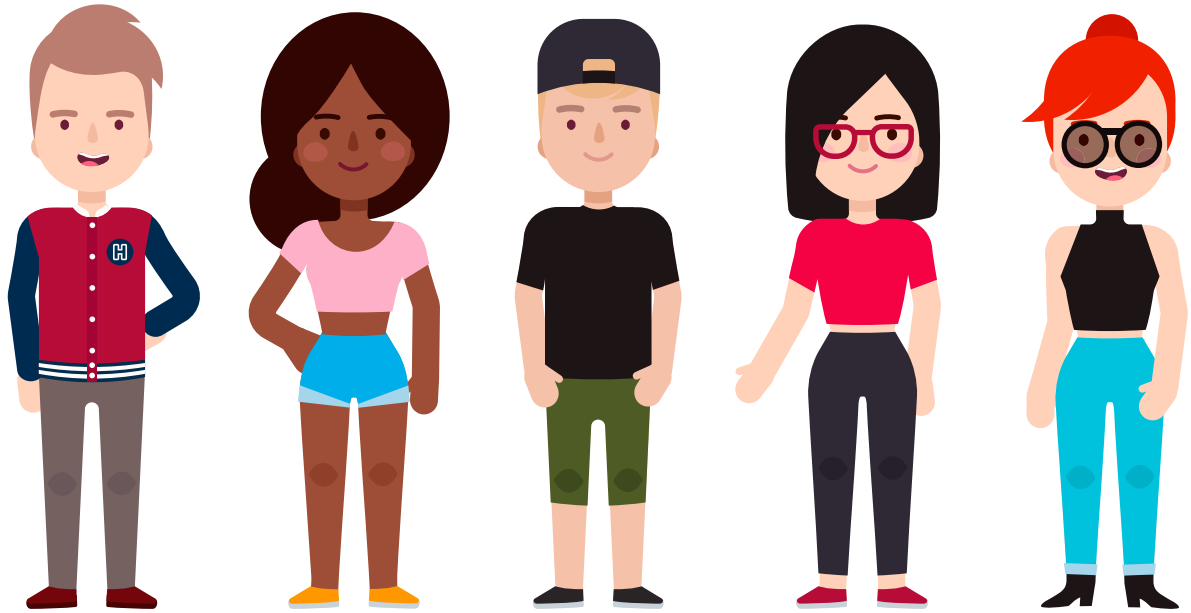
People • Science • Regulation

PDA Letter

Volume LIII • Issue 10 www.pda.org/pdaletter November/December 2017

Millennials

How Manufacturers Are Training the New Generation of Workers



PDA Bookstore New Release

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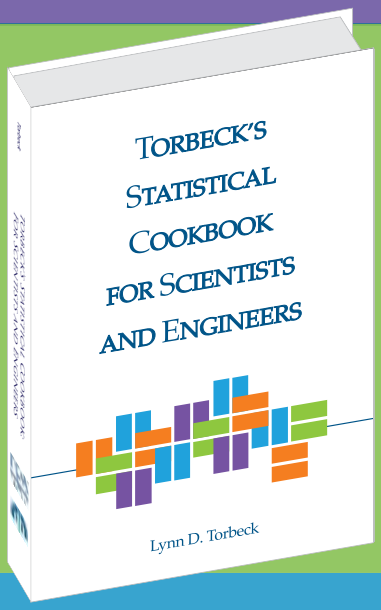
Enter campaign code **TSCK** during Checkout.



Torbeck's Statistical Cookbook For Scientists and Engineers

By: Lynn D. Torbeck

PDA MEMBER PRICE: ~~$210~~ $178.50
PDA NON-MEMBER PRICE: ~~$259~~ $220.15
HARDCOVER: ITEM NO. 17344
DIGITAL: ITEM NO. 18040

In the *Statistical Cookbook for Scientists and Engineers*, you will find tried and true, practical statistical "recipes" that provide a book of specific and unique statistical modules useful for evaluation of industrial studies. These modules are designed for the busy industrial worker, who needs to apply statistical techniques with the assurance he or she is using the technique correctly.

These modules were developed based upon years of experience in the field and training at many facilities, including the U.S. FDA, and are intended to fill a niche that is not currently addressed by other statistical books. Each module uses the same format with modifications. Where helpful, a worked example is presented in a parallel format to the procedure.

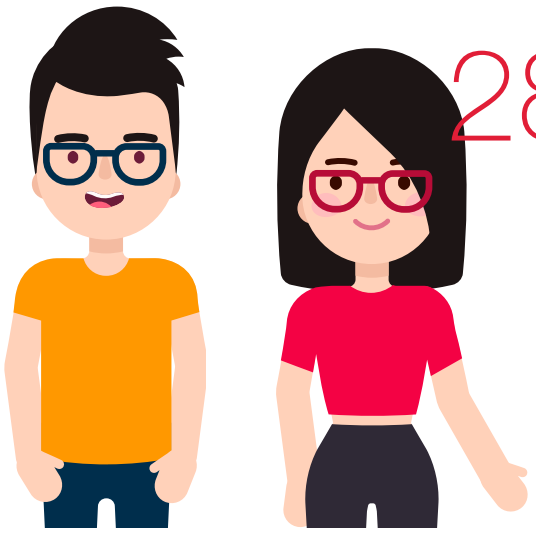
Scientists and engineers engaged in healthcare as well as other industrial manufacturing will find this text an invaluable resource.

go.pda.org/TSCK

About the Author

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

November/December 2017 PDA Letter



Millennials

How Manufacturers Are Training the New Generation of Workers

Rebecca Stauffer, PDA

Millennials recently surpassed Generation Xers as the largest generation in the U.S. labor force. Defined by the U.S. Census Bureau as those born between 1982 and 2000, millennials came of age in a time of great technological change and economic uncertainty. It is no surprise that workplace survey after workplace survey show this generation seeks specific requirements in order to stay fulfilled at their jobs.

Cover Art Illustrated by Karol Keane

InfoGraphic

Gen Xers versus Millennials

How do they differ when it comes to training and technology?

Isolator Surfaces and Contamination Risks to Personnel

GMP Cleaning Requirements for Nonproduct Contact Surfaces

Richard Denk, SKAN AG, et al.

When it comes to protection of cleanroom personnel and product, the possibility for contamination both within and on the exterior of an isolator exists.

AIDC is a Sign of Things to Come

Part I: What is AIDC and How Will it Impact Pharma Manufacturing?

Napoleon Monroe, New Directions Consulting

In 1974, a pack of Wrigley's chewing gum became the first retail item to be scanned with a Universal Product Code (UPC). IBM and the retail industry led the development and implementation of the UPC, but the healthcare industry did not embrace standardized bar coding.

PDA Letter

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

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

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Subscriptions are not available.

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Departments

Digital Exclusives

> **On the Issue** | Next Generation Manufacturing
Amgen's **Arleen Paulino** discusses next generation manufacturing at the company's facility in Singapore at the *2017 PDA/FDA Joint Regulatory Conference.*

pda.org/letter

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The Parenteral Drug Association presents:

3rd PDA Europe Annual Meeting

MARK YOUR CALENDAR

26-27 June 2018

Marriott Hotel

Berlin | Germany

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Video Opens New Frontiers in 2017

So far in 2017, more than 56,000 individuals have visited the *PDA Letter* website. And the year is not yet over! Ever since we relaunched the Letter website in September 2015, it has consistently remained in the top ten pages visited across the entire PDA website.

I am proud to say that each month we have also posted some type of digital exclusive content, be it an online-only article or a video. Digital exclusives do not appear in print. We also regularly post a few print articles online weeks ahead of print. Each Tuesday, you can find some new type of content on the Letter website, so I encourage you to visit the site each week: www.pda.org/pdaletter.

In addition, almost 10,000 of you have watched an "On the Issue" video over the course of 2017. Last year, we put out seven On the Issue videos and, this year, we are on track to post nine. With each video we produce, we get better and better at our production technique and editing. You will notice that our latest videos have a different look and feel than earlier videos. We are trying to make them less static and more dynamic.

Our videos cover a wide range of topics. This year, On the Issue videos have covered flexible manufacturing, quality culture, cleanroom disinfection, straight-through processing, cell and gene therapies, continuous microbial monitoring and next generation manufacturing. We also recently filmed a video on contamination recovery rates at the *12th Annual PDA Global Conference on Pharmaceutical Microbiology.* This should be posted on our website by the end of the year.

Rebecca Stauffer

Filming BMS' Paula Peacos at the PDA micro conference in Bethesda, Md.

(You can also view On the Issue videos by subscribing to PDA's YouTube channel: https://www.youtube.com/user/ParenteralDrugAssoc/featured).

I must confess: we like recording the videos and putting them together. I work with a subsection of our *PDA Letter* Editorial Committee to identify subjects that would make a good visual story and develop a script. On the day of filming, the Publishing team finds a location and sets up our equipment, including lighting and audio equipment. **Katja Yount,** the *PDA Letter's* designer, serves as our lighting and film advisor. Did I mention we now have some new lights?

In fact, if you come to a PDA conference, you might see us tucked away setting up in some quiet corner. But we also film at the PDA headquarters in Bethesda, Md., as well.

I hope we can produce more videos in 2018. If you have an idea for a topic, I encourage you to contact me. We are open to suggestions!

A Full Year of Publishing Projects

Walter Morris

A weekly email newsletter, a PDA-owned guide on preventing contamination and the rebranding of "PDA Surveys" as "PDA Research" were among the many new initiatives launched by the PDA Publishing team in 2017. All of these served to enhance PDA's publication offerings to members.

The "news uPDAte" hit member's inboxes for the first time in May. This e-newsletter, which we developed using InLoop's "intelligent newstracker" artificial intelligence system, provides members a customizable news feed that draws on relevant news sources covering the PDA niche. The news uPDAte website also includes a comprehensive online buyer's guide. If you do not get the news feed and want it, simply go to http://www.pda.myindustrytracker.com and sign up for the weekly email. Soon, we will place news feeds on various topics of interest throughout the PDA website. If you oversee a PDA Connect[SM] community, use this resource to stimulate conversations!

In December, we are publishing *Handbook on Contamination Prevention for Nonsterile Pharmaceutical Manufacturing,* which was generously given to PDA by Johnson & Johnson. Author **Andrew Dick,** Senior Manager, Source Quality North America, Microbiology Center of Excellence and Laboratory Controls, Johnson & Johnson, has participated in the PDA pharmaceutical microbiology conference and on a PDA task force. Andy felt the Handbook was a great tool for the community, so stepped up to convert it into a PDA-owned book!

PDA task forces routinely survey the industry to help develop PDA technical reports and other products for the membership. In past years, these have been published as "PDA Surveys." These surveys, however, represent an important part of the research conducted by PDA members and the Scientific and Regulatory Affairs staff, and as such, will be rebranded as "PDA Research." The first "PDA Research" survey is *Aseptic Processing Survey,* scheduled to publish in December.

"New" is not the only highlight of 2017. PDA's oldest member benefit, *PDA Journal of Pharmaceutical Science and Technology,* continued presenting high-quality, manufacturing-related research and case studies, extensive reviews and thought-provoking commentaries. Journal Editor **Govind Rao** pulled off a real coup, obtaining an interview with former Pepsi and Apple CEO **John Sculley** (July–Aug., pp 259–260). The two discussed the broken U.S. healthcare system and Sculley's efforts to push IT as a way of fixing it.

Just as timely, the Journal published four articles on pharmaceutical glass. There is no need for me to restate the ongoing issues with pharmaceutical glass, but these articles provide glimpses into the serious ongoing efforts to fix quality problems. "Enhancing patient safety through the use of pharmaceutical glass designed to prevent cracked containers" (currently in the "Accepted Articles" section of the website) and "Historical review of glasses used in parenteral packaging" (July–Aug., pp 279–296) are by authors from Corning Incorporated. The other papers are authored by teams from Jansen AG, with Corning, and Amgen (Jan–Feb., pp 50–58, and Sept.–Oct., pp. 379–392).

When it comes to the *PDA Letter,* enough cannot be said about how successful the transition from myself as the Managing Editor to **Rebecca Stauffer** has been. In her Editor's Message, she details the success of our "visual articles" program, better known as the "On the Issue" video series. We produced nine in 2017. I've become the de facto movie producer and, as Rebecca mentioned, it has actually added a fun challenge to our daily work. We are grateful that PDA has so many camera-ready members!

We hope all PDA members are benefiting from the Publishing team's hard work!

The Parenteral Drug Association presents the...

2017 PDA Cell and Gene Therapy Conference

December 5-6, 2017 | San Diego, CA
Exhibition: December 5-6
#2017CGT

The Journey of Cell and Gene Therapy – Bringing Science to Reality

With the recent U.S. FDA approval for the first cellular therapy for treatment of human patients, cell and gene therapies are gaining traction as next-generation medicines to treat life-threatening diseases. Therefore, it is critical that companies have a clear understanding of how novel approaches are being applied to the development and commercialization of these bio/pharmaceutical products.

Attend the *2017 PDA Cell and Gene Therapy Conference* to find out about current and future applications for these novel treatments, including the emerging field of immunotherapy. Emphasis will be placed on the science and technologies needed to bring these innovative products to market and, ultimately, to the patient.

Hear directly from a FDA CMC Product Reviewer with the Office of Tissue and Advanced Therapies in CBER regarding challenges faced by product developers in the industry. The Conference will also feature presentations from pioneering academic researchers and industry experts who have helped to drive these novel treatments forward.

The robust agenda will also include sessions on:

- Navigating the Regulatory Environment, Understanding the Challenges, and Sharing Solutions
- Development of a Process Control Strategy Leveraging Big Data to Speed Cell and Gene Therapy Product Development
- Process Validation and Process Comparability for Cell and Gene Therapy Products
- Facility, Process Design, and Containment
- Quality Systems and Compliance

To learn more and register, please visit pda.org/2017CellGene

Joint Statement from PDA and ISPE

October 11, 2017

The pharmaceutical and biopharmaceutical community faces many challenges in our changing global environment. New technologies are required for manufacturing and control of a more diverse product portfolio; new techniques are needed for managing a global supply chain; and regular information is needed about the changing regulatory landscape.

Fortunately, there are nonprofit organizations that work through their members to educate our industry, and also work together to define and disseminate consensus guidance and best practices. Nonprofit organizations fund these activities through membership dues, publication sales, and, in large part, through registration fees from education conferences and training courses. We pride ourselves on providing neutral, high-quality and reliable information to our members and attendees.

Today, we see an increasing number of for-profit conference organizers who duplicate the content developed by nonprofit organizations, employ aggressive marketing techniques and charge high prices for that content. This siphons much needed support from nonprofit organizations such as ours.

As leaders of two global member-driven organizations, ISPE and PDA, with nearly 30,000 members between us, we value the support that the community gives us. We are committed to fulfilling our missions, to guide our members and stakeholders toward using the best science and engineering to continue to provide high-quality, safe and effective medicines to serve patients.

Furthermore, we are committed to continuing our collaborations that provide unbiased platforms for dialogue, such as in cross-industry initiatives and interassociation groups, among others, that benefit the global pharmaceutical and biopharmaceutical community.

John Bournas
President and CEO International Society for Pharmaceutical Engineering (ISPE)

Richard Johnson
President and CEO
Parenteral Drug Association (PDA)

PDA in the News

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

BioProcess International

September 19, 2017
"The Unican Concept: Engineering Dual Capability into Single-Use Vessels"
— Terry Hudson, Ekta Mahajan, Kelsey Dent and Edward Chan
https://goo.gl/WbQXzR

European Pharmaceutical Review

August 31, 2017
"A comprehensive review of the newly revised European Pharmacopoeia chapter 5.1.6"
—Michael J. Miller
https://goo.gl/zGLuHW

FDANews

September 12, 2017
"PDA Conference: Baxter Cuts 483 Rate With Quality Matrix"

Healthcare Packaging

September 11, 2017
"Live from PDA/FDA: 5 Key Landscape Takeaways"
— Keren Sookne
https://goo.gl/bE7JAC

September 11, 2017
"Live from PDA/FDA: Culture of Quality"
— Liz Tierney
https://goo.gl/oa1gbj

September 13, 2017
"Live from PDA/FDA: 3D Printing Applications"
— Keren Sookne
https://goo.gl/G1XcTr

September 14, 2017
"PDA/FDA: Trends in Compliance and Enforcement"
— Keren Sookne
https://goo.gl/DE85Rj

Outsourcing-Pharma

September 12, 2017
"Cost of bad quality is much higher than cost of producing good quality, says PDA task force"
— Melissa Fassbender
https://goo.gl/vQtNEG

Pink Sheet

October 5, 2017
"EU Defends Plans To Keep 'PUPSIT' Testing In Revised EU GMP Annex 1"
— Joanne Eglovitch

MHRA Inspector Covers Reasons for Annex 1 Update

The Annex 1 revision process continues and the document is expected to be out soon. Although, according to **Andrew Hopkins,** Expert GMDP Inspector, UK MHRA, in his talk at the opening session of the *2017 PDA Annex 1 Workshop* on Oct. 2 in Washington, D.C., he did not have a time frame for when the document would be available.

Hopkins' presentation provided extensive coverage of the reasons behind the revision. In his words, EMA recognized the document needed "tidying up." The revision is expected to include Quality Risk Management (QRM) principles and address the need for manufacturers to keep up with new technologies.

Additionally, the revised Annex 1 will keep the requirement that manufacturers conduct pre-use, post-sterilization integrity testing, commonly referred to as "PUPSIT."

Gabriele Gori, VP, Head of Quality Audit and Risk Management, GSK Vaccines, and **Hal Baseman,** Chief Operating Officer, ValSource, currently head the PDA task force looking into the Annex 1 revision and working closely with European regulators. Members of this task force published the two-part *Points to Consider for Aseptic Processing* document in 2015 and 2016 in advance of the Annex 1 revision. Both Part 1 and Part 2 can be purchased from the PDA Bookstore (www.pda.org/bookstore).

(l-r) Andrew Hopkins, MHRA, and session moderator, Hal Baseman, ValSource

PDA Volunteer Spotlight

Lain-Tze Lee

- General Manager
- *Genhealth Pharma*
- Member Since | **2005**
- Current City | **Hsinchu, Taiwan**

I set my goals as aggressively as possible

As President of the PDA Taiwan Chapter, what are the top three accomplishments you are most proud of?
Helping the Taiwan FDA be a member of PIC/S, serving as a professional GMP training center in Taiwan and establishing a GMP system for medical gases in Taiwan.

What do you enjoy the most in your role as President?
The chapter serves as a platform for sharing and communicating within the pharmaceutical industry, government administration and academia in Taiwan. As President, what I enjoy the most is the opportunity to meet both domestic and foreign pharmaceutical experts, and discuss with them the latest advancements in technology.

What advice would you give PDA members?
The purpose of GMP is not to pass inspection, but to enhance the quality of drugs to protect the safety of patients.

What inspires you to volunteer with PDA?
In the early years of my career, I worked for the Industrial Technology Research Institute. In order to implement results from my research, I found that PDA was the best platform for exchanging information on pharmaceutical technologies. This led me to chapter activities and volunteering with the chapter.

How has PDA contributed to your career?
I have built three pharmaceutical plants. The assistance I obtained from the Taiwan chapter helped me pass the PIC/S inspection.

What lessons has your work life taught you?
Do not promise what you cannot deliver. Do not overextend your resources and get a reputation for poor performance. Do not tell the customer what he or she wants to hear. Tell them what they need to know; they will respect you for it.

When you were a child, what did you want to be when you grew up?
I wished to become President of Taiwan, but I have found that being President of the PDA Taiwan Chapter is my greatest honor.

Record Scholarships Awarded at NE Chapter Dinner

Steven Jones, Validation Support, New England Chapter Communication Commitee Chairperson Member at Large

We were delighted to see the close interest and engagement of our attendees at the most recent New England Chapter dinner meeting. In response to member requests, we held the meeting in Westford, Mass., a more convenient location than past meetings for those living/working northwest of Boston. This change was received positively by both attendees and sponsors, and we saw many fresh faces, in addition to "regulars."

The event started with a lively and well-attended sponsor exhibition and networking reception. We thank our Sponsors, who make our events and our scholarship fund possible.

This year, we were delighted to award $18,000 in total scholarships to six students from Middlesex Community College (MCC)—a record for the chapter! The students were selected based on their academic records and their involvement in and contribution to our student chapter at MCC. Scholarship winners are: **James Carroll, Tayaba Naz** and **James Nichols** for the $5,000 Transfer to a 4-Year Program Award, and **Hetalben Patel, Zeel Patel** and **Matt Peranelli** for the $1,000 2nd-Year Continuation Award. Congratulations and best wishes for continued success in your biotechnology education! Platinum Sponsors Boston Analytical and Masy BioServices, Gold Sponsors Avista Pharma, DPS, ICQ and Lyophilization Technologies, and Silver Sponsors Commissioning Agents and Complya all contributed directly to the scholarship program.

Following the announcement of the scholarship winners, the evening's talks on change management and quality metrics began. **Mike Jovanis** presented strategies on how to break down organizational silos to transform change management within a GMP company. In his talk, Jovanis emphasized the importance of breaking down silos between groups, changing mindsets to embrace innovative ways of doing things, empowering people to make decisions with accessible information and encouraging collaboration across functional areas. A robust Q&A session ensued at the end of his presentation.

Next, **Philippe Gaudreau,** led an interactive presentation and session based on outcomes from his company SOLABS' 2017 Quality Metrics Data Survey. This survey followed the 2016 FDA draft guidance on quality metrics. The survey was launched to understand how life science companies have responded to these requirements, and Fifty companies responded to it. Some of the survey questions discussed with the audience were:

- Are you currently collecting necessary data, and how frequently?
- Do you collect data and calculate additional metrics to measure quality system and subsystem performance?
- Do you collect any other data to evaluate the quality culture at your company?

There was excellent participation from the audience, and some very thoughtful responses.

The chapter is currently planning an exciting slate of similar meetings for 2018 spread out across the New England region. We hope to see you there!

PDA Who's Who

James Carroll, University of Massachusetts Lowell

Philippe Gaudreau, CEO, SOLABS

Mike Jovanis, Vice President, Veeva Vault Quality Product Suite

Tayaba Naz, Northeastern University

James Nichols, University of Massachusetts Lowell

Matt Peranelli, Student, Middlesex Community College

Hetalben Patel, PhD, Senior Scientist, Pfizer

Zeel Patel, Research Assistant, Drexel University College of Medicine

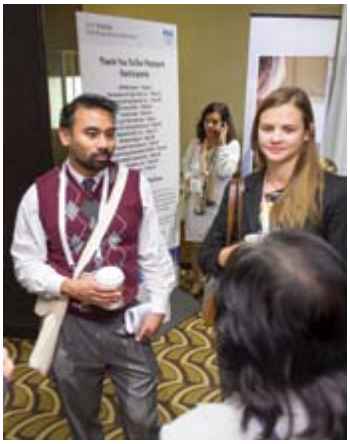
Networking Lights Up PDA/FDA JRC Exhibit Hall

Rebecca Stauffer, PDA

327 gallons of coffee consumed. 2,004 pastries devoured. And 800 granola bars served.

Attendees at this year's *PDA/FDA Joint Regulatory Conference* took advantage of refreshment breaks to enjoy generous helpings of snacks and make new connections as well as reaffirm existing ones. The exhibit area proved cozy and attendees visited exhibit booths with fervor. Though some attendees may have just been drawn to free chocolates and such wonderful tchotchkes as notepads, pens and even the occasional fidget spinner (thanks to exhibitor Veeva Systems for the light up ones!).

All in all, PDA hopes everyone who attended the conference not only learned a lot from the sessions but also formed some new friendships and connections within the industry. We hope everyone can meet up again Sept. 24–26 for the *2018 PDA/FDA Joint Regulatory Conference*.



PDA on the Move

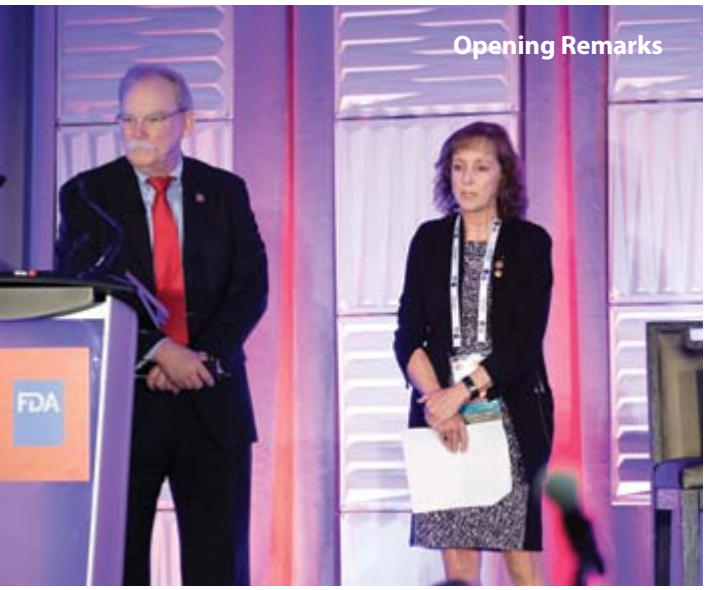
Amy McDaniel recently left her position as Director of Technical Operations at Pfizer for a microbiology role in CDER at the U.S. FDA.

PDA wants to hear about your career transitions and recognitions. Have you recently been promoted, switched jobs or received a special recognition? Let us know by email at submissions@pda.org.

At the end of October, CAPT **Sharon Thoma,** PharmD, National Expert of Pharmaceuticals, United States Public Health Service, Office of Regulatory Affairs, retired from FDA.

David (Dave) Doleski, Acting Deputy Director, Office of Process and Facilities, CDER, FDA, is leaving the Agency Nov. 9 to become Compliance Head at Sanofi Genzyme.

PDA Photostream www.flickr.com/parenteral-drug



(l-r) Richard Johnson, PDA President; Rebecca Devine, PhD, Regulatory Consultant and PDA Chair-Elect

2017 PDA/FDA Joint Regulatory Conference

Sept. 11–13 | Washington, D.C.

Steven Mendivil (right) talks to new PDA members at the Orientation breakfast

(l-r) Maria Guazzaroni Jacobs, PhD, Pfizer; David Cummings, CDER, U.S. FDA; Peter Marks, MD, PhD, CBER; Rosemarie Hunziker, PhD, U.S. National Institutes of Health

(l-r) Guy Villax, Hovione; John Pinion II, Ultragenyx Pharmaceutical

(l-r) Amy McKee, MD, FDA

PDA Photostream www.flickr.com/parenteral-drug

A1
Data Integrity

(l-r) Renee Kyro, AbbVie; Cormac Dalton, PhD, AbbVie; Simone Pitts, FDA; Carmelo Rosa, CDER, FDA

B1
Quality Systems: Maturity Models and Continuous Improvement

(l-r) Kevin Cloonan, Baxter; Brooke Higgins, CDER, FDA

C1
Expedited Pathways: Developing a Quality Product under Accelerated Timelines

(l-r) Sau "Larry" Lee, PhD, CDER, FDA; Earl Dye, PhD, Genetech

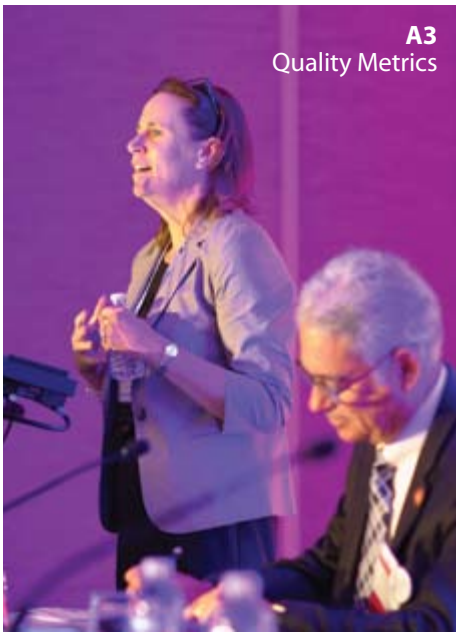
A2
Quality Culture and Enabling Lifecycle Quality Improvement

(l-r) Thomas Friedli, University of St. Gallen; David Jaworski, CDER, FDA; Cylia Chen-Ooi, Amgen; Thomas Cosgrove, CDER, FDA

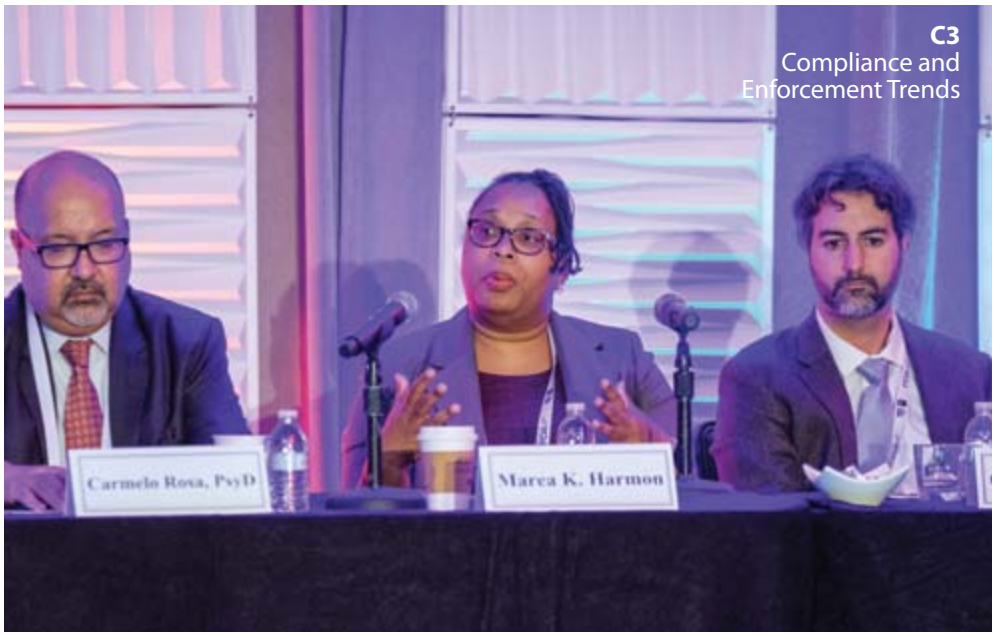
B2
ICH Q12 Change Management and Risk Management

(l-r) Ashley Boam, CDER, FDA; Andrew Chang, PhD, Novo Nordisk

PDA Photostream www.flickr.com/parenteral-drug



(l-r) Valerie Whelan, Amgen; Steven Mendivil, Amgen



(l-r) Carmelo Rosa, CDER, FDA; Marea Harmon, CVM, FDA; Robert McElwain, CBER, FDA

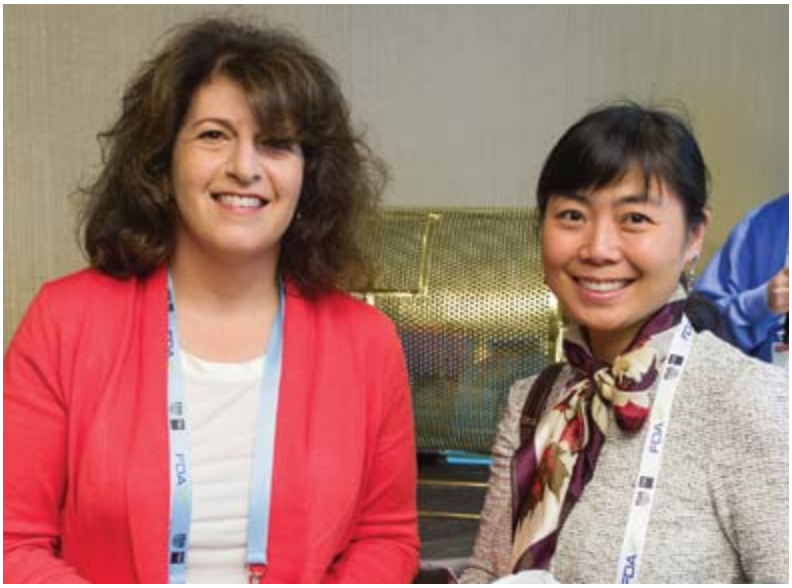
(l-r) Laurie Norwood, CBER, FDA; Susan Batcha, Novartis; Peter Turecek, Shire; Alexey Khrenov, PhD, CBER, FDA; Susan Kirshner, CDER, FDA; Anthony Lorenzo, CBER, FDA

(l-r) Colleen Hoyt, FDA; Theresa Mullin, PhD, CDER, FDA; Michael Oehlsen, PhD, CVM, FDA; Niraj Mehta, PhD, FDA; Joan Blair, CBER, FDA

(l-r) Alonza Cruse, Office of Regulatory Affairs, FDA

PDA Photostream www.flickr.com/parenteral-drug

Passport Drawings



Passport Drawings

Networking/Exhibitors

2017 PDA PAC iAM Workshop
Sept. 13–14 | Washington, D.C.

(l-r) Kara Follmann, Pfizer; Kassidy Good, Mylan; Suzanne Kiani, Mylan; Karolyn Gale, Emergent BioSolutions

(l-r) Mihaela Simianu, PhD, Pharmtech Associates; Emma Ramnarine, Genentech/Roche; Mahesh Ramanadham, PharmD, U.S. FDA; Andrew Chang, PhD, Novo Nordisk

(l-r) Ursula Busse, PhD, Novartis; Sharmista Chatterjee, PhD, FDA; Robert Iser, FDA; Susanne Martz, PhD, GSK; Frank Montgomery, AstraZeneca; Morten Munk, NNE; Mahesh Ramanadham, PharmD, FDA; Anders Vinther, PhD, Sanofi Pasteur

SNAPShot

2017 PDA/FDA Joint Regulatory Conference

IG Corner

Potency Assays, Aging Facilities Prove Twin Challenges for Vaccine Manufacturers

Rebecca Stauffer, PDA

The challenge of using the right potency assays and the regulatory issues of aging facilities served as focal points of discussion at the Vaccines Interest Group meeting, Sept. 11, at the *2017 PDA/FDA Joint Regulatory Conference.*

Interest group meeting leaders, **Jane Halpern,** PhD, Health Specialist, Vaccine Translational Research Branch, Vaccine Research Program, DAIDS, NIAID, U.S. National Institutes of Health, and **Sara Gagneten,** PhD, Associate Director for Regulatory Policy, Division of Viral Products, CBER, U.S. FDA, headed off the discussion on potency assays. A common challenge for all animal-based vaccines is variability. This often becomes apparent during the transition from in vivo to in vitro testing. Sometimes manufacturers accumulate data from clinical studies conducted for different purposes; this additional data may be used to correlate animal tests with human tests.

While Gagneten conceded that FDA continues to conduct research tests on potency assays, she cautioned that the Agency does not view itself as being able to impose specific potency tests.

Following the discussion on potency assays. **Michael Schwartz,** Director, Global Regulatory Affairs, GSK Vaccines, and **Linda Kramer,** Director, Global Regulatory Affairs, Establishments, GSK Vaccines, gave a short presentation on regulatory and compliance issues facing aging facilities. The main concerns, according to Kramer, are the potential for contamination, inspection issues, potential for drug shortages and the impact of modernization (recapitalization, time, product holds and process validation).

Vaccine manufacturers faced with an aging facility will have to make some hard decisions regarding modernization, Kramer further explained. If a manufacturer decides to outsource some or all of the process to a CMO, quality agreements come into play. If the manufacturer chooses to modernize the facility, the process may even need to be changed. And if the manufacturer chooses to build a new site filled with modern equipment, "that's going to take time, money and validation."

Naturally, any modernization plan will require involvement with FDA. Kramer recommends going to FDA with a well-thought-out modernization plan outlining defined expectations for the discussion.

Anyone interested in getting involved with the Vaccines Interest Group is encouraged to contact PDA at sci_reg@pda.org.

Journal *Preview*

The Nov./Dec. issue of the *PDA Journal of Pharmaceutical Science and Technology* includes the latest research around a myriad of topics, including packaging, validation of a system and pharmaceutical microbiology. Make sure you don't miss an issue and sign up for eTOC alerts. Go to http://journal.pda.org/cgi/alerts to sign up today!

Letter

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

Research

Ken G. Victor, et al., "Method Development for Container Closure Integrity Evaluation via Headspace Gas Ingress by Using Frequency Modulation Spectroscopy"

Alberto Leyva, et al., "Demonstration of the Maintaining of the Validated State of a System Used to Generate Water for Injection by Thermocompression Distillation"

Lloyd Waxman, Vinod D. Vilivalam, "A Comparison of Protein Stability in Prefillable Syringes Made of Glass and Plastic"

Masakazu Tsuchiya, "Factors Affecting Reduction of Reference Endotoxin Standard Activity Caused by Chelating Agent/Detergent Matrices: Kinetic Analysis of Low Endotoxin Recovery"

Technology/Application

Annalaura Carducci, et al., "Development of Methods for Recovering Endotoxins from Surfaces and from Air in Production Environment of Injectable Drugs"

Robert A. Schaut, et al., "Enhancing patient safety through the use of a pharmaceutical glass designed to prevent cracked containers"

Worst-Case Analysis of Cell Growth in SUS

Samuel Dorey, Sartorius

Single-use technologies are widely used in the bioprocessing industry as they bring a number of advantages over traditional stainless steel solutions.

Increasingly, these technologies are being used in more critical process steps. Yet biopharmaceutical manufacturers have raised concerns about their application and the risk that toxic or inhibitory substances could be released from the materials used for their construction. One solution could be to analyze the potential for cell growth inhibition using a worst-case analysis method.

With this in mind, a team of researchers conducted a study to demonstrate the relationship between results from cell growth tests and the concentration of extracted compounds as quantified by HPLC-UV and LC-MS. The extractable data is focused on the compound *bis*(2,4-di-*tert*-butylphenyl)phosphate (bDtBPP,), which is formed when an antioxidant used in polyethylene based single-use containers degrades. Antioxidants are necessary, however, to keep film properties stable, and cannot be easily removed.

For this study, the amount of bDtBPP has been quantified for different single-use films with a suitably developed method of detection using worst-case ethanol extraction. The study demonstrates the relationship between this analytical method and cell growth data from different films, thereby, facilitating the establishment of new film quality checks.

Extraction Methods

Eleven different films were extracted with pure ethanol. Films were gamma irradiated at 25–45 kGy. The extraction was performed with a surface-to-volume ratio of 1.5 cm²/mL and incubated at 40 °C for 3, 21, 70 and 120 days in static mode. Extracts were analyzed by HPLC-UV (with a flow rate of 1 mL/min with a gradient of acetonitrile and water. The injection volume was 20 µL and the detector had a wavelength at 220 nm.

Other sets of gamma-irradiated bags (50 kGy) with S71 and S80 films were filled with pure ethanol with surface-to-volume ratio of 1.5 cm²/mL and incubated at 40 °C for 3 or 21 days under static conditions. Extracts were analyzed by LC-MS (with a flow rate of 0.5 mL/min with a gradient of acetonitrile and water with ammonium acetate.

Extraction was conducted for three days with ActiCHO medium in 0.8 L sample bags (3 cm²/mL) at 37 °C without agitation. A glass bottle was used as reference. For the biological compatibility assay, the extracts were transferred to six well plates and spiked with human IgG1 producing CHO-DG44 cells. An inoculum cell density of 0.2 × 106 cells/mL was applied. During the assay, the cells were grown in a CO2 incubator under agitation at 160 rpm with a temperature of 36.8 °C, 80% relative humidity and 7.5% CO2. Each experimental condition was conducted in triplicate over three days.

Pure ethanol (EtOH) is able to extract low molecular weight chemical compounds, representing a worst-case extraction medium for biotech industry applications where aqueous solutions are more commonly used. Alcohols like ethanol can be regarded as optimal solvents for extractable investigations.

Ethanol extractions were performed on samples of the S71, S80 and S40 films. **Table 1** shows that the concentration of extracted bDtBPP is below the level of detection of 0.05 µg/mL under the study conditions. The results also show the lot-to-lot film consistency of the bDtBPP extractable concentration.

The results from the negative film reference show a constant bDtBPP concentration of 1.95 µg/mL–1.99 µg/mL irrespective of the extraction time. The ethanol extracts from the bags were also analyzed by the more sensitive LC-MS method. In parallel, water extractions were performed on the S71 and S80 films. No bDtBPP was detected after three days of contact time, either by HPLC-UV or by LC-MS.

Additionally, bDtBPP in ethanol solutions, at a level of 0.05 µg/mL after some days of contact time, indicates that no bDtBPP will be found in aqueous solutions after an even longer contact time.

Films from other suppliers were extracted with 100% ethanol were extracted by HPLC-UV to highlight the presence of bDtBPP **(Figure 1).** bDtBPP was detected in extracts from all of films C to I that have a polyethylene (PE) inner layer. The concentration within the extracts was between 0.5 and 1.5 µg/mL for all films except for the extract of film F, which

Table 1 bDtBPP Quantification by HPLC-UV in Bag Extracts in Contact with Pure Ethanol at Different Time Points at 40 °C

Film (sample name)	Solvent	Gamma-irradiation dose [kGy]	bDtBPP quantification [µg/mL]			
			t=3days	t=21days	t=70days	t=120days
S40	EtOH	50	ND	ND	ND	ND
S71 lot 1	EtOH	50	ND	ND	ND	ND
S71 lot 2	EtOH	50	ND	ND	ND	ND
S71 lot 3	EtOH	50	ND	ND	ND	ND
S80 lot 1	EtOH	50	ND	ND	ND	ND
S80 lot 2	EtOH	50	ND	ND	ND	ND
S80 lot 3	EtOH	50	ND	ND	ND	ND
Negative film reference	EtOH	50	1.95	1.96	1.99	1.96

Note: ND = not detected

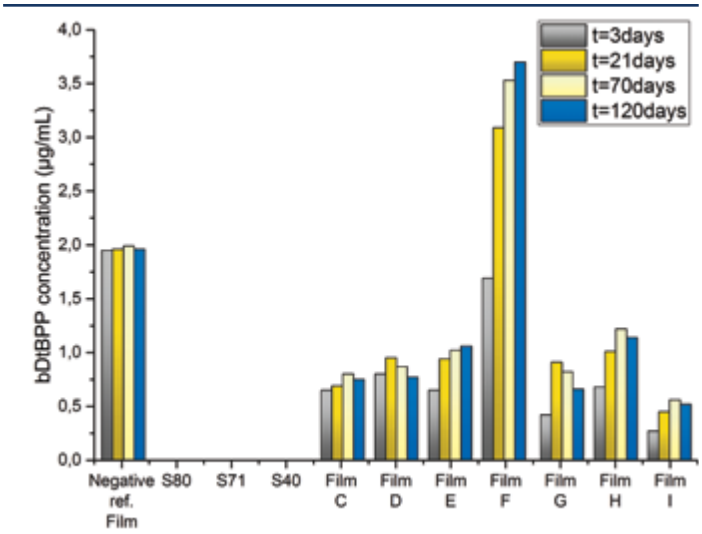


Figure 1 bDtBPP Quantification by HPLC-UV in Bag Extracts in Contact with Pure Ethanol at Different Time Points

contained a higher bDtBPP concentration of ~2 to ~4 µg/mL. The ethanol extracts from the S71, S80 and S40 film samples contained no detectable trace of bDtBPP (<0.05 µg/mL).

Cell Growth Inhibition

The impact on the biological performance of S40, S80 and S71 film formulation was also evaluated. Results on all films are depicted in **Figure 2.**

From these results, it can be concluded that cell growth inhibition is not influenced by total film thickness, contact layer thickness or the contact layer material. This shows that the additives added to the polymers in the resin recipe are key film parameters influencing cell culture.

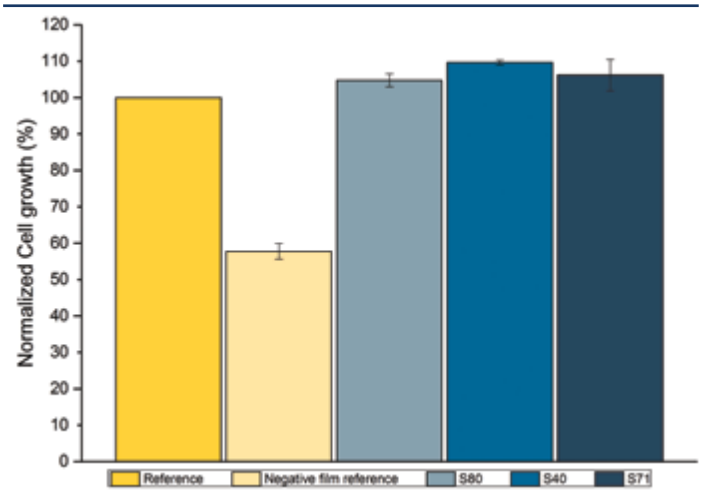


Figure 2 Cell Growth Assay Outputs on Different Films Expressed as % of Reference

The relationship between the analytical results for bDtBPP quantification by analytical methods has been established. The analysis and the detection of bDtBPP is not possible in a cell culture medium by chromatographic methods as there is interference with media compounds present in high concentrations. Extraction studies have been performed with pure water under worst-case conditions but did not demonstrate the necessary sensitivity. The bDtBPP concentration was determined to be less than the limit of detection (LOD) of 0.05 µg/mL in the ethanol extracts of the S71, S80 and S40 (**Table 2**).

Table 2 Quantification by LC-MS in Bag Extracts in Contact with Pure Water

Film (sample name)	Solvent	Gamma-irradiation dose [kGy]	bDtBPP quantification [µg/mL] t=3days at 40°C
S80 lot 1	WFI	50	ND
S80 lot 2	WFI	50	ND
S80 lot 3	WFI	50	ND

Moreover, the negative film reference releases in pure ethanol a quantity of bDtBPP up to ~2 µg/mL **(Figure 1).** From the data presented in **Figure 2,** one can see that the three SSB film types do not exhibit any cell growth inhibition effect.

Considering that this amount of bDtBPP has been extracted under worst-case conditions with ethanol, it can be concluded that bDtBPP levels at <0.05 µg/mL will not affect cell lines in bioprocesses (media are water-based solutions). The analytics provides the possibility to assess the potential impact of the bDtBPP presence on cell growth performance, depending on the amount of bDtBPP and the sensitivity of the cell lines.

Summary

Worst-case extractable studies with ethanol were used to evaluate the suitability of films for cell growth applications. It can be assumed that ethanol extracts with a bDtBPP concentration lower than 0.05 µg/mL will not show any impact on cell growth. The established extraction method with pure ethanol allows the characterization of film materials and shows that the bDtBPP concentration is below the EC50 value previously reported in literature for aqueous solutions. Knowing that this amount of bDtBPP has been extracted in worst-case conditions, it can be assumed that bDtBPP levels will not affect cell lines in biotech processes.

The analytics provide the possibility to assess the impact of bDtBPP presence on cell growth performance, depending on the amount of bDtBPP and the sensitivity of the cell lines. This approach to identifying extractable compounds is, therefore, an invaluable tool for the evaluation of plastic single-use systems.

About the Author

Samuel Dorey is a Senior Scientist at Sartorius Stedim Biotech specializing in polymer characterization, polymer selection, extractables and leachables, analytical chemistry, impact of the gamma irradiation, polymer interaction and chemical migration through films.

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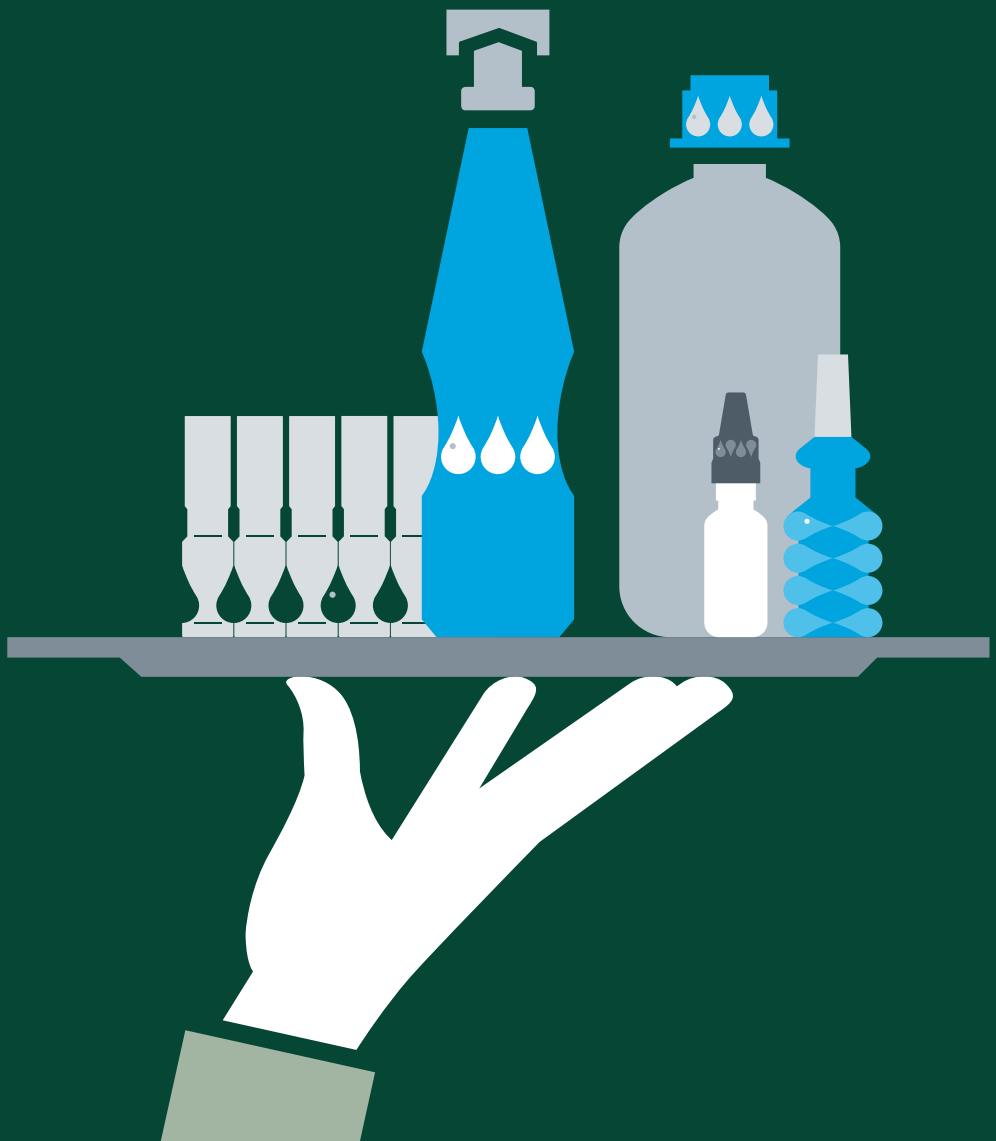


PDA Staff Gown Up for Site Visit at Pilot Plant

Marilyn Foster and Jahanvi (Janie) Miller, PDA

As part of PDA's staff development opportunities, five staff members representing PDA's Education, Marketing, Publications and Scientific and Regulatory Affairs departments, were treated to a tour of the MedImmune pilot facility in Gaithersburg, Md., Aug. 11, to learn how parenterals are started, manufactured and distributed. MedImmune is the global biologics research and development arm of AstraZeneca, focusing on the discovery, development and commercialization of small molecule and biologic prescription medicines. It is one of nine buildings on the Gaithersburg campus.

(front l-r) Kimberly McIntire; Roxene Edwards; Jahanvi (Janie) Miller; Stephanie Grinan (back l-r) Marilyn Foster

Ken Herko, Associate Director, and **Jason Stone**, Associate Director, Quality Assurance, welcomed the group, provided an overview of AstraZeneca's local and global enterprise and pointed out what to expect on the tour. They also answered questions as they traveled with PDA staff to the gowning station. Stressing the importance of maintaining a sterile environment, they explained that the purpose of the protective gear is, "not so much to protect you from the medicines, but to protect the medicines from any microbiological detritus you might bring into the facility."

Properly gowned in sterile jumpsuits, boots, gloves, hairnets and protective glasses, the two led the group through a corridor of observation windows that looked onto cell banks, media and cell culture prep actively in production. They explained how raw materials are tested and processed, identified the purpose of various equipment, described how they are cleaned and prepped for changeover and detailed the measures the company takes to ensure quality and prevent microbiological contamination.

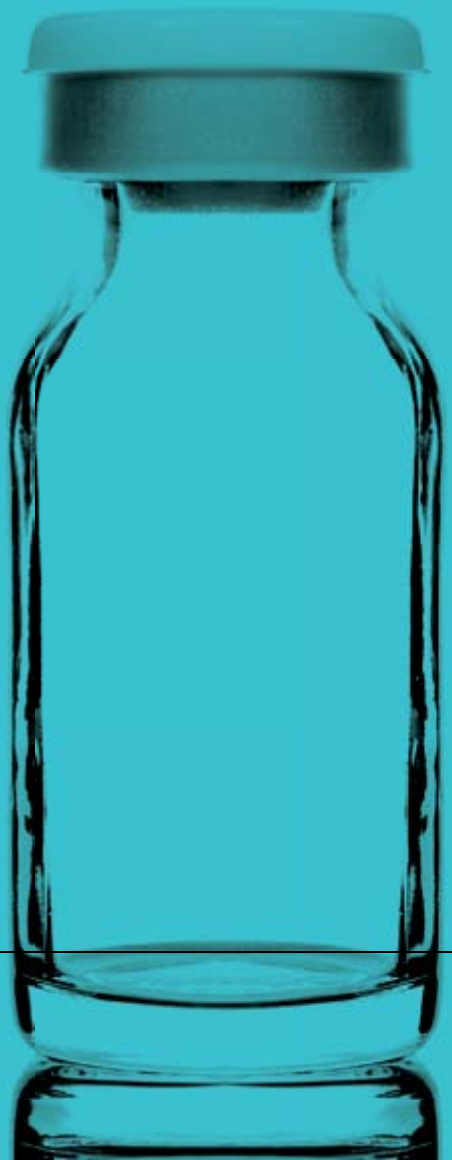
The five PDA staff members who attended the site visit found it quite enlightening. None of them have a background in parenteral manufacturing so experiencing the shop floor gowned up allowed them to better understand the daily challenges PDA members face. All agreed that the visit will help them effectively communicate with PDA members in the future.

PDA would like to thank **Ian Hart,** Director of Development, Manufacturing Sciences, MedImmune, and **Stephan Krause**, PhD, Associate Director–QA/QC/Validation, MedImmune LLC, who worked with **Jahanvi (Janie) Miller** of PDA's Science and Regulatory staff to facilitate this site visit and provide an enjoyable and educational experience.

The Parenteral Drug Association presents:

Parenteral Packaging

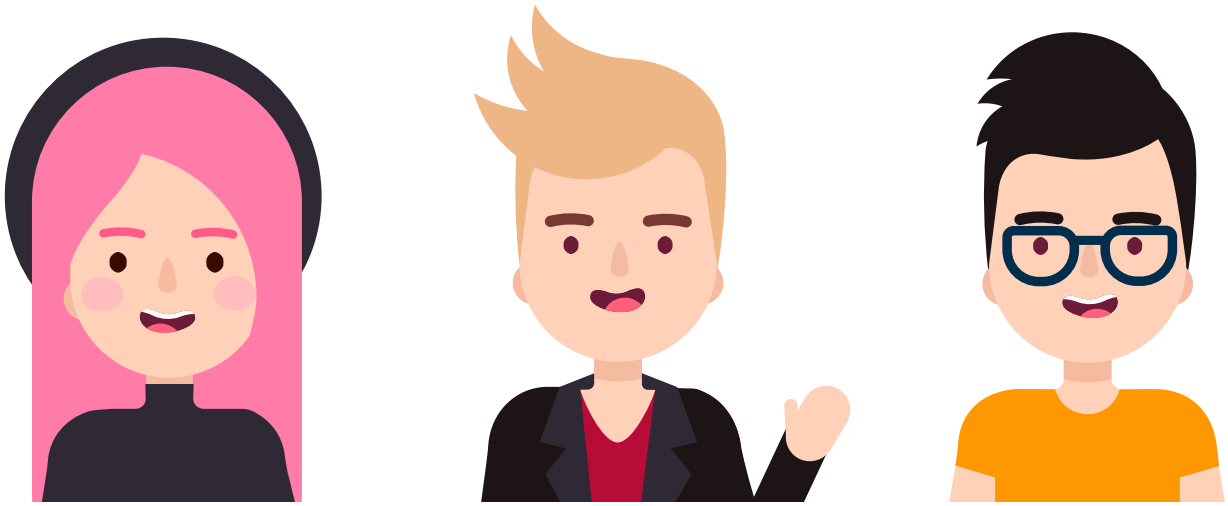
Container Closure Best Practices Throughout the Product Life Cycle



MARK YOUR CALENDAR

27-28 February 2018

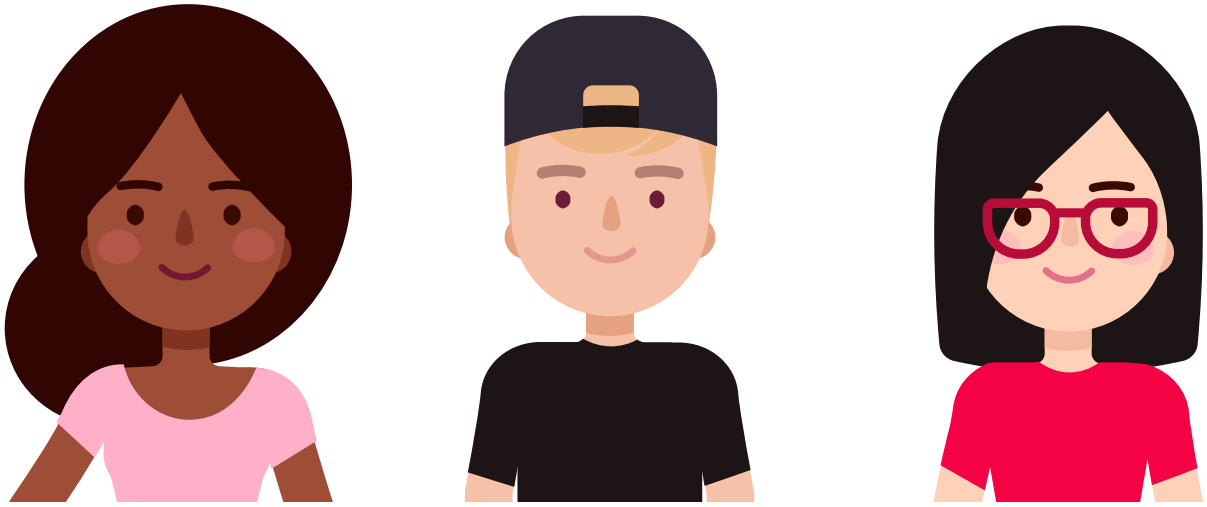
Prague | Czech Republic



Millennials

How Manufacturers Are Training the New Generation of Workers

Rebecca Stauffer, PDA



Millennials recently surpassed Generation Xers as the largest generation in the U.S. labor force ***(1).*** Defined by the U.S. Census Bureau as those born between 1982 and 2000, millennials came of age in a time of great technological change and economic uncertainty. It is no surprise that workplace survey after workplace survey show this generation seeks specific requirements in order to stay fulfilled at their jobs. Flexibility in when and where they work. Greater collaboration among colleagues. Ability to integrate technology into their roles. And companies that fail to deliver these requirements face the ever-present threat of their millennial employees seeking greener pastures, as they are more likely to switch jobs than other generations ***(2).*** This is not strictly a U.S.-only challenge for employers either; although fewer in number, European millennials also seek flexibility and emphasis on technology yet also remain open to other employment opportunities ***(3).***

While open floor plans, generous work-from-home opportunities and extensive reliance on personal mobile devices during the workday make sense at a Silicon Valley startup or a creative marketing firm, such millennial-centered perks may not be as feasible for a GMP environment. Nevertheless, pharmaceutical manufacturers are working to refine their training and professional development programs to not only attract millennials but retain them.

Some in the industry feel that millennials could have used more preparation within their university programs before entering the GMP workforce.

> Millennials do not want a lump sum approach to training

"Unfortunately, there is still a big experiential gap between university preparation and industrial reality," said **Manuel Belmonte,** Learning and Development Manager, Patheon. He specifically cited education around sterile manufacturing of injectables as particularly lacking.

Milton Ruiz, Senior Manager, Quality Management Systems, Portola Pharmaceuticals, agreed that standard university science programs do not cover GMP adequately.

"When it comes to the process of sterilization, they teach you about the science behind it, but when it comes to hands-on and what that looks like day-to-day, I don't think they do an effective job of setting people up."

"I think the schools do a pretty good job training them technically on the science of what is there. But I don't think they do a very good job of preparing them to be in a regulated environment," concurred **Timothy Gillum,** PhD, Director, Quality Training, Baxter.

Of the educational background of Millennial staff, his colleague, **Dawn Nixon,** Director, Business, Human Resources, Baxter, said, "Sometimes I think they lack the practical application of what it is to work in that type of environment. We know that collaboration is key for millennials. They like to be able to work on the go. They like to integrate technology into what they're doing. And a lot of that presents challenges to how you really interact in a sterile manufacturing environment."

In fact, Gillum pointed out that, as a traditional manufacturer, he thinks GMP should even be touched on at the *high school* level as many of their operators have only a high school education.

At the same time, some university programs are starting to address the unique requirements of sterile manufacturing. A few even offer programs in it. Ruiz has seen accredited university programs in vial manufacturing that teach what he terms the "sterile envelope" and how to work within a biotechnology environment. **Maik Jornitz,** CEO, G-Con Manufacturing, has also seen changes at the university level.

"Nowadays, I see more upcoming training courses and academic initiatives to prepare the next generation of manufacturing personnel. Within universities, there are also a multitude of new therapies being generated, which means that process technologies are utilized and trained," he explained.

Firms Explore New Training Frontiers

Regardless of the quality of university programs in covering sterile manufacturing, companies are modifying their training programs to address how millennials prefer to learn new information. Baxter is embarking on an overhaul of its training programs to address the needs of millennials on both the floor and in the lab.

"We really are trying to bring our learning programs into the current technology age, not only to appeal to millennial employees but also to the larger global employee population," Nixon said, adding, "even broader than just our learning programs, we are starting to incorporate more collaboration tools, bringing mentoring, learning and experience to employees where they need to get it and where they are working."

And those on the manufacturing floor are not being left out.

"We are moving more to microlearning," Gillum said. "Microlearning" refers to breaking up on-the-job training into bite-size bits of information. For example, instead of holding a two- or three-hour session, shift meetings might include five- to 15-minute segments of hand-based training activities. He compared it to paying for something in monthly installments as opposed to a one-time lump sum payment. And millennials do not want a lump sum approach to training.

The challenge for Baxter, he explained further, is modifying the training to suit both those in the lab and staff on the floor. A line operator filling IV bags does not have the same access to a workstation with an online training program as a manager in the microbiology lab. The company is considering placing a tablet-based station on the manufacturing floor for operators to access training as the need arises.

Other companies are also looking at the microlearning approach. Biotech firm Portola Pharmaceuticals outsources its manufacturing. This has exposed Ruiz to how other companies are modifying their training as Millennials come on board.

"The challenge from my experience was when you had these baby boomers or Gen Xers who were kind of expecting training to be very straight-forward and 'Here is what I am going to tell you' versus the millennials that liked constant change," he said. He is now seeing more companies offering training programs that "go in the middle" by offering moderately lengthy training with more bite-size pieces.

"I firmly believe in collaborative training and not separate training blocks for just target groups. That would create separation instead of unity and interactive experience exchange," Jornitz said, further explaining that training should be interesting, fun and hands-on.

Training should also be customized for each audience, said Belmonte. He also wants to see collaborative training that involves both millennials and more experienced staff. ➤

Article at a Glance

- New training programs address needs of millennial staff on floor and in the lab
- Mentoring between generations is key
- Millennials will be at the forefront of Industry 4.0

2017-2018 PDA Upcoming Events

SAVE THE DATE for PDA's 2017-2018 Events

NOVEMBER

14-16
■ **Validation of Moist Heat Sterilization Processes**
Bethesda, MD
pda.org/2017NovMH

14-17
Facilities and Engineering Course Series
Bethesda, MD
pda.org/2017FacilitiesCS

15-16
COURSE IN GERMAN LANGUAGE
Track und Trace – Implementierung von Serialisisierung, Fälschungssicherheit und Verifizierung
Leipzig, Deutschland
pda.org/EU/TRACK-UND-TRACE2017

21-22
Outsourcing & Contract Manufacturing Conference
Munich, Germany
pda.org/EU/Outsourcing2017

23-24
Outsourcing, Technology Transfer, and CMO-Client Relationships
Munich, Germany
pda.org/EU/cmo-tt-17

23-24
Practical Guide for Root Cause Investigations – Methodology and Tool Kit
Munich, Germany
pda.org/EU/RootCause2017

23-24
Risk Management in Technology Transfer
Munich, Germany
pda.org/EU/RM2017

28-29
2017 PDA Modern Biopharmaceutical Processing Conference
Singapore
pda.org/2017BiopharmSingapore

DECEMBER

4-7
■ **Fundamentals of Aseptic Processing**
Bethesda, MD
pda.org/2017DecFundAP

5-6
2017 PDA Cell and Gene Therapy Conference
San Diego, CA
pda.org/2017CellGene

7-8
Evaluation, Validation and Implementation of Alternative and Rapid Microbiological Testing Methods
Bethesda, MD
pda.org/2017Rapid

11-14
PDA Quality Risk Management Certificate Program
Bethesda, MD
pda.org/2017QRMTP

JANUARY

22-26
■ **PDA Aseptic Processing, Option 1 Week 2: Feb. 19-23**
Bethesda, MD
pda.org/2018Aseptic1

23-24
2018 PDA Glass Quality Conference
Bethesda, MD
pda.org/2018Glass

30-31
PDA Quality Culture Transformation
Thousand Oaks, CA
pda.org/2018Transform

FEBRUARY

25-28
NEW COURSE
Downstream Processing (DSP) – Purification of Biomolecules
Clausthal-Zellerfeld, Germany
pda.org/UC/DSP2018

27-28
Parenteral Packaging Conference
Rome, Italy
pda.org/EU/ParPack2018

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

PDA
Parenteral Drug Association

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

27-1
NEW COURSE
CBP – Continuous Bioprocessing of Biomolecules
Clausthal-Zellerfeld, Germany
pda.org/UC/CBP2018

28
PDA Southern California Chapter 7th Annual Industry Summit and Exhibitor Showcase
Yorba Linda, CA
pda.org/SoCal2018IS

28-2
Human Factors Course Series
Bethesda, MD
pda.org/2018HF

MARCH

6-7
NEW COURSE
Strategies for Formulations Development: How to Get the Right Data in the Right Amount at the Right Time
Bethesda, Md
pda.org/2018SFD

12-16
■ **PDA Aseptic Processing, Option 2**
Week 2: Apr. 9-13
Bethesda, MD
pda.org/2018aseptic2

19-21
2018 PDA Annual Meeting
Orlando, FL
pda.org/2018Annual

21-22
2018 PDA Manufacturing Intelligence
Orlando, FL
pda.org/2018MI

22-23
2018 PDA Annual Meeting Course Series
Orlando, FL
pda.org/2018AnnualCourses

27-29
■ **Airflow Visualization Techniques and Practices, Option 1**
Bethesda, MD
pda.org/2018MarAir

27-29
■ **Validation of Biotechnology-Related Cleaning Processes, Option 1**
Bethesda, MD
pda.org/2018MarValBiotech

ADDITIONAL SIGNATURE EVENTS IN 2018

MAY

15-16
Virus Forum
Florence, Italy
pda.org/EU/Virus2018

JUNE

26-27
3rd PDA Europe Annual Meeting
Berlin, Germany
pda.org/EU/Annual2018

SEPTEMBER

11-12
11th Workshop on Monoclonal Antibodies
Munich, Germany
pda.org/EU/MABS2018

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

OCTOBER

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

15-16
PDA Europe Pharmaceutical Microbiology
Berlin, Germany
pda.org/EU/PharmaMicro
(Some sessions simulcast with PDA North America)

15-17
13th Annual PDA Conference on Pharmaceutical Microbiology
Bethesda, MD
pda.org/2018Micro
(Some sessions simulcast with PDA Europe)

"We cannot waste the curiosity and creativity of millennials but, on the other hand, we cannot waste the experience of [experienced personnel]," he explained. "In this sense, workshops could help by enabling multiple generations of staff to share knowledge and ideas."

Additionally, "paper has to be eliminated as much as possible," as this represents the older way of documenting training, Belmonte explained.

Building Ties Across Generations

In addition to new types of training, companies are also building up their mentoring programs. Baxter offers a variety of mentoring programs, including what Nixon refers to as an "open source" program where personnel can sign up to be paired informally with a mentor. Both parties work together to manage the relationship, suiting it to their unique needs. The manufacturing, operations and quality groups offer a rotational program that provides mentoring in different aspects, so that participants can get a taste of other roles.

Ruiz also sees mentorship as playing a vital role in getting millennial employees up to speed.

"Everybody has to feel like they bring something of value. If you have an older generation, you want them to be mentors to help teach the intangibles to the millennials," he said. Millennials may have "tactical skills" but lack what he calls "intangible skills." These are the communication and strategic-thinking skills necessary for long-term planning.

"I believe that having millennials be mentored, guided and taught on the intangibles of being successful is the way to get both [demographic groups] to be intergenerational. And as a result, I believe these millennials will also teach some of the older workers some new skills," Ruiz said.

Belmonte views mentorship as a recipe with the ingredients of "respect, trust, synergy and success."

"The first two ingredients serve as the basis of good collaboration within different generations, while the third leads to the fourth," he explained.

> "this generation has no qualms about acting on the urge to seek better opportunities"

Mentoring also allows for millennial staff to build better ties with staff from earlier generations.

"Both have to come together to learn from each other, to improve together and create an environment of collaboration and advancement," emphasized Jornitz. "In instances one sees 'experience contempt,' which may not allow for new ideas, even in training. I believe we need to learn from each other to constantly improve."

Mentoring is also another way for companies to retain millennials. Often labelled "job hoppers," this generation has no qualms about acting on the urge to seek better opportunities ***(2).*** Belmonte attributes this to the fact that many started their careers in the midst of a global financial crisis with little to no memory of the prosperity of the 1980s and late 1990s. Ruiz also pointed out that he is seeing more companies on the manufacturing side hiring contract staff for fixed terms (usually three years), with no expectation that employees will stay on full time.

Many companies, however, still seek employees looking for long-term tenure. Baxter is moving away from a performance rating system to one that encourages more frequent check-ins. The company is also in the beginning stages of implementing a LinkedIn-type internal platform that allows personnel to provide feedback and give recommendations for staff. Additionally, the company is also appealing to millennials' altruistic side by providing opportunities for staff to give back to the community. The company hopes these steps will encourage millennial staff to stay on with the company and grow their careers within.

Millennials Embrace Industry 4.0

Just as training is becoming more high tech, so too are manufacturing processes. Although pharma has lagged behind other industries when it comes to implementing Industry 4.0 or Factory-of-the-Future technologies, involving the digitization and automation of manufacturing, the industry is slowly evolving in this space. And this is an area where millennials can truly shine.

Belmonte's company, Patheon, is currently investing in Industry 4.0 projects, and even has millennials involved as project leaders. When it comes to millennials and Industry 4.0, he said, "It's the best current combination you can choose."

Ruiz even sees Industry 4.0 as a strength for the millennial generation.

"I see them in the background, creating the automation and working in that area," he said. "That is where I see more millennials contributing, being part of manufacturing on that end as it becomes more and more automated."

Industry 4.0 is one of the areas where millennials' ability to adapt to constant change will allow this generation of manufacturing staff to leave its mark. It also doesn't hurt to remember that millennials will one day be the mentors of succeeding generations.

"Eventually, millennials will start hitting that age where they're 45 or 50 years old," Ruiz said. "Then a whole new generation comes in, and they're inexperienced with intangibles and the cycle just keeps on going on."

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Continued at bottom of page 56

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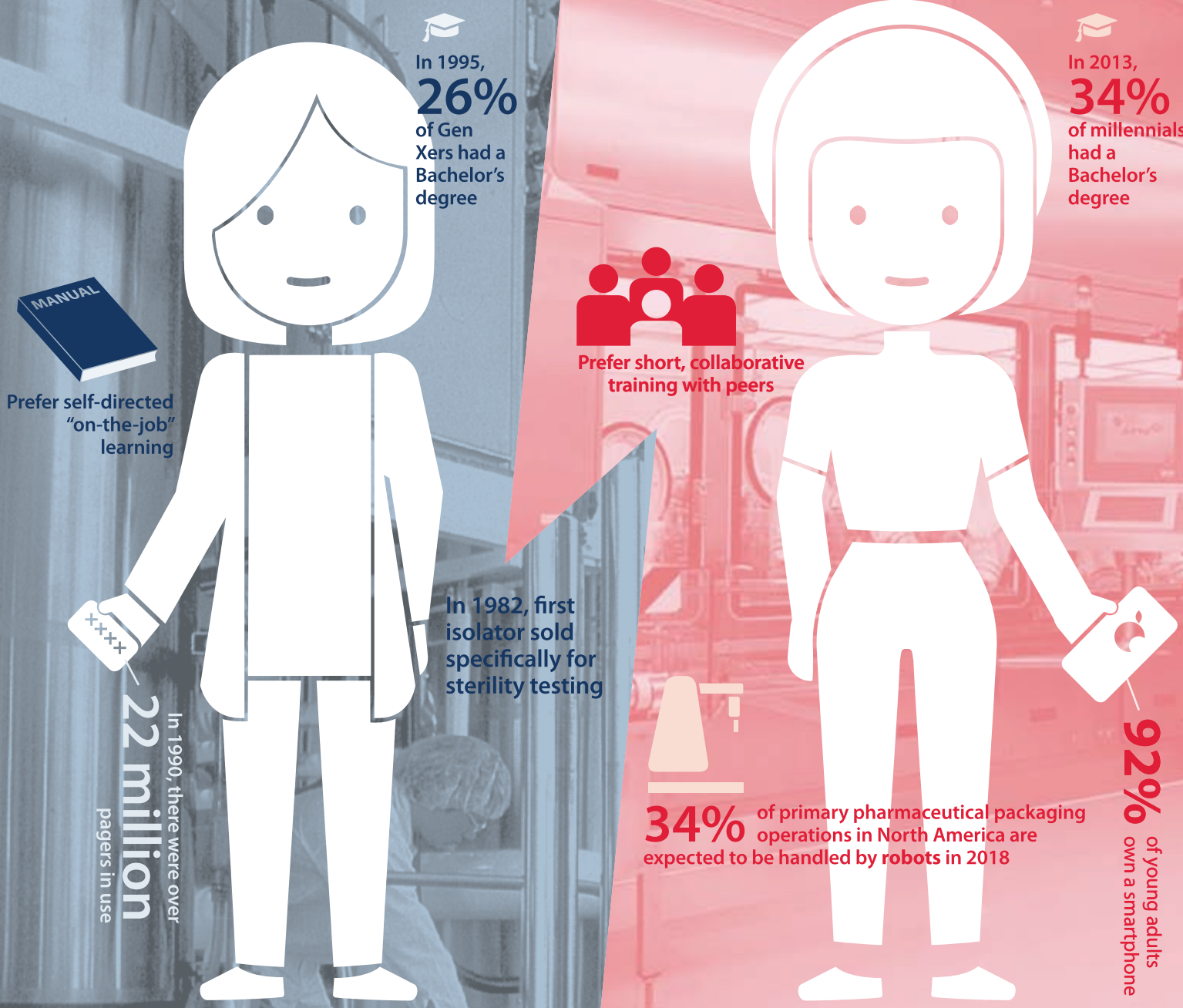
Born between 1982 and 2000



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Isolator Surfaces and Contamination Risks to Personnel

GMP Cleaning Requirements for Nonproduct Contact Surfaces

Richard Denk, SKAN AG, et al.

When it comes to protection of cleanroom personnel and product, the possibility for contamination both within and outside an isolator exists.

The issue is of particular interest in the manufacturing of pharmaceutical products with highly potent APIs (HPAPIs). Manufacturers must assess isolator design, the routes by which HPAPI can spread (transfer or contact via nonproduct contact surfaces) and the possibilities for containment with a view to evaluating possible contamination risks within an isolator. Additionally, the cleaning process and cleaning limits for nonproduct contact surfaces within an isolator operated under aseptic conditions, as well as cleaning and air concentration limits outside the isolator, should also be considered.

Validation of the cleanliness of nonproduct contact surfaces has increased in popularity since EMA proposed the following measures to demonstrate effective management of the cross-contamination risk in Chapter 5.21 of Part 1 of the GMP guidelines: **"Depending on the contamination risk,** verification of cleaning of non product contact surfaces and monitoring of air within the manufacturing area...in order to demonstrate effectiveness of control measures against airborne contamination or contamination by mechanical transfer;..."

In aseptic manufacturing, isolators are used to reduce direct access by personnel to the critical stages of manufacture (fill–finish) and to contain the cleanroom area in which critical stages take place. As an example, the fill–finish area within an isolator is designed as Zone A/ISO Class 5, and the area outside is Zone D/ISO Class 8 for the European Union and ISO Class 7 for the United States. Protection of personnel handling HPAPIs is another reason for using isolators.

But how does a classic aseptic isolator differ from an isolator used for the aseptic manufacture of HPAPIs? A classic isolator

is supplied with conditioned air for Zone A via unidirectional air flow. The return air from the isolator to the recirculation fan travels through the double wall of the isolator ***(1).*** Spread of released HPAPIs from the isolator to the isolator plenum is possible; therefore, the classic isolator is not suitable for use of HPAPIs (**Figure 1**).

An HPAPI isolator, on the other hand, features an additional filter level before the air return into the isolator plenum. This filter level is located directly before the air return ducts, preventing HPAPIs from spreading into return air ducts and the isolator plenum. See **Figure 2** for a single-wall isolator with appropriate filter

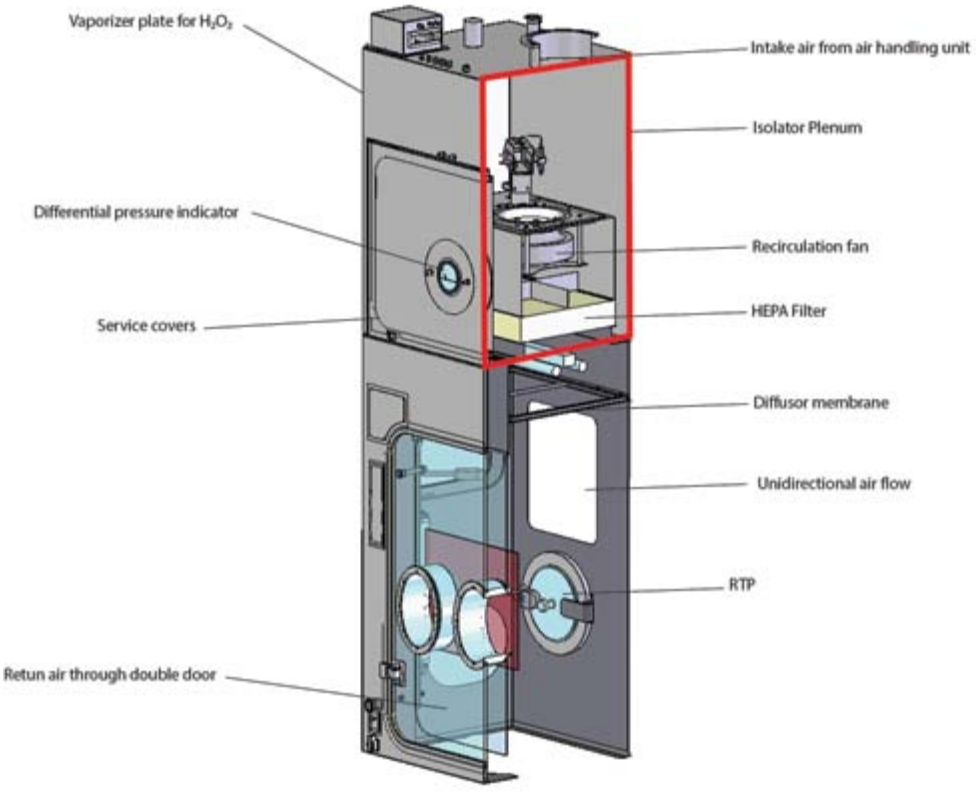

Figure 1 Isolator With Double-Walled Air Return Chamber

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technology between the isolator process chamber and the air return ducts for use with HPAPIs ***(2).***

The primary concern in the manufacture of HPAPIs is to prevent the substance from spreading outside Zone A into the air return ducts and isolator plenum. At the same time, it is also advisable to limit the spread of substances within the isolator chamber; technical measures are required to keep this spread to an absolute minimum. These can include various pressure cascades from the critical manufacturing area to noncritical areas.

The critical HPAPI exposure stages of aseptic manufacturing are the filling process, the fitting of the stoppers and the loading and unloading of the freeze dryer **(Figure 3).**

There are various scenarios in which highly potent/toxic substance can spread within the isolator. The key issue here is contamination of the line when a product is being manufactured at that moment. Here, there is no direct risk of cross-contamination, especially as only one product can be manufactured in a given space at any point in time. But if this contamination is not removed effectively during cleaning, this can result in potential cross-contamination risk for the next product manufactured using the same facility.

Product spread can be caused by the breakage of containers such as vials, ampoules, syringes, etc. For the sake of simplicity, this article refers to vials, but this should be understood to include other forms of primary packaging.

The following may cause product spread in an isolator:

1. Turbulence due to air flow (pressure cascades) within the isolator line
2. Contaminated gloves
3. Mechanical transfer systems such as conveyors, carousels, transport carriages for moving equipment to other sections of the isolator, etc.
4. Contact contamination due, for example, to damaged vials and gloves, or contaminated stainless steel or plastic surfaces
5. Transfer of contaminated settle plates (viable sampler)

So how can these be prevented? The following are some considerations for preventing cross-contamination:

Air flow

The spread of airborne particles or aerosols can be determined in advance during the

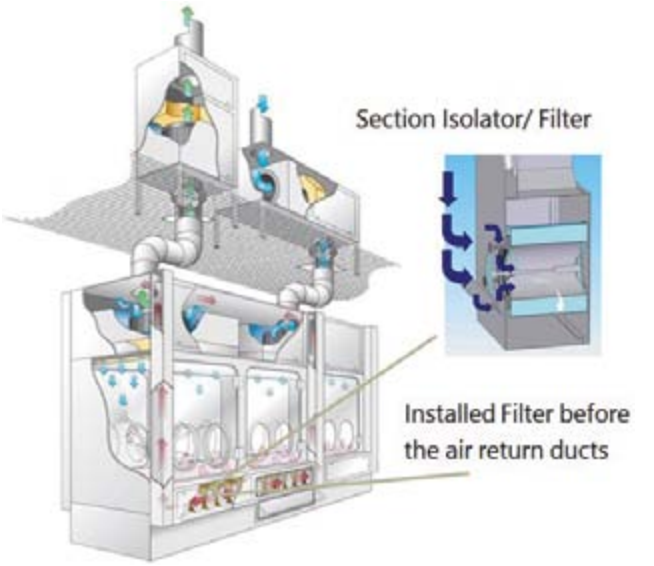

Figure 2 Filter Before the Air Return Ducts

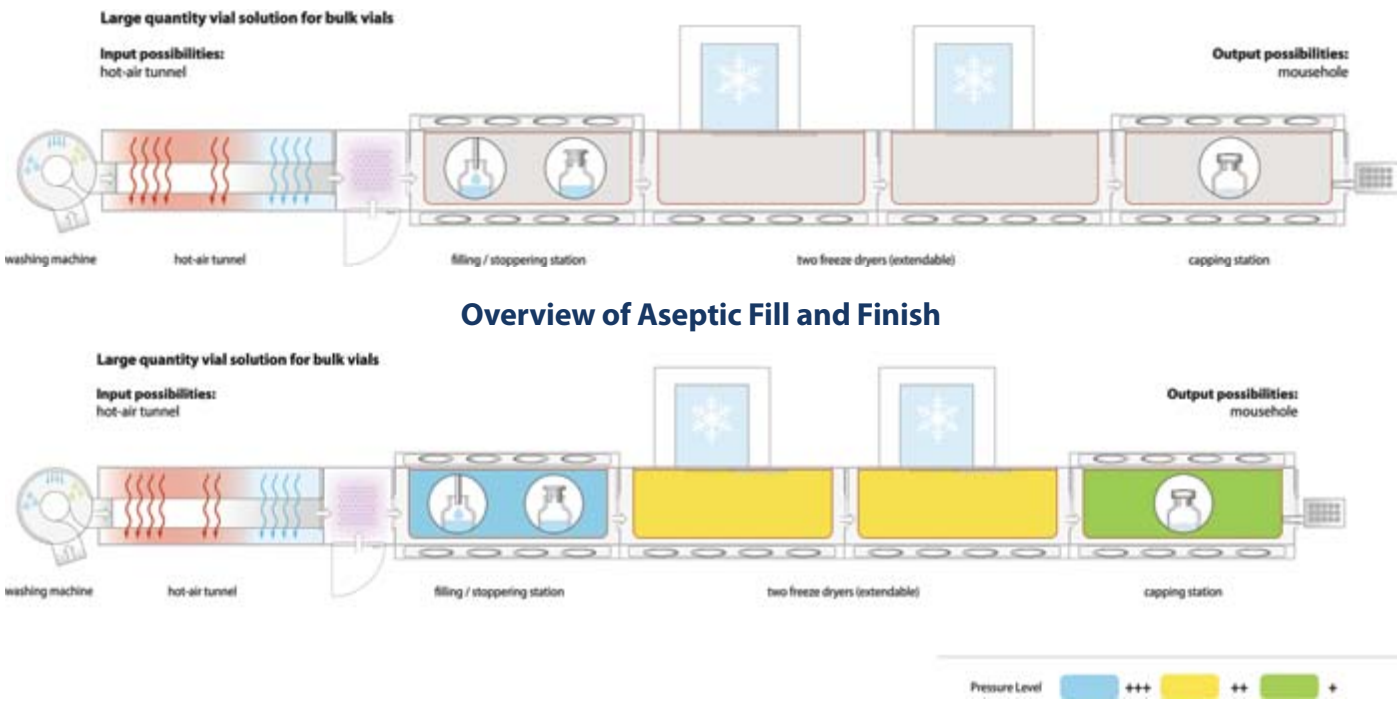

Figure 3 Pressure Cascades in the Individual Isolator Sections *(Picture shows examples with no relation to a containment application)*

planning stage through simulations. These help when it comes to positioning the filters before the air return ducts, and in designing the air flow to the filters. In addition, modifications can be made to the design of areas in which air flow is found to be turbulent.

Mechanical transfer

During the aseptic fill–finish process, vials, syringes, etc., are transferred using conveyors, separating systems, lifting and transfer systems. These transfer systems can also result in the carryover of highly active substances into neighboring areas. This carryover is critical in the following situations:

- Open filling of vials, syringes, etc. The filling process leads to the release of aerosols that can build up on, dry out and then be released from surfaces/transfer systems/filling equipment such as filling needles

- Breakage of vials. Vial breakage can occur at any time during the manufacturing process and result in contamination of mechanical transfer systems; particularly critical points include separation of the vials, transfer of the vials via carousels, loading and unloading of the freeze dryer, and finally, crimping of the vials

Contact contamination

Contact contamination within the isolator can be the result of various causes and distribution routes. One common cause is breakage of one or more vials. The following forms of breakage are possible:

- Breakage of a vial contaminates other directly adjacent vials which are then moved on, contaminating more vials on contact

- Breakage of a vial contaminates surfaces such as the floor of the isolator and fixtures within the isolator; if liquids are not removed in a timely manner, they dry up, and the dried active substance may then be spread by the air flow

- Manual cleaning of vial breakage by the operator using gloves attached to the isolator; this can result in contamination of the gloves and cleaning equipment and, depending on where the vial breakage occurs, the route to the next port through which the contaminated cleaning equipment is removed from the isolator can be contaminated

While the forms of contamination mentioned above generally do not yet represent a direct risk of cross-contamination, they can be a challenge in terms of cleaning and should be kept to an absolute minimum. The cleanability of facilities should also be optimized by means of "hygienic

design" and by using specific equipment/material which will be changed at the end of a campaign or, at least, prior to a product change to efficiently reduce the risk of cross-contamination (see below). Insufficient cleaning can quickly lead to contamination problems for the next product manufactured on the same line.

New Guidelines for Risk Assessments

In line with the new EU GMP Guidelines, Chapter 3 and Chapter 5, a risk assessment has to be performed with regard to potential cross-contamination of one product with another—the objective being assuring patient safety.

The risk assessment should summarize the structural and operational controls that are in place as elements of the facility risk management program to reinforce approved processes to minimize and mitigate the risk to product quality.

Reasons for cross-contamination can be manifold and caused by technical as well as organizational deficiencies. Insufficient cleaning of equipment, poor facility design or inappropriate design of the HVAC system may be reasons, as well as contamination via personnel or primary packing material. But also the design of the production process itself can cause cross-contamination, for example, due to open product handling during transfer or sampling operations in shared plants. It is extremely important to control cross-contamination to levels below the acceptance criteria.

A comprehensive risk assessment process includes the assessment of risks related to environment, health and safety (EH&S risk assessment) and risks related to potential cross-contamination and product quality (GMP risk assessment).

Cleaning validation is one crucial element in risk management to ensure that patient safety is not at risk. The latest guidance from the EMA on health-based limits for cleaning validation is provided in the *Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities* ***(3).***

> **"the design of the production process itself can be the cause for cross-contamination"**

It is important to consider the whole material flow, e.g., from dispensing to packaging, personnel flow (gowning, movements from one area to another or to corridors, etc.) and general HVAC and facility layout.

Risk assessment methodologies, such as ICH Q9, should be applied.

One example for a risk assessment methodology is FMEA. This methodology requires that for each process step, the following questions be addressed:

- **Probability:** What is the probability of a cross-contamination at levels higher than the acceptable health-based limits?
- **Severity:** What would be the effect of this carryover in the patient, based on the toxicological characteristics of the contaminant and the maximum possible carryover?
- **Detectability:** How easily would a cross-contamination be detected?

Before the facility is commissioned, a riboflavin test can be carried out to determine how the active substance spreads within an aseptic isolator during the filling process. Filling 1 g riboflavin suspended in 1,000 ml of water into prepared vials in the isolator makes it possible to monitor the spread of the substance during the manufacturing process and subsequent cleaning process, as well as the risk of cross-contamination ***(4).*** The test results can then be used to define sampling points for swab tests in the cleaning validation process.

Certain potentially critical situations or operations should also be assessed, and if necessary, simulated:

- Vial breakage in the filling area and during freeze drying
- Vial breakage in critical areas within the isolator, such as vial separation or crimping
- Removal of liquid/powder and vial, and subsequent cleaning in the event of vial breakage
- Unloading of contaminated cleaning equipment
- Connection and disconnection of the HPAPI buffer container in the isolator

Depending on the surface properties of nonproduct contact parts such as plastics used to transfer or separate the vials, it may be necessary to dedicate them to a specific product. The surfaces of plastics are not qualifiable, cleaning cannot be validated, or the effort involved in cleaning is disproportionate in comparison with the use of product-dedicated parts.

[Editor's Note: The rest of the article, including additional figures and tables and information about the authors and the reference list can be found on the *PDA Letter* website.**]**

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AIDC is a Sign of Things to Come

Part I: What is AIDC and How Will it Impact Pharma Manufacturing?

Napoleon Monroe, New Directions Consulting

In 1974, a pack of Wrigley's chewing gum became the first retail item to be scanned with a Universal Product Code (UPC). IBM and the retail industry led the development and implementation of the UPC, but the healthcare industry did not embrace standardized bar coding.

This continued into the 21st century. In 2006, a senior healthcare executive told me that automated identity and data capture (AIDC) in healthcare "would never happen in his lifetime." He is still alive.

Enter the regulators and the legislators. In 2013, two U.S. regulations, the Unique Device Identifier (UDI) regulation and the Drug Supply Chain Security Act (DSCSA), set standards for AIDC in healthcare ***(1,2).*** A major selling point of both regulations was that AIDC would help avoid counterfeiting and facilitate recalls. Since 2013, deadlines for both have been extended. Potential uses and effects of AIDC in healthcare are slowly taking shape and are far broader than the initially stated regulatory objectives due to the growing digitization of the industry.

The AIDC legislation and regulations enabled, and even required for the first time, future widespread use of more informative AIDC in the U.S. healthcare industry. The National Drug Code (NDC), which has been used on drugs and some devices for many years, only contains manufacturer and product names in a linear barcode. For years, lot (or batch) and expiry text has been required on manufacturer healthcare labels, but there was no standardized AIDC format for this information. The limitations of and administrative issues related to NDC codes severely restricted product control and cost-saving possibilities.

The 2013 regulations require encoded lot and expiry information and even serialization as well as mandates on entering company and product identifiers into databases accessible to government agencies, such as the U.S. FDA's Global UDI Database (GUDID), and for prescription drug product transfer reporting requirements.

There is no cost or pricing data in the FDA databases; however, providers and others are leveraging the GUDID and similar databases abroad to build very sophisticated databases. These will prove to be useful in contracting functions.

AIDC: Inevitable Part of Digitization

Retail is far more fully digitized than healthcare. Before UPC barcodes, individual merchants had to place stickers on products. Digitization of healthcare is inevitable, and AIDC is coming to healthcare as part of digitization. As in retail, AIDC marking at source will limit the addition of labels, aka "stickering," elsewhere in the supply chain.

For manufacturers not to make the most of the AIDC technology seems a terrible waste. While I firmly believe that AIDC can enable healthcare services, production and distribution automation, data integration, and cost savings over the long term, the path forward clearly is not simple.

GS1, the issuing agency for the UPC and one of the U.S.- and EU-accredited issuing agencies for UDI and DSCSA symbologies, along with RxTrace, have been good sources for information on DSCSA and UDI as interpretations have evolved.

Greg Bylo, U.S. Vice President, Healthcare, GS1, who is leading the initiative to drive the industry's adoption and usage of GS1 standards, characterizes the issue as follows:

"Most companies ask themselves [what path to follow] and struggle with determining the correct decision and the value that would result from a serialization effort," says Bylo. "So the question is: 'Do I do nothing; do I use a lot/batch approach; or do I serialize my products?'"

Bylo further points out that each option offers different possibilities with different cost implications. He lists the questions a company should ask for each option:

1. How much **control** of my products in the supply chain should I have?

2. How **expensive** are my products? Does tracking my products afford me better control of these expensive assets?

3. How much **risk** can we assume if something goes wrong? With lot/batch, I will have one level of risk; with serialization I will have significantly less risk, since I will be able to bound the issue in smaller groups and not an entire batch/lot.

4. How do I want to handle a **recall?** With lot/batch how many products will be impacted versus serialization controls where a company can bound the recall by serial number.

The choice is ultimately one of risk and cost. At the same time, AIDC presents some challenges that may make manufacturers wary to fully embrace it. These are:

- Complexity. The United States has led in healthcare AIDC implementation, but the task has proven far harder than anticipated.

- Resistance to change. Healthcare is fragmented. Many competing interests have resisted change. Some may fear transparency.

- Concerns about data security. These are valid. The finance industry had the same concerns about data security as digitization became common. But this industry developed preventive measures just like pharma can.

- Cost. The initial costs of implementation are high. Marking products with AIDC symbologies is only the first step; the IT costs are usually far greater. The resulting efficiencies, opportunities and returns on investment will only be realized beyond the short term. Some companies fail to consider potential offsetting benefits. Many vendors and consultants offer services to assist. Good help is not cheap.

- Lack of clarity. Regulations are evolving in very uncertain business and political environments. In the United States, some hope for a healthcare regulatory reversal. They hope that value-based purchasing and accountable care will simply go away. This is not likely given the need to resolve out-of-control healthcare costs, economies of scale for large entities and already heavy investments in AIDC.

- Differences in drug and device regulatory requirements. In the United States, drugs, biologics and devices are covered by different sets of regulations and FDA centers. There are similarities, but also major differences. Even differences in the language used in drug and device regulations can cause difficulties. Product names and risk classes are not well standardized. Combination products present their own issues. Many companies manufacture both pharma and devices.

- Differences in regulatory systems from country to country. Harmonization of requirements is desirable. Marking requirements seem to be moving toward similar endpoints. Products are in different classes in different countries. Risk classifications abroad differ from those in the United States. Full harmonization of data requirements seems impossible. Abroad, the pace of adoption is even more uncertain. Some healthcare trusts in the United Kingdom have begun mandating the adoption of the Pan-European Public Procurement On-Line (PEPPOL). PEPPOL requires AIDC marking and submission of manufacturer, product and cost data. While the implementation timing has been postponed, currently Classes 3 and 2 A&B will have to be in the PEPPOL system by March 31, 2018. Adoption of PEPPOL in healthcare across much of Europe and beyond is predicted. How the differences in UDI implementation dates would be viewed in CE audits is another open question.

Serialization is essential to having granular information to manage products. It allows the manufacturer, a manufacturer's subcontractor or others to identify a specific product as it moves through the supply chain and to associate that specific product with the user and other factors in near real time.

Certain product changes may not normally occasion a lot or batch number change by a product manufacturer or marketer. Lot or batch numbers are often not sufficient for managing because distributors, as well as drug packaging, software and excipient vendors, might not record or report some potentially meaningful changes. Some examples of these types of changes (which some might consider inconsequential, but may actually be important) could be component processing changes, raw material lot changes or "minor" procedural changes.

Distributors do not record the lot or batch numbers distributed to every customer. Therefore, having only lot or batch numbers can result in unknowns and unnecessarily large recalls. Knowing what specific (serialized) product a specific customer received can validate the appropriateness of a return for credit. Serialization also enables limitation of grey market activities.

It is difficult to know how much to include in such a 40,000-foot overview. I hope this information stimulates thought. In Part II, I will discuss serialization challenges and opportunities for combination products.

[Editor's note: Part II can be found on the *PDA Letter* website. It will also appear in the January 2018 print issue**].**

This article contains opinions and is not regulatory guidance. The author and his clients have interests in the use of AIDC in healthcare.

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About the Author

Napoleon Monroe's expertise includes product development, licensing, regulatory processes, risk management and international marketing, with experience managing business relationships in more than 30 countries.

SNAPShot

IG Corner

Pharmacopeial Interest Group Strives to Meet Mission

Janeen Skutnik-Wilkinson, Biogen, (Interest Group Coleader) and Karen Ginsbury, PCI (Former Coleader)

PDA's Pharmacopeial Interest Group has been active since 2011. Recently, we took some time to review the Pharmacopeial Interest Group's five-point mission statement and see how the interest group is meeting these five goals. Below are our findings:

Advocate globally for greater pharmacopoeial cooperation, harmonization (both prospective and retrospective) and working long term toward the ultimate goal of a single international publication

When WHO published a Good Pharmacopoeial Practices draft guidance, the interest group rapidly assembled a task force and sent in general comments in a tight timeframe. Within one day of receiving our general comments, WHO asked for our detailed comments and we sent those in. Clearly, the interest group has a voice and represents the general consensus of PDA's membership.

Monitor compendial activities and publications and provide periodic reports to RAQAB and PDA members

If you take a look at the group's PDA Connect℠ site, you will see that our members are kept abreast of updates through this medium. But, there is also a call for members to make posts—so please start doing that. All posts are welcome.

Prepare position papers on compendial initiatives and proposals not being addressed by other PDA Committees

The interest group regularly discusses compendial concerns at face-to-face meetings at PDA's Annual Meeting and Joint Regulatory Conference with the U.S. FDA. Additionally, PDA is hosting its *Pharmacopoeia Conference* next May in Vienna, cochaired by **Janeen Skutnik-Wilkinson,** Staff Associate Compliance & Standards, Biogen, and **Susanne Keitel,** PhD, Director, EDQM. The theme of the conference is fast-tracking pharmacopeial convergence/harmonization and the future direction of pharmacopeias. We would like to

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publish more position papers on compendial initiatives, but that needs volunteer input, so reach out to us!

Represent PDA at the USP Stakeholders Forum

We do not always manage to get a PDA-specific person there, although, we try. But any PDA member planning to attend a USP forum is always welcome to contact the interest group and let us know if they are interested in serving as a PDA representative. The interest group's leaders would work with such a volunteer on where PDA stands with issues under discussion at the meeting and how to obtain formal feedback.

Proactively identify compendial topics and advocate PDA's position

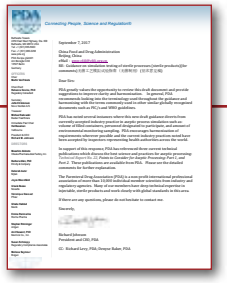
We don't always manage to do this, and we need help here, too. If you hear of a compendial issue, let the group know!

Additionally, this interest group recently gave an update to PDA's Regulatory Affairs and Quality Advisory Board (RAQAB), its Advisory Board umbrella, summarizing the group's activities. One of the actions identified was to obtain volunteers and "spread the word" among PDA's membership base, and this update is intended to achieve just that. Anyone wanting to become active in this interest group can contact **Denyse Baker** at PDA (baker@pda.org) and let us know what you would like to take on.

In summary, the interest group has been and continues to be active. It clearly has a place at PDA and is beneficial to members and to RAQAB and the Board of Directors. There is a need to channel the group's activities better and grow a set of committed industry volunteers who work with pharmacopeias day in and day out and, therefore, can easily update the group. We hope to hear from those interested in volunteering and we would be delighted to receive feedback from anyone with fresh ideas.

We also want to welcome **Anette Yan Marcussen,** the new coleader of the interest group. She replaces **Karen Ginsbury,** who is stepping down. She looks forward to taking the interest group into 2018.

CFDA Encouraged to Review PDA Docs



September 7, 2017

China Food and Drug Administration
Beijing, China
email: gmp-cfdi@cfdi.org.cn
RE: Guidance on simulation testing of sterile processes (sterile products) (for comments)
无菌工艺模拟试验指南 (无菌制剂) (征求意见稿)

Dear Sirs:

PDA greatly values the opportunity to review this draft document and provide suggestions to improve clarity and harmonization. In general, PDA recommends looking into the terminology used throughout the guidance and harmonising with the terms commonly used in other similar globally recognized documents such as PIC/s and WHO guidelines.

PDA has noted several instances where this new draft guidance diverts from currently accepted industry practice in aseptic process simulation such as: volume of filled containers, personnel designated to participate, and amount of environmental monitoring sampling. PDA encourages harmonization of requirements wherever possible and the current industry practices noted have been accepted by inspectors representing health authorities across the world.

In support of this response, PDA has referenced three current technical publications which discuss the best science and practices for aseptic processing: *Technical Report No. 22, Points to Consider for Aseptic Processing: Part 1, and Part 2.* These publications are available from PDA. Please see the detailed comments for further explanation.

The Parenteral Drug Association (PDA) is a non-profit international professional association of more than 10,000 individual member scientists from industry and regulatory agencies. Many of our members have deep technical expertise in injectable, sterile products and work closely with global standards in this area.

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

Sincerely,
Richard Johnson
President and CEO, PDA
CC: Richard Levy, PDA; Denyse Baker, PDA

PDA Commenting Task Force

Anette Yan Marcussen, Novo Nordisk A/S (lead)

Hongyang Li, Novartis

Hal Baseman, ValSource

Jette Elkjaer Johansen, Novo Nordisk A/S

Cylia Chen-Ooi, Amgen

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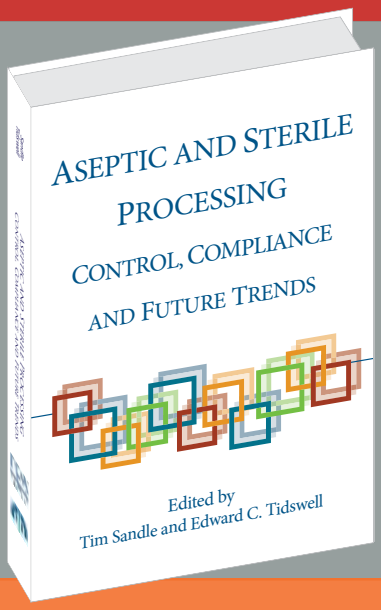

Aseptic and Sterile Processing: Control, Compliance and Future Trends

Edited by: Tim Sandle and Edward C. Tidswell

PDA MEMBER PRICE: $260

PDA NON-MEMBER PRICE: $325

HARDCOVER: ITEM NO. 17342

DIGITAL: ITEM NO. 18038

The *Aseptic and Sterile Processing: Control, Compliance and Future Trends* is the most important text discussing aseptic and sterile manufacturing that has been published in the last decade! This text looks at both today and tomorrow in regard to these two vital processing procedures.

The Editors of this book realized that there was an urgent imperative for these subjects to be reassessed and represented. To achieve this objective, along with many subject matter experts, they produced a book that is designed for those involved with aseptic and sterile processing to take away many learning points and apply these principles to aseptic and sterile processing, within the pharmaceutical and healthcare sectors.

It is the aim of the Editors to help readers reassess legacy definitions and historical understandings and move them toward concepts that will help them think in new ways about equipment and processes in order to reach the highest standards and evaluate them through science-based risk assessments.

Table of Contents:

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PDA and IFPMA Foster Discussion on PAC

Ursula Busse, PhD, Novartis

Global regulatory harmonization and expanded reliance on pharmaceutical quality systems (PQS) within companies will be key to reducing the complexity around post-approval changes (PAC), according to several speakers at the *2017 PDA PAC iAM Workshop*, Sept. 13–14, following the *2017 PDA/FDA Joint Regulatory Conference.*

The workshop was co-sponsored by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA). Chaired by **Ursula Busse,** PhD, Head, Quality Intelligence and External Relations, Novartis, and **Lisa Skeens,** PhD, Vice President, Global Regulatory Affairs, Pfizer, the workshop provided insights into several international initiatives such as ICH Q12: *Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management*, touched on practical aspects of PAC implementation and provided an overview of the PDA PAC iAM[SM] task force's current work. It reflected the most current thinking on the concepts and tools proposed to facilitate PAC and spur manufacturing innovation during a product's commercial phase. Participants actively engaged in discussion and were also given an opportunity to provide responses to survey questions in real time using their personal mobile devices during the meeting.

In recent years, both ICH and WHO have launched several worldwide initiatives to address the issue of PAC, with support from both PDA and IFPMA. The lack of a harmonized global regulatory framework for PAC leads to supply chain complexity, slows down the pace of manufacturing innovation and increases the risk of quality failures.

In the opening plenary session of the workshop, **Anders Vinther,** PhD, Chief Quality Officer, Sanofi Pasteur, and co-chair of the PDA PAC iAM[SM] task force, called for a global dialogue between industry and regulators to resolve current PAC regulatory challenges. **Bob Iser,** Director, Office of Process and Facilities, CDER, FDA, and member of the ICH Expert Working Group (EWG) responsible for ICH Q12, mentioned that ongoing dialogue within the group has already paved the way for closer alignment among different regulatory agencies, including new ICH member organizations. He emphasized that implementation of ICH Q12 principles, not the document alone, will improve the situation. **Isabelle Colmagne-Poulard,** Senior Director, Regulatory CMC Strategic and Technical Advisor, Global Regulatory Affairs and Quality Assurance, Merck KGaA, then spoke on behalf of IFPMA about international initiatives complementary to ICH's science- and risk-based dialogue around PAC. In particular, she cited the WHO's efforts in strengthening national regulatory systems while striving for global regulatory convergence. And she highlighted reliance on a company's pharmaceutical quality system (PQS) to manage low-risk changes to reduce regulatory reporting burden.

The next two plenary sessions then delved into some of the principles and tools proposed by ICH Q12. **Frank Montgomery,** Global Head, Regulatory CMC, AstraZeneca, and member of the ICH Q12 EWG, spoke about Established Conditions (ECs) and change categorization, as well as the anticipated benefits of ECs and how to realize them. Iser provided the regulator's point of view. Both outlined how the risk- and science-based approach of the EC concept will reduce the amount of information that needs to be assessed by a regulator. They also underscored the importance of sound knowledge management, as reporting categories for changes will be linked to the level of product and process understanding. A real-time survey of attendees during the session showed that some companies are already applying the EC concept to their PAC management, and that most see the value of leveraging it universally.

The next day, **Emma Ramnarine,** Senior Director Global Biologics, Genentech Roche, and co-chair of the PDA PAC iAM[SM] task force, provided insights into the dynamics of the product lifecycle. She pointed to her company's Post-Approval Lifecycle Management plan as an example. **Mahesh Ramanadham,** PharmD, Acting Director of the Division of Inspection Assessment, CDER, FDA, and member of the ICH Q12 EWG, introduced the Product Lifecycle Management document as an effective tool to be used for communication between a company and regulatory agencies and, within an agency, between assessors and inspectors. Both touched on the importance of establishing an effective PQS and sharing knowledge between industry and regulatory agencies to reduce PAC notification requirements.

In addition to these presentations, attendees also broke into groups to discuss case studies. Here, participants explored concepts proposed by ICH Q12 to better manage PAC and then applied the science- and risk-based approaches cited by the speakers. ECs, change categorization and reporting categories in the context of a company's PQS were discussed in different roundtable settings. Participants also provided feedback to the PDA technical report team currently developing a document centered on PAC change management protocols (PACMP) as a potential solution to PAC complexity. These interactive activities showed that participants clearly prioritize knowledge management and quality risk management in their change management systems to gain regulatory flexibility.

Following these roundtable discussions, the closing panel provided insights on initiatives in manufacturing innovation and global solutions aimed at resolving PAC regulatory complexity. **Morten Munk,** Global Technology Partner, NNE, spoke on behalf of PDA's Aging Facilities Task Force on the challenges encountered by the current PAC regulatory environment, which slows down the rate of manufacturing innovation. **Sharmista** ➤

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Chatterjee, Division Director, Division of Process Assessment, FDA, explained the FDA Emerging Technology Team's role in encouraging the adoption of novel manufacturing technologies. She said that information exchange between regulatory authorities can enable faster adoption of innovative technologies in other regions. **Susanne Martz,** PhD, Senior Vice President of Quality Vaccines, GSK Vaccines, and member of IFPMA's Vaccines Heads of Quality Group, outlined the quality group's ongoing work to advocate for streamlined and more predictable global PAC approvals. Their efforts are geared toward reducing the rate of vaccine shortages, currently, a major worldwide healthcare issue.

The workshop turned out to be highly interactive as panelists and speakers addressed myriad questions. The presentations showed that ICH Q12, once appropriately implemented, should increase opportunities to make changes without prior approval, benefitting both industry and regulators alike. This should incentivize manufacturers to invest in product lifecycle management and PQS. All global efforts combined should foster regulatory harmonization of PAC regulations, encourage adoption of shared principles and facilitate continual improvement to spur manufacturing innovation globally.

Did the workshop change participants' opinions about current initiatives and their impact on PAC management? Yes and no, according to the real-time surveys: Views about effect of these initiatives on the current situation did not change: 75% of respondents still believed the initiatives would have a favorable impact, while 25% felt that PAC management will just be different. Participants also highlighted two additional critical success factors for these initiatives, in addition to trust, harmonization and dialogue: courage and examples to share across industry. Ultimately, PDA plans to support standardization across industry and implementation of shared principles.

The workshop underscored the strong link between an effective PQS and successful lifecycle management. It showed that companies can gain regulatory flexibility in PAC management if they apply the principles of ICH Q8–11. A sound scientific understanding of products and processes, coupled with consistent application of quality risk management, embedded in an effective PQS, will provide the basis for ICH Q12 realization.

Keep up with the latest trends in Aseptic Processing

PDA Parenteral Drug Association

2018 SCHEDULE

OPTION 1
Week 1: January 22-26
Week 2: February 19-23

OPTION 2
Week 1: March 12-16
Week 2: April 9-13

OPTION 3
Week 1: May 7-11
Week 2: June 4-8

OPTION 4
Week 1: July 23-27
Week 2: August 13-17

OPTION 5
Week 1: September 17-21
Week 2: October 15-19

FOR MORE INFORMATION CONTACT:
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PDA Training and Research Institute
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For more than 70 years, PDA has been recognized worldwide as a leader in aseptic processing. With the advent of new biological therapies, the importance of proper aseptic processing has never been greater. Turn to PDA for the most comprehensive aseptic processing education, taught in PDA's unique, onsite cleanroom filling facility.

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Regulatory Briefs

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

North America

ORA, CDER Align on Manufacturing

The U.S. FDA continues to restructure its field activities, moving away from a geographic focus to a structure based on program-aligned commodity areas. As part of this process, CDER and the Office of Regulatory Affairs (ORA) recently began implementing a concept of operations agreement that better aligns drug review programs with facility inspections. Both field and review staff will work together as part of a team-based approach that provides a holistic overview of all elements that create risk, from drug substance to drug product to manufacturing.

The Agency hopes this alignment will help prevent manufacturing delays due to inspection issues.

Asia/Pacific

TGA Responds to Increase in Clearance Docs

Due to the increase in GMP clearance applications, Australia's Therapeutic Goods Administration (TGA) is implementing new process improvements. TGA estimates that 60% of clearance applications do not include all the supported evidence necessary to demonstrate that a manufacturing site meets requirements for supplying product to the Australian market. For all applications submitted on or after Sept. 26, TGA will conduct an application assessment once all outstanding fees have been paid. If the assessment finds certain information is missing, the agency will provide a written outline of the deficiencies noted.

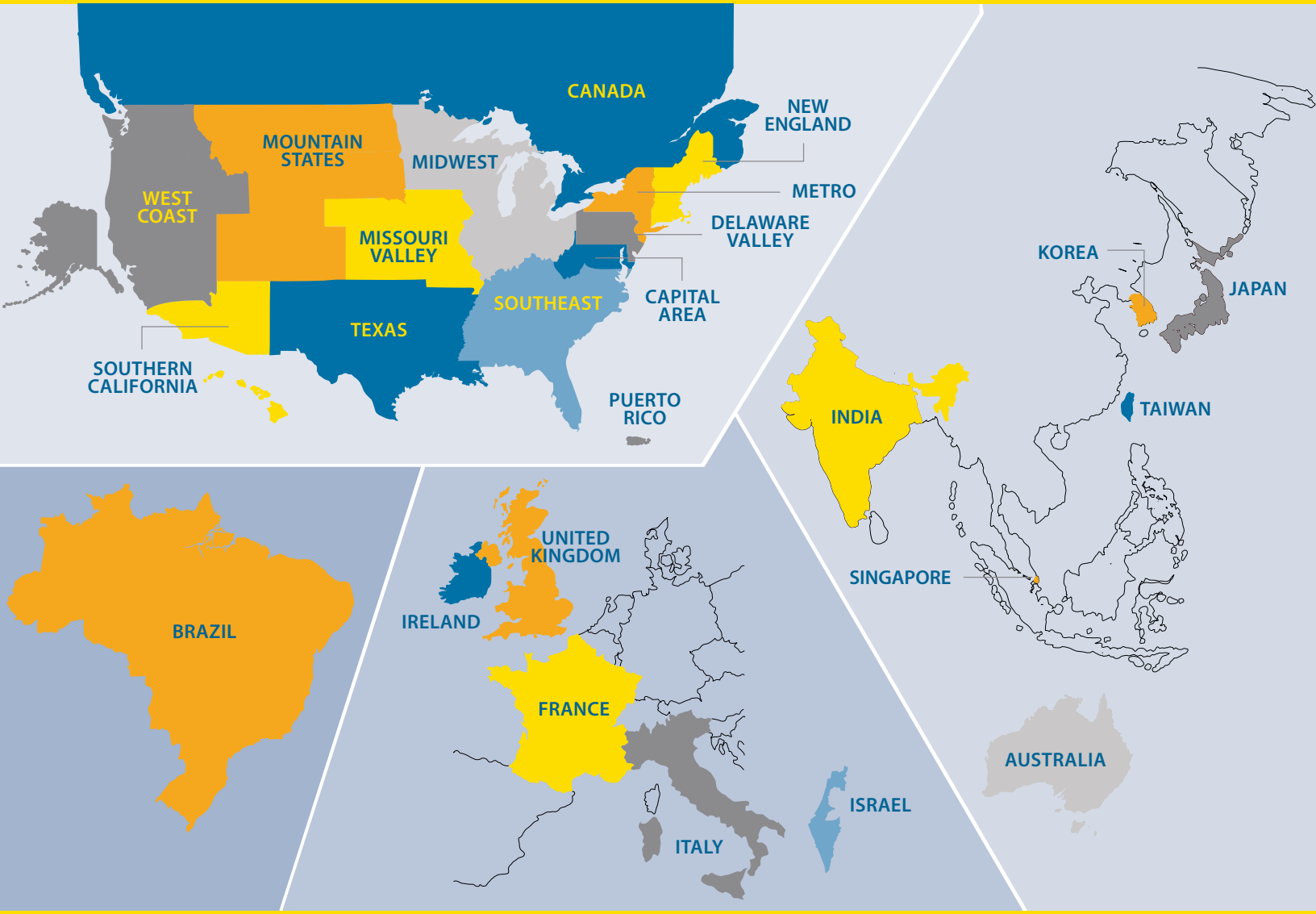
Applications submitted before Sept. 26 will have a one-time opportunity for sponsors to submit outstanding supporting information prior to assessment. TGA is also currently working on a revised GMP clearance guidance document and new Web-based Clearance Application Assistance Tool.

India: Stability Data Required

In August, India's Central Drugs Standard Control Organisation (CDSCO) notified all regional drug controllers that they must better enforce requirements for Indian manufacturers to submit quality data for nonpatent and proprietary medicines. CDSCO requires this data at the time of submission. Data should show that drug product is stable under storage conditions.

PDA Chapters

Your Local PDA Connection



Are you curious about the issues unique to your region?

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

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

A Risk Assessment is an Opportunity Assessment

A Participant's View of the 2017 PDA QRM Workshop

David Hubmayr, CSL Behring

It was a pleasure attending the *2017 PDA Quality Risk Management for Manufacturing Systems Workshop* this June in Chicago. This interactive workshop featured thought-provoking presentations from leaders in quality risk management (QRM) and opportunities to discuss specific QRM scenarios in breakout groups. As an attendee, I want to share some of what I learned with the wider PDA membership.

Effective QRM is key to product quality. To master future challenges, our industry needs to take a collaborative approach with regulators as pharma is a challenging environment with more complex products, increased reporting to regulators, and expansive globalization of supply chains. Continuous manufacturing and personalized medicine are some of the disruptive trends affecting the industry.

The industry remains committed to maintaining the bar high on product quality. Keeping the promise of high quality means a deep understanding of the product and process, built on identifying and proactively managing risks inherent to real-life production processes. QRM is, therefore, not solely a regulatory need; it is an essential tool for the company to know that products are safe.

Quality has, and is, value. Bad quality has significant influence on both the patient and the brand. An integrated, cross-functional culture of risk- and science-based decision-making is key. Cross-functionality ensures different functional expertise in the working group for the holistic approach. QRM must always be backed by senior leadership as it may require dedicated resource allocation.

Effort put into risk management processes is sometimes extensive, which makes it essential to start with a clear risk question, followed by a Manufacturing System Characterization, using either a Process Risk Assessment or by System Risk Assessment. A broad lineup of risk management tools is available—there is no one-size-fits-all solution. Nonexhaustive examples of risk management tools consist of basic risk management facilitation methods (flowcharts, check sheets, etc.), Failure Mode Effects Analysis (FMEA), Failure Mode Effects and Criticality Analysis (FMECA), Fault Tree Analysis (FTA), Hazard Analysis and Critical Control Points (HACCP), Hazard Operability Analysis (HAZOP), Preliminary Hazard Analysis (PHA), risk ranking and filtering, and supporting statistical tools. It might be appropriate to adapt these tools for specific issues. Risks can also be assessed and managed by internal procedures (Standard Operating Procedures).

Significantly reducing the probability of occurrence of risks backs the basic homework of qualification, validation, monitoring, training of people, etc.

It pays back in many ways to:

- Dive into the Risk Assessment (RA)
- Implement risk control activities occurring throughout the design
- Integrate commissioning and qualification phase and operational phase of a system
- Reduce the operational and quality risks associated with the system
- Support a successful commissioning and qualification
- Assure ongoing system effectiveness and continued process verification.

A good RA states the risks, impact and what is done for management, and the risk rating goes straight into control. An opposite example is an RA with a predetermined outcome—one of the top-ranking reasons an RA fails.

Companies often struggle to implement and/or develop an effective and supporting QRM system due to the fear of taking the risks virtually linked in current QRM system implementation. But playing it safe merely follows an audit-proven approach. Another impacting factor is the lack of understanding to deal meaningfully with available data from clinical development and/or routine GMP process. It pays to manage available data and to think about what types of data are needed prior to the creation of data.

The focus should be to determine if an RA truly adds value, e.g., there is no RA needed to tell that the labeling must be correct as that is simple GMP.

Risk management is not a one-time task, it follows a risk management lifecycle which includes a periodic reevaluation of risk management activities using new data and experience over time as, e.g., discrepancy management and investigation data, customer complaint and adverse event data, change control data, internal audit data, walk-through inspection and external inspection data, predictive/preventive maintenance data, calibration data, work orders, manufacturing system monitoring trends, regulatory guidance and standards, and related industry trending data and scientific publications. The risk review can either be event-based or time-based. The risk review covers the important task to span the bridge between QRM and knowledge management and is an effective tool to measure risk reduction as well. A QRM process must always be accompanied by an integrated risk communication, aligning stakeholders and process environment on risks.

Ultimately, I took away from this workshop that a well set-up, diversely structured and coherently communicated QRM process is a powerful tool to keep our promise to patients.

About the Author

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

"This is the best PDA Course I have ever taken!"

–Stephan Krause, PDA Member

Be Transformed!!

What are most important positive quality culture behaviors that impact product quality?

Can you identify which mature quality attributes have the biggest impact on quality culture behavior?

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Take the first step on a journey to transform your Quality Culture with resources developed by PDA volunteers specifically for pharmaceutical manufacturing sites.

Following a successful pilot conducted over the last 18 months, PDA is pleased to launch the Quality Culture Transformation Resources to the industry.

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When you enroll in this new program, PDA will train your assessors, teach you how to use the Maturity Model, offer an anonymous survey to your site staff and give you access to PDA's composite benchmarking results so you know where you stand with your peers.

Your site leadership will be able to gauge employees' views of quality culture and have a better understanding of where to take action, how to track progress, and which decisions to take to improve the site culture.

PDA Quality Culture Transformation Resources

Your registration fee includes:

1. **COURSE**: TWO seats in hands-on active learning in a two-day course on "Quality Culture Transformation"
2. **TOOL:** Quantitative assessment of current quality culture at TWO manufacturing sites
3. **SURVEY:** Blinded, direct employee feedback on aspects of your Quality Culture at TWO sites
4. **BENCHMARK:** Compare your results against more than 40 sites from 24 companies in North America, Europe, and Asia that have already completed Quality Culture Assessments.

Who Should Participate

This program will benefit pharmaceutical and biopharmaceutical manufacturing leaders who want to measure quality culture maturity at their plant sites and identify areas for improvement. It will also prepare your assessors to conduct site evaluations in a consistent and verifiable manner using the PDA Model and Tools.

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Voices of the Board continued from page 58

industry to develop a practical guidance, which will be intended for use along with existing compendial, regulatory and industry standards. The Zero Defects for Visible Particles in Injectables Task Force intends to identify gaps in current risk assessments and methods used to detect and quantify visible particles. This information will then be used to develop a best practices document to potentially reduce defects related to particles.

There are multiple workstreams working to identify a visible particle size threshold, analytical method gap analysis (for elastomer and glass components) and validation strategies. These workstreams consist of global representatives from pharmaceutical manufacturers as well as suppliers to ensure a well-balanced perspective on best practices. PDA intends to expand the resources relating to visible particulates in support of continuous improvement and development of new best practices for the industry and our members.

Solving Industry Problems Equals Serving Patients Worldwide: The lack of a harmonized global regulatory framework for PAC results in supply chain complexity, slows down the pace of manufacturing innovation and increases the risk of quality failures. In Sept. 2017, PDA cosponsored with the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) a very successful PAC workshop, featuring speakers and panelists from the U.S. FDA, the ICH Q12 Expert Working Group, IFPMA and industry **[Editor's note:** See p. 48 for a summary of this workshop**.]**

Through the Post Approval Change Innovation for Availability of Medicines (PAC iAM℠) initiative, PDA continues to raise awareness, dialog and collaboration between industry and regulators on global solutions for PAC. PDA's specific focus is on providing practical solutions to the industry for 1) the application of science- and risk-based approaches for PAC management, and 2) methods for leveraging an effective pharmaceutical quality system to reduce the regulatory burden for PAC. PAC iAM℠ has also provided a number of valuable resources for the industry through Points to Consider papers, webinars, presentations and informational articles on PAC (accessible at www.pda.org/pac). PDA will also be publishing a technical report with specific PAC examples. If you are interested in joining PDA's efforts on PAC, feel free to contact us.

It is my pleasure to conclude that PDA has never been more respected, strong and secure. PDA is uniquely positioned to connect people, science and regulation® to influence industry and regulatory solutions to serve patients. So, I encourage you to join your colleagues from around the world to help PDA enhance the quality and reliability of medicines so we all can live up to our responsibility to serve patients!

Millennials continued from page 32

(accessed Oct. 26, 2017)
2. Adkins, A. "Millennials: The Job-Hopping Generation." *Gallup News.* (May 12, 2016) http://news.gallup.com/businessjournal/191459/millennials-job-hopping-generation.aspx (accessed Oct. 26, 2017)
3. Eckert, G. and Deal, J. "A European Perspective on Millennials." *IEDP.com*. (June 8, 2012) http://www.iedp.com/articles/a-european-perspective-on-millennials/ (accessed Oct. 26, 2017)

About the Experts

Following years of experience in manufacturing, quality and operational excellence, **Manuel Belmonte** is the Learning and Development Manager of the Patheon Ferentino site (now part of Thermo Fisher Scientific).

Milton Ruiz has 20 years of experience in the pharma/biotech industries with a career focus on learning and development within a GxP environment. He has worked for Portola, Gilead Sciences and Genentech.

Timothy Gillum, PhD, has worked both in academic and business environments for more than 20 years with a focus on learning and change management within regulated environments.

Dawn Nixon has 15 years of global human resources experience partnering with business leaders across multiple industries, competencies and functions to transform their organizations and change the way they operate.

Maik Jornitz is a distinguished technical expert with close to 30 years of experience in bioprocesses, especially sterilizing grade filtration and single-use technologies, including regulatory requirements, integrity testing, systems design and optimization.

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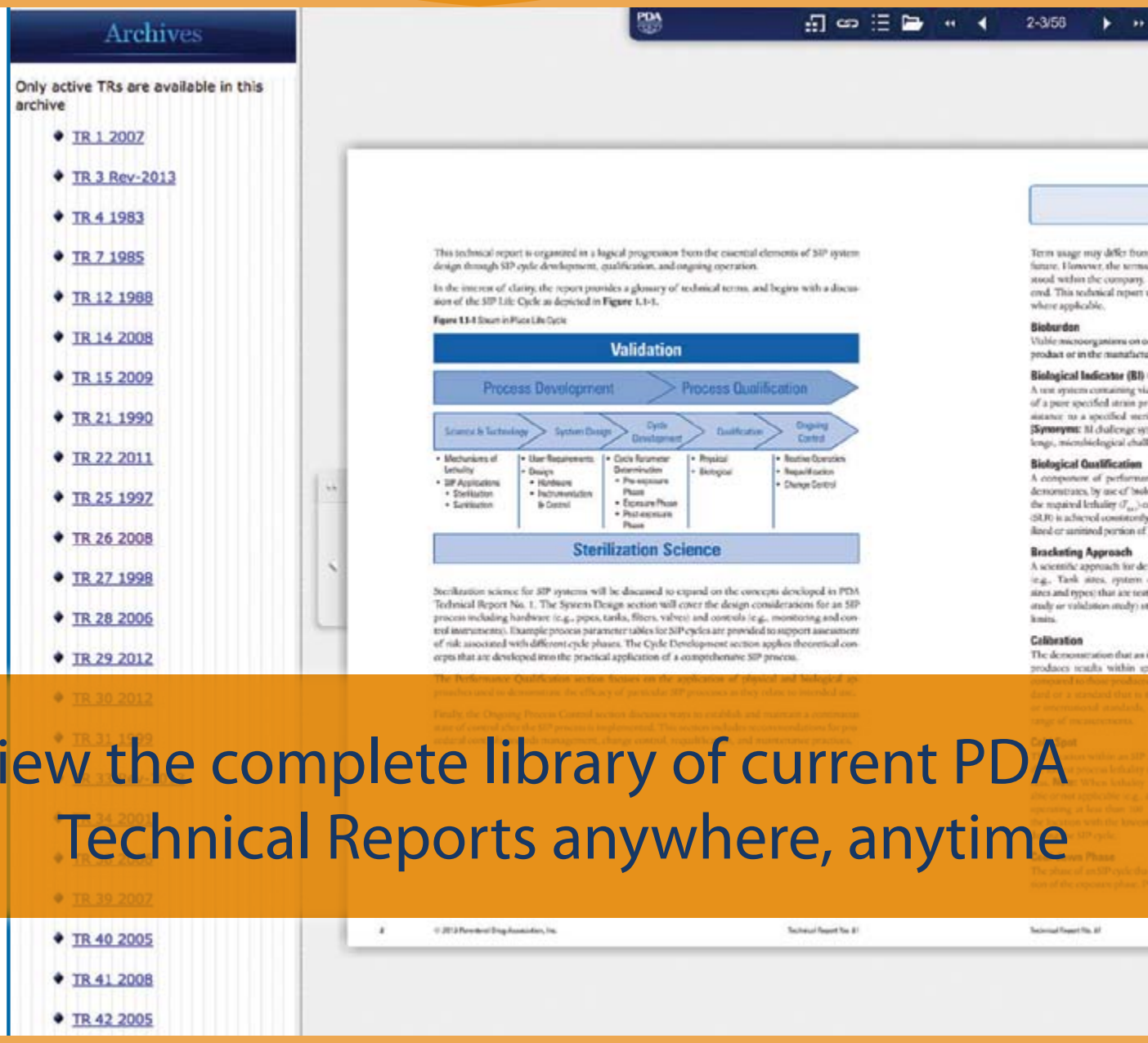

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2017: A Fast-Paced Year for PDA

Martin VanTrieste

As Chair of the PDA Board of Directors, I am proud and honored by what PDA's staff, volunteers and over 10,000 members have accomplished in helping our industry to **serve patients.**

Serving patients is a privilege and that privilege comes with significant responsibilities. It is not easy living up to these responsibilities; PDA was created over 70 years ago to help us all live up to those responsibilities.

PDA's success is because of the hard work, determination and diversity of PDA's staff, volunteers and members. In fact, PDA is one of the most diverse organizations with which I have had the privilege to be associated. There is a great deal of diversity within PDA, from our members all the way to the Board of Directors. This diversity allows PDA to get many different perspectives on what is needed to serve patients.

Our growing membership reflects our growing diversity. PDA added over 1,000 new members in 2017, including 424 young professionals, or students. Our members are located in 78 countries with over 2,500 of them actively volunteering for PDA.

Now, I want to take this time to highlight just a few initiatives: efforts to serve global patients, the elimination of visible particles and harmonization of post-approval changes (PAC).

Science Has No Borders: PDA has chapters in Australia, Brazil, Canada, France, India, Ireland, Israel, Italy, Japan, Korea, Singapore, Taiwan, the United Kingdom and United States along with a European headquarters in Berlin.

We are also exploring adding chapters in other countries like Cuba, Mexico and Russia. Our international activity has grown by hosting more meetings and training activities in countries outside the United States and Europe, including China, Japan, South Korea, South Africa, India and Australia. PDA also offers training courses in languages other than English. We have applied for a license to do business in Cuba and are exploring partnerships with other countries (e.g., potential building of training facilities in other regions of the world). In 2016, 35% of our conference attendance and 32% of our education attendance was from outside the United States.

Working Collaboratively to Improve Product Quality by Eliminating Visible Particles: PDA members have been very active in developing best practices relating to visible particulate matter. The PDA Paper, "Industry Perspective on the Medical Risk of Visible Particles in Injectable Drug Products" has been viewed over 9000 times in the *PDA Journal of Pharmaceutical Science and Technology*. There is a desire to have a clearly defined particle specification (e.g., size, type and quantity) based on the risk of harm to patients. While such specificity is desirable, the lack of relevant clinical trials limits the ability to establish specifications as is typically done for other "impurities." A large body of anecdotal information has been used to guide our understanding of clinical risk of visible particles to date. These are useful and provide guidance, but not an exact limit for setting acceptance criteria for injectable products and the primary packaging used in their preparation. This, coupled with the normal variability of human visual inspection, has led to a wide range of practices and limits applied to particles in injectable drug products and their packaging materials. Due to the level of commitment of our members in providing consensus-based guidance to the industry, the Pharmaceutical Manufacturing Forum has tasked us with taking a deeper dive into this topic.

A new task force has formed to align on a common, harmonized rationale across the

Continued at top of page 56

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Amgen's Cylia Chen-Ooi — Defining the Quality Culture

PDA Education Instructor Mary Carver — Cleaning and Disinfection for Pharmaceutical Manufacturing

ValSource's David Hussong — USP Microbiology General Chapters

A Discussion with PAC iAM Task Force Chairs Anders Vinther and Emma Ramnarine

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

www.pda.org/pdaletter

The Parenteral Drug Association presents the...

2017 PDA Modern Biopharmaceutical Processing Conference

November 28-29, 2017 | Singapore
Exhibition: November 28-29
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- Processing, especially in single-use systems
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- Technology transfers and upscaling from research to manufacturing site
- Challenges of temperature-controlled distribution of biopharmaceuticals in the global supply chain

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Learn more and register today at **pda.org/2017BiopharmSingapore**