a reasonable likelihood of serious health consequences resulting from the manufacture of a drug product, FDA in collaboration with the Civil Division of the U.S. Department of Justice, may file a complaint against a drug manufacturer under the U.S. Food, Drug, and Cosmetic Act (FDCA) or the Federal Claims Act (FCA) to extract substantial penalties for such cGMP violations.

Two Conflicting Legal Verdicts

One such complaint was filed against Ranbaxy USA, Inc., a subsidiary of Indian generic pharmaceutical manufacturer Ranbaxy Laboratories Ltd, alleging that Ranbaxy falsified stability testing data and intentionally departed from the stability testing protocols it disclosed to FDA.

On May 13, 2013, the U.S. Department of Justice announced that Ranbaxy pled guilty to seven felony counts arising out of the manufacture and distribution of adulterated drugs and agreed to pay a criminal fine and forfeiture totaling $150 mill. Ranbaxy also agreed to settle civil false claims and state law claims for $350 mill. arising out of Medicare and Medicaid reimbursement for such drugs.

The consent decree required Ranbaxy to comply with data integrity requirements before FDA would resume reviewing drug applications containing any data or information from three Ranbaxy facilities in India. The consent decree also prevented Ranbaxy from manufacturing drugs at four facilities for introduction into the United States, until such drugs could be manufactured at those facilities in compliance with applicable quality standards. In addition, FDA withdrew its tentative approval of two ANDAs which it had previously granted to Ranbaxy because the compliance status of one or more of the facilities referenced in the applications was unacceptable to support tentative approval.

While the Ranbaxy case highlights the Justice Department's willingness to use both the FDCA and the FCA to impose substantial penalties on drug manufacturers as a means of penalizing cGMP violations, a recent decision in *Rostholder v. Omnicare* (745 F.3d 694 (4th Cir.2004)) limits the use of the FCA by private individuals to bring actions in the name of the government alleging FCA violations.

In *Rostholder*, a private individual sought to bring claims under the FCA, alleging that Omnicare, a provider of pharmacy services, knowingly or recklessly violated cGMP regulations causing some drugs to be adulterated and ineligible for reimbursement and that any reimbursement for the drugs was "false or fraudulent" under the FCA. The Court rejected the argument, on the basis that a defendant is liable under the FCA only where it has made a false statement or engaged in a fraudulent course of conduct, and drugs are eligible for reimbursement under Medicare and Medicaid so long as they have been approved by FDA. The FCA does not expressly bar reimbursement for drugs manufactured in violation of cGMP regulations because compliance with cGMP regulations is not a requirement for reimbursement under Medicare and Medicaid.

In view of *Rostholder*, the Justice Department now faces significant obstacles in using cGMP violations as a basis for substantial civil liability under the FCA. Despite *Rostholder,* the Justice Department continues to bring non-FCA related actions against pharmaceutical companies for violations of cGMP regulations and the FDA continues to issue warning letters.

Data Integrity Codified

CGMP regulations are codified at Title 21 of the Code of Federal Regulations and set the minimum requirements for the methods, facilities, and controls used in manufacturing, processing and packing of a drug product.

The cGMP regulations at 21 CFR § 211 and § 212 set the cGMP requirements with respect to data integrity:

- § 211.68 requires that "backup data are exact and complete" and "secure from alteration, inadvertent erasures, or loss" and that "output from the computer … be checked for accuracy"
- § 212.110(b) requires that data be "stored to prevent deterioration or loss"
- §§ 211.100 and 211.160 require that certain activities be "documented at the time of performance" and that laboratory controls be "scientifically sound"
- § 211.180 requires that records be retained as "original records," or "true

Article at a Glance

- FDA continues to cite data integrity violations in warning letters
- Strong quality culture helps ensure data integrity
- A quality culture that works for one company may not work for another

copies," or other "accurate reproductions of the original records"

- §§ 211.188, 211.194, and 212.60(g) require "complete information," "complete data derived from all tests," "complete record of all data," and "complete records of all tests performed"

- §§ 211.22, 211.192, and 211.194(a) require that production and control records be "reviewed" and that laboratory records be "reviewed for accuracy, completeness, and compliance with established standards"

- §§ 211.182, 211.186(a), 211.188(b)(11), and 211.194(a)(8) require that records be "checked," "verified," or "reviewed").

As noted in several of the warning letters, any failure to meet these cGMP regulations can amount to a data integrity failure and a violation of cGMP regulations.

So, in light of these, what are best practices for cGMP compliance?

"Since data is central to drug manufacturing, maintaining the integrity of that data to be in compliance with cGMP regulations has always been central to everything the pharmaceutical industry does to support the quality, safety and efficacy of a drug product," says **Anil Sawant,** PhD, Senior Vice President, Global Quality Compliance, Merck & Co.

Looking for a global regulatory perspective on data integrity? Expert GMP Inspector David Churchward from the UK MHRA will speak Sept. 18 at the *2019 PDA Data Integrity Workshop* in Washington, D.C.

> **"In the absence of management support of a quality culture, quality systems can break down and lead to cGMP noncompliance"**

In December 2018, the FDA released its guidance "Data Integrity and Compliance with Drug cGMP – Questions and Answers – Guidance for Industry." This guidance recommends that pharmaceutical companies follow this guidance to ensure compliance with best practices for cGMP compliance.

According to **Karen Takahashi,** senior policy advisor in the FDA's Office of Pharmaceutical Quality, a pharma company should follow flexible and risk-based strategies to prevent and detect data integrity issues. A pharma company is required to employ strategies to ensure the completeness, consistency, and accuracy of data. Complete, consistent, and accurate data should be attributable, legible, and contemporaneously recorded, whether as an original or a true copy, and accurate.

This means, she explains, that a pharma company should employ strategies for the design, operation, and monitoring of systems and controls based on risk to patient, process, and product. Risk assessments should include an evaluation of data criticality, control mechanisms, and the impact on product quality and to ensure complete, consistent, and accurate data when there are higher risk consequences.

Takahashi also emphasizes a pharma company should approach quality culture according to what works for that company. What works in one company or in a given situation may not work in other instances. A pharma company must have a management with executive responsibility that will create a quality culture where employees understand that data integrity is an organizational core value and feel empowered to identify and promptly report real and potential data integrity issues and make recommendations for operational improvement. In the absence of management support of a quality culture, quality systems can break down and lead to cGMP noncompliance.

To ensure the integrity of data, FDA follows a multilayered approach which starts with setting clear and appropriate expectations of manufacturers and applicants regarding data integrity. Multiple experts evaluate application content before approval and when certain changes are made after approval. FDA also conducts onsite inspections and testing as needed, conducts ongoing surveillance of manufacturing activities, and responds to reports of quality problems.

FDA also conducts a preapproval inspection process of manufacturing sites and conducts a thorough assessment of applications prior to approval and when companies submit information about changes to their manufacturing processes. The preapproval inspections might entail an evaluation of data integrity onsite when deemed appropriate.

"To be within the cGMP requirements and follow the FDA guidance, it is recommended that a pharma company maintains an active compliance program where all affected employees are made aware of cGMP requirements and are continuously trained to generate and evaluate the quality and criticality of the data so that it can recorded and reported in accordance with cGMP requirements," says Sawant.

He adds, "an active compliance program requires a quality culture with a management with executive responsibility and accountability where employees are encouraged to come forward with any cGMP violations which are observed. ➤

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David M. Churchward, MSc, Deputy Unit Manager, Inspectorate Strategy and Innovation (Expert GMP Inspector), *MHRA, UK*

Tom Cosgrove, Partner, *Covington & Burling LLP*, formerly with *FDA*

Carmelo Rosa, PsyD, Division Director, Office of Manufacturing and Product Quality, CDER, *FDA*

Aditi Thakur, Acting Quality Assessment Lead, Office of Pharmaceutical Quality, CDER, *FDA*

The detailed agenda, including the full lineup of speakers, can be found at ***pda.org/2019DIWorkshop***

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An active compliance program should also follow a holistic approach integrating the relevant people, quality management systems and electronic data capture processes. It should also be supported by internal auditing, monitoring quality agreements with all suppliers, remediating cGMP-related issues, and responding promptly and thoroughly to any FDA warning letters.

Conclusion

With the ongoing prospect of regulatory actions, it behooves a drug manufacturer to follow certain best practices to be in compliance with cGMP regulations.

"The pharmaceutical industry must continue to introduce procedures, policies, and share data integrity best practices via technical reports especially as the industry continues to automate, digitize, and introduce new manufacturing technologies. This will go a long way in providing assurance that a pharma company will ensure the integrity of the data throughout the cGMP data lifecycle," concludes Sawant.

PDA Data Integrity Resources

PDA/DHI Book: Assuring Data Integrity for Life Sciences

Points to Consider: Best Practices for Document/Data Management and Control and Preparing for Data Integrity Inspections

Points to Consider: Fundamental Concepts for Data Integrity

Elements of a Code of Conduct for Data Integrity

PDA Technical Report No. 80: Data Integrity Management System for Pharmaceutical Laboratories

Information about these resources can be found at the PDA Data Integrity page: www.pda.org/dataintegrity. In addition, a technical report team is currently putting together a technical report specific to manufacturing systems.

About the Author

Lina Genovesi writes about pharmaceutical, regulatory, science and business topics.

Follow the Audit Trail Breadcrumbs

Audit Trail Reviews Crucial for Maintaining Data Integrity

Ann Milliman, Baxter Healthcare Corporation

Data integrity is a hot topic for the U.S. FDA and other global regulatory agencies. Two crucial aspects, in particular, have been cited by regulators: audit trails and audit trail reviews.

Both are used to confirm the correctness of data. Per 21 CFR Part 11, controls for electronic systems should include: "secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information." Without this, it is not possible to reconstruct the sequence of events documenting the *who, what, when* and *why*.

Yet these regulations do not provide specifics on what information should be in an audit trail or define how to perform an audit trail review. As a result, there is significant confusion around how to conduct an audit trail review. It is not uncommon to see minimalistic audit trail reviews that lack appropriate information, such as where the audit trail is located. It is commonly thought that every piece of data needs to be reviewed. Some companies resist conducting audit trail reviews as it is believed to take up too much time during routine laboratory operations.

Yet companies do not realize that often what is needed for an audit trail is already covered as part of existing data review/approval.

Another common thought is that one audit trail review process can be performed for all instruments. But instruments vary in terms of analyst and audit trail capabilities; therefore, one set of criteria cannot be applied generically across the board. Also, the characteristics of an audit trail differ among instruments. Thus, audit trail reviews for each instrument need to have specifics in terms of what to review and where to find the audit trail.

Step-by-Step Audit Trail Review Process

It is helpful to understand the FDA perspective. In general, the audit trail review needs to:

- Be part of the routine data review/approval process
- Look for abnormalities or inconsistencies with the generation and/or processing of data
- Be completed prior to final approval or release of data
- Be conducted by someone independent who knows the instrument

Both U.S. and EU regulations state it is acceptable to use a risk assessment when defining the audit trail review based off of the

> **All audit trail reviews must include a statement outlining who performed the review and the date it occurred**

potential effect on product quality, safety and record integrity. The audit trail review process requires the following steps:

- Determining the available information in the instrument's software and/or other utility that maintains the instrument data to ALCOA+ standards
- Defining the critical information
  — "Critical information" is defined as that which establishes the *who, what, when, and why* in the audit trail
- Defining the audit trail review based on the defined critical information

As part of an audit trail review, the user, time and date of an event or action must always be verified. To define additional critical information, some key questions about the extent to which analysts can alter parameters, methods and data should be asked.

- If an established nonmodifiable method exists, was it verified that the correct method was chosen?
- Was the parameter choice confirmed for situations when analysts create or modify such parameters?
- Were parameters applied correctly during integration of high-performance liquid chromatography chromatograms?
- Does the test match what is defined in the SOP?
- Were parameters applied correctly during integration of high-performance liquid chromatography chromatograms? This part of the audit trail review includes confirming that samples are used appropriately, e.g., samples are not used for conditioning the column prior to the run.
- Does an analyst have the ability to modify or delete records? If so, then the modifications and deletions need to be reviewed along with an accompanying reason and confirmation that no suspicious patterns are present. If the analyst cannot do any of the above, the only item to review in addition to user, time and date is that all records have been reported (i.e., there are no duplicate or trial/unofficial records).

Once the necessary information is identified, it must be found in the audit trail. Some instruments may not have what would be considered a typical audit trail—in these cases, the necessary information is often found in unexpected places. For instruments with controlling software that do not have any intrinsic audit trail capability, a secondary program to capture the *who, what, when and why* of actions can be added to the instruments. Some instruments create a nonmodifiable file. If these files are saved directly onto a locked server where they cannot be deleted or moved and the clock is locked, the audit trail review consists of verifying the user creation of files with the specified date and time along with confirmation that all records have been reported.

All audit trail reviews must include a statement outlining who performed the review and the date it occurred. There must also be a statement that no issues were found. To avoid additional forms, a statement can be added to the instrument SOP noting that that the reviewer has performed the audit trail review per the SOP and no discrepancies were found. In an R&D setting, this may be acceptable, but for manufacturing, a separate form as part of batch record may be a better option. Either way, the form must be based on what is reviewed in the audit trail for the given instrument.

To ensure a proper audit trail review, analysts who generate data must have duties separate from administrators who can establish accounts and transfer/delete data when appropriate without an audit trail. If analysts can modify or delete files without documenting the change, this must be addressed before establishing an audit trail review for the instrument. Defining the data needed as part of the audit trail review during validation, establishes ➤

the necessary data controls to maintain ALCOA+ expectations.

A few final points. Audit trails and audit trail reviews apply to analytical instruments and manufacturing equipment. As each instrument is unique, a helpful option is to place the audit trail review process within the instrument SOP rather than have one overall audit trail review procedure. The steps outlined above apply to an audit trail review during data review which is typically performed each time data is released/approved. There is also an expectation to perform an audit trail review at the system level that evaluates modification of locked methods and administrator modifications, such as user access and privilege modifications, data deletion and archiving. This can be done periodically (e.g., annually) rather than for each dataset.

The audit trail review is the last check to prevent unsuitable product from being released. As a real-world example showing the importance of an audit trail review, a company a few years back received many lack of effect complaints on a lot of product. It was determined that the lot was made half as potent compared to its label claim due to an unintended error.

Why was this not caught during release testing? When reviewing the audit trail for the release test data, it was found that the analyst tested the lot and the result came out half as potent. The analyst retested the lot where it passed, and the lot was released based on this second passing result. The first result was not reported or investigated. It was only after the numerous lack of effect complaints that the error was found. In this case, the audit trail showed the duplicate test, but no audit trail review was performed during data review. As a result, patients received subpotent product. Yet an audit trail review would have identified the extra test result and a subsequent investigation would have found the manufacturing error prior to releasing the lot.

With the increased focus on data integrity and common observations for audit trails and audit trail reviews, it is imperative to have robust audit trails and audit trail reviews. After all, the audit trail review is the last step to ensure safe and effective products are released.

About the Author

Ann Milliman has over 15 years of product quality and quality systems experience in the pharmaceutical/medical device industry. This includes cross functional work in product development and market support as well in establishing and assessing quality systems.

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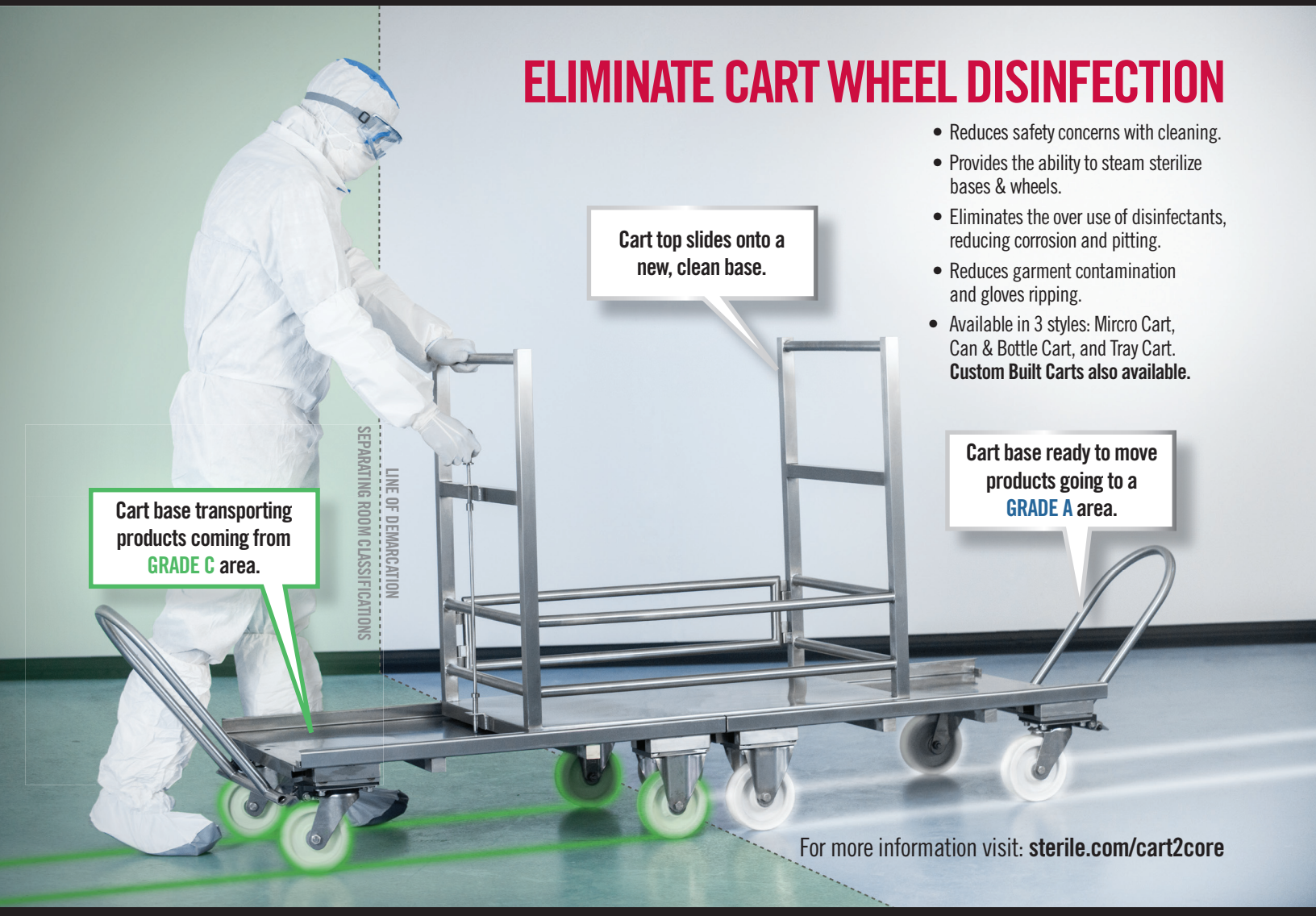

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New Technology Meets Old Data Integrity Challenges

Kir Henrici, The Henrici Group, Monica Cahilly, Green Mountain Quality Assurance, and Peter Baker, Green Mountain Quality Assurance

The ecosystem of life science data has experienced a seismic shift. Industry 4.0, the Internet of Things and next generation intelligence have enabled unprecedented capabilities in using data to support product development, process excellence, compliance and innovation. We are now in a new era suffused with promise for health and well-being.

Want to learn more about data integrity in the age of big data and Industry 4.0? Consider attending the *2019 PDA Data Integrity Workshop,* Sept. 18–19, in Washington, D.C. www.pda.org/2019diworkshop

But as this big data revolution sends shockwaves through every corner of our industry, and inspired futurists flurry to adopt new technologies, build analytical models and tinker with artificial intelligence (AI), stewards of data integrity might find themselves reeling.

The renewed focus on established data integrity requirements has resulted from regulatory inspections identifying critical, and, at times, fraudulent data integrity breaches. Organizations have rallied, tilting efforts toward remediation and process improvements, while ALCOA, standing for "attributable, legible contemporaneous, original and accurate," has become the abiding standard for ensuring the integrity of GMP data.

In this emerging landscape, the industry can be divided into proactive and reactive players, further subdivided by size and technology with—unfortunately—the occasional miscreant, leaving data integrity champions with their hands full. Regulators, experts and quality assurance (QA) leaders all wrestle with creating cohesive rules, assessment strategies, communications and training to enable data integrity. As manufacturing processes have become more complex due to the range of paper-based and automated systems, hybrid systems and complex data acquisition models, new perspectives are desperately needed.

QA Meets IT: A Success Story?

Some companies have turned to ITQA functions to ensure the integrity of data managed by computerized systems. By enabling the IT department to manage data integrity compliance in an increasingly digitalized environment, theoretically, the integrity of computerized data would be better ensured. Yet manufacturers are finding ITQA departments lack the requisite GMP expertise necessary to assess the data lifecycle and its impact on product quality and patient safety.

Compliance gaps and breaches continue to occur. In the best of cases, traditional

This is an opportunity…to pioneer next generation data integrity

QA departments learn computer system validation principles on the fly through regulatory and industry guidance documents. In the worst of cases, QA finds themselves assessing product quality in response to a breach. In either scenario, it can be argued that innovation has outpaced the rules.

Meanwhile, big keeps getting bigger.

In the life sciences, data is being generated at an exponential pace. Wearables, sensors, smartphone wellness applications, smart manufacturing, digital technologies and software programs have enabled exchange, creating a borderless data ecosystem in the cloud. Data is now an asset. In the big data revolution, this burgeoning, disparate and, at times, ominous collection of data is just the beginning. The value is in the intelligence, or analytics. Data modelling, algorithms and deep learning will drive next generation life science innovation.

Catching Up to New Technology

From the perspective of data integrity compliance, the situation is thorny. The big data revolution has been the stomping ground of IT, engineers and computational scientists. For QA, the knowledge and experience of big data and AI has been thin. QA can no longer simply rely on an ALCOA checklist. "Wranglers" of big data repositories must manipulate data for usability. When software platforms perform the "wrangling," the programs learn from the decision-making of the user and complete the "manipulations" independently. The transparency of such manipulations, in particular, deletions, may not be visible to QA.

Although data lineage is a data quality attribute among data scientists, and in theory, connects the output to its raw data point, when it comes to big data, this pathway is circuitous, and data may be "scrubbed" prior to review. "Scrubbing," i.e., well-intentioned decisions to delete information considered erroneous, may itself introduce risks.

Another challenge is the large number of algorithms, including some that operate without human intervention and do not afford visibility into the decision-making process.

All of these challenges fuel a call to action. This is an opportunity (and some might say responsibility) to pioneer next generation data integrity. Champions of data integrity can swap shy for savvy and win the interdisciplinary skills necessary to en- ➤

hance the QA paradigm and enable agile compliance in tenor with big data and AI disruption, thus empowering innovation.

And now for some good news.

Global regulators are recognizing the profound benefits of big data and AI, and the subsequent need for regulatory change. The U.S. FDA, for example, has been a leader and early adopter with programs such as the Sentinel Initiative for post-marketing surveillance of big data datasets generated by health insurers, and its INFORMED initiative aimed at implementing big data analytics to inform oncological regulatory science. The Agency is also data mining via AI tools and methodology to detect "signals" across internal databases and collect safety data. These initiatives offer insight into FDA's thinking in terms of compliance, for example, the forming of multidisciplinary teams, the need to standardize data and analytical models and the value of data sharing. According to former FDA Commissioner **Scott Gottlieb,** in an *FDA Voices* blog post from August 2018, FDA is actively "developing a new regulatory framework to promote innovation in this space and support the use of AI-based technologies" ***(1).*** Less than a year later, FDA released a discussion paper and request for feedback, proposing a regulatory framework for changes in algorithms that may impact technological efficacy and patient safety ***(2).***

Additionally, EMA and the Heads of Medicines Agencies (HMA) have established a joint task force to "investigate the potential role of 'big data' in the context of medicines development and regulation in the European Union" ***(3).*** In February, the task force published the HMA-EMA Joint Big Data Taskforce Summary Report, a seminal body of work that acknowledges that in regard to big data and AI the "uncertainties about the quality of the data, the models and the level of quality management used undermine the confidence in the validity and reliability of the evidence generated" ***(4).*** The good news is the summary report is conclusive on the benefits of big data and AI, offering robust learnings, recommendations and strategic objectives to support a roadmap.

> "Data integrity is a major component of big data and AI"

As global regulators continue to cite data integrity issues during GMP inspections, the industry can expect to see further requirements that address data integrity for big data technologies. Recent FDA Warning Letters evidence that the Agency maintains little tolerance for intentional or unintentional breaches in data integrity. We can expect that FDA will retain this mode of thinking as applied to emerging big data technologies, considering the Agency's overall mission to both protect and promote public health.

We are privileged, as data integrity pioneers in spirited collaboration with our industry partners, to support global regulators in the adoption of big data and AI innovative healthcare in commitment to the lives and well-being of patients.

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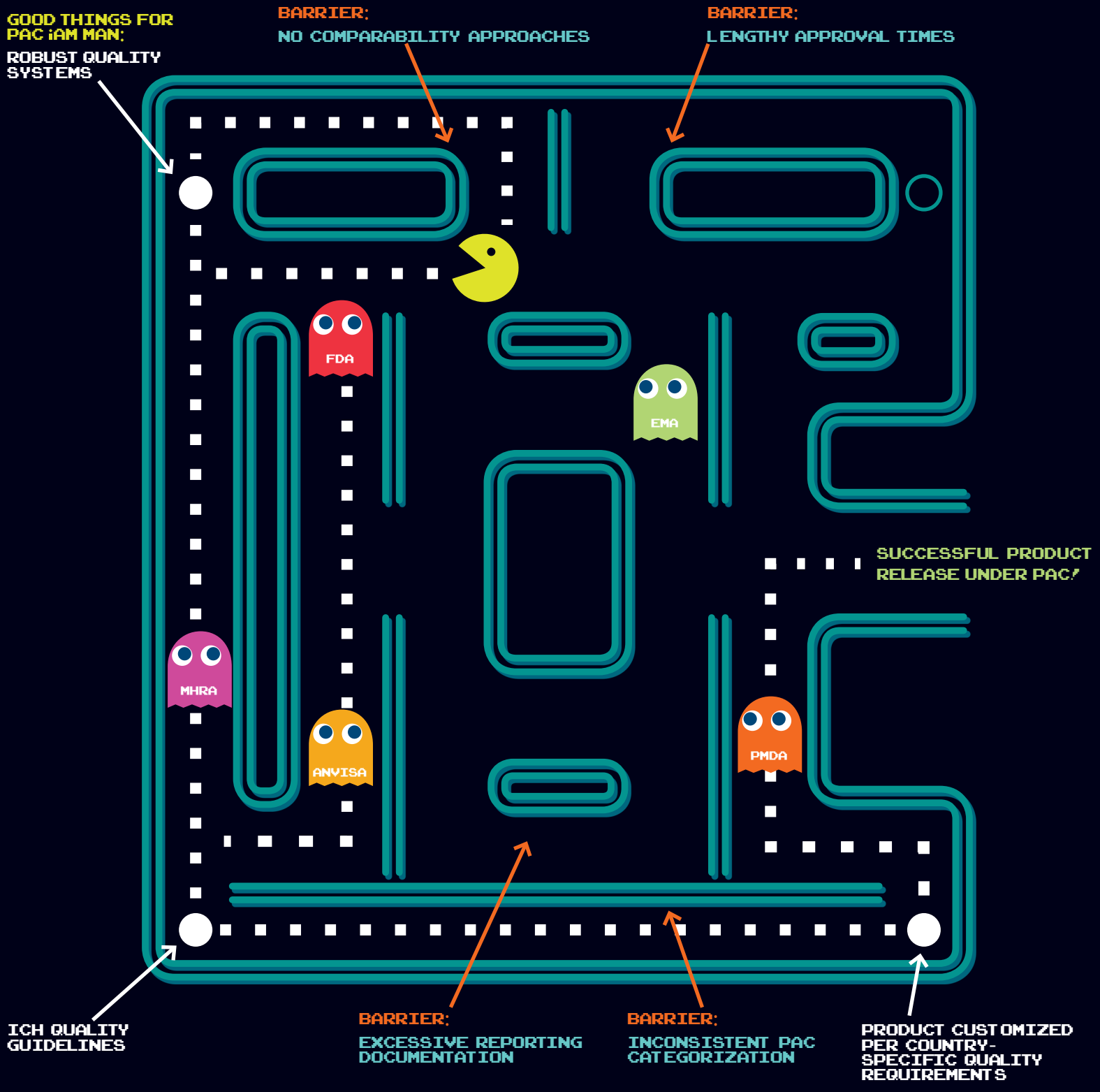

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- **Global Conferences and Workshops** on topics such as glass quality, parenteral packaging, container closure integrity testing, and pre-filled syringes
- A broad array of **Topic-specific Training Courses**
- **Technical Reports and Resources,** 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

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

Full Support for WHO WFI Guidance

April 15, 2019

World Health Organization
Medicines Quality Assurance
kopps@who.int
jonessi@who.int

Reference: Production of Water for Injection by Means Other Than Distillation (February 2019) Draft Guidance

Dear World Health Organization,

PDA appreciates the opportunity to World Health Consultation on: Production of Water for Injection by Means Other Than Distillation. PDA fully supports the WHO's Production of Water for Injection by Means Other Than Distillation (February 2019) Draft Guidance, as it advocates a risk-based lifecycle approach. The WHO draft guidance deems to incorporate the latest changes in European Pharmacopoeia and other global regulatory and standards guidances. PDA supports flexible approaches for products currently manufactured to avoid interruption of supply of essential medicines. PDA is also working to harmonize language across guidances as a global effort to increase the implementation of standard processes.

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

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

Sincerely,
Richard Johnson
President and CEO, PDA
Cc: Tina Morris, Falk Klar, Janie Miller

PDA Commenting Team

Igor Gorsky, ConcordiaValSource

Phil DeSantis, DeSantis Consulting Associates

To see the full comments grid, go to https://tinyurl.com/y2qcxol4

PDA's full database of regulatory comments is now under the "Global Community" "Member Resources" tab at the top of the home page.

A Weeklong Look at Quality Risk Management

Susan Schniepp, Regulatory Compliance Associates

PDA is excited to announce that U.S. FDA CDER Director **Janet Woodcock**, MD, has agreed to be the keynote speaker for a new conference concept that will focus entirely on quality. The inaugural *PDA Quality Week* will consist of three distinct conferences, each one focusing on a different aspect related to quality risk management (QRM).

The first conference for the week is titled *Risk Management in the Regulatory Landscape* and will provide participants a foundation in QRM. Lively panel discussion will cover various aspects of risk management. There will also be case studies to exemplify how risk management is being integrated into everyday activities.

2019 PDA Quality Week

Washington, D.C.

Dec. 9–13

www.pda.org/2019qualityweek

The second event of the week is a workshop, *Building a Foundation and Culture for Quality Risk Management Integration.* This workshop will focus on the basic foundational elements needed to incorporate risk management thinking into company culture throughout an organization. This includes what barriers might exist when integrating risk management and practical solutions to overcoming obstacles in a risk management program. Participants will have an opportunity to plan how they might help their organization implement a total risk management program.

The final conference of the week, *Optimizing Quality Risk Management,* will build on the two previous meetings, identifying strategies for successfully implementing an effective QRM program. Attendees will learn how to implement, document, train and identify the different roles needed for success. There will also be opportunities to share experiences and identify opportunities to collaborate both within their company and externally with organizations like PDA.

Although each of the phases is related to each other, they are designed to be standalone conferences, offering attendees the flexibility to participate in as many of the activities provided.

Stay tuned for more information about the *2019 PDA Quality Week!*

pda.org/2019RapidMicro

2019 PDA Rapid Microbiological Methods Workshop

The momentum is building!

Industry and regulatory experts from across the globe will address challenges and offer first-hand insights and real-world practices on the evaluation and implementation of rapid microbiological methods.

The agenda features presentations from:

Bill M. Carpenter, MS, Senior Manager, QC Microbiology, *Biogen, Inc.*

Luis E. Jimenez, Sr., PhD, Associate Professor, *Bergen Community College*

Jeffrey W. Weber, Senior Project Manager, PAT, Global Technology Services, *Pfizer Inc.*

Get your pressing questions answered during the final Ask the Experts and Regulators Panel Discussion!

Don't let travel hold you back! This Workshop will be live streamed. Experience the same great content without additional time away from the office (or lab)!

To learn more and register, visit *pda.org/2019RapidMicro*

OCTOBER 23-24 | ROCKVILLE, MD

14TH ANNUAL PDA GLOBAL CONFERENCE ON PHARMACEUTICAL MICROBIOLOGY: OCT. 21-23
EXHIBITION: OCT. 23-24
TRAINING COURSES: OCT. 25
#PDARapidMicro

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pda.org/EU/Bio2019

2019 PDA EUROPE

BioManufacturing

3-4 SEPTEMBER 2019
MUNICH, GERMANY
EXHIBITION: 3-4 SEPTEMBER
TRAINING: 5-6 SEPTEMBER
IG MEETINGS: 2 + 5 SEPTEMBER

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Foreign Particles in Bull's Eye of Global Reg Agencies

Hirohito Katayama, PhD, Bayer Yakuhin, and John Shabushnig, PhD, Insight Pharma Consulting

A fill/finish process for injectable products must ensure that the formulation is accurately filled into the container (e.g., ampoule, vial, syringe, bag). The container must also protect product throughout the shelf-life. The container should be free of foreign particles and sealed without damage that could affect container integrity.

The container closure system and fill/finish process should be selected based on development studies and a careful validation process per GMP. Despite these controls, there may still be variation in the process environment or the critical dimensions of container closure system components, possibly resulting in poor quality. Therefore, global regulators require injectable products to have a 100% visual inspection control with special attention given to properly sealed containers. For containers sealed by fusion (i.e., ampoules or bags), a 100% container integrity test must be performed. For other containers, adequate tests must be in place to ensure integrity of all containers of a batch.

2019 PDA Pharmaceutical Product Quality Testing Conference

Tokyo, Japan
Oct. 29-30
www.pda.org/2019japan

With these challenges in mind, the *2019 PDA Pharmaceutical Product Quality Testing Conference* will highlight current regulations and pharmacopeial requirements in Japan/Asia-Pacific, Europe and the United States. Recent regulatory activities including recalls, warning letters and industry experiences will be discussed.

A special session will give an update on the test procedures, equipment and technologies used for visual inspection. The key focus of this session will include:

- Elements of a good visual inspection process, including qualification of personnel, the inspection process, sampling strategy, defect library and how do deal with difficult-to-inspect containers
- Good container integrity control, including selection of a compatible inspection method, defining "properly" sealed for a product, validation strategies and the latest regulatory considerations.

A two-day training course on visual inspection is also planned to further enhance learning on this important topic in conjunction with the meeting.

Published online first
PDA
letter.pda.org

Holistic Verification Requires a New Mindset

David Hubmayr, CSL Behring

Patient-focused pharma requires a risk- and science-based verification approach that supersedes the traditional phases of commissioning, qualification and the firmly established method of specified parameter range testing that includes worst-case scenarios. To deliver on the promise to patients, the holistic verification approach offers the potential for beneficial outcomes.

The holistic verification approach is based on already proven concepts acknowledged by regulators and built around patients. This method overstretches the entire product and process lifecycle, starting from scratch at the research stage with the Target Product Profile, and on through the entire product development process. Leading a collaboration with vendors is critical to the success of this approach.

Quality-by-design is a linchpin of holistic verification, since quality can never be tested into a product but must be designed into it. Quality risk management, supported by a process Failure Mode and Effect Analysis (pFMEA) lifecycle document, allows the effective use of gained knowledge throughout this journey.

A pFMEA setup as a risk management tool grades potential risks using data generated during development based on severity, probability of occurrence and detectability. The emphasis here is on the use of available data. Gut feelings and educated guesses are still too often consulted as a basis for grading, clearly contradicting the risk- and science-based approach. Another emphasis is on the process control strategy as the goal of product and process development is to design and establish a formulation composition consistently meeting patients` needs for the respective therapeutic purpose. The development of a robust manufacturing process which ensures that product quality targets are met should be accompanied by critical quality attributes linked to process parameters. Achieving quality by designing it into the manufacturing process facilitates the development of an effective process control strategy.

Once the product and manufacturing processes are defined, end user requirements drive the stage gate process toward an engineering solution. Here, both product quality relevant (i.e., Good X Practice) and nonproduct quality relevant (i.e., non-Good X Practice) requirements are initiated. These cover the basic design up to multiple, more detailed, design reviews (e.g., 30/60/90%), stretching out till issuance for construction (IFC)/approval for construction (AFC).

The end user sets requirements in a user requirement specification (URS) document. There are two methods that can be used here. A company can supplement a URS with manufacturing, engineering and automation (L1 to L3) information or split into a process user requirement which divides into multiple technical requirement specifications, if applicable. Following the establishment of a URS, risk analysis is necessary. This analysis should focus on the design as this is the stage when weaknesses in functionality can be assessed. The selection of an appropriate risk assessment tool at this level and the amount and quality of data available to support the design focused risk assessment often varies due to the levels of novelty and complexity.

Using a design risk assessment, putting available GMP controls first and waiving severity (S), probability of occurrence (O) and detectability (D) gradings establishes a thorough review of design and functionality. Generating gradings based on subjectivity limits the effectiveness of control strategies in adequately managing risks as risk is proportional to uncertainty—and uncertainty is inversely proportional to knowledge. After grading of S, O and D, the risk priority number is calculated. Keep in mind, this is not an absolute number. Risk priority numbers are a product of ordinal scale numbers and any mathematical operation (e.g., multiplication) is questionable. Close attention must be paid to the validity of the RPN calculation, only acting on GMP controls when the RPN exceeds a defined threshold puts patients unnecessary at risk. It is not possible to eliminate subjectivity entirely, but evidence-based estimation of risk/residual risks can reduce it.

In addition, controls that prevent (e.g., eliminating hazard by redesigning the item in question) and controls that protect (e.g., building in new and improved detection mechanisms) must be in scope.

The Role of Vendors

Following agreement on a vendor, detailed specifications (e.g., functional, design, software, hardware and process) come into play. The formal documentation outlining acceptance of the proposed realization is the design qualification (DQ) document. Once the DQ is approved, things move into the construction/compilation phase.

But if a vendor is involved, how can companies ensure success? A nontechnical quality kickoff with the accepted vendor is essential and cannot be stressed enough. An element of the holistic verification approach is to use vendor documentation to document successfully passed tests. These should not have to be repeated due to documentation not meeting appropriate standards. Relying on vendor documentation means substituting a company's own documentation. At the same time, the quality of the vendor documentation must be high enough to be presentable during an inspection.

Deploying holistic verification raises the degree of freedom for determining the point in time for testing requirements and the format for documenting testing. Testing can occur whenever a vendor is ready, or the engineering system is mature enough. There is no need to wait for handover into a "formal" qualification phase.

Whenever a vendor is ready for an inspection, or the engineering system is mature enough, testing can happen and be documented with no need to progress through a "formal" qualification phase anymore, issue "formal" qualification documentation and, especially, produce independent quality preapproval verification documentation. This certainly shortens implementation timelines and significantly lowers the risk of detecting expensive insufficiencies in too-late stages. Following all testing, a verification report shows compliance status and fit-for-purpose.

In conclusion, the holistic verification approach is backed by familiar concepts. Keep in mind that global regulators have identified continual improvement and innovation not as "nice-to-haves" but as basic expectations. And both are essential activities within a pharmaceutical quality system. In practice, implementation of holistic verification requires cross-discipline teamwork, yet the hurdles to this can be overcome. The real showstoppers require changing current mindsets with a strong push of qualified, future-focused management at all levels.

About the Author

David Hubmayr is member of the Integrated Commissioning and Qualification Expert Group at CSL Behring. He is responsible for qualification compliance.

Common Goals Make Everyone Stronger

Joyce Bloomfield

The combined efforts of our talented membership allow us to meet one common goal: supplying safe products to the world's patients.

This common goal aligns all our members on critical regulatory expectations. In addition to our many members within the industry, a large number of PDA members work for global regulatory agencies. Having had the distinct privilege to work for the pharmaceutical industry and the U.S. FDA, I identify with both, and recognize that whether we work for a company or for a regulatory agency, we are all equally driven by a deep passion for patient safety and health.

We all benefit when we work together to develop the best approaches to GMP. Our members drive the development of new technology through sharing knowledge at PDA Education courses, workshops and conferences. This sharing of knowledge paves the way for effective internal audit and inspection programs.

It has been my privilege to participate in many PDA meetings on critical industry topics. My favorite conference has always been the *PDA/FDA Joint Regulatory Conference.* I recall how I coveted attending this conference as a regulator. Even when I switched to working for a company, I continued to attend the conference. As I became more involved with PDA, I eventually contributed to shaping the conference as a member of the program planning committee.

Why do I enjoy attending the *PDA/FDA Joint Regulatory Conference?* This conference brings regulators and industry representatives face to face to discuss turnkey topics in the areas of manufacturing, quality, regulation and compliance. Each year, the conference evolves due to the needs of the pharma community. The program planning committee works months in advance to identify the most pressing trends affecting industry. Topics at this conference impact the development and content of many PDA documents—leading to practical guidance on applying regulations that best serves patients.

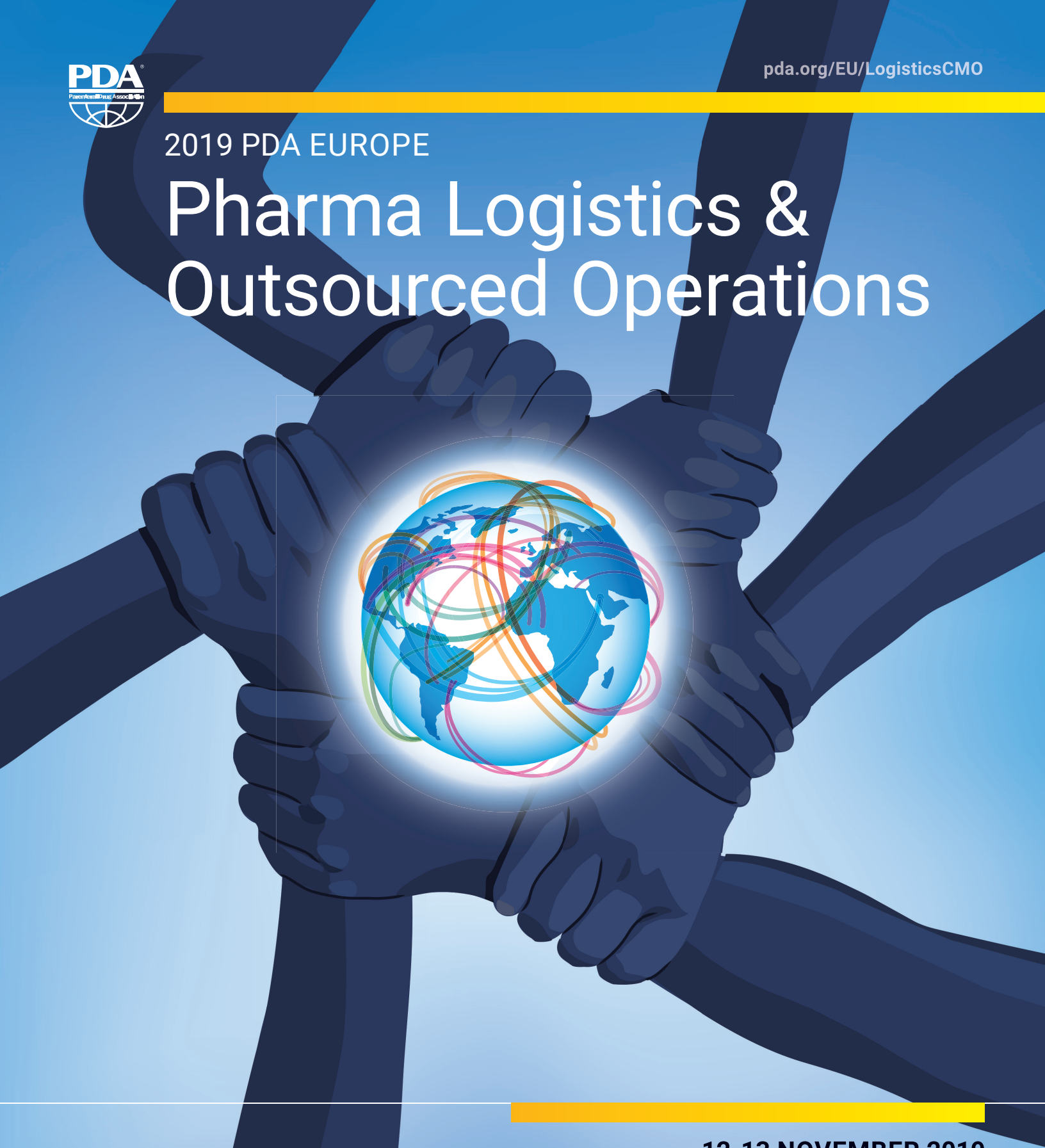
Beyond the *PDA/FDA Joint Regulatory Conference,* PDA staff and volunteers work seamlessly throughout the year to provide useful information to benefit all of us. There is no greater passion than those volunteers from companies and regulatory agencies of all sizes forging the way, going well beyond the call of duty to truly make a difference.

At the end of the day, the goals of industry and regulators are equivalent. Both want safe, available medicine for the world's patients. For me, there is no greater satisfaction as a PDA board member than to have been a part of this great journey by working together toward common goals that make everyone stronger.

pda.org/EU/LogisticsCMO

2019 PDA EUROPE

Pharma Logistics & Outsourced Operations



12-13 NOVEMBER 2019
LISBON, PORTUGAL
EXHIBITION: 12-13 NOVEMBER
IG MEETING: 14 NOVEMBER

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2019 PDA Quality Week

Mastering Risk Management for Organizational Success

MEET OUR KEYNOTE SPEAKERS!

Thomas Stanton, Author, *Enterprise Risk Management (ERM): A Powerful Federal Management Tool*

Janet Woodcock, MD, Director, CDER, *FDA*

Make plans to attend the inaugural *2019 PDA Quality Week*!

Gain the skills you need to implement and optimize a quality risk management (QRM) program in your organization – directly from global industry and regulatory experts!

- ***Risk Management in the Regulatory Landscape Conference*** **| December 9-10**
  Discover the current QRM global regulatory expectations and how regulatory agencies are using risk-based decisions to determine inspection frequencies and provide oversight.
- ***Building a Foundation and Culture for Quality Risk Management Integration Workshop*** **| December 11**
  Listen to real-world case studies from organizations that have established QRM programs and learn the steps for creating a strong quality culture as a prerequisite for a successful QRM program.
- ***Optimizing Quality Risk Management Conference*** **| December 12-13**
  Master the process of successfully applying risk-based approaches to optimize the overall lifecycle management of a product, as envisioned by ICH Q12.

Register by October 25 and save up to $600!

Register for two events and save 10% or register for all three events and save 15%!

To learn more and register, visit *pda.org/2019QualityWeek*

DECEMBER 9-13 | WASHINGTON, DC

EXHIBITION: **DEC. 10-11**

RISK MANAGEMENT IN THE REGULATORY LANDSCAPE CONFERENCE: **DEC. 9-10**

BUILDING A FOUNDATION AND CULTURE FOR QUALITY RISK MANAGEMENT INTEGRATION WORKSHOP: **DEC. 11**

OPTIMIZING QUALITY RISK MANAGEMENT CONFERENCE: **DEC. 12-13**

#PDAQualityWeek

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