People • Science • Regulation

PDA Letter

Volume LV • Issue 10 www.pda.org/pdaletter November/December 2019

FDA Takes Close Look at Innovation 30

PDA
Parenteral Drug Association

pda.org/2020Annual

2020 PDA Annual Meeting

REGISTER BY JAN. 30, 2020 AND SAVE UP TO $600

Don't miss the early registration deadline!

The *2020 PDA Annual Meeting* is looking to the future of pharmaceutical manufacturing by examining how companies are developing new modalities and adapting to the current manufacturing environment through the modernization of aging facilities and the adoption of innovative approaches and processes.

CALLING ALL YOUNG PROFESSIONALS

Meet other ambitious life science professionals entering the field and build strong business connections with established leaders.

Attend special sessions and networking events planned with YOU in mind.

This Conference is shaping up to be an eye-opening look into the promising future of pharmaceutical manufacturing.

To learn more and register, visit
pda.org/2020Annual

MARCH 30-APRIL 1 | RALEIGH, NC

EXHIBITION: MARCH 30-APRIL 1
2020 PDA PHARMACEUTICAL MANUFACTURING DATA SCIENCE WORKSHOP: APRIL 2
TRAINING COURSES: APRIL 3
#PDAAnnual

CONNECTING PEOPLE SCIENCE AND REGULATION®

November/December 2019 PDA Letter

FDA Takes Close Look at Innovation

Rebecca Stauffer, PDA

Industry 4.0. Artificial intelligence. Big data. Even continuous manufacturing. All of these new technologies will drive the future of pharmaceutical and biopharmaceutical manufacturing. Yet questions persist as to how the U.S. FDA and other global regulatory agencies will address these new technologies, leaving some companies reluctant to fully embrace these advances as early adopters.

Cover Photo by Christopher Ames

Robotics and Big Data Key to Lab of the Future

Peter Crane, Synthace

I had the good fortune to attend the *Digital Robot Pharma Fab* workshop and the *4th PDA Europe Annual Meeting* in Amsterdam this past June.

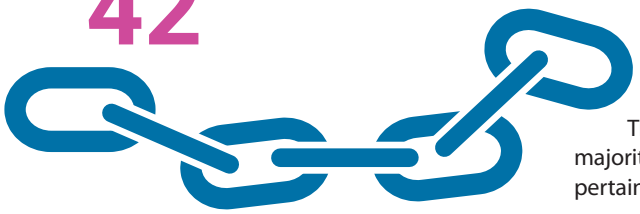
Add Sherlock Holmes to Your Investigation Team

The Role of a Microbiologist in Teams Investigating Product Failures Due to Manufacturing Issues

Tony Cundell, PhD, Microbiological Consulting, LLC

You have reported a microbial test failure to your site's management following confirmation by a laboratory investigation. You then assemble a cross-functional team to investigate the most likely cause of the failure during manufacturing.

InfoGraphic



Data Integrity: Remediation and Quality Culture

The *2019 Data Integrity Workshop* opened with a real-time survey of attendees, the majority representing pharma/biopharma manufacturing. Here are some highlights that pertain to remediation and quality culture.

PDA Letter

Volume LV • Issue 10 www.pda.org/pdaletter

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

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

Subscriptions are not available.

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

Departments

Digital Exclusives

> Strategic Application of Advanced Analytics for CGT Development
Advanced analytical data can help ensure a stable pipeline of cell and gene therapy products and even address CMC issues.

pda.org/letter

PDA GLOBAL HEADQUARTERS
4350 East West Hwy., Suite 600
Bethesda, MD 20814 USA
Tel: +1 (301) 656-5900
Fax: +1 (301) 986-0296
info@pda.org
www.pda.org

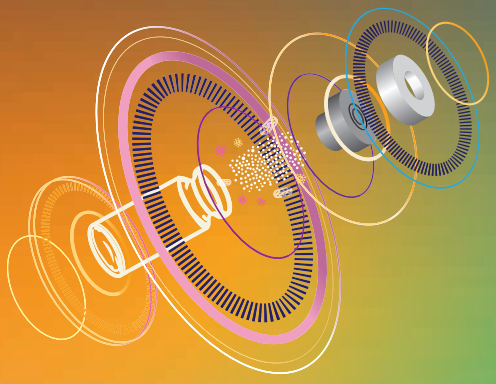
PDA EUROPE — AM BORSIGTURM 60
Am Borsigturm 60
13507 Berlin, Germany
Tel: 49 30 4365508-0
Fax: +49 30 4365508-66
info-europe@pda.org

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

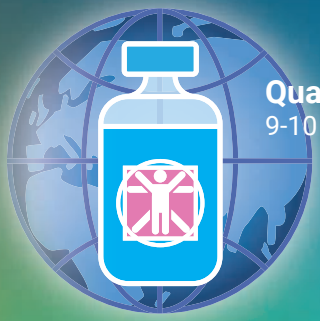
pda.org/global-event-calendar

PDA EUROPE

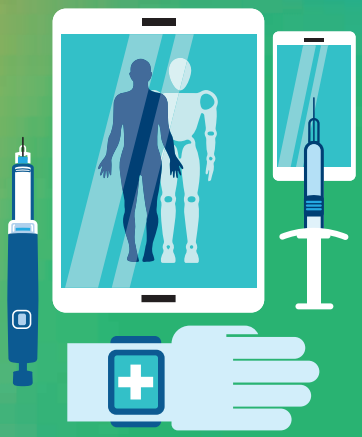
2020 Highlights



Parenteral Packaging
25-26 FEBRUARY



Quality and Regulations
9-10 JUNE



Medical Devices and Digital Healthcare
8-9 SEPTEMBER

Aseptic Animal Health
20-21 OCTOBER

25-26 February	Parenteral Packaging	Basel, Switzerland
21-22 April	Visual Inspection Forum	Berlin, Germany
9-10 June	Quality and Regulations Conference	Dublin, Ireland
22-23 June	Virus Forum	Brussels, Belgium
24-25 June	Advanced Therapy Medicinal Products	Brussels, Belgium
8-9 September	Medical Devices and Digital Healthcare	TBC, Europe
22-23 September	BioManufacturing	TBC, Europe
24 September	Pharmaceutical Freeze Drying Technology	TBC, Europe
20-21 October	Aseptic Animal Health	TBC, Europe

CONNECTING PEOPLE SCIENCE AND REGULATION®

pda.org/2020Annual

The 2020 PDA Annual Meeting is *the* Place to Connect with Key Decision Makers

Looking to align your company with world-class content, introduce new products and services to your target audience, and make valuable new connections with industry influencers?

Then make plans now to exhibit at or sponsor the *2020 PDA Annual Meeting*, **March 30-April 1at the Raleigh Convention Center in Raleigh, NC.**

PDA offers a wide variety of highly visible and cost-effective options to increase your brand awareness among this broad audience of industry "movers and shakers," including:

- Conference Mobile App
- Lanyards
- Tote Bags
- Aisle Banners
- Insert in Conference Tote Bags
- Sponsorship of the Walk/Run
- Hotel Key Cards
- Sponsorship of Reception, Refreshment Breaks, or Lunch
- Wireless Internet
- Much More!

Take advantage of this early opportunity to secure the ideal booth location or sponsorship opportunity to showcase your company's products and services!

To learn more about sponsorship and exhibition opportunities, contact **David Hall**, Vice President, Sales, *PDA*, at hall@pda.org or +1 (240) 688-4405.

CONNECTING PEOPLE SCIENCE AND REGULATION®

MARCH 30-APRIL 1 | RALEIGH, NC
EXHIBITION: MARCH 30-APRIL 1
#PDAAnnual

Hot Topics Covered in 2019

As the year frantically marches to a close, I want to offer some highlights as we close out 2019 and enter 2020.

With the European Union's Annex 1 revision stretched out into 2019, frequent *PDA Letter* contributor, past-PDA Chair, and longtime PDA volunteer and instructor **Hal Baseman** (who is practically a fixture at PDA headquarters!) authored the February cover story on the controversial recommendation for pre-use, post-sterilization integrity testing (PUPSIT) of sterilized filters. Hal explained that PUPSIT could introduce unnecessary risks. Currently, Hal and other longtime PDA volunteers and filtration experts—including Past-Chair **Maik Jornitz**—are conducting research into, among other things, the "masking effect" of PUPSIT. Hal, Maik and PDA's Vice President of Scientific and Regulatory Affairs **Tina Morris** offered an in-depth assessment of this research in an article posted the Friday before the Labor Day holiday in the United States ("PUPSIT and the Annex 1 Revision"). We realized the importance of this research when hundreds of readers had viewed the article by the end of the holiday. Apparently, nothing stops PDA members from getting the information they need!

The February issue also included an infographic based off a survey we conducted of readers' concerns about the proposed Annex 1 revision. In 2020, we will continue to produce infographics highlighting similar topics.

In the October *PDA Letter,* we published our first major profile of an industry thought leader, **Jeffrey Galvin.** Jeffrey went into great detail about his experiences in Silicon Valley and how that translated to his work in cell and gene therapies. Moving forward, we want to profile other industry thought leaders and readers are encouraged to send in recommendations.

We continued our successful "On the Issue" video series. Topics covered in these videos throughout the year have included gloveless isolators, cross-contamination control, container closure integrity and visual inspection. We also filmed some of the Young Professionals who volunteered for PDA at the *2019 Annual Meeting*. Additional videos were filmed at the *2019 PDA Joint/Regulatory Conference* and the *14th Annual PDA Global Conference on Pharmaceutical Microbiology.* These will be available next year.

2020 promises to be a noteworthy year for the *PDA Letter*. As I mentioned in my previous Editor's Message, we will continue to focus on the *PDA Letter* website as the primary content hub. We will also work on quarterly regional editions with content tailored for our readers in Europe and the Asia-Pacific region.

The year has moved fast (as everyone always says) and we are picking up the pace into 2020 and beyond. Get your seatbelts on!

Rebecca Stauffer

@RebeccaStauPDA
www.linkedin.com/in/rebecca-stauffer-782b2310

Online Pubs Expand Access and Areas of Focus

Walter Morris, Senior Director of Publishing

@Walt_PDA
www.linkedin.com/in/walter-morris-82191a4

Over the last decade, PDA's publishing shifted from the traditional print format to online, or electronic publishing. This transition started with our technical reports in 2008, when PDA ceased mailing new technical reports with the *PDA Journal of Pharmaceutical Science and Technology* (*PDA JPST*) in favor of posting them to the online PDA Bookstore as PDF files. A year later, we partnered with HighWire Press, Inc. to provide the online edition of *PDA JPST*, saving even more trees and postage. In 2010, we expanded the online *PDA JPST* to include all issues dating back to 1980. A year later, we launched the online submission and review tool, and soon thereafter, we initiated our version of "publish ahead of press"—i.e., "Accepted Articles"—to reduce the time it took manuscripts to become referenceable resources. We also launched the Technical Report Portal, which gives all standard members access to every active technical report online.

The reaction to moving these critical member-benefit publications to the Web was predictably very positive. In the case of *PDA JPST,* the online version, complete with advanced search capabilities and other features, made the publication a vastly more useful vehicle for research. Virtual technical reports were a bit of a harder "sell" to PDA's community, but overall, members enjoy the ability to download their free PDF version of each new report so that they can "take" them anywhere on their laptops. And when an older report is needed, using the portal is infinitely more convenient than rifling through old booklets or bothering colleagues in the office for a copy!

In 2019, we completed a much-needed upgrade to the *PDA JPST* website and made improvements to the online submission and review website. I wrote extensively about the design and features of the new *PDA JPST* website in the Sept/Oct edition (https://doi.org/10.5731/pdajpst.2019.001115).

The *PDA Letter*—PDA's flagship member publication—lagged behind its sister membership publications when it came to electronic publishing. As of 2015, only PDF versions of the *PDA Letter* were posted along with a limited selection of articles online in HTML. In essence, the *PDA Letter* was crafted as a "print-first" publication, and online content was secondary.

That started changing in 2016 with the launch of the new *PDA Letter* Web portal. With it, we launched our "On the Issue" videocast and published-ahead-of-print and online-only articles.

As Managing Editor **Rebecca Stauffer** in her many, wonderful Editor's Messages this year, the evolution of the *PDA Letter* continues in 2020. A new effort is underway to expand the Letter's online content and to create regional editions to better serve the needs of our members in Europe and Asia. To help expand the online content, we will reduce the print editions from ten to six so that we can shift our focus and resources to online. The print editions will be a collection of content posted online in the previous two months. We are finally flipping the script for the Letter in that it will be a truly "online-first" publication.

It is of the upmost importance that PDA's member benefit publications meet the needs of our members. If you feel these changes do not serve you well, or if you have any other comments or suggestions, we need to hear from you. Please contact me or Rebecca to let us know how we can better serve you. Also, if you are on Twitter and LinkedIn, follow us!

pda.org/FundamentalsAP

Fundamentals of Aseptic Processing

In 2020, this training course is being offered on the following dates:

JAN. 13-16 | BETHESDA, MD
FEB. 10-13 | BETHESDA, MD
APRIL 13-16 | TONGANOXIE, KS
JUNE 22-25 | BETHESDA, MD
AUG. 17-20 | BETHESDA, MD

Gain an understanding of the principles, processes, and systems related to aseptic operations with this interactive training course.

Improve job performance through newly acquired practical knowledge and skills.

Topics to be addressed include:

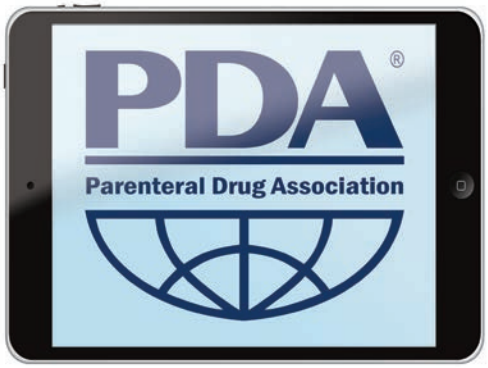
- Facility/Equipment/ Process Design
- Environmental Monitoring
- Airflow Studies
- Aseptic Gowning
- Disinfectant Efficacy
- Sanitization Techniques
- Filtration Processes
- Moist Heat Sterilization
- Aseptic Process Simulations (Media Fills)
- Reading and Evaluating Microbial Results
- Visual Inspection

CONNECTING PEOPLE SCIENCE AND REGULATION®

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

PDA In the News

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



American Pharmaceutical Review
Aug. 27, 2019
"Product Temperature Monitoring and Control via Thermal Imaging during Continuous Freeze-Drying of Pharmaceutical Unit Doses"
—Pieter-Jan Van Bockstal, Jos Corver and Thomas De Beer
tinyurl.com/yy4aovr4

BioPharm International
Aug. 1, 2019
"Moving From Compliance to Quality"
— Agnes Shanley
tinyurl.com/y3gd959e

Cleanroom Technology
Sept. 6, 2019
"How to design a cleanroom monitoring system"
— Hasim Solmaz
tinyurl.com/y3v6bgt5

Healthcare Packaging
Oct. 4, 2019
"Particles in Parenterals: 2019 Update"
— Dirk Rodgers
tinyurl.com/y6bykrgk

International Pharmaceutical Quality
Oct. 29, 2019
"USP Views Early Broad Stakeholder Engagement as Essential in Developing Performance-Based Standards for Biologics"
— (includes summaries of talks from *2019 PDA/FDA JRC*)

Maas & Peither GMP Publishing
July 23, 2019
"PDA Annual Meeting 2019 – Part 1"
— Thomas Peither
tinyurl.com/y5yf35zm

Pink Sheet

Aug. 20, 2019
"Pfizer/Mylan: Pending Clash Of Quality Systems Could Determine Fate Of New Firm"
— Bowman Cox

Sept. 20, 2019
"FDA: Key FY 2019 Warning Letter Trend Is Inadequate Testing For API Impurities"
— Joanne Eglovitch

Oct. 8, 2019
"Manufacturing Quality United States Some Pointers From The US FDA On How To Conduct Better Out-Of-Spec Investigations"
— Joanne Eglovitch

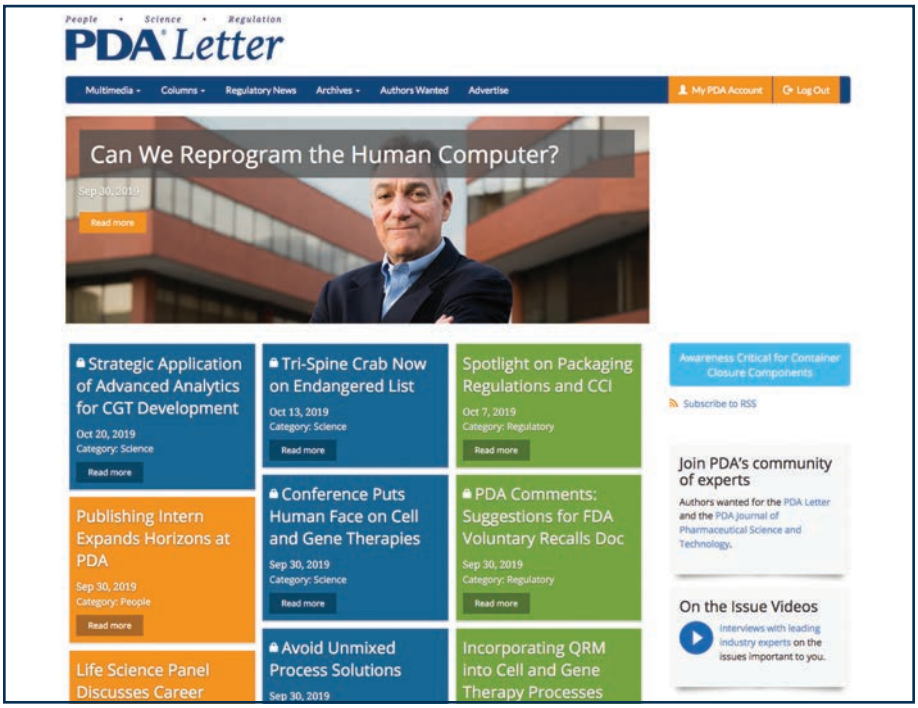
Call for Volunteers: Regional Editions of *PDA Letter*

Beginning next year, the *PDA Letter* editors will publish four quarterly regional editions in PDF format—two aimed at readers in Europe and two for readers in the Asia-Pacific region. Some articles may even be in local languages.

To accomplish this monumental but exciting task, the *PDA Letter* is seeking volunteers in these two regions for their assistance. This includes identifying potential authors, covering local PDA conferences and chapter events and curating content from the main *PDA Letter* website for inclusion in the issues.

The ideal volunteers should have more than five years of industry experience and some publishing experience is preferred.

If this opportunity interests you, please email the Managing Editor at stauffer@pda.org.



PDA Volunteer Spotlight

Karolyn Gale

- **Director, Regulatory Affairs**
- *Emergent BioSolutions Inc.*
- Member Since | **2017**
- Current City | **Winnipeg**, Canada
- Originally From | Dryden, Canada

It is so energizing to share and learn from others' experiences

How did you hear about PDA and why did you join?
I have been in regulatory affairs in the pharmaceutical industry for over 19 years and often heard of PDA in passing. In 2013, I moved into the biologics space at a manufacturing site for bulk biologic manufacturing and aseptic filling. At this time, I started truly leveraging PDA's technical reports.

Then, in 2016, a colleague of mine asked if I would be interested in providing feedback with PDA on a U.S. FDA draft guidance. This spurred another colleague to ask about my interest in working on the ICH Q12: *Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management Core Guideline Guidance for Industry* initiative with PDA. I have been hooked ever since.

How has PDA contributed to your professional career?
It has given me the opportunity to build a network of colleagues from across the industry. Additionally, I have had the opportunity to influence the issues that are so important to our daily working lives from a global regulatory and compliance perspective.

Do you have any advice for new volunteers?
Remember to use the time as a learning experience. You will learn at the same time as you work with your peers.

What is the greatest advice someone has given you?
One of the best pieces of advice I have ever received—and it is almost always true in work and in life—is to "sleep on it." It is so true that things always look better with some rest and some time to think through the facets of an issue.

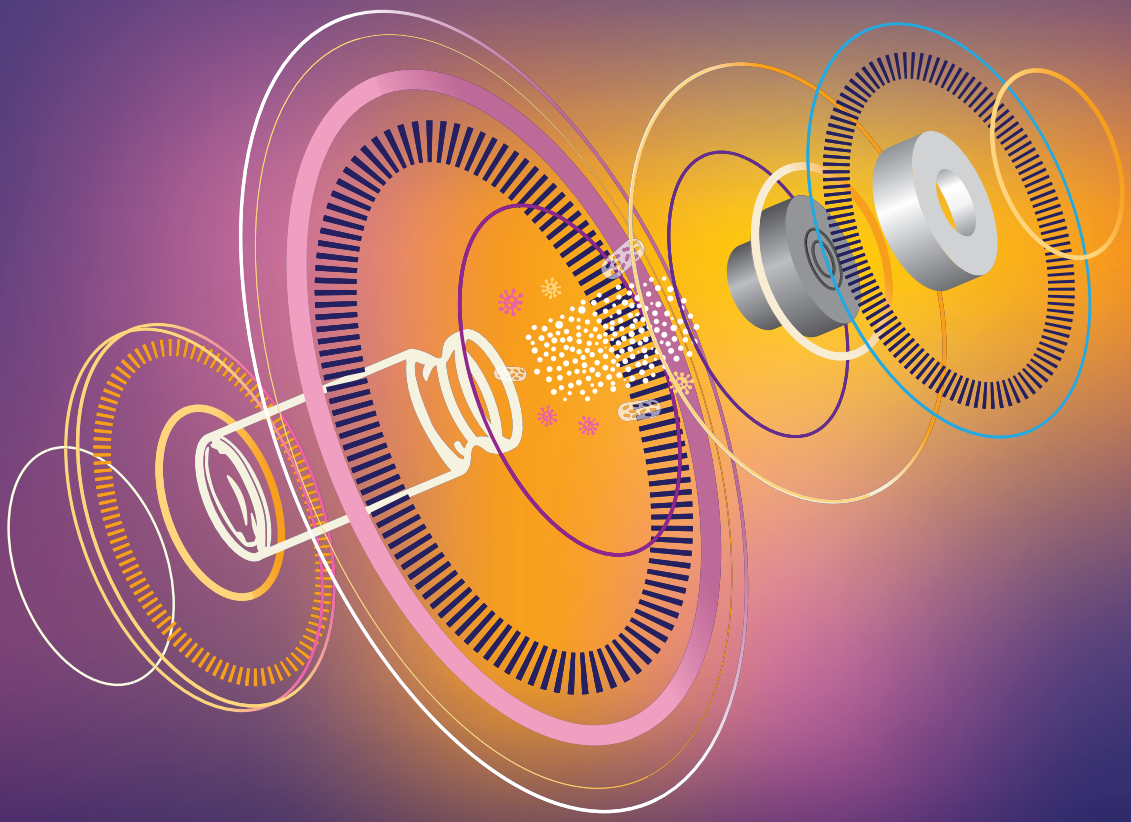
Which authors do you regularly read?
Right now, I am reading some great leadership books including **Brené Brown's** *Dare to Lead.* Brown also delivered a great TED Talk on vulnerability and has a new Netflix special.

PDA
Parenteral Drug Association

pda.org/EU/ParPack2020

2020 PDA EUROPE

Parenteral Packaging



25-26 FEBRUARY 2020
BASEL, SWITZERLAND
EXHIBITION: 25-26 FEBRUARY
EDUCATION & TRAINING: 27-28 FEBRUARY

MARK YOUR CALENDAR

CONNECTING PEOPLE SCIENCE AND REGULATION®

Chapter Update

Published online first

Life Science Panel Discusses Career Journeys

Christy Wong, Keck Graduate Institute, Student Chapter Communication Chairperson, PDA Southern California Chapter

Building a career in the life sciences industry requires using past failures as a foundation for future successes.

This was one of the main points expressed by a panel of life science leaders at the sophomore *Leaders in Life Sciences* event arranged by PDA's Southern California Chapter at the Genentech facilities in Oceanside, Calif., July 25. An evening filled with networking, delicious food, and thoughtful conversation, the event boasted over 140 attendees and 16 exhibitors.

It began with a networking session sponsored by iNK Digital Networking and Samsung. Attendees had the option of professionally connecting through iNK, a newly launched mobile app aimed to facilitate networking and streamline the exchange of business cards and information. A Samsung-operated photo booth was also available for the attendees to capture potential LinkedIn photos in a unique and entertaining way.

The chapter was honored to have PDA President **Richard Johnson** and other distinguished industry leaders participate in the event. The panelists were **Alan Taaghol, Gayle Derfus, Kevin Charrier, Nazeli Dertsakian** and **Valerie Whelan. E.J. Brandreth** served as the moderator.

After Chapter President **Randy George's** opening remarks, **Annmarie Duran** was recognized as the chapter's Board Member of the Quarter for Q2. She is Member-At-Large Committee Chairperson, Philanthropy and Donations and Events and Venues. Next, Chapter Vendor Outreach Chairperson **Herbert Matheson** recognized all the sponsors and exhibitors. Per the chapter's custom, each annual sponsor and exhibitor was given an opportunity to speak about their company's products and services for two minutes. Chapter Treasurer **Greg Mills** concluded the opening remarks by thanking Genentech for hosting the event and helping organize the venue, security and catering.

The panelists then commenced the discussion by talking about their professional journeys, including lessons learned throughout their years in the industry. They spoke about turning points in their careers, emphasizing that positive catalysts arise in the face of difficulty. Charrier exemplified the aforementioned maxim when he struggled for over half a decade to achieve regulatory compliance after his company received a U.S. FDA consent decree. He proclaimed that the hardship he endured during this period not only built resilience, but also served

But the room for innovation is rather large

as a learning experience that he draws from even years later in a different role.

The seasoned veterans also revealed the major influences in their careers. Three common influences for all were: failure, constructive feedback and communication. Each of these have been contributors to professional growth. Johnson, whose career has spanned from microbiology to engineering, pointed out that the journey of growth and evolution is not without hard work and curiosity. He also advised young professionals to not be afraid to try different things. Experimentation helps realize interests and motivations.

The panel also spoke about current industry trends, most notably, the advent of big data. The conversation revolved around the impact of technological advancement on already existing processes. The group concurred that the integration of big data in manufacturing processes is still a feat to be worked on, given, as Taaghol pointed out, big data has rendered both GCP and GMP processes less applicable than before. Whelan echoed this sentiment, noting that regulators are still working on adapting big data to speed up the process of providing products to patients. In order to make the best decisions, Dertsakian explained that generating the right data precludes its adaptation.

The group also touched on the caveats of big data, with data security being at the forefront. Both Charrier and Taaghol expressed concern about potential opportunities for data breaches involving cloud systems. This is a challenge that both regulators and the industry stakeholders will inevitably face together.

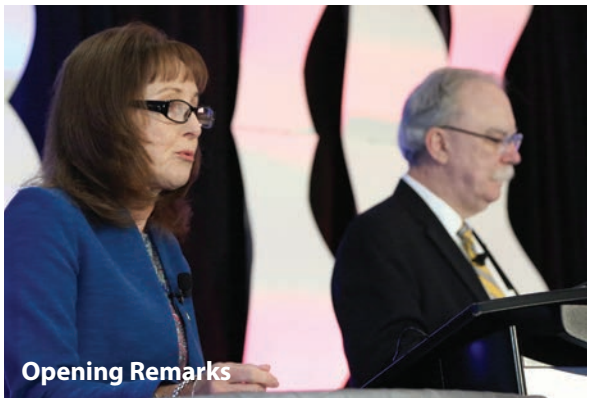
The panelists also gave their thoughts on the future of the life sciences industry. Derfus spoke about continuously rising cost pressures, and the challenge of creating cost-effective processes as a result. She emphasized that innovations in the lab must also be reproduced in manufacturing. But the room for innovation is rather large. Johnson pointed out that there is now a plethora of novel therapies available for patients than in the past. He furthermore proclaimed that the rise of an aging population is a definite springboard for innovation. The rate of advancement, however, is largely dictated by regulation and infrastructure. Brandreth added that both regulators and the industry should aim to move away from Eroom's Law, and perhaps instead inch towards its semordnilap: Moore's Law.

George concluded the event by awarding a sizable donation to Science Rare Bears,

Continued at bottom of page 18

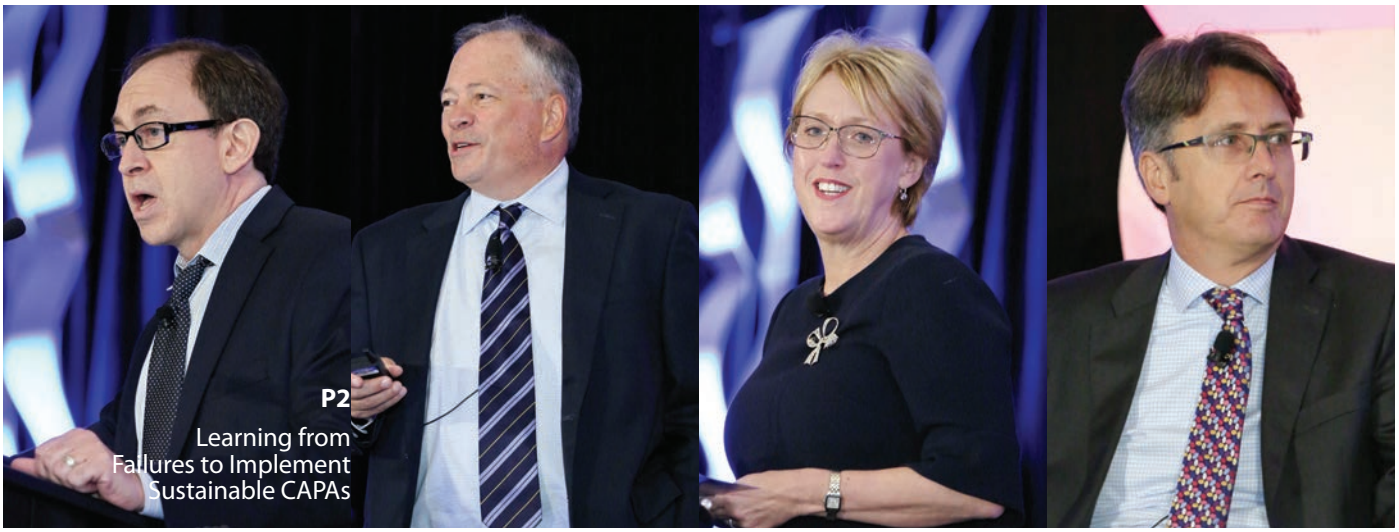
2019 PDA/FDA Joint Regulatory Conference

September 16–18 | Washington, D.C.



(l-r) Rebecca Devine, PDA Chair; Richard Johnson, PDA President

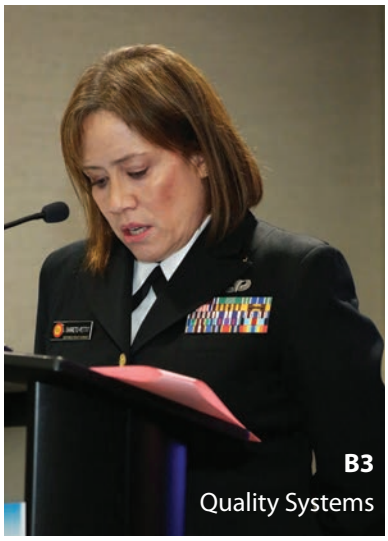
(l-r) David Jaworski, U.S. FDA; John Ayres, MD, Pharma Safety Solutions; Patrizia Cavazzoni, MD, FDA



(l-r) Rick Friedman, FDA; Gerard Greco, Takeda; Jackie Elbonne, Bristol-Myers Squibb; Ronan Farrell, PhD, Roche/Genentech

PDA Photostream www.flickr.com/parenteral-drug

(l-r) Michael Levy, CDER, FDA; Martine Hartogensis, CVM, FDA; Melissa Mendoza, CBER, FDA; John Diehl, ORA,FDA; John Ayres, MD, Pharma Safety Solutions



Ileana Barreto-Pettit, ORA, FDA

(l-r) Hal Baseman, ValSource; Bryan Riley, PhD, FDA; Chakradhar Padala, PhD, Amgen; Lynnsey Renn, PhD, FDA; Shane Killian, Janssen

(l-r) David Churchward, MHRA; Marea Harmon, CVM, FDA; Brooke Higgins, CDER, FDA; Jose Melendez, ORA, FDA; Carmelo Rosa, CDER, FDA

2019 PDA/FDA Joint Regulatory Conference

(Upper l-r) Bing Cai, PhD, CDER, FDA; Zhihao Peter Qiu, PhD, CDER, FDA; Ramesh Raghavachari, PhD, CDER, FDA
(Lower l-r) Renee Blosser, CVM, FDA; Mai Huynh, CVM, FDA; Derek Smith, PhD, CDER, FDA

PDA Chapter Update continued from page 15

a community outreach program for children with rare diseases. The chapter frequently recognizes organizations in the life sciences community for their good work and supports their initiatives through monetary donations.

The success of this occasion would not have been reached without the contributions of Genentech, Southern California PDA Chapter board officers, members at large, volunteers, student chapter members, sponsors and exhibitors. A huge thanks to everyone for their help and support for an event well done!

PDA Who's Who

E.J. Brandreth, Senior Vice President of Quality, Inovio Pharmaceuticals

Kevin Charrier, Vice President of Quality, Par Pharmaceuticals Inc.

Gayle Derfus, Senior Director of Cell Line and Upstream Process Development, Gilead Sciences

Nazeli Dertsakian, General Manager, Vice President, Genentech Oceanside Biologics Operations

Annmarie Duran, Life Sciences Consultant

Randy George, Director of Sales, ValGenesis

Richard Johnson, PDA President

Herbert Matheson, President, VTI Life Sciences

Greg Mills, Director, AXRTECH

Alan Taaghol, PhD, Director of Global Quality Engineering, Kite Pharma

Valerie Whelan, Vice President R&D, Quality, Amgen

Sheba Zaman, Head of Product Specialists and Training Services, Novatek International

PDA
Parenteral Drug Association

history@pda.org

Share Your PDA History!




Be a Part of PDA History

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.

SNAPShot

How to Implement an Effective Big Data Strategy

An Update on the Governance and Controls Technical Report

Richard F. Shakour, Merck & Co., Mark DiMartino, Amgen, Chris Garvin, Amgen, Wilfred Mascarenhas, Eli Lilly &Co., Rob Dimitri, Takeda, and Venkat Parakala, Merck & Co.

Big data from pharmaceutical manufacturing is being collected at an accelerated rate, beyond even the human capability to process it using traditional mechanisms (volume, variety, veracity and velocity). Process automation and data capture capabilities are pervasive, so we are generating and capturing more data than ever. There is a shift from governing and protecting data as it is being generated to governing the generation of data driven insights. In particular, there is a move to using that data to:

- Accelerate development of new therapies
- Provide insights into emerging risks
- Offer affordable medicine to our patients
- Increase internal and external diagnostics and collaborations

The Governance and Controls subteam of PDA's Manufacturing Intelligence Task Force has been looking into these challenges, specifically, the need for governance and active controls of data and information. The team consists of representatives from business, IT and quality spanning multiple biopharmaceutical companies.

Big data challenges require rethinking conventional processes, roles and standards that ensure the effective and efficient use of information and technology to drive value. Additionally, there is a need to incorporate the predictive/prescriptive analytical capabilities emerging from the broader technology landscape in a regulated environment. The Governance and Controls team will be looking into the challenges illustrated in **Figure 1.**

The Governance and Controls team will be publishing a PDA technical report intended to provide practical guidance and best practices needed throughout the data lifecycle. The intention is to propose processes and technologies that can generate and enable manufacturing

Data Governance Challenges and Opportunities…

- **Data Optimization and Scalability** enabled by simplifying data architecture
- Establishing **end-to-end data governmance,** and associated processes enables clear accountability, stewardship and managing change
- **Building** Governance into Technology
- **Sepcifying** Data Quality requirements
- **Utilizing tools** to automate controls and ongoing monitoring
- **Maximize value** by defining key KPIs, Early risk identification and resolution (predictive)

Figure 1 Challenges and Opportunities in Capturing and Using Data Effectively

data insights through purposeful implementation of processes, roles and standards. Furthermore, it will provide best practices in enabling organizations to obtain more reliable data. **Figure 2** illustrates some of the components the team will be assessing in establishing effective data governance and controls within the data lifecycle.

Figure 2 End-to-End Data Governance and Controls (People, Process and Data)

Many companies design their big data strategies with minimal thought to data governance and appropriate controls. Typically, this enables organizations to accelerate their journey in collecting data, however, this shortsightedness leads to roadblocks when it comes to effectively analyzing and visualizing data.

Data governance and controls must have the flexibility to expand or contract as needed but must also be robust enough to ensure consistency and sustainability. The intent is to provide guidance for global use which applies to both new and existing (i.e., legacy) manufacturing big data/analytical models.

How to Qualify Your Disinfectants

Michael Hodgkinson, Orvera Scientific

Setting up a sound program for qualification of disinfectants is a critical component of any contamination control program in a facility manufacturing sterile drug products ***(1).*** Yet subtle changes in a facility and its environmental control performance are often overlooked. This oversight can lead to qualification documentation that does not fully support the program over time.

The following is a framework for managing disinfectant qualification over the lifecycle of a program that takes into account subtle changes, ensuring effective disinfectant qualification.

Setting up a disinfectant qualification program to be manageable over time requires a proper foundation. This starts with selecting agents that align with the process' requirements and scientific principles. A typical facility uses sanitizers (e.g., alcohol), disinfectants (e.g., quaternary ammonia compounds) and sporicidal agents (e.g., hydrogen peroxide and peracetic acid mixtures).

The selected agents must be firmly established prior to embarking any qualification studies. Qualification studies are not simple and come with considerable costs, so it is in a company's best interest to ensure there is no required rework of the initial qualification. Those responsible for contamination control, operations and health and safety should collaborate together when choosing the agents for a new facility. The selection process must consider compatibility with the facility and equipment surfaces, operation types, microbiocidal needs and the disinfection approach. In-suspension studies offer valuable data for agent selection and can be leveraged from the vendor's technical files. In-suspension studies consist of adding a small volume of a prepared culture directly to the chemical agent for a specified time, neutralizing the agent and then attempting to recover the spiked microorganism.

Once the chemical agents have been chosen, the facility and equipment surfaces can be assessed. Risk assessment is a valuable tool for this stage of the program. Understanding the surfaces to be decontaminated and the criticality of the surfaces in relation to the manufacturing process are important aspects to understanding disinfection risk. The risk assessment should consider the following at a minimum:

- Materials of construction of equipment, materials and facility surfaces
- Cleanability of such materials (i.e., surface finish or porosity)
- Material criticality in relation to the process (proximity to critical operations)
- Agents that will be used on specific surfaces
- Relative amount of surface area of the material in the facility (utilization)
- Corrosion potential, mechanical resistance to scratching
- Use of any persistent microbial coatings (e.g., silver).

The output of this risk assessment provides the framework for entering the first stages of disinfectant qualification.

Carrier Studies

Carrier studies are laboratory studies to demonstrate efficacy of the chemical agent against a panel of microorganisms, on a variety of carriers (surfaces). While some debate the merit of these studies, given how different they are from the actual in-situ disinfection process, they are a regulatory expectation and their data are often requested during a regulatory inspection. Carrier studies also provide a good baseline analysis of the agent efficacy against surfaces found in the facility.

Carrier materials should represent the facility, materials and equipment surfaces and worst-case elements of the program as identified in the risk assessment. It is not necessary to test each and every surface that will be exposed to the disinfectants. A surface-family approach can be taken to create brackets of material surfaces. **Table 1** provides an overview of a potential set of surface-families, their family members and some general notes on risk profile. ➤

pda.org

Keep pace with the latest industry trends with PDA,

the leading global provider of science, technology, and regulatory information and education for the bio/pharmaceutical industry.

PDA® Parenteral Drug Association

TAKE ADVANTAGE OF:

- **Technical Reports,** which are peer-reviewed global consensus documents providing expert guidance on important scientific and regulatory issues
- **Conferences and Workshops** on trending topics
- Practical information and implementable solutions gained through **Hands-on Education and Training Courses**
- **Technical Resources** offering sound advice and best practices on established and emerging topics
- Access to a **Global Network** of more than 10,000 industry and regulatory professionals

CONNECTING PEOPLE SCIENCE AND REGULATION®

To learn more about all that PDA has to offer, visit pda.org

Table 1 Example of Surface-Family Grouping Strategy for Coupon Selection

Family	Family Surfaces	Risk Profile
Stainless Steels	316L stainless steel 304 stainless steel	Proximity to product, smooth surface finishes, highly used in facility
Soft Plastics	Sterile consumable bags Curtains	Associated with material movement into critical areas, smooth surface finishes, highly used in facility
Hard Plastics	Panels Barriers Machine parts	Proximity to product, smooth and porous surface finishes, highly used in facility
Glass	Vessels Windows	Not used close to product, smooth surface finishes, low use in facility
Elastomers	Latex gloves Isolator / RABS gloves	Proximity to product, smooth surface finishes, highly used in facility
Painted Surfaces	Floors Walls	Removed from direct impact on product, smooth surface finishes, highly used in facility—large surface area
Composite Surfaces	Modular cleanroom walls Barriers	Removed from direct impact on product, smooth to porous surface finishes, highly used in facility—large surface area

The surface-family grouping exercise allows for the selection of a reduced number of carrier surfaces for the carrier study. In most cases, one material can be selected as a worst-case from each family. For example, in the stainless-steel family, 304 stainless steel can be selected as a worst-case carrier material as it is generally less smooth than polished 316L used in the facility.

Next, the microorganisms to be challenged in the carrier study must be selected. A panel of microorganisms including bacteria, yeast and mould are required. It is important to include a selection in-house isolates from the facility's environmental monitoring program in the panel. Environmental monitoring trend reports are leveraged to determine what microorganisms are most ubiquitous in your facility. Consideration can also be given to what surfaces they are being recovered from. For new facilities, American Type Culture Collection (ATCC) cultures can be used until the facility's microflora are better understood.

The carrier study can now be performed. In general, the study consists of spiking the panel of microorganisms on to the selected surfaces, drying the inoculum, applying the chemical agent for the contact time, neutralizing the agent and then testing the surfaces for the microorganism (either looking for total kill or enumerating). Carrier surface materials and microorganisms are matched to the agents being used on those surfaces. Generally, disinfectants and sanitizers are tested against vegetative microorganisms and sporicidal agents are tested against bacterial and fungal spores. Disinfectant preparation and use aspects should be considered in the study design to ensure agents are tested at the end of permitted in-use times.

Disinfectant preparation and use aspects should be considered in the study design

In-Situ Studies

In-situ studies are studies performed in the actual manufacturing area using the actual disinfection procedures and are a more accurate measure of the effectiveness of the disinfection program. These studies incorporate aspects of the program that are not covered by the carrier studies such as the use of tools like wipers and mops, facility airflow considerations and disinfection technique. These studies will also incorporate any cleaning agents used in the process prior to application of disinfectants, sanitizers and sporicidal agents.

PDA Technical Report No. 70: Fundamentals of Cleaning and Disinfection Programs for Aseptic Manufacturing Facilities offers two potential approaches to conducting these studies ***(2).*** One of the approaches is performing environmental monitoring before and after facility start up. When a facility is first commissioned or has been in an extended maintenance shutdown, baseline environmental monitoring samples can be taken in the facility prior to any cleaning or disinfection steps. Following rough cleaning and removal of soils, environmental monitoring samples are taken again. Then the facility cleaning and disinfection steps are followed to bring the facility up to the classified state. This typically involves several cleaning and disinfection steps with the different chemical agents used in the program. After each cleaning and disinfection step, environmental monitoring samples are taken. At the conclusion of this process, the study should demonstrate that the stepwise cleaning and disinfection process is capable of returning the facility to its classified state from the original dirty state.

Lifecycle Considerations

After completing qualification of disinfectants through laboratory and in-situ

Qualification of disinfectants requires careful consideration of risks

studies, maintenance of the program over the facility lifecycle begins. This includes trending of environmental monitoring results, monitoring of facility isolate recovery rates, risk review and monitoring changes to the facility. It goes without saying that any changes to chemical agents, tools or procedures used in the site disinfection program must be assessed in real time before implementation.

The facility environmental monitoring trend results should be carefully analyzed on an ongoing basis with consideration of the disinfectant qualification program for shifts in performance. Shifts in performance could be related to increases in recovery rates on surfaces or changes in the microflora recovered. Any significant changes should be evaluated to determine if any follow up studies regarding disinfectant qualification are required.

Risk assessments that support the program must be reviewed on a periodic basis to ensure they remain accurate over time as the facility changes. Changes to material surface utilization and any other changes that impact the assessment may cause a required revision to these documents. New surfaces introduced to the facility must be evaluated for how they fit into the surface-family groups either through this risk-review process or through the change management process.

Conclusion

Disinfection is an important aspect of contamination control in any facility manufacturing sterile drug products. Qualification of disinfectants requires careful consideration of risks in determining the scope of laboratory carrier studies and in-situ studies. Risk assessment tools are important in creating a systematic approach to scoping the studies and setting up the program for ongoing management of lifecycle changes.

References

1. USP <1072> Disinfectants and Antiseptics, USP 42 Feb 1 2019
2. Vellutato, A. *PDA Technical Report No. 70: Fundamentals of Cleaning and Disinfection Programs for Aseptic Manufacturing Facilities.* PDA, Bethesda, MD, 2015.

About the Author

Michael Hodgkinson has over 20 years of experience in the sterile pharmaceutical, therapeutic biologicals and vaccines manufacturing industry.

PDA
Parenteral Drug Association

pda.org/EU/QR2020

2020 PDA EUROPE

Quality and Regulations Conference

9-10 JUNE 2020
DUBLIN, IRELAND
EXHIBITION: 9-10 JUNE
TRAINING: 11-12 JUNE

SAVE THE DATE

CONNECTING PEOPLE SCIENCE AND REGULATION®

Published online first
PDA letter.pda.org

Tri-Spine Crab Now on Endangered List

What the Decline in *T. tridentatus* Means for our Industry

James Cooper

Photo by Magnus Manske

Recently, the International Union for Conservation of Nature (IUCN) added *Tachypleus tridentatus,* the tri-spine or Chinese horseshoe crab, to its list of endangered species ***(1).*** IUCN reports that abundance of *T. tridentatus* is falling sharply in the South China Sea and other Asian waters, where it ranges from southern Japan to Indonesia ***(1).*** This decline is primarily caused by habitat loss, overfishing for human consumption and production of *tachypleus* amebocyte lysate (TAL).

In the absence of regulatory policy to return TAL crabs to the sea, they are subject to human consumption and production of chitin. No spawning was observed in a recent survey of 27 nationally known spawning sites. Overharvesting results in 100% mortality ***(2).*** Continued fishing threats are not considered reversible in China and Vietnam ***(1).***

TAL is produced by eight firms in China and sold primarily as single-test vials. These firms produce about 15% of the amebocyte lysate global market. Naturally, they will turn to *limulus* amebocyte lysate (LAL) as the horseshoe crab population is exhausted in the Chinese region. There are plans to help these users conduct endotoxin testing with more efficient use of LAL. New firms seeking to bleed Limulus for non-FDA regulated LAL production will be subject to strict use and possession regulations of member states of the Atlantic States Marine Resources Commission (ASMFC), the federal Commission that oversees conservation of marine resources such as *Limulus polyphemus,* the American horseshoe crab.

The ASMFC reports in their Horseshoe Crab Stock Assessment that LAL production has no detrimental impact on HSC sustainability or availability of horseshoe crab eggs for migratory shorebirds in Delaware Bay ***(3).*** Marine biologists agree that use of horseshoe crabs as bait for eel and whelk, habitat loss and bycatch destruction are the most damaging threats. The Assessment signifies that no threats exist that necessitate either discontinuation of LAL production or the use of alternatives methods.

The endangered status of *T. tridentatus* is a vivid reminder that a similar fate would have befallen *limulus* were it not for the protection that LAL provides. *Limulus* stock has been subject to exploitation for fertilizer and livestock feed in the past and currently for marine eel and whelk baiting, where crabs are sectioned and placed in traps. About 700,000 horseshoe crabs are harvested annually from coastal waters for the bait fishery. From the outset, early LAL researchers adopted a return-to-sea policy, influencing the U.S. FDA to make catch-and-release a condition for FDA licensure of LAL in 1973.

The global lysate market is about $400 million. Lysate firms have the essential responsibility of providing over 70 million test units annually for assuring the safety of parenteral products. HSC are collected by hand harvest or by trawling. About equal numbers of male and female are collected for LAL and returned to sea after use.

Mortality does not occur during the LAL-related bleeding process of donor crabs, which is analogous to human blood donation. A 1983 study of the long-term impact of bleeding on a large number of crabs in a Florida bay estimated that bleeding increased the risk of mortality by about 10% ***(4).*** The Stock Assessment considers this number trivial in comparison to other threats, such as baiting, habitat loss and predators.

The public was generally unaware of horseshoe crabs until they learned about the value of their blood to healthcare. Currently, thousands of people volunteer their time for tagging studies and spawning surveys each spring along designated beaches to become part of citizen science events that heighten their awareness of horseshoe crabs and their important ecological relationships ***(5).*** Horseshoe crab numbers are increasing in mid-Atlantic, southern states and Delaware Bay ***(3).*** Yet numbers are not stable in areas where bait fishing for eel and whelk remains allowed. The collection of horseshoe crabs for bait was banned in 1991 in South Carolina and in 2006 in New Jersey. Horseshoe crabs thrive where LAL is produced and baiting is prohibited.

In summary, the conservation practices of the LAL industry and ASMFC have secured the future of the American horseshoe crab. Unless similar practices are enacted, *T. tridentatus* has a less promising future.

References

1. IUCN 2019. IUCN List of Threatened Species: Tri-spine horseshoe crab *Tachypleus tridentatus.*
2. Global Revenue for Amebocyte Lysate—2016 World Market, QY Research Group
3. Atlantic States Marine Resources Commission. 2019. ASMFC Stock Assessment Overview: Horseshoe crab.
4. Rudloe, A. "The effect of heavy bleeding on mortality of the horseshoe crab, *Limulus polyphemus,* in the natural environment." *Journal of Invertebrate Pathology* 42 (1983):167–76.
5. Swan, B. "Migrations of adult horseshoe crabs *Limulus polyphemus,* in the middle atlantic bight: 1 17-year tagging study." *Esturaries* 25 (2005):28–40.

About the Author

James Cooper, PharmD, is an innovator of the bacterial endotoxins test (BET) for parenteral products. He founded Endosafe Inc. in 1987, an LAL production unit which is now part of Charles River Laboratories.

PDA Upcoming Events

NOVEMBER

6-8 Train the Trainer Training Course Series
Bethesda, MD | *pda.org/2019TrainerTCS*

- 5 Design, Develop, and Implement a Training Course
- 6 Designing/Presenting GXP Training Programs to Meet FDA Requirements
- 7-8 Learning, Knowledge Management, and Impact: Moving from Theory to Practice

7-8 Isolator Technology – Option 2
Bethesda, MD | *pda.org/2019IsolatorTech2*

11-15 Quality Risk Management Certificate Program – Option 2
Bethesda, MD | *pda.org/2019QRM2*

- 11 Foundations of Quality Risk Management
- 12-13 Quality Risk Management: Risk Control and Risk-Based Decision-Making
- 12-14 Practical Application of Quality Risk Assessment Tools
- 15 Quality Risk Management for the Design, Qualification, and Operation of Manufacturing Systems

12-13 2019 PDA Drug Delivery of Injectables Conference
Taipei City, Taiwan | *pda.org/2019taiwan*

- 14-15 Drug Delivery Device and Combination Product Risk Management and Safety Assurance Cases
- 14-15 Extractables and Leachables for Parenteral Applications

12-13 Pharma Logistics and Outsourced Operations
Lisbon, Portugal | *pda.org/EU/LogisticsCMO*

- 14 Supply Chain Management Interest Group Meeting

12-14 TR No. 62: Recommended Practices for Manual Aseptic Processes Training Course
Bethesda, MD | *pda.org/2019TR62training*

18-22 Cleaning Training Course Series – Option 2
Bethesda, MD | *pda.org/2019CleaningTCS*

- 18-19 Fundamentals of Cleaning and Disinfectant Programs for Aseptic Manufacturing Facilities
- 20-22 Validation of Biotechnology-Related Cleaning Processes

20-21 Strategies for Formulations Development – How to Get the Right Data in the Right Amount at the Right Time
Bethesda, MD | *pda.org/2019SFD*

26-27 Single-Use-Systems: A New Age of Drug Making
Göttingen, Germany | *pda.org/EU/TC-SUS19*

DECEMBER

2-5 Fundamentals of Aseptic Processing Option 6
Bethesda, MD | *pda.org/2019DecFundAP*

9-13 2019 PDA Quality Week
Washington, DC | *pda.org/2019qualityweek*

- 9-10 2019 PDA Risk Management in the Regulatory Landscape Conference
- 11 2019 PDA Building a Foundation and Culture for Quality Risk Management Integration Workshop
- 12-13 2019 PDA Optimizing Quality Risk Management Conference

12-13 Single Use Systems for the Manufacturing of Parenteral Products
Bethesda, MD | *pda.org/2019SUS*

12-13 Open BioPharma Training Course Series
Carlsbad, CA | *pda.org/2019OpenBioPharmaTCS*

- 12-13 Fundamentals of Cleanroom Operations
- 12-13 Fundamentals of an Environmental Monitoring Program

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

LOOKING AHEAD TO 2020

FEBRUARY

25-26 2020 PDA Europe Parenteral Packaging
Basel, Switzerland | *pda.org/EU/ParPack2020*

MARCH/APRIL

3/30-4/1 2020 PDA Annual Meeting
Raleigh, NC | *pda.org/2020Annual*

2 2020 PDA Pharmaceutical Manufacturing Data Science Workshop

21-22 2020 PDA Europe Visual Inspection Forum
Berlin, Germany | *pda.org/EU/VIForum2020*

JUNE

9-10 2020 PDA Europe Quality and Regulations Conference
Save the Date

22-23 2020 PDA Europe Virus Forum
Brussels, Belgium | *pda.org/EU/Virus2020*

24-25 2020 PDA Europe Advanced Therapy Medicinal Products Conference
Brussels, Belgium | *pda.org/EU/ATMPs2020*

SEPTEMBER

8-9 2020 PDA Europe Medical Devices and Digital Healthcare Conference
Save the Date

OCTOBER

5-6 2020 PDA Universe of Pre-Filled Syringes and Injection Devices
Las Vegas, NV | *pda.org/2020UPS*

7 2020 PDA Combination Products Workshop

19-21 15th Annual PDA Global Conference on Pharmaceutical Microbiology
Washington, DC | *pda.org/2020Micro*

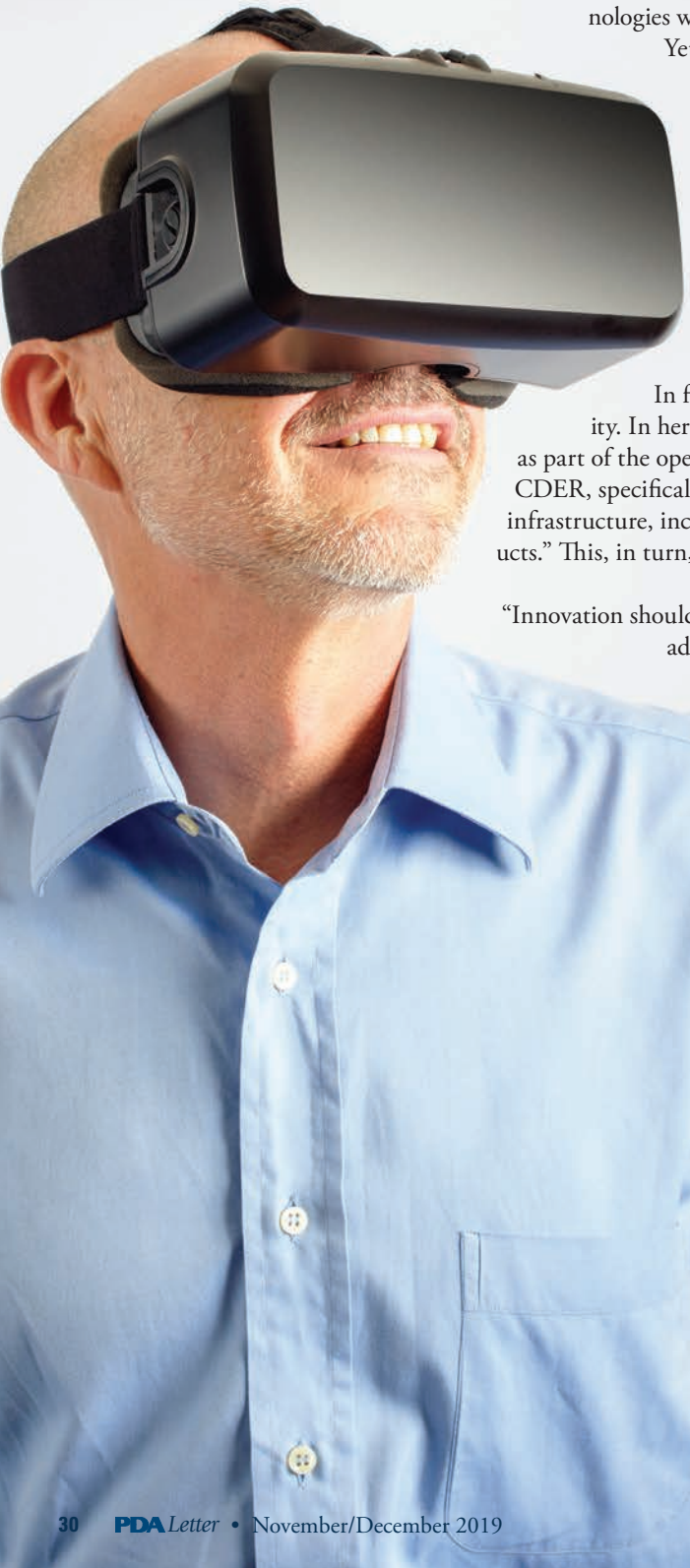
21-22 2020 PDA Rapid Microbiological Methods Workshop

20-21 2020 PDA Europe Aseptic Animal Health Conference
Save the Date

■ This course is taught in PDA's U.S. Manufacturing Training Facility.

FDA Takes Close Look at Innovation

Rebecca Stauffer, PDA



Industry 4.0. Artificial intelligence. Big data. Even continuous manufacturing. All of these new technologies will drive the future of pharmaceutical and biopharmaceutical manufacturing. Yet questions persist as to how the U.S. FDA and other global regulatory agencies will address these new technologies, leaving some companies reluctant to fully embrace these advances as early adopters.

Some answers, while not necessarily definitive, could be found at the *2019 PDA/FDA Joint Regulatory Conference* in Washington, D.C., Sept. 16–18. From the opening to the closing talks, both regulatory and industry representatives expressed the need to integrate more advanced manufacturing technologies into everyday processes and the critical role of collaboration between industry and regulators.

In fact, some of the FDA speakers pointed to innovation as a way to improve quality. In her presentation, "Advancing Drug Innovation through Investment in Quality," as part of the opening plenary, **Patrizia Cavazzoni,** MD, Deputy Director for Operations, CDER, specifically cited how innovation is necessary to create a "more modern manufacturing infrastructure, including advanced technology for manufacturing of drugs and biological products." This, in turn, will help reduce the threat of drug shortages due to fewer drug recalls.

"Innovation should help establish the quality system," she said. "FDA continues to be a strong advocate for, and to support, modernization of the pharmaceutical industry, and we recognize that adopting innovative approaches to manufacturing may present technical and regulatory challenges. For instance, companies may have a concern that using such technologies would result in delays while FDA reviewers familiarize themselves with the technologies."

Cavazzoni pointed to CDER's Emerging Technology Program as one way FDA is addressing this concern. This group seeks to "promote the adoption of innovative approaches to pharmaceutical product design and manufacturing." Manufacturers looking to implement such technology can communicate their concerns directly to the FDA members comprising the Emerging Technologies Team (ETT). This early interaction is supposed to help address any regulatory concerns early on before the technology is used.

> I really do think you can make a business case for improving the quality

Augmented Reality in the Cleanroom

The ETT came up again later that day in the breakout session, "Augmented Reality and Artificial Intelligence: Conceptualization through Implementation." **Bob Bowden,** PhD, Senior Director, Cell Collection, Advanced Therapeutics Supply Chain, Janssen, discussed his company's approach to using augmented intelligence during manufacturing operations. Currently, in the beginning stages of implementation, his company plans to use what he refers to as "augmented intelligence"—a device or system that enhances human capabilities "to augment the intelligence of our operators in a cGMP environment."

In particular, the operators within the company's cell therapy manufacturing facility wanted an approach that would let them view the batch record and batch record status without directly handling a paper batch record. In addition, the operators wanted to interact with only one interface instead of six to seven systems to complete a process.

Bowden's team took these needs into account, developing an approach relying on an augmented reality headset. Similar to virtual reality, augmented reality overlays computer-generated graphics on physical space. Pokemon Go is an example of such a technology. In fact, augmented reality is already being used in other manufacturing sectors, such as agricultural equipment and aviation. The company is now conducting use cases involving an augmented reality headset outside of the cleanroom as the company wants to be absolutely certain of the capabilities of the technology before bringing it into the cleanroom.

But what about the regulatory side? According to Bowden, his company's main regulatory concern about the headset device involves 21 CFR Part 11, the FDA regulations applying to electronic signatures. He believes that since the data passes through the device and this existing data is not altered means it does not fall under Part 11.

At this time, the device is being used on the production floor as some technical limitations still need to be overcome.

During the Q&A portion of the session, **David Jaworski,** Senior Policy Advisor, CDER, FDA, joined the panel. The first question was directed at him, asking for the Agency's perspective on artificial intelligence and machine learning.

"We are evaluating a lot of the new technologies, usually on a one-on-one case right now," he replied. "We do have the ETT process over in CDER and we have a similar process in CDRH, so there is the ability to come in and discuss these concepts in advance…in the development stage. We would encourage people to open up those communication channels early. Right now, it is more exploratory."

Later, another question referenced Cavazzoni's point about the potential for manufacturing innovation to reduce drug shortages.

"I think some companies tend to underestimate the impact of looking at some of this technology and innovation upon the quality of their products," Jaworski said. "And I really do think you can make a business case for improving the quality that then is going to reduce the shortages…the technology may be technically very complex, but it is the design of the process, the design of the software that you are going to use, the design of the equipment that you are going to bring in to your facility, that really needs to be looked at at the beginning. Try to really concentrate on these things in advance instead of waiting for a problem to occur downstream."

In fact, Jaworski explained that sometimes he has seen companies using older, existing technologies that result in quality issues when a more advanced piece of technology could have prevented the problems from occurring. ➤

Article at a Glance

- U.S. FDA speakers point to innovation as a way to alleviate issues due to manufacturing quality
- Continuous manufacturing adoption encouraged, says FDA speaker
- Agency also exploring ways to innovate internal operations using new technology

"All of these things if you look at them, there is always something that could have been done early in the design process to really reduce that potential, and it may be technically challenging on the upstream side in your workflow but on the downstream side you will have much better results. I think when that all plays out, it can help eliminate drug shortages… if you concentrate on the quality aspects, then the ability to provide medication to patients in the end will be satisfied."

Continuous Manufacturing Keeps Up

The next day, **Sharmista Chatterjee,** Supervisory Chemist, CDER, FDA, provided more details on the ETT. The team is headed by **Sau (Larry) Lee** from the Office of Pharmaceutical Quality and consists of 22 members including herself. The team is cross-functional within CDER, featuring representation from the Office of Pharmaceutical Quality, Office of Compliance and Office of Regulatory Affairs. The ETT provided support for FDA's approval of the first new drug product produced via continuous manufacturing and the first switch from batch to continuous manufacturing for a previously approved product ***(1).***

She views continuous manufacturing as another way for manufacturers to reduce quality issues.

"A quality product of any kind consistently meets the expectations of the user," Chatterjee explained. "Drugs are no different."

FDA has seen applications for continuous manufacturing for both small and large batches. For small batches, this includes both drug substance and drug product. Chatterjee has also seen continuous aseptic spray drying. For large molecules, applications have included continuous manufacturing for downstream processes, end-to-end integrated bioprocesses and a small manufacturing platform for continuous bioprocesses (i.e., pharmacy on demand).

Since launching the ETT program in late 2014, Chatterjee explained that continuous manufacturing requests sent to the ETT have included multiple face-to-face meetings or teleconferences between manufacturers and the Team. Many had site visits with ETT members prior to submitting the application.

Approvals for continuous manufacturing have included Vertex's ORKAMBI, Janssen's Pezista, Eli Lilly's Verzenio, Vertex's Symdeko and Pfizer's Daurismo.

In February 2019, FDA released a draft guidance on continuous manufacturing. The primary objectives of this guidance are to communicate that FDA supports continuous manufacturing, that it is consistent with the FDA Quality Initiative and there are no regulatory hurdles for implementation of continuous manufacturing. FDA received over 20 comments. The comments included recommendations for further clarity on what has to be included in the regulatory submission concerning a site's pharmaceutical quality system, concerns about "intermingling" of cGMP expectations with design expectations, further information with respect to requirements for process analytical technology data storage and the risk-based approach for model maintenance over the product lifecycle and requests to only include topics unique to continuous manufacturing and avoid topics raised in other guidances.

FDA plans to move forward with the guidance while taking the comments into account. Chatterjee said that the content of the draft guidance served as the basis for the Agency's perspective when drafting ICH Q13: *Continuous Manufacturing for Drug Substances and Drug Products.*

FDA Center Leaders Talk Tech

During the "Center Updates" on the last day of the conference, advanced manufacturing technologies came up as a topic of discussion. In fact, **Peter Marks,** MD, PhD, Director, CBER, FDA, explained how his Center is even embracing some of the same technologies internally.

"A.I. is something that is increasingly being used in various spaces. We are using it at the Center in a variety of ways in terms of exploring what it can do for us. For instance, sifting through thousands of adverse events and helping us understand where there is a real signal," he said. "If A.I. can help flag a high percent of them and basically triage 95% of them, and categorize them, that would actually free up staff and allow people to concentrate on other things."

In addition, he said that some companies are now submitting applications to CBER containing big datasets, such as whole genome sequencing. This is an area where A.I. can really shine and Marks stated that a high performance computing group at CBER is working on it.

"It [A.I.] is clearly the wave of the future," Marks said. "I do not think we are going to see a computer doing reviews of the applications but certainly it can help us tremendously with regulatory review, particularly in the post-market setting. It may turn out that A.I. is very useful in helping us figure out whether there are safety signals, particularly, as we build very large databases."

Alonza Cruse, Director, Office of Pharmaceutical Quality Operations, Office of Regulatory Affairs, also weighed in on A.I. and other technologies.

"[It requires] a whole new skillset and understanding but I think it is one [technology] that is important because drug manufacturing companies are using A.I…they are using this to look for, and to rehab, issues."

Cruse envisions FDA inspectors walking into a facility and using A.I. to decide which areas to focus on. He sees A.I. as just one way to help with decision-making.

"A.I. can help us selectively reach more informed decisions."

Reference

1. "Impact Story: Regulatory Science is Strengthening U.S. Drug Product Manufacturing." *Regulatory Science in Action*. FDA.gov (Feb. 5, 2019) tinyurl.com/yxopbqxf

Alsonza Cruse spoke about FDA realignment at the *2018 PDA JRC*. Read it online at www.pda.org/PDALetter

Legendary

At Contec, we don't just make cleanroom products – we've transformed the cleanroom industry. We don't just follow best practices, we created them. So know that when you clean with Contec, you're not just cleaning – you're putting up the industry's strongest defense against contaminants.

CONTEC® | WHATEVER IT TAKES™

Robotics and Big Data Key to Lab of the Future

Peter Crane, Synthace

I had the good fortune to attend the *Digital Robot Pharma Fab* workshop and the *4th PDA Europe Annual Meeting* in Amsterdam this past June.

For those of you unfamiliar with the term, "Fab," the word refers to an automated and digitally empowered factory (manufacturing, QC and packaging) that integrates robotics with artificial intelligence and a suite of end-to-end digital tools.

The *Digital Robot Pharma Fab* preconference workshop highlighted the key role the "Fab" will play in the future of the pharmaceutical industry. I learned that in 2017, there were approximately 2.1 million industrial robots installed across all industries—with a large percentage in Asia-Pacific countries. By next year, this number is projected to reach 3.8 million globally, a 22% compound annual growth rate a year.

Despite this, only 4187 robots were sold to the pharma industry in 2017. What does this mean? Well, for one, clearly pharma must now meet the levels of digitization and automation adopted in other industries, such as the automotive industry.

Fortunately, the *4th PDA Europe Annual Meeting* included a number of sessions dedicated to ensuring pharma rises to the level of these other, fully digitized industries. So what was the one theme consistent throughout? Well, while we need more robots, we also need more advanced systems to collect, collate, structure and interrogate large datasets. Without this data aspect, robots, wherever they may be and in whatever form they are, will not reach their full potential. In addition, without the implementation of software above the robotic ➤

MAXIMIZE EFFICIENCY
You'll find the solutions here.

NEW TECHNOLOGIES
You'll see innovation here.

LEARN FROM EXPERTS
You'll learn from subject matter experts here.

ACCERLATE TO MARKET
You'll find everything you need, from science through commercialization, to cost effectively develop and manufacture product here.

Experience science through commercialization

SAVE THE DATE
APRIL 28-30, 2020
JAVITS CENTER, NYC

NEED TO ATTEND? NEED TO EXHIBIT?
Register to attend OR submit to exhibit: INTERPHEX.COM

INTERPHEX

PDA Parenteral Drug Association
Premier Association Sponsor

pda.org/EU/Animal2020

2020 PDA EUROPE

Aseptic Animal Health

20-21 OCTOBER 2020

SAVE THE DATE

CONNECTING PEOPLE SCIENCE AND REGULATION®

> **Organizations must be willing to move toward a more agile, collaborative and less siloed culture**

hardware, we will simply create robotic siloes rather than the fully automated and integrated digital Fab.

Other talks on deep learning, blockchain and GMP validation of technologies also touched on this idea. In particular, the session, "Artificial Intellgence in Pharma," resonated with me. **Sebastian Brandes** from Criterion AI, a company based in Copenhagen, Denmark, asked attendees if they are okay with service versus industrial versus cobots (collaborative robotst that interact closely with humans in a shared workspace, and AI, deep learning and machine learning?

In the same session, **Kasper Larsen** from Novo Nordisk demonstrated that by applying Principal Component Analysis (PCA) methods and a random forest algorithm, his team identified a key source of variability in a packing process. The variability in question? A specific day of the year, which they subsequently correlated to humidity. This example shows how a company could realize the power of machine and deep learning by first focusing on the data, then collecting further data before delivering diverse, structured, annotated and interoperable information.

As I left the conference and headed back to London, there were several points I mulled over. After some time to put put my thoughts together, I want to now give you my four main takeaways from the *4th PDA Europe Annual Meeting* and preconference workshop.

4 Points to Ponder in the Age of Fab

1. Many companies are looking to evaluate in-house solutions for automation, data management and data analysis.

In other industries, such as the integrated circuit industry, we have seen a move away from in-house solutions, which are often unsupported, difficult to update and more of a proof of concept, toward the use of best-of-breed, fully integrated and independent vendors. While pharma is still tentatively exploring digital and automation solutions, I expect the trend for in-house projects to continue, but with strong movement toward specialist vendors in the near term. The key advantage here being you do not need to hire this talent, plus, aspects such as security, operating system updates and compatibility are fully taken care of.

I would also take this as a call to current or future vendors to lead the field with innovative next generation products, rather than simply responding to specifications with incremental innovation.

2. There are some really interesting approaches to automation and robotics being trialled.

One such example, shown by Ferring Pharmaceuticals's **Robert Roennback** in the workshop, is a scale-out model whereby microfactory systems are distributed in containers. These units are standalone systems enabling a geographically responsive approach to product production, QC and distribution.

As I viewed this presentation, I recognized its potential to alleviate the challenges facing the autologous cell therapy industry. I wonder whether such an approach (microfactories) may allow for the increased geographical supply of these breakthrough products, thus reducing the logistics burden.

3. Robotics are a fantastic and tangible option for the needs of pharma today.

But the definition of a robot, a system that can "sense, compute, act" to me means that with the rapid development of process analytical technologies, we may be moving to a future whereby we have end-to-end "robotic" processes comprised of largely "nonrobotic" (in the traditional sense) operations.

4. There was a lot of discussion about data scientists and technology, and how you integrate these into an organization.

From my own experiences in the industry, it requires a commitment to a common language (e.g., API in tech versus API in pharma) and also a willingness for extreme openness. Having siloes of "data people" rarely works. Organizations must be willing to move toward a more agile, collaborative and less siloed culture. Whether pharma is prepared to move to such a culture remains to be seen.

Overall the *4th PDA Europe Annual Meeting* and *Digital Robot Pharma Fab* proved a fantastic glance into the later stages of the industry's value chain.

About the Author

Peter Crane, DPhil, is the corporate strategy manager at Synthace. At Synthace he is responsible for new market exploration/expansion and thought leadership around the Lab of the Future.

Add Sherlock Holmes to Your Investigation Team

The Role of a Microbiologist in Teams Investigating Product Failures Due to Manufacturing Issues

Tony Cundell, PhD, Microbiological Consulting, LLC

You have reported a microbial test failure to your site's management following confirmation by a laboratory investigation. Now, you must assemble a cross-functional team to investigate the most likely cause of failure during manufacturing.

How can your team effectively investigate this testing failure? Consider including a microbiologist among the team members. A microbiologist increases the likelihood of a successful investigation by bringing their expertise to the investigation. Think of it as adding **Sherlock Holmes** to your team of investigators.

Getting Started

The ideal microbiologist must have broad experience in microbiological investigations, product formulation and manufacturing processes. Furthermore, it is preferred that they are familiar with the actual product implicated in the failure. Without this expertise, it is less likely that the root cause of the failure will be determined, and the investigation may be limited to merely checking the required boxes and rounding up the usual suspects. The microbiologist should be engaged from the beginning as microbiological investigations are time sensitive due to microorganisms' transitory nature.

The first step is a walk-through of the manufacturing area for orientation and to identify unusual situations that may be directly linked to the contamination.

To be successful, this microbiologist must:

- have access to all related microbial testing results,
- the cooperation of manufacturing employees at all levels, and
- free rein to interview staff in the manufacturing area, inspect processing equipment, take follow-up samples and review change control and batch records without prior managerial approval.

In a few cases, access to customer complaint records may be necessary. For failures related to purchased pharmaceutical ingredients, the microbiologist should join any audit team visiting the ingredient supplier as part of an investigation.

Avoiding Bias

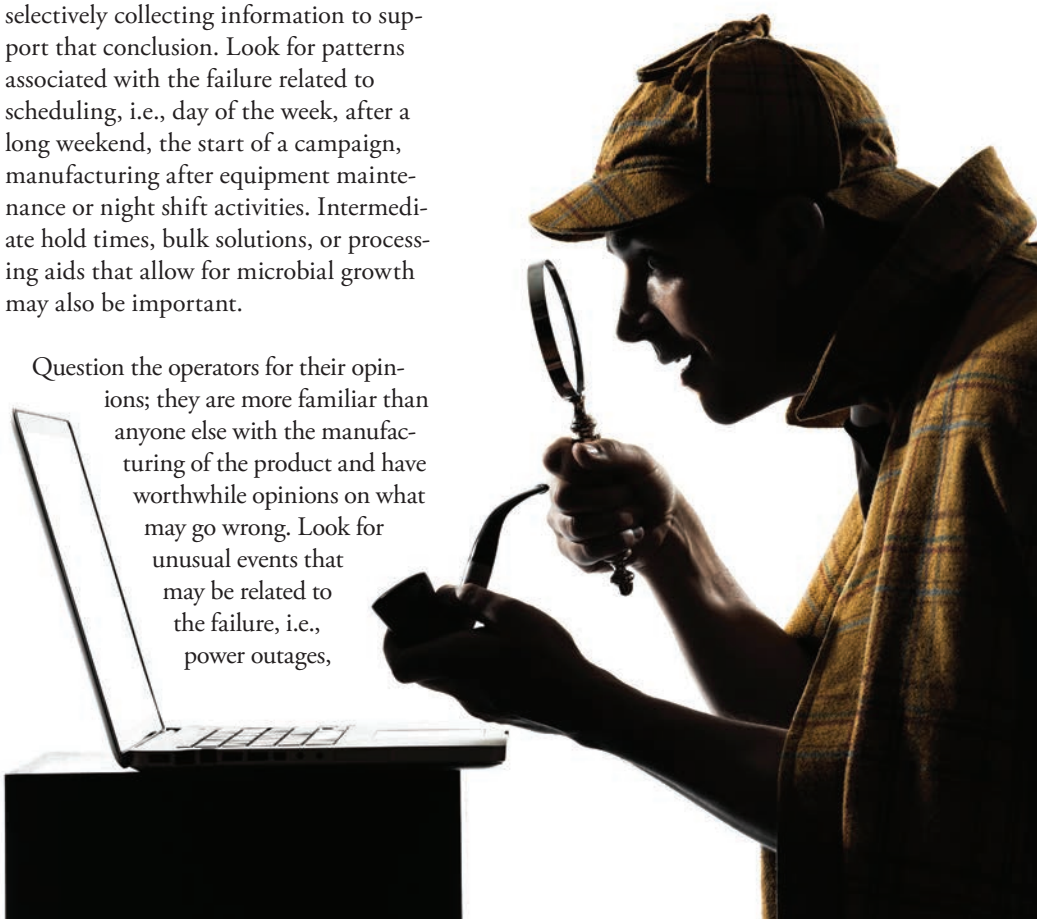
Contrary to the widely held belief that microbial failure investigations are usually inconclusive, my experience has shown that the causes of the microbial contamination can be ascertained via aggressive investigations by teams supported by an experienced microbiologist. In the absence of a definitive cause, the most probable causes can be suggested based on the information gathered plus follow-up observations, testing and record review. To avoid confirmation bias, the team must be willing to reject their original hypothesis as to the probable cause, in light of the evidence subsequently collected. Another bias to avoid is hindsight bias. This can occurr when previous successful investigations are exaggerated, unduly influencing the current investigation.

Be aware that early information obtained during the investigation can lead the team to prematurely reach a conclusion, selectively collecting information to support that conclusion. Look for patterns associated with the failure related to scheduling, i.e., day of the week, after a long weekend, the start of a campaign, manufacturing after equipment maintenance or night shift activities. Intermediate hold times, bulk solutions, or processing aids that allow for microbial growth may also be important.

Question the operators for their opinions; they are more familiar than anyone else with the manufacturing of the product and have worthwhile opinions on what may go wrong. Look for unusual events that may be related to the failure, i.e., power outages, equipment failures, excessive processing times, floods, staffing changes or even union grievances. Investigation checklists or fishbone diagrams of the manufacturing process can be helpful to avoid overlooking an input to the manufacturing that may potentially be the source of the contamination. They also provide a rational roadmap and offer evidence to upper management or an external auditor of the investigation's comprehensiveness. Knowledge, experience and communications within the team and perseverance are the critical elements of a successful manufacturing investigation.

Different Approaches

There are two schools of thought in the approach to decision-making that are applicable to these investigations ***(1).*** Nobel prize-winning behavioral economist **Daniel Kahneman** and his colleagues classify decision-making as either intuitive (irrational) or rational, depending on whether it was based on tacit or explicit knowledge. An intuitive investigation is based on gut feeling, and reflects the belief ➤



SMA MicroParticle ICS
Non-Viable Particle Counters

THE NEXT LEVEL OF PARTICLE COUNTING

UNMATCHED ENVIRONMENTAL CONTROL

STERILE.COM

For more information, visit our website at **sterile.com/particlecounters**

vai
VELTEK ASSOCIATES, INC.

pda.org/CompoundingTCS

The Parenteral Drug Association (PDA), the leading provider of bio/pharmaceutical industry education and training, is pleased to introduce the all-new

Compounding Training Course Series

Gain expert solutions to common compounding pharmacy challenges that pose risks to patients.

PDA has introduced a new Compounding Training Course Series – designed specifically for compounding pharmacy professionals. The three training courses in this series will help compounding pharmacy staff understand the practices and techniques that ensure safe pharmaceutical preparations meet the personalized needs of patients. Participants will also discover important background information along with practical skills and solutions to the problems that compounding pharmacies are facing.

Compounding Pharmacy – Improving Aseptic Operations

This training course provides an in-depth understanding of microbial control and prevention of cross-contamination for better quality compounded preparations. Gain important skills in aseptic technique through hands-on learning activities, including environmental monitoring, smoke studies, gowning, and aseptic filling of media.

In addition, you will learn how to:

- Achieve and maintain environmental control
- Achieve sterilization and be able to differentiate between sterilization and sanitation

Cleaning Compounding Environments – Understanding Contaminants and How to Remove Them

Inconsistent cleaning and disinfection practices can lead to contaminated drugs. This training course will examine the theory behind cleaning and disinfecting surfaces and provide practical information for the successful selection and use of tools to clean and apply disinfectants. Get hands-on experience in effective and proper use of cleaning tools in typical compounding environments.

Gain a foundational understanding of:

- The microbial risks to sterile compounding
- Contaminant sources and the behavior necessary for effective control
- Best practices for cleaning and disinfection based on the newly published version of USP <797> and other regulatory guidelines
- The relationship between the environmental control systems, cleaning tools and protocols, and compounded pharmaceutical product quality

Compounding Pharmacy – Key Concepts in Microbiological Quality Control

This training course will help close the knowledge gap about how compounders should be performing their microbiological quality control testing and will address control measures that should be implemented to contribute toward sterility assurance of products.

Find out:

- Why a robust quality control program is critical to ensuring microbiological integrity of products
- What testing is needed
- How to select appropriate testing methods
- How to properly perform testing
- How to develop and interpret results

OPTION 1 STARTING IN FEBRUARY 2020!

For more information or to register, visit ***pda.org/CompoundingTCS***

"that experts are always right," whereas a rational investigation is rule-based, comprehensive and may be considered more cGMP compliant. **Table 1** highlights the difference in these two approaches, sometimes referred to as System 1 or 2 ***(2).***

Expert intuition can be fallible, and, in some cases, straight up wrong (e.g., sports analyses), especially if the opinions are not evidence-based and attempt to predict long-term outcomes. Intuition that is a collection of knowledge-based skills and acquired through experience and frequent feedback, however, is more reliable. Consider other professionals that rely on intuitive judgment, such as primary care physicians, firefighters or police detectives. These individuals also internalize their experience and receive frequent feedback from what they observe and their interaction with people. Research has shown that evidence-based medicine, artificial intelligence and the use of simple algorithms markedly improves the performance of clinicians.

The microbiologist belongs in the latter category due to their knowledge of microorganisms, product formulation, manufacturing processes and past experience with investigations. In practice, a failure investigation is not black and white; it has a dual track approach that uses both Systems 1 and 2. In the interest of timeliness (critical in investigations of microbial contamination) a microbiologist has an advantage as they use a more intuitive approach. The Quality Control Unit representative, practiced in document review, takes a more rule-based approach. For example, the microbiologist tours the production area, talks to operators, inspects equipment, takes samples and follows up on possible leads while the QC representative concentrates on batch record/facility operation reviews, considering compliance with internal policies and procedures and industry standards. With the right leadership, the full investigational team can reconcile the differences in these approaches.

A Fictional Counterpart

Microbiologists tasked with investigations should channel their inner Sherlock Holmes, who relied on "abductive reasoning" reasoning, not deductive as we have all been led to believe. Abductive reasoning is a form of logic, which starts with an observation or set of observations seeking to find the simplest and most likely explanation for the observations. This process, unlike deductive reasoning, yields a plausible conclusion, i.e., the best available, most likely or most probable conclusion. This matches the needs of microbial failure investigations due to their apparent randomness and uncertainty of distribution and growth of microorganisms.

Table 1 Comparison between System 1 and 2 Approaches to Investigations

Intuitive Investigations (System 1)	Rational or Rule-based Investigations (System 2)
Unconscious reasoning	Conscious reasoning
Implicit	Explicit
Automated	Controlled
Lower effort	Higher effort
Rapid resolution	Slower resolution
Default process	Inhibitory
Associative	Rule-based
Contextualized	Abstract
Domain specific	Domain general
Older approach	Newer approach
Nonverbal	Linked to language
Recognition, perception and orientation	Rule-following, comparisons & options weighing
Independent of working memory	Limited by working memory capacity
Nonlogical	Logical
Parallel process	Serial process

But the microbiologist may encounter challenges working within a multifunctional investigatory team. This goes hand in hand with the benefits of working in a team. What are common pitfalls in working within a team? There may be tension from the competing objectives of problem solving, product manufacturing and release and cGMP compliance. Clearly identifying the problem and its boundaries, with the goal of obtaining the most likely cause based on investigation findings is crucial. Misidentifying the cause of the failure means any corrective and preventive actions implemented will waste resources and failures may recur, and even become chronic, resulting in economic loss.

Decision-making should be by consensus. The level of participation and the acceptance of informed opinion should be driven by technical expertise, access to information and not superiority of position within the organization, i.e., an authority bias. Furthermore, the team should avoid another common bias—groupthink.

The chair of the investigation team should encourage full participation by the microbiologist and other team members. This ensures the investigation is evidence-based, manages conflict, and brings the investigation to a timely conclusion.

Every team investigating a testing failure should take into account the advantages of including a microbiologist among the team. This ensures a successful investigation to prevent recurrence of the event.

References

1. Kahneman, D. *Thinking, Fast and Slow.* New York, NY, Farrar, Straus and Giroux, 2013.
2. Sandle, T. *Risk Management and Risk Assessment for Pharmaceutical Manufacturing: A Contamination Control Perspective.* North Charleston, South Carolina, CreateSpace, 2013.
3. Slovic, P. *The Feeling of Risk.* New York, NY, Routledge, 2010.

About the Author

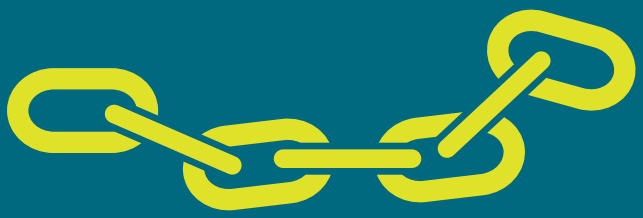
Tony Cundell, PhD, consults with a number of pharmaceutical companies and other healthcare firms.

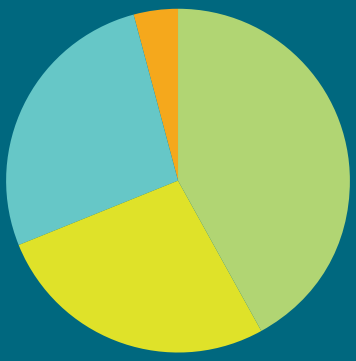
Data Integrity: Remediation and Quality Culture

The *2019 Data Integrity Workshop* opened with a real-time survey of attendees, the majority representing pharma/biopharma manufacturing. Below are some highlights that pertain to remediation and quality culture.

Remediation Efforts

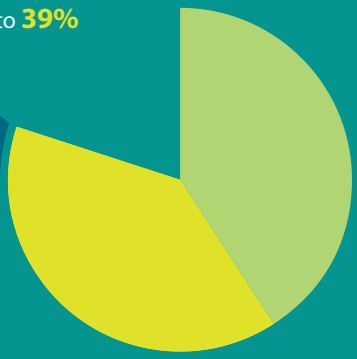
When it comes to the role of quality culture in data integrity, **42%** were focused on remediation efforts while **27%** just began focusing on it within the last year. **27%** have it integrated within continuous improvement and just **4%** link it to next generation data integrity.





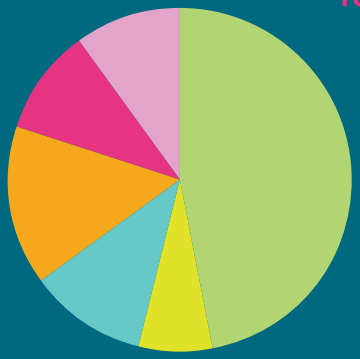
The same is true for the role quality culture plays with laboratory data integrity; the majority of respondents **(50%)** focused on remediation efforts.

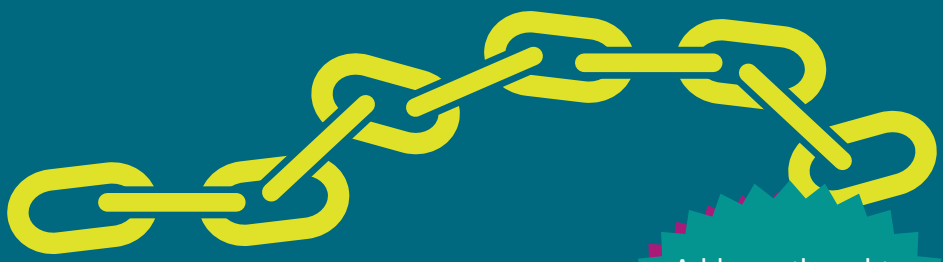
But when it comes to how quality culture sits in relation to manufacturing programs, **41%** have just started building it out within the past year, compared to **39%** on remediation efforts.



Data Integrity Program

When asked what area they have implemented a data integrity program in, **47%** said manufacturing with only **7%** for GvP, **11%** GCP, **15%** GLP, **10%** Regulatory and **10%** R&D.





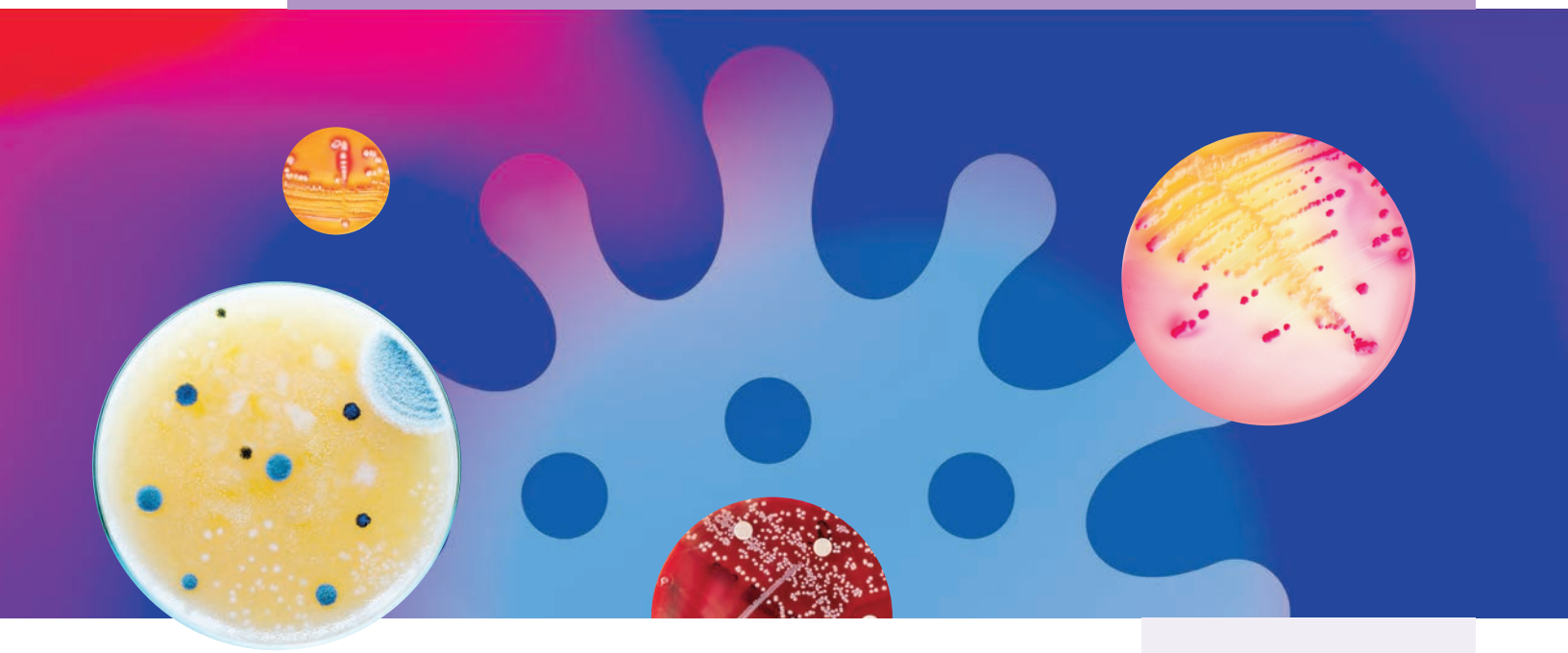
Add your thoughts on data integrity in the Data Integrity Interest Group forum on PDA Connect℠.

community.pda.org

pda.org/2020Micro

15th Annual PDA Global Conference on Pharmaceutical Microbiology

REGISTER BY AUG. 10, 2020 AND SAVE UP TO $600!



Save the date for the *15th Annual PDA Global Conference on Pharmaceutical Microbiology*!

Continue the tradition of exploration into the most relevant topics in pharmaceutical microbiology at this best-in-class Conference.

Stay tuned for more information including abstract submission details, agenda updates, and keynote speaker announcements.

To learn more and register, visit *pda.org/2020Micro*

PLEASE NOTE THAT WE'RE MAKING A MOVE!

Next year's Conference will be held at the Grand Hyatt in Washington, DC!

OCTOBER 19-21 | WASHINGTON, DC

EXHIBITION: OCT. 19-20
2020 PDA RAPID MICROBIOLOGICAL METHODS WORKSHOP: OCT. 21-22
TRAINING COURSES: OCT. 22
#PDAMicro

CONNECTING PEOPLE SCIENCE AND REGULATION®

PDA
Parenteral Drug Association

www.pda.org/pdaletter

On the Issue Videos by the *PDA Letter*

Interviews with leading industry experts on the issues important to you

Watch the following experts:

- Skan's Richard Denk — Cross-Contamination
- Emergent's Kevin Gadient — Gloveless Isolator System
- Merck's Kenneth Boone — Recovery of Anaerobic Organisms
- Roche's Aaron Goerke — Big Data

For more information on all PDA videos, podcasts and other interviews, please visit us at www.pda.org/pdaletter

CONNECTING PEOPLE SCIENCE AND REGULATION®

PDA Responds to EMA Combo Product Reg

30 August 2019

Quality Working Party
Committee for Medicinal Products for Human Use
European Medicines Agency
PO Box 71010
1008 BA Amsterdam
The Netherlands

Reference: Guideline on the quality requirements for drug-device combinations (draft)

EMA/CHMP/QWP/BWP/259165/2019

Dear Madam or Sir:

PDA appreciates the opportunity to comment on the draft guideline on the quality requirements for drug-device combinations, EMA/CHMP/QWP/BWP/259165/2019. We present our comments in the attached table.

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 have been prepared by a committee of PDA members with expertise in pharmaceutical and biopharmaceutical manufacturing on behalf of PDA's Biotechnology Advisory Board and Board of Directors.

If you have any questions, please do not hesitate to contact me via email at johnson@pda.org.

Sincerely,
Richard Johnson
President and CEO, PDA

cc: Tina Morris, PDA; Ruth Miller, PDA; Falk Klar, PDA

PDA Commenting Task Force

Gabriele Gori, GSK Vaccines
Lee Leichter, P/L Biomedical
Karin Baer, Boehringer Ingelheim
Demetra Macheras, AbbVie
Hendri Harmoko, Becton Dickinson
Louise Place, Cambridge Design
Sarah Clark, Eli Lilly

PDA
Parenteral Drug Association

pda.org/refer

Get Rewarded for Referring PDA!

When you refer a colleague to join PDA, they'll get $10 and you'll get $10!

HOW IT WORKS:

PDA wants to say thank you to its loyal members who refer their friends and colleagues.

When you refer a colleague to join PDA, that person will receive $10 off the PDA Individual Membership fee.

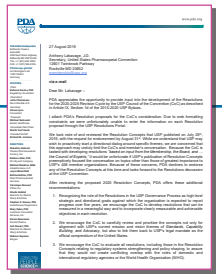
And, as a thank you for the referral, you will receive a $10 Visa gift card when that person joins. There is no limit – the more people you refer, the more you benefit.

It's a win for everyone!

Visit pda.org/refer and start to "Give $10 and Get $10" today!

CONNECTING PEOPLE SCIENCE AND REGULATION®

PDA Input on USP 2020-2025 Revision Cycle



27 August 2019

Anthony Lakavage, J.D.
Secretary, United States Pharmacopeial Convention
12601 Twinbrook Parkway
Rockville MD 20852
membership@usp.org

via e-mail

Dear Mr. Lakavage –

PDA appreciates the opportunity to provide input into the development of the Resolutions for the 2020-2025 Revision Cycle by the USP Council of the Convention (CoC) as described in Article IX, Section 1d of the 2015-2020 USP Bylaws.

I attach PDA's Resolution proposals for the CoC's consideration. Due to web formatting constraints we were unfortunately unable to enter the information on each Resolution proposal through the USP Resolutions Portal.

We took note of and reviewed the Resolution Concepts that USP published on July 29th, 2019, with the request for endorsement by August 31st. While we understand that USP may wish to proactively start a directional dialog around specific themes, we are concerned that this approach may unduly limit the CoC's and member's conversation. Because the CoC is tasked with developing resolutions *"based on input from the Membership, the Board, and … the Council of Experts,"* it would be unfortunate if USP's publication of Resolution Concepts preemptively focused the conversation on topics other than those of greatest importance to USP's 458 member organizations. Because of these concerns, PDA declines to endorse any of the Resolution Concepts at this time and looks forward to the Resolutions discussion at the USP Convention.

After reviewing the proposed 2020 Resolution Concepts, PDA offers these additional recommendations:

1. Recognizing the role of the Resolutions in the USP Governance Process as high level strategic and directional goals against which the organization is expected to report progress over five years, we encourage the CoC to develop resolutions that can be measured in a meaningful way and to incorporate clearly measurable and achievable objectives in each resolution.
2. We encourage the CoC to carefully review and prioritize the concepts not only for alignment with USP's current mission and vision themes of *Standards, Capability Building, and Advocacy,* but also to link them back to USP's legal mandate as the official compendium of the United States.
3. We encourage the CoC to evaluate all resolutions, including those in the Resolution Concepts relating to regulatory systems strengthening and policy shaping, to assure that they would not create conflicting overlap with the roles of domestic and international regulatory agencies or the World Health Organization (WHO).

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, and is an ANSI-accredited standards development organization. Our input has been prepared by a committee of experts in regulatory affairs and standards-setting on behalf of our Regulatory Affairs and Quality Advisory Board and Board of Directors.

If you have any questions, please do not hesitate to contact PDA's delegate to the USP Convention, Dr. Tina Morris via email at tmorris@pda.org.

Sincerely,
Richard Johnson
President and CEO, PDA

cc: Tina Morris, PDA; Ruth Miller, PDA; Falk Klar, PDA

PDA Commenting Task Force

Bettine Boltres, West
Michael De Felippis, Eli Lilly
Susan Schniepp, Regulatory Compliance Associates
Stephan Krause, AstraZeneca Biologics
Janeen Skutnik-Wilkinson, Biogen
Karin Baer, Boehringer Ingelheim
Earl Zablackis, Sanofi-Pasteur
John Ayres, Pharma Safety Solutions
Frithjof Holtz, Merck KGaA
Gopi Vudathala, Intarcia Therapeutics

Published online first

An Inside Look at the 2019 PDA Quality Week

Eva Urban, Celgene, Susan Schniepp, Regulatory Compliance Associates, Lori Richter, ValSource, and Ghada Haddad, Merck

Are you ready to implement the quality risk management (QRM) requirements included in the soon-to-be released Annex 1 document? Are you aware that ICH is planning on revising ICH Q9: *Quality Risk Management* to provide guidance on the applications of QRM concepts? Whether you answer "yes" or "no" to these two questions, you should plan to attend the *2019 PDA Quality Week.*

PDA is focusing on the complex subject of QRM for an entire week in December. The week is comprised of three unique, individual-but-contiguous miniconferences designed to educate attendees on all aspects of QRM. Participants can attend one, two or all three. Each miniconference provides a different perspective on QRM. The first conference focuses on the emerging regulatory landscape, framing the requirements of the regulations that govern this important but elusive concept. The second event is a one-day workshop that encourages attendees to actively participate in defining successful risk management applications that can be translated to the workplace. The third related miniconference focuses on the challenges and opportunities an organization faces when developing a holistic QRM program.

PDA has secured thought leaders on QRM for all three events including **Dr. Janet Woodcock, Dr. Greg Claycamp,** from the U.S. FDA, **David Churchward** from MHRA, **Guy Villax,** CEO of Hovione, **Dr. Anil Sawant,** PDA board member and Senior Vice President, Global Quality Compliance, Merck & Co., Inc., **Martin VanTrieste,** Past PDA Chair and CEO of Civica Inc., **Martin Nemec,** PhD from Health Canada and **Hal Baseman,** Past PDA Chair and Chief Operations Officer, ValSource. In one session, attendees can communicate suggestions directly to members of the ICH Q9 working group behind the Q9 revision.

The *2019 PDA Quality Week* promises to be one of the most comprehensive programs that addresses QRM. Do not miss this opportunity to collaborate with industry thought leaders and provide input on how QRM requirements should be implemented by our industry.

2019 PDA Quality Week
Washington, D.C.
Dec. 9–13
www.pda.org/2019qualityweek

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

The *PDA Letter* and *PDA JPST*

Interested in Peer Reviewing?
The *PDA JPST* is looking for peer reviewers!

CONNECTING PEOPLE SCIENCE AND REGULATION®

For more information on PDA publishing please visit:

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

Get Your Data Integrity Basics Down for Success

Silvia Martins, Five Validation

In recent years, regulatory investigators have observed an increase in violations involving data integrity ***(1).*** Inconsistencies related to data integrity pose risks to product safety, effectiveness and quality. At the same time, pharmaceutical manufacturing is growing ever more digitized, raising the criticality of data integrity even further. In light of these technological changes, it pays for companies to invest in a data integrity strategy.

The major regulatory agencies continue to focus audits on data integrity and remain committed to monitoring fraud cases around the world, even sharing cases of nonconformity with other agencies to get a global picture of how the issue has been addressed by industries.

Naturally, pharmacuetical companies are taking a closer look at the state of data integrity within their companies. The first task that must be considered when developing best practices for data integrity is to record the current situation of the company via data inventory. This entails reviewing compliance based on current procedures for managing critical data.

Next, the validation and QA teams must work together jointly to author a risk analysis to define which data falls under GMP and GDP (GxP) and are part of batch release. This step is intended to prevent all company data, even those not subject to GxP, from being included the data integrity process, as this would increase the cost and complexity of the production process. The master plan and procedures should consider this information so that the quality system has clearly defined which data will be subject to data integrity best practices.

All final data regarding the production process, such as metadata, which carry information about raw data (e.g., photogpraphs accompanying product claims, environmental monitoring records, training documentation, etc.) should be part of reviewing data integrity processes ***(2,3).***

In order to ensure that the decision-making process is well informed and the information reliable, the events or actions that led to such decisions should be well documented. This action is crucial to ensuring data integrity, in addition to serving as a key part of a structured Quality Management System (QMS).

The data supporting such decisions need to be complete as well as accurate, legible, contemporary, original and attributable, i.e., follow ALCOA principles. These basic GxP principles ensure the reliability of the data and they are not new.

It is essential to invest in employee training

ALCOA Principles of Data Integrity

The ALCOA concept is based on the accurate, complete and consistent recording and management of a data or information, either on paper or electronically.

The data on which these decisions are based should therefore be complete as well as being attributable, legible, contemporaneous, original and accurate, commonly referred to as "ALCOA." The basic principles and the related good practice expectations that assure data reliability. Below are examples of each of the ALCOA principles:

Attributable – Data can be assigned to the individual performing the task

Legible – Data can be read by eye or electronically and retained in a permanent format

Contemporaneous – Data is created at the time the activity is performed

Original – Data is in the same format as it was initially generated, or as a "verified copy," which retains content and meaning

Accurate – Data is true/reflective of the activity or measurement performed

Some actions may be taken within the production process that contribute to data integrity requirements. These can consist of the following:

- Keep a watch available in activity areas to avoid mistaken notes of time
- Facilitate operators' access to documents related to the activities they perform to avoid recording data after the fact
- Control unfilled forms to minimize the risk of wrong information recorded
- Control access to computer systems to prioritize traceability of data
- Avoid transcription of data and using printers directly connected to equipment
- Facilitate access to raw data by those responsible for data review to minimize regulators finding nonconformities

8 Essential Steps for Data Integrity

So, how can pharmaceutical manufacturers develop a culture that supports high levels of data integrity? There are eight steps that must be taken to build such an invironment.

1. Ensure limited and authorized individual access control
2. Define, clearly, complete records
3. Define, clearly, access profiles
4. Evaluate and record the evaluation of all relevant GxP records
5. Implement, monitor and review critical audit trail logs before product release
6. Backup data regularly

PDA Parenteral Drug Association

trarchive.pda.org

PDA's Technical Report Portal

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

CONNECTING PEOPLE SCIENCE AND REGULATION®

trarchive.pda.org

For licensing options contact Janny Chua at chua@pda.org

Data integrity can be a great opportunity for digital transformation

7. Include information security features and integrity in computer system validation approach
8. Train users

Regarding the last point, it is essential to invest in employee training to deal with relevant data integrity requirements and to create an in-company culture of attention to procedures so that employees feel responsible for the integrity of the data generated in their area, production stage or analysis.

Go Digital to Ensure Data Integrity

Well-implemented computer systems can streamline processes and make data entry more efficient and organized. Tools in compliance with FDA 21 CFR Part 11 and robust data integrity policies can help improve processes, no matter what stage of digital transformation journey a company is in.

A robust data integrity initiative can bring a company closer to digital transformation since companies are automating their production processes with incredible speed to optimize time and reduce costs. Paper-based processes remain slow and susceptible to human error.

Companies that automate their processes and embrace digital transformation will see gains in quality while companies still reliant on manual processes will experience low efficiency due to delays from outdated manufacturing proceesses and increased regulatory risk. Pharmaceutical manufacturers must implement innovative software and systems that streamline paper-based activities to increase efficiency and maintain compliance.

While other manufacturing industries discuss Industry 4.0 and big data, pharmaceutical manufacturers are still securing the integrity of their regulatory records. Data integrity compliance tends to be reactive and many see data as a liability. Yet data integrity can be a great opportunity for digital transformation.

For years, pharmaceutical manufactuers have claimed they had difficulty in adopting innovative manufacturing solutions due to regulatory requirements. Now, global regulators are increasingly adopting risk-based approaches that offer companies tools such as risk assessments and control strategies for managing product quality. Efficient analysis of stored data enables continuous improvements.

Data integrity and digital transformation go hand-in-hand. For example, data integrity reinforces GMP in automation and IT. By incorporating quality culture principles, manufacturers can ensure that the entire organization is in line with current challenges and future improvements.

Data Transformation for Compliance

Many businesses today are scrutinizing their operations to figure out how to join the digital transformation revolution. They understand that to become more competitive, they need processes that are integrated and scalable. They understand that controlling and making use of robust data is the key to success.

Unfortunately, poor data practices, which can cost a lot of money, are often overlooked. When it comes to the impact caused by poor data quality, the figures speak for themselves.

To turn that enormous loss into opportunities, CIOs and CEOs need to better operationalize data at enterprise scale—making qualified, clean and reliable data available to employees to then analyze to make fast, informed decisions. With the new emphasis on agility through digital transformation, CEOs now have the power to enable rapid change within their businesses by developing digital strategies with data at the core. These leaders have to change the departmental view that data is solely an asset used primarily by data scientists and expand it to cover data used across the entire enterprise.

CIOs and quality managers need to rethink their role within the broader organization—shifting from simply being a caretaker of utility-type technologies that run the business to be facilitators that help users leverage data to gain performance and make good decisions.

References

1. Data Integrity: Sindusfarma Guideline for Pharmaceutical Industry (Brazil, Portuguese language)
2. European Medicines Agency Questions and answers: Good manufacturing practice – Data Integrity
3. WHO Annex 5 Guidance on good data and record management practices.

About the Author

Silvia Martins is a CTO at Five Validation with almost 20 years of experience in Computer System Validation, GAMP5, FDA 21 CFR Part11, trained in CSV and Data Integrity in UK, Germany and Denmark. An enthusiast of compliant paperless pharmaceutical industries, she has been dedicating her last four years in designing GO!FIVE®, a SaaS-based VLMS Validation Lifecycle Management Software developed by Five Validation.

2019: A Global Launch for PDA

Rebecca Devine, Biopharmaceutical Consultant

As Chair of the Board, I am excited to write about another successful year for PDA. We are celebrating 73 years of connecting people, science and regulation®. We launched a number of initiatives that we will continue to support in the coming years.

Our standards program, which we launched in 2017, took significant strides in 2019. In September, we published our first standard on purchasing controls for public comment. We also added new standards, bringing the total in the pipeline to six.

PDA continued to work with other organizations. This year, we partnered with the BioPhorum Operations Group, ICH, PQRI and ISPE. ICH recognized PDA as a training partner. With ISPE, we formed collaboration on Root Cause Analysis guidance. We were also one of the sponsors for the Kilmer Conference this year.

Earlier this year, PDA launched its new Asia-Pacific office in Singapore. We also offered conferences in South Korea, Japan and Taiwan and continue to work heavily with chapters in the Asia-Pacific region. Additionally, we expanded our training courses in India, starting with the "Aseptic Processing Training Program," which has been well-received and has proven popular with students in that country.

Looking ahead, we have also prepared a new PDA Strategic Plan. The goals for the new Strategic Plan are to differentiate and expand our volunteer pipeline, including more volunteers in the Asia-Pacific region, and working more with our Young Professional members. We want to think globally and act regionally. These goals have been developed through outreach, including surveys and collaboration with key volunteer groups. We obtained a significant amount of volunteer input and feedback as the plan developed.

I want to thank my colleagues on the Board of Directors, PDA President **Richard Johnson,** PDA staff, our volunteers and the membership for making 2019 a successful year in a time of expanding global collaboration and innovation.

pda.org/2020UPS

2020 PDA Universe of Pre-Filled Syringes and Injection Devices

REGISTER BY JULY 27, 2020 AND SAVE UP TO $600!

PDA is taking Pre-Filled to Las Vegas!

We're bringing together industry heavyweights, experts from academia, and regulatory representatives for this must-attend event. We will focus on the emerging issues related to development, materials, manufacturing processes, injection methods and safety devices, and regulatory requirements.

Get the latest information including abstract submission details, agenda updates, and keynote speaker announcements when you sign up for the event newsletter.

To learn more and register, visit *pda.org/2020UPS*

CONNECTING PEOPLE SCIENCE AND REGULATION®

OCTOBER 5-6 | LAS VEGAS, NV

EXHIBITION: OCT. 5-6
2020 PDA COMBINATION PRODUCTS WORKSHOP: OCT. 7
TRAINING COURSES: OCT. 8
#PDAUPS

2019 PDA Quality Week

Mastering Risk Management for Organizational Success

Come prepared to roll up your sleeves and learn by doing when you attend the ***2019 PDA Building a Foundation and Culture for Quality Risk Management Integration Workshop*!**

The Workshop, Dec. 11, part of the ***2019 PDA Quality Week***, features interactive sessions to help you better understand the importance of quality culture and its relationship to quality risk management.

Highlights include:

- **Breaking the Barriers to a Successful Risk Culture**
  Address specific risk culture challenges in the "World Café Poster Session." Spend designated time at a series of posters to identify management methods and approaches to tackle each risk culture challenge
- **Choose Your Own Adventure: Managing Risk Communication**
  Benefit from lively dialogue and critical thinking as you break into small teams to unravel a case study where decisions must be made and communication must be clear. Each team will share its journey and rationale for resolutions reached.

This exciting Workshop is bookended by two informative Conferences on related QRM topics:

- **Risk Management in the Regulatory Landscape Conference | Dec. 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.
- **Optimizing Quality Risk Management Conference | Dec. 12-13**
  See how risk-based approaches can foster success in your organization and optimize the overall lifecycle management of a product, as envisioned by ICH Q12.

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

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

DECEMBER 9-13 | WASHINGTON, DC

EXHIBITION: **DEC. 9-11**
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

CONNECTING PEOPLE SCIENCE AND REGULATION®