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PDA Letter

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Revised USP Micro Chapters Address Changing Technologies

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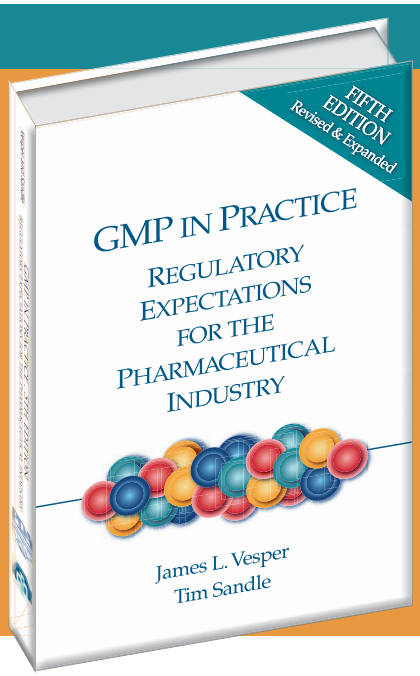
PDA Bookstore New Release



GMP in Practice: Regulatory Expectations for the Pharmaceutical Industry, Fifth Edition, Revised & Expanded

By: James L. Vesper and Tim Sandle

PDA MEMBER PRICE: $240

PDA NON-MEMBER PRICE: $299

HARDCOVER: ITEM NO. 17349

DIGITAL: ITEM NO. 18054

The Long-Awaited Revision and Update of GMP in Practice is Here!

Have you ever asked yourself, "Where in the Good Manufacturing Practices (GMPs) does it say I have to do follow certain methods?" If so, look no further than PDA's *GMP in Practice: Regulatory Expectations for the Pharmaceutical Industry, fifth edition, Revised & Expanded*.

As companies strive to harmonize global requirements for quality systems, the 5th edition of this text provides an overview of the 34 essential global cGMP requirements that are typically included in a modern pharmaceutical quality system, including data integrity and how they have evolved. Explore risk-related questions, delve into several expectations for each quality system element encompasses, and review real-world examples from cGMP regulations from the US FDA, Health Canada, the European Union, the World Health Organization, and the International Conference on Harmonization (ICH).

If you're looking for an enhanced understanding of GMP in practice, this text is a must-have for your reference collection.

Purchase it now!

go.pda.org/GMP5

September 2018 PDA Letter

Show Issue

The *2018 PDA Universe of Pre-Filled Syringes and Injection Devices* showcases the latest in drug delivery technology.

2018 PDA Universe of Pre-Filled Syringes and Injection Devices

13th Annual PDA Global Conference on Pharmaceutical Microbiology

The *13th Annual PDA Global Conference on Pharmaceutical Microbiology* looks at the current state of pharmaceutical microbiology.

Revised USP Micro Chapters Address Changing Technologies

David Hussong, PhD, Eagle Analytical Services, Radhakrishna Tirumalai, PhD, USP, Edward Tidswell, PhD, Merck, and Don Singer, GSK

As technological advancements around microbiological testing continue to grow within the pharmaceutical industry, USP's Microbiology Expert Committee seeks to update some of its microbiology chapters. For each five-year cycle, the Expert Committee has an established workplan intended to help meet USP's standards-setting goals. Some of the workplan's major initiatives in the current USP cycle (2015–2020) include sterilization processes and sterility assurance, parametric release, depyrogenation, endotoxin testing, rapid sterility testing of short-life products and *Burkholderia cepacia* complex.

Cover Art Illustrated by Katja Yount with help from Rapid Micro Biosystems

Viewpoints on the EU Annex 1 Revision

Last December, the EU Annex 1 revision was released, drawing considerable industry attention. This issue features two authors' perspectives on different parts of the revision. **Walid El Azab** looks at proposed changes to the sections on sterilization and moist steam while **James Tucker** analyzes revisions to the section on cleaning and disinfection.

InfoGraphic

Common Issues Found in Nonsterile Drug Facilities

A look at eight years of U.S. FDA warning letters and EMA noncompliance reports.

PDA Letter

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

Departments

Digital Exclusives

> Evaluating Cell Viability After Cryopreservation
How can companies address the challenges of using cryopreservation techniques on living cells used for regenerative medicines?

> Reclaiming Efficiency Amid Serialization Nightmares
Learn how the OEE equation may help with preventing serialization disasters.

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People are the largest source of contamination. If their garments are compromised, your process could be too. Kimtech* is asking you to take a closer look at your reusable apparel. Is it protecting your process and your people? Or is it a potential cause of contamination?

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2018 PDA Cell and Gene Therapy Conference

Advancing into Commercialization

The field of cell and gene therapy has grown tremendously over the last few years. Hear from the top experts in the field at the *2018 PDA Cell and Gene Conference*, **Oct. 23-24**, about cutting-edge developments and the latest regulations and gain the tools you need to navigate market approvals in this innovative field.

Hear **Peter Marks, MD, PhD**, Director, CBER, U.S. FDA, present the Regulatory Perspective on Considerations for Development and Commercialization of Cell and Gene Therapies.

Plenary sessions and panel discussions will include:

- Navigating the Progress and Promise of Gene Editing
- Applying Analytics to the Development and Manufacture of Cell and Gene Therapy Products
- Automation of Cell Therapy Product Manufacturing
- Current Advancements in Product Realization and Lifecycle Management
- Supply Chain and Logistics surrounding the Delivery of Personalized Medicines

Don't miss the Exhibition where vendors and suppliers will showcase their latest technologies and offer solutions to help accelerate the development and manufacture of advanced therapies for market approval.

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

PDA Parenteral Drug Association

October 23-24, 2018 | Bethesda, MD
Exhibition: October 23-24
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Content to Drive Discussion

As I write this, it is hard to believe that the hazy days of August (well, hazy for us on the East Coast of the United States) are slipping away. As such, I am looking ahead to our schedule for the rest of the year.

PDA has a busy slate of fall meetings in the United States, Europe and Asia throughout October and November. You can read about two of the largest upcoming events throughout this issue: *2018 PDA Universe of Pre-Filled Syringes and Injection Devices (UPS)* and *13th Annual PDA Global Conference on Pharmaceutical Microbiology*.

"Biologics Packaging Presents Risks" (p. 19) looks at some innovative types of packaging that address the challenges of packaging biologics in prefilled syringes. The author's company is one of a considerable number of packaging exhibitors at the UPS conference in Orlando, Fla., in early October. I encourage you to spend time during refreshment breaks talking with some of them. I know I enjoyed doing this at last year's UPS event!

In addition, a number of talks will address packaging concerns related to prefilled syringes. I see that SHL Connect's **Markus Bauss** and Groninger's **Egmont Semmler** are codelivering a presentation on smart packaging. Both of them spoke on this topic at last year's meeting as well and I found it very enlightening.

Our cover story was written by members of the USP Microbiology Expert Committee and provides an overview of changes planned for some of USP's microbiology chapters. **David Hussong,** one of the coauthors, will also present the USP update at the *13th Annual PDA Global Conference on Pharmaceutical Microbiology.* If you plan to attend this meeting, I encourage you to read through this article and make note of any questions you may have in advance of his talk.

Even if you do not plan to attend either meeting, I am sure that these articles, along with the rest of the issue, contain useful information. If you have any feedback about any of the content, I always welcome Letters to the Editor.

For those of you who plan to attend one or both meetings, contact me if you are interested in writing a summary for the Letter. It is always interesting to read another perspective on a meeting, especially if it is one I attended.

And as the end of 2018 comes closer in sight, I want to mention another *PDA Letter*-related volunteer opportunity: the *PDA Letter* Editorial Committee. This group of volunteers reviews Letter submissions with an eye toward subject matter and helps plan the editorial themes for the subsequent year. If you are interested, email me with "PDA Letter Editorial Committee" in the subject line with your name, affiliation and expertise.

Rebecca Stauffer

Vote for the 2019 PDA Board of Directors

As a PDA member, you have the power to help set the strategic direction of the Association by voting in this year's Board of Directors election. Voting opens Sept. 10 and closes at 11:59 p.m. U.S. EST on Nov. 7.

Members in good standing as of Aug. 30 can vote online beginning Sept. 10 at the PDA website (www.pda.org/vote) and at PDA conferences held between Sept. 24 and Nov. 7 in the United States and Europe.

For information about the candidates, visit www.pda.org/election.

Director Candidates

Bettine Boltres, PhD

Stephan Krause, PhD

Brigitte Reutter-Haerle

Anil Sawant, PhD

Melissa Seymour, MBA

Art Vellutato, Jr.

Vote Online

You will need your member ID and password.

www.pda.org/vote

If there are any questions about the voting process, please email **vote@pda.org** or call (301) 656-5900

PDA Wants You!

Four New Volunteer Opportunities Available

Interested in sharing your knowledge and furthering your connections? Below are four new volunteer opportunities with PDA.

Standards Development Volunteers

PDA is very pleased to announce the launch of its standards development program! We are seeking volunteers to assist in developing, writing and fine-tuning one (or both) of the following proposed standards:

- BSR/PDA Standard 01-201x, Enhanced Purchasing Controls to Support the Bio-Pharmaceutical, Pharmaceutical, Medical Devices and Combination Products Industries (new standard)
- BSR/PDA Standard 02-201x, Cryopreservation of Cells for Use in Cell Therapies and Regenerative Medicine Manufacturing (new standard)

The deadline to submit a notification of interest is Sept. 28. Nominees/volunteers should have knowledge or experience in the specific areas outlined in the proposal and must apply by contacting PDA's Standards Manager at standards@pda.org.

Spanish Technical Report Translator

PDA is currently looking for a volunteer fluent in both English and Spanish interested in translating technical documents, such as PDA technical reports, into Spanish. In addition, PDA is also seeking volunteers to serve on a Translation Review Committee who will review translated technical reports by comparing them to the original English version for the purposes of determining their accuracy.

PDA Journal Editorial Board

PDA is establishing an all-volunteer Editorial Board for the *PDA Journal of Pharmaceutical Science and Technology* comprising qualified experts with working knowledge of existing and/or emerging science and technologies important to PDA members. This expertise should include, but is not limited to, the following areas: aseptic processing/sterilization, pharmaceutical and biopharmaceutical manufacturing science, supply chain, packaging science, drug delivery, pharmaceutical microbiology and viral clearance.

Both the technical report translator and editorial board opportunities are open until filled. To apply or ask questions regarding the time commitments, responsibilities, etc., contact the Volunteer Coordinator at volunteer@pda.org.

For more information about these opportunities, visit www.pda.org/membership/volunteer-opportunities/upcoming-volunteer-opportunities.

PDA Volunteer Spotlight

Lori Richter

- Senior Consultant
- *ValSource*
- Member Since | 2010
- Current City | Sacramento, California
- Originally From | Live Oak, California

I love working together with regulators to improve the future of the industry

What do you like about volunteering for PDA?
I enjoy volunteering for PDA because it allows me to work with like-minded people in the industry. This serves as a great learning opportunity and a chance to collaborate with others who are also interested in improving various processes throughout the industry.

Of your PDA volunteer experiences, which have you enjoyed the most?
I really enjoyed being on the team that produced *PDA Technical Report No. 54-5: Quality Risk Management for the Design, Qualification, and Operation of Manufacturing Systems.* This project pulled together various subject matter experts to collectively build a document that explained quality risk management (QRM), starting with design then following the lifecycle of the manufacturing process.

The resulting technical report was a "how-to" on the practical application of QRM.

What have been your most memorable PDA connections?
During a *PDA/FDA Joint Regulatory Conference* a few years ago, I met **Kelly Waldron,** another QRM expert. We sat next to each other during a plenary session in the ballroom and had a good chuckle over how two people working in something as specific as QRM ended up sitting next to each other at this huge conference. We then met for lunch where I introduced her to **Ghada Haddad,** a PDA board member and QRM expert. By the end of lunch, Ghada had decided we needed to work together to bring clarity to QRM and its true practical applications. That was the moment TR 54-5 was born. Now, a few years later, Kelly and I work together as consultants.

When you were a child, what did you want to be when you grew up?
I wanted to be a veterinarian. I loved animals and grew up in a rural community. For many years, I was in 4-H and raised pigs and rabbits for the county fair. We often had to treat the animals for their various illnesses, and I was in love with the idea of caring for them and ensuring they remained healthy for the duration of their lives to fulfill their roles on the farm.

Make PDA Your Bio/Pharmaceutical Manufacturing Resource

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To learn more about how PDA is promoting progress in bio/pharmaceutical manufacturing, visit us at www.pda.org

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India Chapter Goes into the Cold

Chapter Workshop Explores State of Cold Chain Management in India

Biny Joseph, PDA India Chapter Coordinator

The future of cold chain management was on display at a recent PDA India chapter workshop, which overwhelmingly left attendees with a sense of oneness. The workshop, held April 19–20, featured a mix of presentations by industry leaders in the cold chain space.

(l-r) Tej Bazaz; S.G. Belapure; Ravi Chitradurg; Yogesh Lawania; Greg Bassett; Janusz Mielewczyk;, Dinesh Khokal; Ravi Menon; Rustom Mody

Rodney D'Cruz opened the workshop with an overview of the International Air Transport Association (IATA) Center of Excellence for Independent Validators in Pharmaceutical Logistics program. **A. Ramkishan** then began a discussion of the Indian regulatory perspective on cold chain management**.** Both talks generated great discussion.

Another presentation that drew considerable interest came from **Greg Bassett,** who spoke about the changing landscape of cold chain over the last decade. His talk covered such subjects as changing GDPs, increasing complexity in product portfolio and serving multiple countries. For a look at global regulatory expectations, **Dinesh Khokal,** External Affairs Director from Amgen Singapore, spoke about other countries' requirements for cold chain management.

Rustom Mody was another well-received speaker. He spoke extensively on the the demand for a reliable cold chain management system for biologics, emphasizing that efficacy and safety rely heavily on

GDP, Good Handling Practices and Good Storage Practices. Despite technological advances in cold storage monitoring capabilities, India's drug manufacturers continue to experience breaks in the cold chain. Mody alerted the audience to global regulators' increasing concerns about the integrity of temperature-sensitive biopharmaceuticals.

Ravi Menon and **S. G. Belapure** discussed *PDA Technical Report No. 46: Last Mile: Guidance for Good Distribution Practices for Pharmaceutical Products to the End User* and *PDA Technical Report No. 39 (Revised 2007): Guidance for Temperature-Controlled Medicinal Products: Maintaining the Quality of Temperature-Sensitive Medicinal Products through the Transportation Environment,* immediately engaging with the audience who wanted to learn more about these documents. Following this presentation, **Prasanna Devaraneni** addressed vital differences between small molecule therapeutics and biologics in terms of stability and sensitivity before delving into the impact of temperature and other stress factors encountered during cold chain supply on protein structure and, ultimately, on product quality.

When it came to warehouse and transportation qualification, **Janusz Mielewczyk** covered aspects of validation in his engaging talk. **Ravi Chitradurga** discussed data integrity issues in distribution networks while **Tej Bazaz** discussed supply chain security.

Madhura Joshi from Lupin Limited then covered the session on critical aspects of clinical sample management. **Yogesh Lawania** took the last session, exploring how to build efficiency in a temperature-controlled supply chain and distribution system using two case studies through which participants could directly apply the lessons learned to their own work.

PDA Who's Who

Greg Bassett, Executive Director, Amgen Hong Kong

Tej Bazaz, Director, Client Services and Project Management, Fisher BioPharma Services Pvt. Ltd

S. G. Belapure, Managing Director, Zydus Hospira

Ravi Chitradurga, Manager, Distribution Development PAN India, Expeditors International

Rodney D'Cruz, Assistant Director, Passenger and Cargo Services, IATA

Prasanna Devaraneni, Principle Scientist, Formulations Development, Lupin Biotech

Madhura Joshi, Research Scientist, Lupin Limited

Dinesh Khokal, External Affairs Director, Amgen Singapore

Yogesh Lawania, General Manager, Supply Chain, Biocon

Ravi Menon, Additional Director, Production, Serum Institute of India

Janusz Mielewczyk, International QA Senior Manager, Amgen Breda, Netherlands

Rustom Mody, Senior Vice President, Lupin Biotech

A. Ramkishan, Deputy Drug Controller, India Central Drugs Standard Control Organization (CDSCO)

Continued at top of page 45

PDA Photostream www.flickr.com/parenteral-drug

3rd PDA Europe Annual Meeting

June 26–27 | Berlin, Germany

Falk Klar, PDA Europe Vice President

Top: (l-r) Maik Jornitz, G-CON Manufacturing; Hal Baseman, ValSource; Roberto Conocchia, EMA

Bottom: Jette Christensen, Novo Nordisk

Indu Conley, DPS Group

Markus Hayek, Accenture

Aaron Goerke, Roche

Timo Simmen, Janssen J&J

Sebastian Schmitz, Industry 4.0 Maturity Center

(l-r) Paige Kane, Dublin Institute of Technology; Susan Schniepp, Regulatory Compliance Associates; Ursula Busse, PhD, Novartis; Emma Ramnarine, Genentech/Roche

PDA Europe Vice President Falk Klar (left) hands meeting co-chair Jette Chrisensen (right) a Berlin Buddy Bear statue. He also presented PDA Honor Awards to Stefan Merkle (middle) and Siegfried Schmitt (far right).

PDA Photostream www.flickr.com/parenteral-drug

Marc Philipp, Accenture

Christoph Marschall, Ludwig-Maximilians-University

Build Connections at Two PDA Events

Opportunities abound at this year's *PDA Universe of Pre-Filled Syringes and Injection Devices* and *13th Annual PDA Global Conference on Pharmaceutical Microbiology* to expand your list of Outlook contacts. Below are some of the networking opportunities available at both meetings.

Monday, Oct. 8

Networking Reception

Travel to the tropics at this luau-themed reception. Be sure to grab a lei and enjoy tropical music, food and drinks. Guests are welcome to wear their best island casual attire but should be mindful of the potential Florida chill as the event is outside. 7–10 p.m. *(Sponsored in part by Owen Mumford, Sensile Medical and MedImmune)*

Monday, Oct. 15

Networking Reception with Poster Presentations

Join fellow attendees in the Exhibit Area for drinks and refreshments where exhibitors will be on hand to showcase their latest product offerings and poster presenters will discuss their latest research. 5:45–7 p.m.

There will be additional opportunities to network during refreshment breaks throughout both meetings.

SNAPShot

PDA Participates in Nipro Experience Days

Janie (Jahanvi) Miller, PDA

PDA staff and volunteers experienced the future of parenteral packaging among the historical surroundings of the Philadelphia region during Nipro's Experience Days, April 25–26. Those attending the two-day program, including some PDA staff and volunteers, learned a bit about the rich history of the city along with new developments in packaging.

The Nipro team—**Annick Somers,** Senior Vice President of Marketing and **Christoph Grinda,** Marketing Manager—set the stage for this event at Philadelphia's National Constitution Center, with the city's profuse history on full display.

Roger Asselta, leader of PDA Packaging Science Interest Group, opened the first day with a look at market trends and challenges facing pharmaceutical manufacturers and the suppliers developing glass packaging containers. He reviewed glass as a primary packaging material before exploring potential technologies to reduce particulate matter in products while improving the strength of the container.

The day closed with Nipro unveiling its new VIALEX™ technology, intended to improve surface durability and reduce the shedding of glass particles. Following the launch, attendees took part in the evening's activities, beginning with a walk through Constitution Center followed by a networking reception.

Day Two of the Nipro Experience featured a tour of the company's production plant in Millville, N.J., where attendees could view the entire production process from tubing formation to final packaging in pallets. The Nipro production staff coordinated information stations to explain each part of the vial-forming process, beginning with the furnaces that melt the various glass forms. Next came demonstrations of the cooling, inspecting and palletizing processes for delivery of the tubes to customers or transfer to the vial-forming facility. Automated transfer of the tubes to the rotary vial-forming machines quickly provided vials, which attendees could see up close as the vials underwent the VIALEX™ technology process.

PDA appreciated the opportunity to take part in this unveiling and looks forward to the future of new glass technologies that will increase patient safety.

Journal *TOC*

All the Latest on Viral Clearance from the 2017 Viral Clearance Symposium

The September/October edition of the *PDA Journal of Pharmaceutical Science and Technology* features summaries of presentations at the *2017 Viral Clearance Symposium*. Topics covered include virus barrier filters, virus filtration and more! (journal.pda.org)

Editorial

Richard Levy, "Special Viral Clearance Issue and St Gallen PDA Collaboration Paper"

Review

Glen Bolton, Dayue Chen, "Upstream Mitigation Part 1: Cell Bank and Bulk Harvest Testing"

Dayue Chen, Glen Bolton, "Session 1.1 Upstream Mitigation Part 2: Virus Barrier Filter and HTST"

Thomas Kreil, David Roush, "Proceedings of 2017 Viral Clearance Symposium Session 2.1: DSP Unit Operations – Virus Filtration/ Inactivation"

Thomas Kreil, David Roush, "Proceedings of 2017 Viral Clearance Symposium Session 2.2: DDSP Unit Operations – Purification Unit Operations"

Editorial

Stefan Hepbildikler, Sarah Johnson, Johannes Bluemel, "Viral Clearance Symposium 2017 Conclusion"

Franz Nothelfer, Stefan Hepbildikler, "Proceedings of the 2017 Viral Clearance Symposium – Introduction"

Johannes Bluemel, Junfen Ma, "Proceedings of 2017 Viral Clearance Symposium Session 3: Resin Life Time"

Astrid Schwantes, Qi Chen, Rachel Specht, "Proceedings of 2017 Viral Clearance Symposium Session 4: Submission Strategies"

Junfen Ma, Thomas R. Kreill, "Proceedings of 2017 Viral Clearance Symposium Session 5: Facility Risk Mitigation"

Sarah Johnson, David Roush, "Proceedings of 2017 Viral Clearance Symposium Session 6: Ensuring Viral Safety in Continuous Processing"

Research

Paul Buess, et al., "The Impact of Quality Culture on Operational Performance – An Empirical Study from the Pharmaceutical Industry"

Biologics Packaging Presents Risks

Alessandro Morandotti, Ompi

Biological drugs are growing in tandem with an aging, longer-living population. At the same time, biological drugs are very challenging to stabilize and administer due to their larger dosage and complexity, sensitivity and viscosity. Risks include extractables, glass delamination, particles and siliconization. But new prefilled syringe packaging options offer potential solutions to these risks.

Risks Associated with Extractables

Increasing regulatory and compendial attention is being paid to extractables, substances released from the complete drug packaging system after stress treatment (e.g., long-time and high-temperature exposure). In particular, special attention is being placed on tungsten, a material used during glass tip-forming operations. Recent studies show that soluble tungsten polyanions may cause precipitation and/or aggregation of biomolecules, reducing drug efficacy and increasing the risk of immunogenicity.

In the case of sensitive biologics, the concentration of extractables must be lowered as much as possible.

Risks Associated with Delamination

Delamination can be described as the appearance of visible glass particles, known as flakes (lamellae), in injectable preparations. This phenomenon caused several drug-product recalls in 2010–2011 ***(1).***

Many factors determine the delamination propensity of pharmaceutical glass: drug formulation (aggressive buffers, complexing agents, high pH), storage conditions (temperature, time), surface treatment (sulfur, coating) process and drug shelf life (depyrogenation, terminal sterilizations).

Reducing the risk of delamination requires a precise evaluation ***(2),*** starting with choosing the most appropriate glass to optimizing the glass container forming process, subsequent filling operations and the shelf life of the product.

Risks Associated with Particles

The European, U.S. and Japanese Pharmacopeias have set limits and techniques to detect and quantify visible/subvisible particulate in parenteral solutions that might compromise patient safety. Glass containers must actually be free from visible particles ***(3).***

In particular, silicone oil subvisible particles may migrate from a siliconized container to the drug solution. Also, the movement of the stopper during the injection may ease the migration of silicone oil into the drug. This concern can become serious when the number of dispersed particles exceeds the limits set by the pharmacopeias. The presence of silicone oil may also accelerate aggregation in proteins and, when injected, may elicit immunogenic responses ***(4).***

Risks Associated with Siliconization

Prefilled syringes and cartridges operate using a plunger that moves along the inner surface of a glass barrel. To ensure the smooth movement of the plunger, silicone oil is commonly employed as a lubricant. As mentioned previously, there is evidence that proteins may aggregate by interacting with the lubricant. A lubricant is, in any case, necessary to guarantee suitable values of break loose and gliding forces and enable correct administration. The silicone oil layer is characterized by two main parameters: the quantity of silicone oil applied to the container barrel and its distribution. Particular care must be taken in order to deposit only the proper amount, as an excess of silicone oil may detach from the barrel and generate particles. Moreover, the silicone oil must be applied homogeneously throughout the inner surface of the container, in order to ensure a constant degree of lubrication along the plunger path.

Based on these risks, two glass container platforms have been developed. One optimizes conventional prefilled syringe processes and addresses sensitive biologic injectables issues; another was devised as

an innovative solution to streamline the biologic drugs development path using a new technologically advanced coating.

Two New Options for Glass PFS

The platform that optimizes conventional prefilled syringe processes has a number of features. These include a low tungsten manufacturing process, low-adhesive extractables due to an improved adhesive curing process, particle reduction through barrel washing, low delamination propensity, optimized silicone treatment, dimensional device compatibility, improved mechanical resistance and 100% cosmetic camera inspection.

Another innovative glass primary packaging platform is composed of sterile vials, cartridges and syringes with the same internal treatment crosslinked to the surface of the glass. This solution reduces the impact of two main problems—delamination and silicone particles presence—facilitating each step of the drug development phase. Using the same internal coating throughout development improves lifecycle management and avoids validation failures because the drug product stays in contact with the same surface independently from the container shape. This allows a smooth switch at each step of the process, while guaranteeing an ultralow particle level.

The rising number of biologics has placed pressure on manufacturers to pay attention to multiple aspects for guaranteeing drug quality, efficacy and patient safety. In addition, as more patients receive treatment on an outpatient basis, a new generation of glass containers that enable perfect functionality in drug delivery systems is needed. With this in mind, more packaging companies are designing new forms of containers that ensure better chemical and mechanical performance and are specifically dedicated to sophisticated drugs, like those based on monoclonal antibodies or recombinant proteins.

[Editor's Note: The author's company will be exhibiting at the *2018 PDA Universe of Pre-Filled Syringes and Injection Devices*.**]**

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About the Author

Alessandro Morandotti has been working in OMPI since 2001 covering a variety of positions and he is now Product Manager for Syringes.

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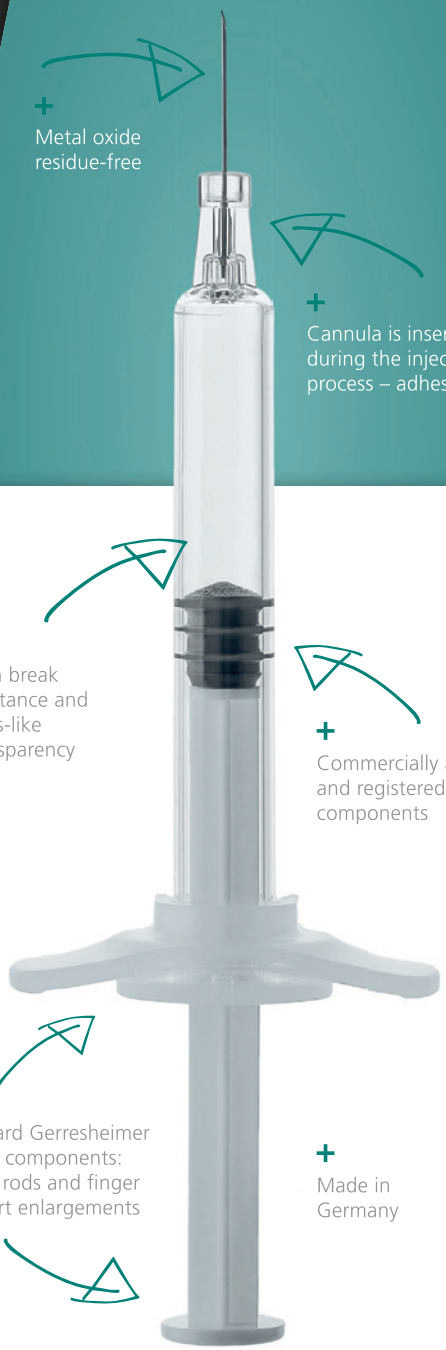

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GERRESHEIMER

13th Annual PDA Global Conference on Pharmaceutical Microbiology

New Trends, New Challenges for BET

Jay Bolden, Eli Lilly and Company, and Ned Mozier, PhD, Pfizer

Endotoxin testing for pharmaceutical production processes has seen a number of advances in recent years, among them discovery of recombinant Factor C (rFC) and development of the monocyte activation test (MAT). At the same time, data integrity has become an issue for various test modes.

Where can industry personnel learn about the latest practices in these areas and discuss emerging trends and issues with global colleagues?

The *2018 PDA Endotoxins Workshop,* immediately following the *13th Annual PDA Global Conference on Pharmaceutical Microbiology,* will provide a forum to discuss these topics in an interactive format.

Recombinant Factor C (rFC)

Although the rFC reagent has been commercially available as an alternative to the traditional horseshoe crab-derived LAL reagent for bacterial endotoxin testing since the early 2000s, industry has been slow to take it up. Keynote speaker **Lynne Ding,** PhD, of the University of Singapore, an rFC patent holder, will present the history of rFC to workshop attendees. An Eli Lilly representative will follow up with a report on a real-world application of rFC in pharmaceutical product and water testing, sharing roadblocks, successes and data.

Monocyte Activation Test (MAT)

MAT is another alternative test, one with the potential to replace the compendial rabbit pyrogen test capable of detecting bacterial endotoxins in addition to nonendotoxin pyrogens. **Peter Bruegger** (Lonza) will present background information on the MAT based on extensive compendial experience in Europe. Then, **Ned Mozier,** PhD, (Pfizer) will convey his real-world experience with MAT.

Data Integrity and Endotoxin Testing

Data integrity continues to be a recurring theme in global regulatory findings. The evolution of the bacterial endotoxins test has led to potential pitfalls for various data reporting mechanisms and the need to implement appropriate controls to ensure data integrity.

Additional topics will include depyrogenation, low endotoxin recovery and other immune-modulating impurities.

2018 PDA Endotoxins Workshop

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

PDA Universe of Pre-Filled Syringes and Injection Devices

Going Beyond Patient Preference

How We Can Improve our Understanding of Patient Needs

Nic Bowman, Pfizer

Patient preference is much discussed and often measured, particularly when choosing features or comparing product against a competing offering. Yet, genuine patient preferences are hard to pin down. Deeply held doubts about validity persist—often aired with the phrase "the company that pays for the preference study gets the preference"—as the preferences expressed may seem superficial, ephemeral or reflective of a patient's perception of what an interviewer wants to hear.

Beyond preference lies motivation perhaps. For any patient, their preference is an expression of their deeper desires and concerns. To best understand the patient, the patient's motivation on this deeper level must be understood.

With this understanding, manufacturers may be better placed to select optimized product solutions or develop a range of solutions that can cover a wide range of patient needs. Better understanding of a patient's motivation may lead to changing behaviors, especially around compliance to medication regimens. This could have a significant impact on an individual's quality of life and even healthcare costs.

So how can the industry learn to better understand the meaning of patient preference? At the *2018 PDA Universe of Pre-Filled Syringes and Injection Devices* conference and exhibition, **Paul Upham** of Roche/Genentech, and **Claire Everitt** of Pfizer will discuss their views on patient-centric products.

The world is changing its view of the patient—patient power is becoming a significant driving force. To stay on top of understanding what the patient really needs, come to the *2018 PDA Universe of Pre-Filled Syringes and Injection Devices*.

2018 PDA Universe of Pre-Filled Syringes and Injection Devices

Orlando, Fla.
Oct. 8–12
www.pda.org/2018pfs

2018 PDA Upcoming Events

SAVE THE DATE for PDA's 2018 Events

SEPTEMBER

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

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

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

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

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

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

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

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

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

OCTOBER

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

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

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

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

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

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

14-17
Prozesschromatographie
Clausthal-Zellerfeld, Germany
pda.org/EU/PC18

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

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

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

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

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

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

17-18
Environmental Monitoring and Contamination Control
Berlin, Germany
pda.org//EU/EMCC18

SEPTEMBER'S FEATURED EVENTS

13th Annual PDA Conference on Pharmaceutical Microbiology Course Series
pda.org/2018MicroCourses

October 18-19, 2018
Bethesda MD

Following the 13th Annual PDA Conference on Pharmaceutical Microbiology

Oct. 18 Investigating Microbial Data Deviations

Oct. 18 Regulatory Aspects of Microbiology in a Non-Sterile Environment

Oct. 19 Microbiological Risk Assessment of a Pharmaceutical Manufacturing Process

Oct. 19 Developing a Microbial Monitoring Plan and Leveraging New Technologies for Effective Sterility Assurance in Aseptic Processes NEW COURSE

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

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

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

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

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

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

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

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

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

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

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

NOVEMBER

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

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

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

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

8-9
Practical Guide for Root Cause Investigations – Methodology & Took Kit
Seville, Spain
pda.org/eu/rootcause2018

8-9
Risk Management in Technology Transfer
Seville, Spain
pda.org/eu/risk-tt-18

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

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

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

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

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

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

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

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

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

DECEMBER

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

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

10-12
NEW COURSE
Quality Risk Management Facilitator Training
Bethesda, MD
pda.org/2018Facilitator

Revised USP Micro Chapters Address Changing Technologies

David Hussong, PhD, Eagle Analytical Services, Radhakrishna Tirumalai, PhD, USP, Edward Tidswell, PhD, Merck, and Donald Singer, GSK

As technological advancements around microbiological testing continue to grow within the pharmaceutical industry, USP's Microbiology Expert Committee seeks to update some of its microbiology chapters. For each five-year cycle, the Expert Committee has an established workplan intended to help meet USP's standards-setting goals. Some of the workplan's major initiatives in the current USP cycle (2015–2020) include sterilization processes and sterility assurance, parametric release, depyrogenation, endotoxin testing, rapid sterility testing of short-life products and a test for the presence of *Burkholderia cepacia* complex.

Sterility Assurance and Sterilization

While all products purported to be sterile must meet the requirements of USP <71> Sterility Tests, sterility assurance is achieved only through validated, robust sterile

> **a parametric program of release should be in place where feasible**

manufacturing processes. Currently, USP <1211> Sterilization and Sterility Assurance of Compendial Articles addresses principles of sterility assurance but provides information on only a few sterilization processes. In response to stakeholder feedback requesting greater information on specific sterilization methods, USP initiated a two-stage revision approach over ten years ago. Phase 1 focused on correcting outdated content with up-to-date information. This became official in the 2010 *USP 33-NF 28*. Phase 2 involved significantly rewriting the general chapter.

The initial focus of Phase 2 was sterilization, followed by content relevant to sterility assurance. In determining how to update the sterilization material in USP <1211> (which had its origins in the late 1980s), the Expert Committee decided to split the content. Information relating to sterilization would be removed from the existing USP <1211> and that chapter renamed "Sterility Assurance"—its main focus. The Expert Committee recognized that a separate sterilization chapter should:

1) Provide a roadmap for the design and control of the process for sterile product manufacture,
2) Introduce a means of extending terminal sterilization to more sensitive products,
3) Offer enhanced detail on all the core elements of sterility assurance, and
4) Include key details to expand application of parametric release.

The result has been development of a new series of general chapters, the <1229.x> series. In support of USP <1229> Sterilization of Compendial Articles, which covers overarching concepts of sterilization, each new general chapter is dedicated to an individual sterilization process or related topic.

To date, 15 general chapters have been developed to provide valuable information and guidance on distinct methods of sterilization. This effort emphasizes that bioburden is the "true" target of sterilization processes, thus, knowledge of its resistance is essential. Another key element involves encouragement of terminal sterilization processes to enhance patient safety.

The Expert Committee also recognized that the notion of completely destroying a large population of highly-resistant biological indicators (BI), worst-case assumptions, and use of overkill sterilization parameters as the arbiter of cycle appropriateness hampers broader adoption of terminal sterilization processing. Therefore, alternative methods of moist heat sterilization cycle design and qualification (including development of bioburden/BI and bioburden methods) are described to aid wider application of terminal sterilization processes to improve process control.

Parametric Release

The sterility test is technically and statistically inadequate to detect anything other than gross contamination. While defining the scope of the USP <1222> Terminally Sterilized Pharmaceutical Products—Parametric Release revision, the Expert Committee recognized that:

a) Increased adoption of parametric release is important because it leads to increased patient safety, and
b) Sterility assurance is not best served by end product tests.

In support of these concepts, a parametric release program must be designed, validated and controlled based on the user's understanding of process control, critical process parameters and risk points. This completely revised content is applicable to all methods of terminal sterilization. In fact, some enhanced or advanced aseptic manufacturing could be candidates for parametric release. One pivotal change in both USP <1222> and USP <1211> is that parametric release is the default mode of product release, not sterility testing. In other words, a parametric program of release should be in place where feasible. Terminally sterilized products should then be released parametrically.

Depyrogenation

During the revision process for the <1229.x> series of chapters, the Expert Committee decided to develop a general chapter <1228.x> series on depyrogenation separate from the chapter on dry heat sterilization in order to better align with current industry practices. The intent of depyrogenation is very different from that of sterilization. Thus, the <1228.x> series of general chapters includes descriptions of various methods used for depyrogenation of materials and product streams. While defining the scope of <1228.x>, the Expert Committee recognized:

a) Changes in current thinking on product lifecycle and advances in parenteral formulation and manufacturing,
b) Renewed industry focus on raw material quality, and
c) Shift in active ingredients from small molecule APIs to biologics.

Article at a Glance

- <1229.x> series of chapters covers individual sterilization processes
- Revised chapter supports expansion of parametric release
- Rapid methods and *B. cepacia* to be addressed in Sept/Oct issue of PF

Interested in more USP microbiology updates? **David Hussong** will present, "Current Activities of the USP Microbiology Expert Committee," Oct. 17 at 8:30 a.m. in the session, "USP Updates," on the last day of the *13th Annual PDA Global Conference on Pharmaceutical Microbiology*. USP's **Radhakrishna S. Tirumalai,** PhD, will moderate the session.

About the USP Microbiology Expert Committee

Through its General Chapters-Microbiology Expert Committee, USP develops and revises general chapters for the advancement of pharmaceutical microbiology consistent with the organization's mission of quality medicines, food ingredients and dietary supplements. The current Expert Committee consists of industry experts and consultants along with U.S. FDA liaisons.

The Microbiology Expert Committee is responsible for general chapters that address microbial test procedures and microbial control of processes and environments. Its responsibilities do not extend to drug or product monographs, which are handled by other USP Expert Committees, although the Microbiology Expert Committee does support the development of microbiological requirements for all monographs via consultation with the relevant monograph Expert Committees. A separate Expert Committee handles monographs and informational general chapters on pharmaceutical waters.

USP General Chapters Microbiology Expert Committee 2015–2020

David Hussong (Chair)
James Akers
James Agalloco
Dilip Ashtekar
Anthony Cundell
Richard Friedman (U.S. FDA)
Dennis Guilfoyle
Rajesh Gupta
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Andrea Ottesen (FDA)
Marla Stevens-Riley(FDA)
Donald Singer
Paul Stinavage
Colleen Thomas (FDA)
Edward Tidswell
Radhakrishna Tirumalai (USP)

> **No standard method exists, however, for the detection of BCC even though they are considered objectionable species**

These changes challenged the narrow, prescriptive requirements for depyrogenation initially proposed for dry heat in the original USP <1211>. To date, five new general chapters have been developed to provide valuable information and guidance on distinct methods of depyrogenation. Referencing the concepts of quality-by-design and risk management, the USP <1228.x> series proposes alternatives to traditional thinking around designing, executing and assessing depyrogenation processes. These concepts include:

a) Using appropriate calibration materials; while current calibration standards (USP reference standard endotoxin or control standard endotoxins) are convenient, some depyrogenation methods, particularly those that are part of product streams, may be better challenged by naturally occurring (or native) endotoxin
b) Demonstrating a reduction of endotoxin to safe levels based on the calculated endotoxin limit rather than establishing a process minimum of 3-log reduction in endotoxin (or lipopolysaccharides, i.e., LPS) activity, irrespective of the initial endotoxin burden or process capability

Endotoxin Testing

The bacterial endotoxins test is a critical requirement for injectable products and medical devices required to be pyrogen-free. In 2012, the U.S. FDA withdrew its 1987 guidance, *Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices.* As a result, stakeholders lost useful guidance on a variety of issues related to "best practices" for the bacterial endotoxins test. To fill this void, a new chapter, USP <1085> Guidelines on the Endotoxins Test, was proposed in the July-August 2018 issue of *Pharmacopeial Forum* ***(1).*** More specifically, this chapter provides guidelines on the bacterial endotoxins test relative, but not limited to, control standard endotoxins, control of standard curves, analyst training and qualification, calculation of endotoxin limits for ingredients, drug products with single and multiple active ingredients and resolution of out-of-specification results.

Rapid Methods

Conventional microbiology tests, such as sterility tests, found in the major pharmacopeias, rely on demonstrating microbial growth. Limitations of these tests include their low sensitivity and their time- and labor-intensive nature. Many cytotherapy or regenerative medicine products, radiopharmaceuticals and compounded pharmacy products are administered to patients prior to receiving results from sterility tests. A more rapid sterility test would be better in such instances from a patient safety perspective. These issues prompted USP to assemble a panel of technology experts and representative stakeholders from the sterile compounding, positron emission tomography, cell therapy and pharmaceutical and contract testing industries. This panel helped USP establish user requirement specifications, review risk-based approaches and recommend suitable technologies for the rapid sterility testing of short-shelf-life products ***(2).*** All of this has led to a new general information chapter on a risk-based approach for rapid sterility tests, USP <1071> Rapid Sterility Testing of Short-Life Products: A Risk-Based Approach, proposed in the September-October 2018 issue of *Pharmacopeial Forum*. The next step involves conducting proof-of-concept studies to demonstrate the reliability of the proposed methods. Based on these

Continued at bottom of page 45

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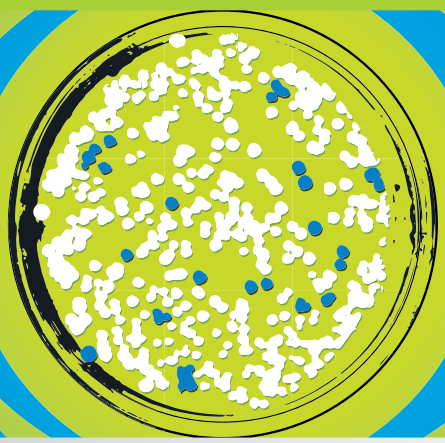

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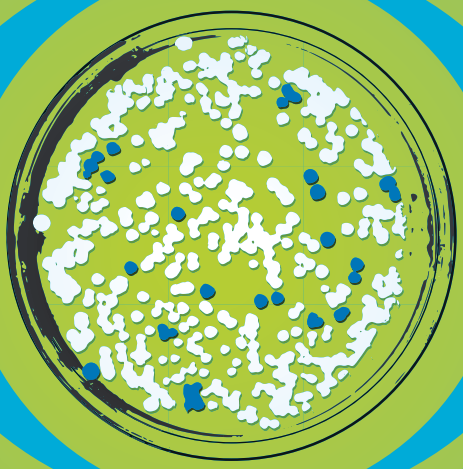

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Viewpoints on the EU Annex 1 Revision

What Annex 1 Means for Sterilization and Moist Steam

Walid El Azab, STERIS Life Science

In December, the European Union released the long-awaited revision of Annex 1. The goal behind the revision was to reinforce the need for manufacturers to stay current with innovative technologies related to sterile manufacturing. To meet this goal, the revision aims to clarify regulatory requirements, introduce quality risk management (QRM) principles, allow for the inclusion of new technologies and innovative processes, make the structure of the document more logical and remove some ambiguities ***(1).***

Despite these lofty goals, however, the draft contains several terms and requirements that are not in line with ISO and pharmacopeial recommendations ***(2).*** At the same time, some requirements of the draft Annex 1 differ from U.S. FDA guidelines or even USP recommendations, including those for both biological indicators testing and feed water used to generate pure steam ***(3).*** Such differences may present challenges for global companies as they must comply with the legislative requirements where the product is marketed ***(4).***

For these reasons, careful review of the draft Annex 1 is needed, particularly the requirements for steam used for sterilization and approaches to steam sterilization of product, equipment and packaging components. Additional revisions cover steam quality and moist steam sterilization. These changes require new parameters for analysis and considerations for developing risk-based justifications.

Pricy, Unnecessary Tests Required?

The draft revision suggests that the minimum feed water quality for a pure steam generator should be "purified water, with a low level of endotoxin." The USP monograph on pure steam, however, requires that the steam be "prepared from water complying with the EPA National Primary Drinking Water Regulations, or with drinking water regulations of the European Union or of Japan, or with WHO drinking water guidelines. It contains no added substance" ***(5).*** The current European Pharmacopoeia (Ph. Eur.) and USP monographs for purified water do not require testing for endotoxins. Finally, based on the USP and Ph. Eur., if the item being sterilized encounters the drug product, pure steam should meet the requirements of water for injection (WFI) when condensed ***(5).***

What does "low level of endotoxin" mean when the specification for the steam is 0.25 endotoxin unit/mL? To reach this so-called "low level of endotoxin," manufacturers would be required to manage their purified water system comparable to a WFI system. Depending on existing purified water system design and routine microbial monitoring data, an increase in preventive cleaning/sanitization may be required to prevent endotoxin contamination and biofilm formation.

Many steam generators have endotoxin removal systems and do not require feed water that meets specified endotoxin levels. But the feed water to the generator should meet the manufacturer's requirements in order to prolong the use-life of the generator and to generate pure steam consistently. Therefore, in most cases, water softening, reverse osmosis, deionization or other water treatment methods are used to condition the feed water.

The requirement of using purified water with a low level of endotoxin to feed a pure steam generator would force some pharmaceutical manufacturers to review and, possibly, modify their utility design which may add expensive testing to feed water that may not be required by the steam generator manufacturer. The inclusion of a higher feed water quality standard in the pharmacopeia should be justified when there is a risk of a wrapped sterilized item, intermediate product or a primary packaged product being directly contaminated by endotoxins.

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Annex 1 and Steam Quality

A quality risk assessment (QRA) should be developed based on analysis of periodic steam requalification and monitoring results, periodic water requalification and monitoring results and the number of microbial out-of-specification results related to steam or feedwater. Furthermore, the QRA should also take into account the capabilities of the pure steam generator (such as endotoxin removal), frequency of corrective maintenance on the pure steam generator, steam distribution and water system design, the number and type of wrapping layers used during the sterilization process, the type of equipment autoclaved (wrapped or not wrapped, direct or nondirect product contact) and any other relevant information. Based on this, a suggested edit to Section 7.17 of the draft is: "The minimum feed water for the pure steam generator should comply with the appropriate pharmacopeial pure steam monograph. However, when the risk of endotoxin contamination is identified, a higher water quality should be required."

The quality of steam used for the sterilization of porous loads and steam-in-place (SIP) should be assessed periodically against validated parameters ***(6).*** Steam quality is assessed through physical, chemical and endotoxin testing ***(7–9).*** The critical steam attributes that should be monitored at scheduled intervals include noncondensable gases, dryness values and superheat and steam condensate quality.

In addition, any other relevant parameters that may impact steam quality or the sterilization process, air removal and leak testing for example, should be part of the monitoring ***(10).*** The validity of the steam quality should be verified at scheduled intervals based on both a quality and business risk assessment.

The QRA should analyze historical steam monitoring data, number of corrective maintenance and technical failures, number of nonconformances, criticality of the items sterilized versus the risk to alter the sterility assurance level and the manufacturer's control of sterilized product not yet released. Business risk should consider financial product value versus testing frequency as well as the control of the item or product sterilized. Finally, verification frequency of steam validity is justified when the quality and business risk is balanced toward patient safety.

The draft Annex 1 revision should support use of a risk-based approach. Manufacturers must always demonstrate a full understanding of their processes to be able to scientifically justify their decisions.

[Editor's Note: An expanded version of this article appears on the Letter website.**]**

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About the Author

Walid El Azab is a Technical Services Manager for the Life Sciences Division of STERIS Corporation.

Draft Annex 1 Separates Cleaning and Disinfection

Is Your Microbiology Lab Ready?

James Tucker, Ecolab Life Sciences

The EU Annex 1 revision released at the end of last year featured many changes; one in particular addresses cleaning and disinfection. It has long been widely accepted that cleaning and disinfection are two distinct processes within the cleanroom environment. The segregation of these two processes is, for the first time, reinforced in the Annex.

Cleaning versus Disinfection

The objective of cleaning is to remove physical soiling that can lead to contamination. This is usually achieved via systems such as vacuums, detergent cleans, wet cleans with water for injection (WFI), isopropyl alcohol (IPA) or even dry cleans with wipes and mops. Disinfection, on the other hand, is designed to kill microorganisms. Disinfectants can be divided into distinct groups: sporicides and broad-spectrum disinfectants. Each consists of various chemistries offering different effects against each type of organism; however, they share a common goal to render the specific target group of microorganisms unable to proliferate.

One key area of the Annex critical to the pharmaceutical industry is the disinfection section, which has replaced the previous sanitization section and is now further expanded.

The requirement for rotation of disinfectants is further clarified, with the statement that more than one type of product should be employed, including periodic use of a sporicidal agent. This indicates that one sporicide and a broad-spectrum disinfectant is sufficient for cleanroom contamination control.

As part of validation requirements for disinfectants, there is an increased emphasis on contact times, surface and manner of application, suggesting that these will be key areas for qualification, validation studies and reviews of validation data moving forward.

The revision includes a requirement to ensure that efficacy is demonstrated throughout the in-use shelf life, which places an increased burden on those making product up from concentrate as opposed to using ready-to-use products. This is because the datasets required to support the product in the final format will need more detail.

Additionally, the revision continues to reference the development of microbial resistance; however, the development of acquired rather than innate resistance is still unproven at in-use concentrations. The requirement for disinfectants to be effective against the flora is a logical approach. For example, bacterial spores will not be killed by alcohols; therefore, a sporicidal agent is required for efficacy against bacterial endospores.

The new Annex also maintains many of the original requirements for monitoring disinfectants and detergents for microbial growth, ensuring product is sterile when used in Grade A and B environments, storing dilutions in previously cleaned containers for defined periods, etc. At the same time, the revision removes the exception for sterility, demonstrating the need for a holistic approach across processes to show the effect on facilities and equipment.

Another key aspect of cleaning and disinfection is the in-practice demonstration of efficacy via environmental monitoring, as this should include monitoring pre- and post-disinfection. Furthermore, the Annex specifies that microbes within Grade A and B environments should be identified to species level, and the impact of this identification on the state of control assessed. This makes it easier to ensure the correct product(s) is(are) being used and identify which corrective action should be followed, as required.

A written plan should be in place for actions to take if environmental monitoring is out of trend or action limits are reached. This will undoubtedly include remedial action as part of the CAPA, which will likely require introducing a sporicide as one particular action.

Residues in Full View

The visual aspect of residues has always been a concern and there are records of pharmaceutical companies being cited for the presence of residues in the cleanroom environment. Annex 1 now calls out the need to control these residues and raises concerns over the potential latent effect of residues as highlighted in sections 6.5 A and B, referencing residues potentially creating a barrier and/or posing a particulate risk to the product. ➤

This article continues on the PDA Letter website www.pda.org/pdaletter

The new Annex 1 now includes a statement in the equipment section that cleaning processes should be validated to show they can remove any residues that would otherwise create a barrier between the sterilizing agent and the equipment surface. In this instance, the word "sterilising" has been challenged as incorrect in reviews of the proposed changes. The changes also highlight that residue removal should occur to prevent chemical and particulate contamination of the product during the process—linking to the requirement for cleaning stages.

There is a new specific statement on cleaning programs which should be effective at removing disinfectant residues. This ties in with low residue requirements and clearly states that it is no longer acceptable practice to allow residues to build up uncontrolled on surfaces.

It is a necessity that products used for decontamination of restricted access barrier systems (RABs)/isolators demonstrate they have no impact on manufactured product sterility testing, therefore, residual impact must be assessed. This assessment is not limited to the sterility testing of isolators; the impact on manufactured product and product contact surfaces should also be considered.

Furthermore, there are significant enhancements to expectations for visual inspection, which fits with the focus on residues and reflects a clear industry trend toward the need to remove residues to protect product quality.

When preparing disinfectants onsite from concentrates, the following need to be considered: increased requirements around filtration, such as limits to the number of connections, cleaning and in place integrity testing; an SAL 10-6 (sterility assurance level of 1 in a million); validation, including parameters such as flow rate, minimum and maximum time in contact with the fluid, validation pre- and post-use; pressures in use and bacterial retention testing. Liquid sterilizing filters should be discarded after processing of a single lot (unless validated).

About the Author

James Tucker has more than ten years' experience in the cleanroom industry, in a range of technical and commercial roles. In his current role, he supports many of the industry's leading manufacturers with their cleaning and disinfection processes and challenges.

PHARMACEUTICAL | PERSONAL CARE

A DIFFERENT PERSPECTIVE ON **ANNEX 1.**

So, you've reviewed the proposed changes to Annex 1 in relation to your manufacturing processes, but...

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Common Issues Found in Nonsterile Drug Facilities

U.S. FDA issued **143** warning letters

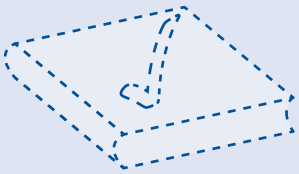
EMA issued **112** noncompliance reports (NCRs)

From January 2008 to February 2016

31% of warning letters and **25%** of NCRs were issued to manufacturers of nonsterile drugs

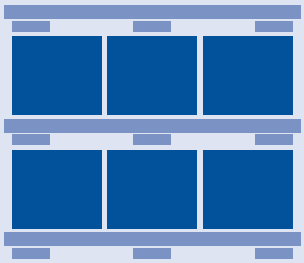
Of these, 115 CGMP violations were identified

What were the most frequent violations?

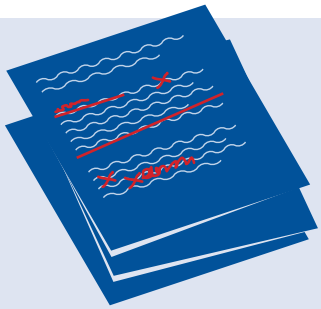


Lack of written production and control procedures

Failure to investigate discrepancies or batch failures



Inadequate stability testing program



Altered records

How can these be prevented?

- ✓ Regular training and awareness
- ✓ More effective documentation reviews

Want to learn more about how to prevent microbial contamination of your facility? Visit the PDA Bookstore to purchase *Contamination Prevention for Nonsterile Pharmaceutical Manufacturing* by J&J's Andrew Dick.

Source

Santos, A.M.C., et al. "A QRM Discussion of Microbial Contamination of Non-sterile Drug Products, Using FDA and EMA Warning Letters Recorded between 2008 and 2016." *PDA Journal of Pharmaceutical Science and Technology* 72 (2018) 62–72.

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Data Integrity in the Age of Metadata and Big Data

Toni Manzano, bigfinite

To adapt to the present reality concerning data management, MHRA published *GXP Data Integrity Guidance and Definitions,* aligned with texts issued by PIC/S, WHO and EMA ***(1–4).*** Released in March 2018, the guidance seeks to achieve a reliable relationship between generation of raw information and related decision-making that occurs during drug manufacturing. Metadata will play a key role in achieving this relationship and it takes a prominent place in the guidance.

In addition to harmonizing data integrity requirements with global guidelines, the document emphasizes the data and technology dependencies that can be found in many manufacturing sites, even referring to the "computerized system" concept some 30 times. Under this technological perspective, the MHRA guideline significantly illustrates the differences between electronic and paper records. Section 6.11 ("Original record and true copy)" of the guidance explains how to properly manage dynamic records, which include electronic records. For these records, technicians can obtain different information depending on the performed query. Static records based on paper, however, require more hands-on manipulation.

When it comes to data management, procedures must be based around how data is acquired, handled and stored. The first phases of this so-called "data governance" are referenced in Section 6.7 ("Recording and collection of data"). Data acquisition and collection should ensure the accuracy and completeness for each record (both terms are present in the ALCOA acronym, i.e., attributable, legible, contemporaneous, original and accurate). In the same section, a statement describes the different behaviors between static and dynamic data treatment. When the existing abilities of electronic systems allow users to handle data in a dynamic manner, a computerized versus print procedure is preferred.

The process of transforming information into knowledge must also be encompassed in integrity surveillance. The guideline describes why an image that represents a signature embedded in a document cannot be considered an electronic signature in Section 6.14 ("Electronic signatures"). The paraph can be drawn and added to a document only when validated software grants that operation.

MHRA operates with a pragmatic frame of mind, pointing to common situations that require special awareness when technology is used to manage critical information. Assigning system administrators functions to others presents opportunities for deception. Section 6.16 ("Computerised system user access/ system administrator roles") specifically says that granting system administrator rights to users involved with generation or consumption of data is not good practice.

Metadata Matters in GXP

As mentioned previously, the document highlights metadata extensively; the term appears 25 times within the text. Section 6.3 ("Metadata") defines it as the mechanism to provide meaning and context to raw data. Metadata is a useful tool to earmark the first "A" of ALCOA, permitting it to be attributable to an individual or to an automatic system that generates data. For instance, the audit trail definition explained in Section 6.13 ("Audit Trail") implicitly uses metadata as the instrument to include the "who, what, when and why" associated with the action that must be traced.

The four "W's" are information that most computerized systems provide automatically without human intervention. From an audit trail perspective, historical records can be easily recreated using the metadata by establishing relationships between the main thread and another event through their related contexts. Generated metadata then becomes an inextricable part of the raw data. There is a fifth "W," representing the "where" attribute, that the guidance does not mention but is supplied by many current software applications. Knowing where the data has been generated is convenient metadata that gives geolocation wrapping to the raw information, better closing the circle to secure the data and its governance.

Metadata, therefore, must be accepted as a crucial part of each generated record in

pharmaceutical manufacturing. Considering that a medium biotech/pharma site produces between 500 terabytes and 10 petabytes per year, this new technology provides enough power to efficiently process this amount of information ***(5).*** The cloud has become a natural solution to managing this massive amount of data. In Section 6.20 ("IT Suppliers and Service Providers"), the guidance introduces cloud providers and the formula XaaS (Infrastructure, Platform and Software as a Service) as valid computerized systems to manage regulated information under the principles and recommendations included in the document. In the same way as a traditional software provider, "as a Service" suppliers must harmonize their offers with a Service Level Agreement according to the GXP requirements. Interestingly, these kinds of services are delegating more responsibilities to cloud providers than to the client. Aspects such as backup, archiving, data retention, data retirement or security (all considered in the MHRA guidelines) are easily offered as a service. The framework that allows cloud providers to offer these specialized services allows industry to focus more on data integrity expertise than the infrastructure.

The MHRA data integrity guideline offers an actual GXP vision about the direction that should be taken when relying on existing technology.

[Editor's Note: This is a follow-up to the author's article published in the July/August issue**.]**

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5. GxP and non GxP data volume generated by medium size pharmaceutical sites that are stored in the bigfinite big data platform as of April 2018.

About the Author

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

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Drug Delivery Combination Products Go "Viral"

Lee Leichter, P/L Biomedical

Twenty-eight years ago, the term "combination products" was coined and defined in the U.S. Federal Food, Drug, and Cosmetic Act. Since then, the U.S. FDA has progressed slowly in the amount of guidance for these products.

Publication of the draft rule on combination product GMPs in 2009 should have served as a wake-up call that drug delivery products were going to be addressed more than in the past. With the publication of the Center for Devices and Radiological Health (CDRH) draft guidance on human factors for medical devices seven years ago, medical device requirements were expected to be implemented for drug delivery products, even if submitted in an NDA or BLA.

Over the past five years, an explosion of new requirements has occurred as has an unprecedented expansion in the scope of products covered. From standalone software to smart packaging new types of products have entered the pharmaceutical market. With these, are new regulations, such as the EU Medical Device Regulations. This intrusion ("infection") of new products and requirements has made for an increasingly complex market. Hence, the indication that drug delivery combination products have gone "viral."

Join invited FDA and EU regulators and industry experts from across the drug-delivery device development spectrum at the *2018 PDA Combination Products Workshop* following the *2018 PDA Universe of Pre-filled Syringes and Injection Devices* conference in discussing matters related to this expansion. Topics include connected health, generic and biosimilar combination products, new technologies, post-marketing requirements and globalization, among others. Sessions will feature two presentations followed by a panel discussion.

2018 PDA Combination Products Workshop

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13th Annual PDA Global Conference on Pharmaceutical Microbiology

A Wealth of New Micro Regulations

Michael Miller, PhD, Microbiology Consultants

The regulatory framework for pharmaceutical microbiology is at a crossroads. Novel technologies present challenges when it comes to their regulation. Cell and gene therapy products. Alternatives to in vivo testing. Alternatives to the LAL assay. Rapid microbiological methods. The list goes on.

Recent regulatory changes to address new technologies include EU Annex 1. In addition, the European and U.S. pharmacopeias are revising chapters covering microbiology. With new technologies and changing regulatory standards, where can those involved with pharmaceutical microbiology, whether on the floor or in the lab, in a company or in a regulatory agency, debate and discuss these changes?

Consider attending the *13th Annual PDA Global Conference on Pharmaceutical Microbiology* in the United States or the *PDA Europe Pharmaceutical Microbiology* conference. This year's conference promises special highlights with selected sessions simulcast live between the two conferences.

Current industry practices associated with microbial contamination control, aseptic manufacturing strategies, data integrity, endotoxin challenges, mycoplasma detection and the implementation of alternative and rapid microbiological methods are just a few of the issues that will be addressed. Aspects of manufacturing and the associated strategies for microbiological control, including gene and cellular products, vaccines and other therapeutic and prophylactic medicines, will also be featured in the joint conference program.

13th Annual PDA Global Conference on Pharmaceutical Microbiology and PDA Europe Pharmaceutical Microbiology conference

Bethesda, Md. and Berlin
Oct. 15–19
www.pda.org/2018micro
www.pda.org/eu/pharmamicro

India Chapter Goes into the Cold continued from page 13

Attendees liked the fact that presenters were open to discussing controversial issues instead of focusing solely on the positives. One attendee, a senior manufacturing executive, stated that the "topics were current and the speakers knowledgeable. I can take the knowledge gained back to work right away."

This event was sponsored by Tofflon as a silver sponsor and Grover International and West Pharma provided exhibits.

Revised USP Micro Chapters Address Changing Technologies continued from page 28

studies, a general chapter will be developed and published in a future *Pharmacopeial Forum* for public comment.

B. cepacia Complex

B. cepacia complex (BCC) species are gram-negative, rod-shaped bacteria that include opportunistic pathogens. Many grow in preserved aqueous oral liquids and topical products and can potentially overcome antimicrobial preservative systems and antiseptics, possibly causing serious infections in individuals with cystic fibrosis and chronic granulomatous disease, mechanically ventilated patients, the immunosuppressed and those with serious underlying disorders. No standard method exists, however, for the detection of BCC even though they are considered an objectionable species in many dosage forms. To meet this critical need, the Expert Committee has developed a general chapter, also proposed in the September-October 2018 issue of *Pharmacopeial Forum*, USP <60> Microbiological Examination of Nonsterile Products—Tests for Burkholderia Cepacia Complex, that includes a method to test for the presence of BCC.

Conclusion

USP is committed to continuous revision and improvement of its standards and values the input of users in the field. Indeed, this input is critical to the success, not only of USP, but also of the industry as a whole. Stakeholder feedback helps to ensure that USP's standards are sufficiently comprehensive in application and scope, reflecting current practices in industry. Thanks to this feedback, the Microbiology Expert Committee hopes that planned revisions of the microbiology chapters address the concerns of those involved in pharmaceutical microbiology.

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2. USP Modern Microbiological Methods Expert Panel, 2017 Stimuli to the Revision Process: The Development of Compendial Rapid Sterility Tests. *Pharmacopeial Forum* 43 (5) Sept.-Oct. 2017

About the Authors

David Hussong is the Chief Technical Officer at Eagle Analytical Services. In 2014, he retired from the U.S. Public Health Service as a Commissioned Corps Officer after 30 years with FDA. In addition, he is currently the chair of the USP Microbiology Expert Committee for the 2015–2020 cycle.

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Edward C. Tidswell, PhD, is Executive Director, Microbiology QA for Merck & Co. with global ownership over microbiological issues, sterilization and sterility assurance.

Donald Singer is a GSK Senior Fellow and Manager of Microbiology for Biopharmaceutical GMP Operations at GSK Research and Development, where he has oversight of microbiology for all sterile clinical products in development.

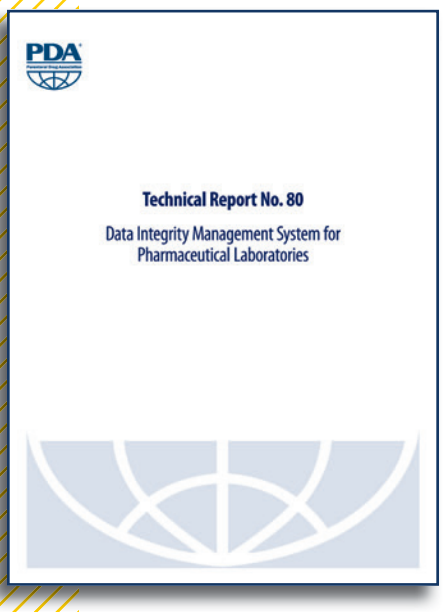
New TR Addresses DI in the Lab

Anil Sawant, PhD, Merck

Data integrity, a multifaceted issue, continues to be in the news and remains a top concern among regulators worldwide. Just recently, Chinese regulators found a local vaccine manufacturer fabricated production and product inspection records. We have heard these kinds of stories—which should not be tolerated in our industry—from various regulators around the globe.

We in the pharma industry have an obligation to engage in behaviors and practices that ensure all stakeholders can trust that decisions are based on information that is accurate, truthful and complete. In 2016, PDA published a voluntary Code of Conduct for Data Integrity to help ensure our moral compass is always pointed toward our patients. The Code of Conduct has been downloaded over 5,000 times since its launch and is now considered a useful resource by regulators.

I choose "multifaceted" to describe data integrity because, beyond the black and white issues of malintent and malfeasance, data integrity issues can also occur when interpreting GMPs written during a time of paper-based operations in an age of digital technology. Applying ALCOA (attributable, legible, contemporaneous, original and accurate) principles to rapidly evolving technologies can be confusing, especially to less technology savvy individuals. To create awareness and expand understanding, members of the PDA Data Integrity Task Force conducted workshops in Washington, D.C., London, Berlin and San Diego in 2016. As the colead of the task force, I had the privilege to hear PDA members voice their concerns, questions and frustrations firsthand. Some of these burning questions were addressed in the PDA "Points to Consider: Best Practices for Document/Data Management and Control and Preparing for Data Integrity Inspections," available in the *PDA Journal of Pharmaceutical Science and Technology.* Other more technical aspects are being included in technical reports.



As the colead of *Technical Report No. 80: Data Integrity Management System for Pharmaceutical Laboratories,* I am proud to announce the launch of this important document, written by subject matter experts from industry, the U.S. FDA and consulting firms. The technical report summarizes potential data integrity risks in microbiology and chemistry laboratories, providing best practices for preventing and mitigating these risks. The report is written for individuals who may not be well-versed in computer technology but are expected to understand its pitfalls and controls. Relevant regulatory requirements and expectations are also included.

I encourage PDA members involved with both microbiology and chemistry laboratories to download the document. It can be accessed in the PDA Bookstore (www.pda.org/bookstore).

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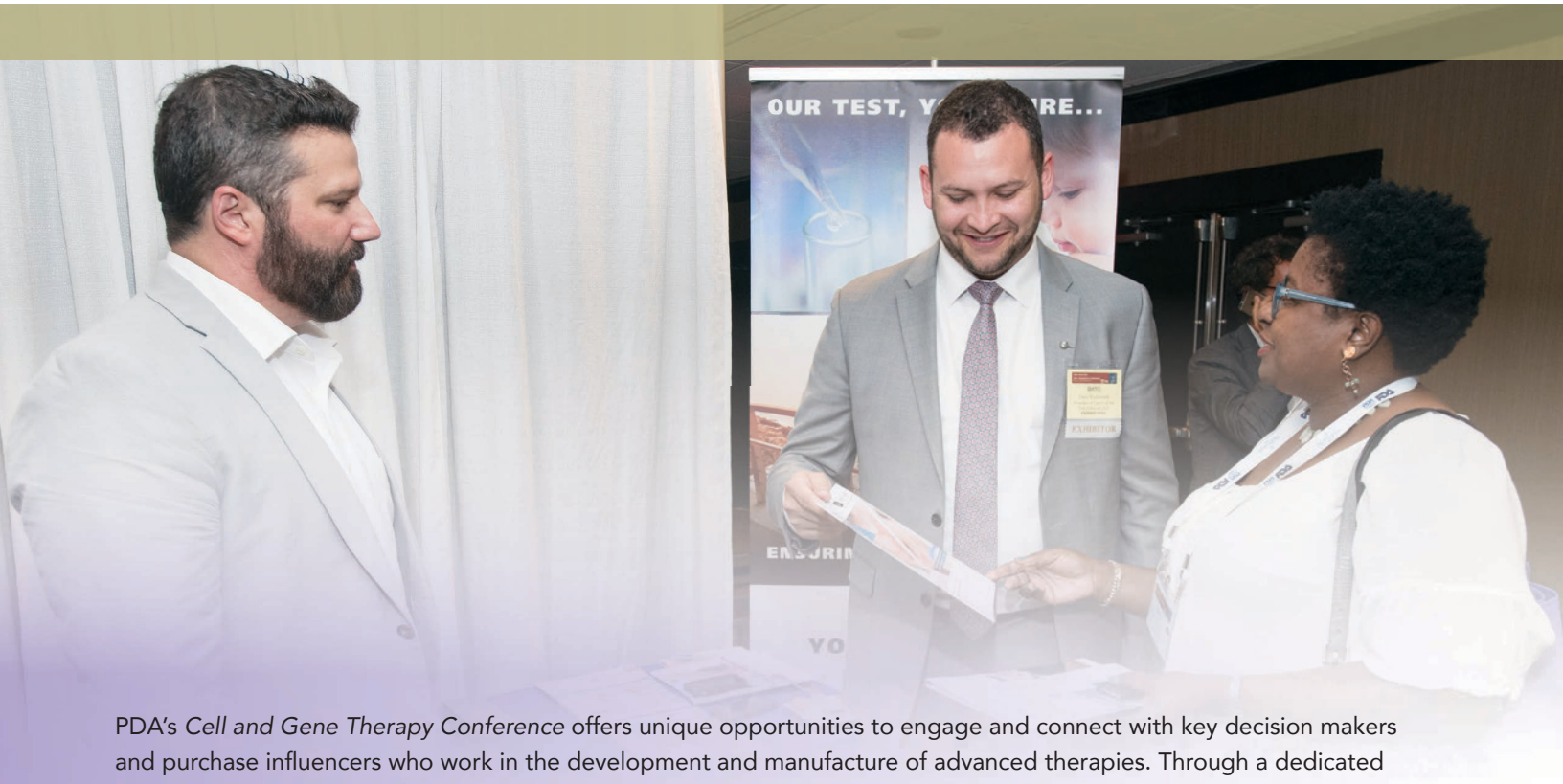

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