People • Science • Regulation

# PDA Letter

Volume LII • Issue 7 www.pda.org/pdaletter July/August 2016

## PDA/FDA JOINT REGULATORY CONFERENCE

# 25TH ANNIVERSARY

1991-2016

## PDA Celebrates 25 Years of Industry, FDA Collaboration 28

# 2017 PDA Annual Meeting

*Manufacturing Innovation: The Next Wave of Sterile and Biopharmaceutical Science, Technologies and Processing*

**April 3-5, 2017 | Anaheim Marriott | Anaheim, CA**

Exhibition: April 3-4 | Post-Meeting Workshop: April 5-6 | Courses: April 6-7

## CALL FOR POSTERS / CASE STUDIES

The Program Planning Committee encourages you to submit an abstract for a one-day poster presentation at the *2017 PDA Annual Meeting*. Case studies are particularly desired. Abstracts must be non-commercial, describe industry developments, strategies or practical implementation, and contribute to the current body of knowledge for biopharmaceutical manufacturing, quality management and technology. Abstracts related to novel manufacturing and analytical technologies are preferable, but those addressing other bioprocessing topics are welcome.

Suggested topics include, but are not limited to:

**Advances in Analytical Sciences & Quality Control Strategies**

- Human Error Prevention
- Process Capability Improvements
- Process Monitoring Plans
- Process Validation/ Lifecycle Approach
- Managing Supply Chain
- Shipping Validation
- Technology and Knowledge Transfer
- Microbial Control Program
- Control Strategy Design
- Quality by Design
- Process Analytical Technology
- Single-Use Bioprocess Technology and Validation
- Cell Line Development
- Cell Culture Systems and Expression Rates
- Continuous Bioprocessing
- High Throughput Analytical Methodology and Automation

**Developments in Patient-Centered Precision Medicine**

- Quality Metrics
- Drug Shortages
- Supply Chain Security (Serialization, Track and Trace, Counterfeit)
- ICH Q12
- Post-approval Change Management and Comparability
- Breakthrough Therapies
- Combination Products
- Managing Data Integrity Risks
- Patient Perspective
- Internet of Things (IoT)
- Science & Risk-Based Approach
- Automation & IT
- Biosimilars

**Next Generation Manufacturing**

- Aging Facilities
- Challenges in Manufacturing
- Single Use Systems Technology
- Emerging Methods for Adventitious Agents Detection and Clearance
- Viral and Microbial Contamination in Biopharmaceutical Manufacturing: Risk Mitigation, Preparedness and Response
- Pharmaceutical Package Integrity Testing: Industry Challenges, Technology and Advancement
- Bioprocess Upstream and Downstream Technology
- Continuous Manufacturing
- Flexible Processes and Facilities
- Biopharmaceutical Fill-Finish
- Robotics
- Drug Delivery Systems
- Anitbody Drug Conjugate (ADC)
- Personalized Medicine
- Formulation & Filling Technology

## ABSTRACTS MUST BE RECEIVED BY OCTOBER 3, 2016 FOR CONSIDERATION.

The committee may also consider abstracts for an oral presentation. (If a slot is available)

Visit **www.pda.org/2017AnnualMeetingCfP** to submit an abstract

Submitting an abstract confirms that an individual has received their company's required approval to present if selected. Submitters will be advised in writing of the status of their abstract **by November 3, 2016.** To confirm participation and be listed in the final program, poster presenters are required to register as a **paid full conference** attendee at the rate of $1,895 member/$2,154 nonmember no later than **January 19, 2017.** After January 19th, poster presenters are required to pay the prevailing registration rate and will be listed in the online program agenda**. Companies with multiple accepted posters are required to register a different individual for each display at the paid full conference rate. *(Only one presentation per individual will be accepted)***

***ATTENTION EXHIBITORS:*** Registrations included with exhibitor packages are not eligible to present a poster. Exhibitors are required to register as a paid full conference attendee to present a poster.

**Each abstract must include the following information to be considered:**

- Full Name
- Professional Title
- Company
- Mailing Address
- Email Address
- Phone Number
- Biography *(Max 200 words)*
- Abstract Overview *(Max 200 words)*
- Abstract Title *(Max 50 words)*
- Abstract Objectives *(Max 100 words)*
- Audience Take Home Benefits *(Max 100 words)*

**QUESTIONS?**

Contact:
**Wanda Neal**
Senior Vice President
Programs & Registration Services
Tel: +1 (301) 656-5900 ext. 111
Email: neal@pda.org

**ABSTRACT REVIEW**

All submitted abstracts will be reviewed by the Program Planning Committee for inclusion as a poster or podium presentation. (If a slot is available)

**www.pda.org/2017Annual**

**ATTENTION EXHIBITORS**

PDA is seeking vendors who provide excellent products/services in support of this conference. Space is limited and is on a first-come, first-served basis. To reserve your space, please contact **David Hall** at hall@pda.org or +1 (301)656-5900 ext.160

*The Parenteral Drug Association presents the...*

# 2016 PDA/FDA Joint Regulatory Conference

*Celebrating 25 Years of Shaping Global Regulatory Strategy*

**September 12-14, 2016 | Washington, DC**

Renaissance Washington, DC Downtown Hotel

**#2016PDAFDA**

## Conference Theme: *Aligning Manufacturing Goals with Patient Needs through Successful Innovation and Compliance*

Continuing a long tradition of collaboration with the common goal of improving the quality of medical products for the public and educational opportunities for the medical products industries, the *2016 PDA/FDA Joint Regulatory Conference* will feature more than 20 sessions highlighting the current challenges and opportunities regarding product quality, science and innovation, and lifecycle management.

For the 25th straight year, this Conference will give you unparalleled access to FDA regulators and industry experts who will enhance your understanding of the implications, expectations and requirements of new regulatory programs. It will also advance efforts toward regulatory harmonization, regulatory science policy and current Good Manufacturing Practices.

Paying homage to this long collaboration between PDA and the FDA, this year's event will also take a retrospective look back on the last 25 years and look ahead to the potential challenges industry may face, the implementation of changes keep up with new technology.

***Be a part of a tradition of excellence! To learn more and to register, visit pda.org/2016PDAFDA.***

Immediately following the Conference, **Sept. 14-15**, PDA will host the *2016 PDA Data Integrity Workshop*. At this Workshop, you'll learn best practices to identify, prevent and remediate issues related to data integrity through interactive case studies, presentations and breakout sessions.

***To learn more and to register, visit pda.org/2016DataEast.***

And, on **Sept. 15-16**, PDA Education will host six courses to complement what you learned at the Conference.

***To learn more and to register, visit pda.org/2016PDACourses.***

**Register by August 2 and save up to $200**

PDA Letter

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# Cover




*Cover Art Illustrated by Caroline Cruz Design*

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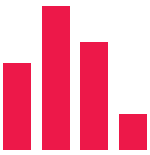




*Articles published in the PDA Letter do not represent the official positions of PDA, Inc., but are the opinions of the authors submitting the articles.*

# PDA HQ Moves, TRI Opens New Lecture/Lunch Rooms

PDA was on the move this spring. With a growing staff and growing course agenda, PDA had outgrown its office space on the second floor and its lecture space on the first floor of Bethesda Towers. There were three options for fixing this "aging facility" problem: move to another building, redesign the existing spaces, or take over new space in the same building.

PDA opted for the third option as the most cost effective and the one least disruptive to operations. And it just so happened that the entire sixth floor of Bethesda Towers and additional space on the first floor became unoccupied at the end of 2015.


In only four short months, the new spaces were redesigned and ready for operation. The move occurred during the U.S. Memorial Day weekend in May, and services to our members were not disrupted at all. Shortly thereafter, PDA sponsored an all-day meeting of the Visual Inspection Interest Group on May 18 in the new classroom.

During the *PDA/FDA Joint Regulatory Conference* in September, PDA will host an invitation-only open house at the new offices, but PDA members can always stop by the office and the Training and Research Institute whenever they are in the Washington, D.C. area.

# 25 for 25: Silver Anniversary Draws 25+ FDA Speakers

More than 25 U.S. FDA regulators are lined up to speak at this year's *PDA/FDA Joint Regulatory Conference*—a record number for this meeting, which celebrates its 25th anniversary this year.

"For 100 years, U.S. FDA regulations have been a central consideration in manufacturing pharmaceutical products for the U.S. market, and around the world. Over the last 25 years, the *PDA/FDA Joint Regulatory Conference* has grown into the key forum for manufacturers around the world to learn how to navigate these requirements," said PDA President **Richard Johnson.**

The conference will mark its 25th anniversary with a mix of presentations by FDA officials and high-level pharmaceutical and biopharmaceutical leaders.

The FDA offices that will be represented at the meeting are:

- Office of the Commissioner
- Center for Drug Evaluation and Research
- Center for Biologics Evaluation and Research
- Center for Veterinary Medicine
- Center for Devices and Radiological Health
- Office of Regulatory Affairs

**Peter Marks,** MD, PhD, Director, CBER, recently confirmed his participation as the keynote speaker.

In addition, **Paul Hargreaves,** Principal Medicines Inspector, Enforcement & Standards Division from the UK regulator, MHRA, will present on PIC/S in the concurrent session, "International Efforts," Sept. 12 at 1:30 p.m.

# PDA Volunteer Spotlight

## Andrew C. Chang, PhD

- Vice President, Quality and Regulatory Compliance, Product Supply Quality
- *Novo Nordisk A/S*
- Member Since | 2008
- Current City | Washington, D.C.
- Originally From | Huangshan City, China

*My involvement has helped me expand my scientific knowledge*

*Andrew likes to golf in his spare time*

**You worked on the recently published *Technical Report No. 74: Reprocessing of Biopharmaceuticals.* Can you describe the experience?**

I worked with an excellent team on this technical report, and all of us are very pleased with how it turned out. I took two lessons from this process. First, it is important to establish the objectives/goals and the scope up front. Second, it helps to have a dedicated team member serve as the project manager to lead and drive the project forward.

**Why do you attend the *PDA/FDA Joint Regulatory Conference?***

The *PDA/FDA Joint Regulatory Conference* provides a forum for the U.S. FDA and its regulated industries to discuss the current hot topics related to quality, manufacturing and cGMP compliance. I have personally benefited by gaining additional knowledge on these topics and awareness of the FDA's focus areas, industry trends and best practices. It is also an excellent place for networking.

**What have you gained from your PDA membership?**

I have been a member of PDA since my previous job as a product reviewer and cGMP inspector at CBER. My involvement has helped me expand my scientific knowledge and build my professional network.

**What drives you to succeed?**

Developing and assuring a steady supply of innovative and high-quality medicines to patients worldwide motivates me to succeed in this industry. At Novo Nordisk, we are striving to defeat diabetes and other serious conditions like hemophilia, growth disorders and obesity. We seek to discover and develop better medicines, manufacture them to meet increasing global demand and make them accessible wherever they are needed.

**What's something not many know about you?**

I enjoy teaching and have provided lectures/training on regulation of biologics for Austria's University of Applied Sciences and China's Peking University.

*The Parenteral Drug Association presents the...*

# 11th Annual PDA Global Conference on Pharmaceutical Microbiology

***Advancing Quality and Safety through Sound Science***

**October 24-26, 2016 | Arlington, VA**

**Hyatt Regency Crystal City**

Exhibition: October 24-25 | 2016 PDA Workshop: Current Challenges in Aseptic Processing, Potential Changes in EMA/PIC/S Annex 1 Revision: October 26-27 | Courses: October 27-28

#2016Micro

**Register before August 11 and save up to $600**

## Conference Theme:
## *Microbial Control: Key to Product Quality and Patient Safety*

At the *11th Annual PDA Global Conference on Pharmaceutical Microbiology*, a distinguished line up of academic, industry and regulatory speakers will share industry experiences, discuss current developments regarding standards and best practices to integrate innovative technologies in today's global market.

Plenary, concurrent and breakfast sessions will explore the following topics:

- **Data Integrity and Compliance**, examining environmental monitoring and laboratory analysis, where reliable data is necessary to support clinical trials, product development and manufacturing.
- **Quality Systems in Microbiology**, developing a strategy for controlling microbial contamination and addressing issues that occur when there is a failure in your microbial quality system.
- **Contamination of a Non-sterile Aqueous Product: A Case Study**, presenting lessons learned from an actual case of non-sterile aqueous product contamination, emphasizing how the FDA and industry collaborated to resolve the problem.

***To learn more and register, please visit pda.org/2016Micro.***

On **Oct. 26-27**, PDA will host the *2016 PDA Workshop: Current Challenges in Aseptic Processing, Potential Changes in EMA/PIC/S Annex 1 Revision* in Arlington, VA. Industry and regulatory professionals will discuss the interpretation of applicable regulations for aseptic processing and explore science- and risk-based approaches that support modern aseptic processing and control strategies.

***For additional information and to register for this Workshop, please visit pda.org/2016Annex1East.***

From **Oct. 27-28**, PDA Education will hold the *11th Annual PDA Global Conference on Pharmaceutical Microbiology Course Series*, which offers four continuing education courses on important pharmaceutical microbiology topics.

***To learn more and register, please visit pda.org/2016mMicroCourses.***

Tales from the Trail

# Speakers Offer EM Insights at Chapter Symposium

**Rebecca Stauffer, PDA**

June 1 marked the first bright, sunny day for many of us on the U.S. East Coast following a rainy May. It also marked the PDA Metro Chapter's 11th annual Day Symposium, *Microbial Monitoring 2016: Environment, Materials and Utilities*. So it only made sense for me to emerge from my soggy office and travel to New Jersey to hear the latest on this topic, enjoy the sunlight, and "get out there and talk to" members of the Metro Chapter.

Considering the overabundance of water on the East Coast in the spring, it was only fitting that the symposium began with **Andrew Collentro's** talk on the importance of microbial monitoring and control for pharmaceutical water systems. Collentro stated that a comprehensive monitoring and control strategy is best, and he advocated for systemic microbial monitoring versus point-of-use monitoring alone.

While reviewing intermittent and continuous water sanitation methods, Collentro predicted ozone would become more popular. He cited not only its "strong history" in other industries, but also changes coming to the *European Pharmacopoeia* in 2017 for WFI. He also touted ozone's short sanitation cycle and the ability to automate and verify results online as other benefits.

Next, **Christine Massaro** offered recommendations for working with high-risk raw materials and finished products. She emphasized the importance of clear communication with vendors and other external partners.

"Get out there, talk to them," she emphasized. "They may be able to get you what you want."

Asking the right questions can uncover a wealth of information about the vendor's approach to environmental monitoring, Massaro said. She frequently delves into a vendor's ability to control bioburden with questions on equipment capability, how qualification runs are conducted for bioburden reduction, and about the process water history.

Following her talk, attendees could "get out and talk" to a number of vendors who were on hand as sponsors of the meeting.

The next session featured Chapter Secretary **Anthony Grilli's** discussion of control considerations for nonsterile

products, which can be something of a challenge due to the wide variety of dosage forms involved and the variable level of concern for different microorganisms.

"Some organisms are more objectionable than others" when it comes to nonsterile products, he explained.

To appropriately sample the environment of nonsterile processes, thorough knowledge of the product, process and risks is required.

Next, **Mousumi Paul** provided a case study on implementing rapid microbial methods in the QC lab. Her group has found success using Lumibyte's MuScan solution for rapid detection of microorganisms. She said that a key lesson from the project is that companies in the industry need to work together to expand acceptance of noncompendial methods.

After lunch, **Karen Zink McCullough,** Vice President of the USP Microbiology Expert Committee, gave an overview of changes to USP chapters covering endotoxin and pyrogen testing. Notably, <151> Pyrogen Test, has been changed to allow for a validated equivalent in vitro pyrogen or bacterial endotoxin test to be used in place of the in vivo rabbit pyrogen test, if appropriate.


McCullough's fellow USP Microbiology Expert Committee colleague **James Agalloco** then offered a holistic overview on the nature of environmental monitoring. He encouraged attendees to avoid viewing monitoring as the same as control and to "respect that microbial control is provided by everything other than monitoring."

A Q&A panel featuring all the speakers served as the conclusion of the meeting. Quite a few attendees probed the panel for their thoughts on low endotoxin recovery (LER), proving this remains a hot topic within the industry.

Stepping out into the bright sunlight afterwards, I reflected that the day's talks served as a ray of sunshine, brightening my knowledge of microbiology and environmental monitoring. And I also

*Continued at bottom of page 13*


**P1: Current Agency Expectations for Approval for Biosimilars**
(l-r) Vincent Anicetti, Coherus Biosciences; Steven Kozlowski, MD, CDER, U.S. FDA; Christopher Holloway, PhD, ERA Consulting; Thomas Gwise, PhD, CDER; Yi Tsong, PhD, CDER

Program Planning Committee member Michael VanDerWerf (center) talks with PDA's Josh Eaton (left) and PDA President Richard Johnson (right)

**P2: Establishing QTPP for Biosimilars**
(l-r) Margaret Karow, PhD, Amgen; Michael VanDerWerf, Teva; Corinna Sonderegger, PhD, Sandoz

**P3: Demonstrating Analytical Similarity**
(l-r) Marjorie Shapiro, PhD, CDER; Barry Cherney, Amgen; Alan Herman, PhD, Coherus Biosciences

**P4: Additional Practical Considerations for Analytical Similarity**
(l-r) Marjorie Shapiro, PhD, CDER; Harry Yang, PhD, MedImmune; Jose Gomes, Pfizer; Alan Herman, PhD, Coherus Biosciences

# Make New Connections at the *2016 PDA/FDA JRC*

They'll be a lot of invigorating talks at this year's *PDA/FDA Joint Regulatory Conference.* You'll probably find yourself bubbling with excitement at the end of a session or two, eager to discuss what you just learned with anyone available and willing to chat. Previous conferences have found the hallways and conference rooms abuzz with conversation about previous sessions as well as anticipation about the next set of talks.

So, PDA invites you to take advantage of the following networking opportunities to meet up with old colleagues as well as make new connections with others in the industry.

### Orientation Breakfast

Monday, Sept. 12, 7–8 a.m.

Are you a new PDA member? Or are you an established member looking to get more involved with PDA? New PDA members can learn more about the Association from PDA's membership team and volunteer leaders while more established members can learn about exciting new opportunities to get involved with PDA—all over a hot breakfast before the start of the conference.

### Networking Reception

Monday, Sept. 12, 6:45–8 p.m.

As a conference attendee, you're invited to attend a networking reception in the Exhibit Area and chat with exhibitors and other attendees. Refreshments will be provided.

### Red, White and Blues Celebration

*(supported in part by FDAzilla)*

Tuesday, Sept. 13, 7–9:30 p.m.

Let's hope the only blues you experience are at our Red, White and Blues Celebration! Music and refreshments will be provided at this shindig celebrating the 25th anniversary of the *PDA/FDA Joint Regulatory Conference.*

There will also be additional opportunities for networking during refreshment breaks throughout the conference.

*Tales from the Trail continued from page 11*

thought of Massaro's words to "get out there, talk to them," and how those could also refer to chapter events. So, I hope you get a chance to "get out there" to your local chapter's next event.

**[Editor's Note:** Karen Zink McCullough will present USP's perspective on LER at PDA's microbiology conference on Oct. 26, in Arlington, Va.**]**

### PDA Who's Who

**James Agalloco,** President, Agalloco & Associates

**Andrew Collentro,** Water Consulting Specialist, WCSI

**Anthony Grilli,** Consultant, Focus Scientific

**Christine Massaro,** Johnson & Johnson

**Karen Zink McCullough,** MMI Associates

**Mousumi Paul,** Associate Director, Engineering Technology Integration, Merck

## Meeting *Preview*

### Interest Group Meeting Schedule

To supplement the regular sessions, a number of PDA Interest Groups gather at the *2016 PDA/FDA Joint Regulatory Conference.* Below is a schedule of interest group sessions falling under the Science and Biotechnology Advisory Boards.

| Monday, September 12 | Tuesday, September 13 |
|---|---|
| 5:30 p.m. – 6:45 p.m. | 5:30 p.m. – 6:45 p.m. |
| Lyophilization Interest Group | Biotechnology Interest Group |
| Sterile Processing and Microbiology/Environmental Monitoring Interest Groups (combined meeting) | Visual Inspection of Parenterals Interest Group (combined with GMP Links to Pharmacovigilance Interest Group) |
| Applied Statistics Interest Group | Combination Products Interest Group |
| Packaging Science Interest Group | Process Validation Interest Group |
| | Facilities and Engineering Interest Group |

# Survey Says…Check Out PDA's Portfolio of Surveys

**Morgan Holland, PDA**

You may have noticed that in addition to our portfolio of technical reports, Points to Consider papers and books, PDA also publishes surveys. In fact, our most recent survey, *2015 Particulate Matter in Difficult to Inspect Parenterals,* was published in May. You may even have wondered how PDA conducts these surveys that contain a lot of useful data about our industry.

PDA surveys are data gathering tools used to collect information from within PDA's membership and the public at large. Surveys may focus on collecting information about individuals or opinions/expertise on a particular topic from PDA's audience. Surveys are one of the research tools that PDA uses to gather data in general and to describe naturally occurring trends or anomalies. These surveys are mostly conducted online, but we conduct surveys using other methods as well. The method chosen depends on the topic of the survey and the demographics of the intended respondents.

PDA conducts these surveys to assess the state of the industries we serve. We explore such topics as regulatory science, quality, analytical methods, manufacturing site operations and processes for pharmaceuticals and biotechnology products. Benchmarking surveys help give PDA the added benefit of understanding the state of these various industries as well as the employable labor force available for various industries. Often times, these surveys are used to supplement PDA technical reports and/or workshops. Published surveys can be found in the PDA bookstore and are available for free download to PDA members within the first 30 days of publication.

We also measure PDA member satisfaction with the help of surveys. Membership satisfaction, dedication and participation are extremely important to PDA. These surveys are research tools used to gain information, from PDA's members. Membership surveys offer an outlet for members to give candid, applicable feedback. These types of surveys are conducted as needed so PDA can maintain up-to-date information of the needs of its members so we can better serve them.

Every industry has its shares of difficulties; a well-built survey can help detect possible obstacles. Through analysis of our surveys, PDA can help foresee probable obstacles and help contribute to contingency plans. When applicable, PDA translates the results into actions that benefit PDA's members and the public alike. PDA surveys can help reduce decision-making risks and increase customer service to its members, fulfilling the professional needs of and bringing additional value to PDA members.

# SAB Supports PDA Interest Group Initiative

**Jahanvi (Janie) Miller, PDA**

PDA's Science Advisory Board (SAB) continues to show support for the interest groups falling under the SAB umbrella. Out of 21 PDA interest groups on the PDA Connect℠ site, the majority fall under SAB. This is at a time when PDA's Advisory Boards are undergoing a major initiative to expand support for their corresponding interest groups.

For the first phase of this initiative, PDA's Advisory Boards must ensure that all interest groups are live on PDA Connect℠ by the end of 2016. The second phase entails expanding leadership opportunities available for interest group members. During the second phase, all interest groups must implement succession policies. PDA's Advisory Boards will continue to support the activities within the interest groups to ensure the members are abreast of industry activities and challenges as well as engaged with PDA initiatives.

PDA interest groups serve as a major source for many PDA activities. Members of interest groups also contribute to PDA conferences and workshops by offering subject matter expertise and exchanging current industry practice, institutional research, ideas and information on global standards. Interest group activities are overseen by the Advisory Boards. Deliverables from these activities include PDA technical reports, Points to Consider documents, surveys, and PDA comments on draft regulatory guidance or regulatory comments.

To get involved in a PDA interest group, visit PDA Connect℠ or attend one of the interest group meetings scheduled for this year's *2016 PDA/FDA Joint Regulatory Conference* (see p. 14 and p. 48 for the schedule of interest group meetings).

## Journal *Preview*

### July/August Issue of PDA Journal Explores the Latest Research on CCIT, Virus Filtration, Packaging and More

For the latest research spanning container closure integrity testing to virus filtration, check out the latest issue of the *PDA Journal of Pharmaceutical Science and Technology.*

*Research*

"Artificial Leaks in Container Closure Integrity Testing: Nonlinear Finite Element Simulation of Aperture Size Originated by a Copper Wire Sandwiched between the Stopper and the Glass Vial"

"Virus Filtration and Flow Variation: An Approach To Evaluate Any Potential Impact on Virus Retention"

"Hydrolysis of Polysorbate 20 and 80 by a Range of Carboxylester Hydrolases"

"There Is Still Room for Improvement: Presentation of a Neutral Borosilicate Glass with Improved Chemical Stability for Parenteral Packaging"

"Real-Time Neutron Imaging to Detect Origin of Blocking in Drug Injection Devices"

"A Spectral Method for Color Quantitation of a Protein Drug Solution"

*Technology/Application*

"Validation of a Spectral Method for Quantitative Measurement of Color in Protein Drug Solutions"

*Commentary*

"A Biopharmaceutical Industry Perspective on the Control of Visible Particles in Biotechnology- Derived Injectable Drug Products"

2015 PDA Europe
The Universe of Pre-filled Syringes & Injection Devices
*Published online first

# Another Step Toward Injection-Free Drug Delivery

**Rebecca Stauffer, PDA**

*During last year's* Universe of Pre-filled Syringes and Injection Devices *conference in Vienna,* ***Stefan Henke,*** *PhD, Managing Director, Innovative Injektions-Systeme (IIS) talked with the* PDA Letter *about the company's Needle Free Injection (NFI) system that uses high speed jets to deliver medicine to the patient.*

***PDA Letter:*** During your presentation, you listed the requirements for your Needle Free Injection (NFI) product: sterile, tailor-made, single-use—that's a lot of requirements. It must be really challenging to manufacture. For the manufacturing process, how do you factor in all these requirements

**Henke:** Well, first of all, we have an aseptic area—a GMP clean room with an isolator—where we manufacture. This needle free injector is built out of 15–20 parts. And all these parts come from special suppliers. We have to make sure the primary container is sterile, of course, and particle-free.

As for the sterile drug chamber for the first Module. We fill the liquid in the isolator into the chamber. Then we put a stopper in it and also a cap to protect this chamber and to keep it sterile. The challenge is that we also cannot have any air bubbles in the chamber because air absorbs the energy of the spring.

Then we put the second module into a Class D room. There, we combine Module 2 with Module 1 (**Figure 1**). The whole filling process occurs in an isolator where we can produce several hundred. Of course, ultimately, we want to produce the product in the thousands.

***PDA Letter:*** Can your device accommodate any injectable product?

**Henke:** It is a unique thing because we cannot predict if every compound is suitable for the same configuration. With the injection simulator, we can test it systematically in a lab and analyze all these configurations..

***PDA Letter:*** Are there any plans to market these simulator studies to other companies?

**Henke:** Yes, this is a target. We are open cooperation projects with other partners. This will require additional work such as human factors analysis, usability studies, etc.

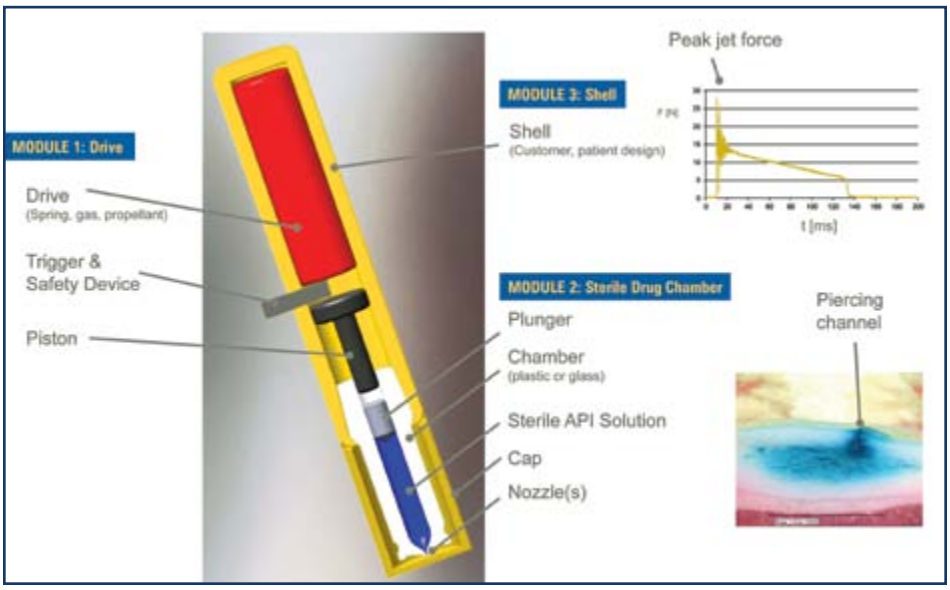
***PDA Letter:*** Has the NFI system been approved by regulators?

**Henke:** The GMP facility is approved in Europe but the whole system is not on the market yet. It's just a proof of concept.

***PDA Letter:*** Are you also seeking U.S. FDA approval?

**Henke:** Yes, of course. Our target markets are clearly in the United States, Europe, Japan and South Korea. We want to market the product initially in developed countries before taking it to the rest of the world.

**Figure 1** IIS NFI – Device




## About the Expert

**Stefan Henke,** PhD, has been Managing Director of IIS Innovative Injektions-Systeme GmbH & Co.KG, Andernach since 2010.

**solutions** | 4Tune Engineering

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# THE **NEXT** GENERATION **RISK** MANAGEMENT PLATFORM

## UNIQUE FEATURES

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Products, Equipment, Facilities and Supply-Chain Risks

Effectively establishing QRM

Knowledge-based FMEAs

## BECOME **FUTURE-READY** FOR A NEW REGULATORY LANDSCAPE

With the increased demands for risk-based decisions, companies need corporate solutions supporting Quality Risk Management throughout the lifecycle of their products. iRISK™ enables just that by applying the best principles and tools to ensure that your risk activities are aligned with FDA, GMP Annex 15, EMA and ICH guide-lines.

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> "Having all tools connected is extremely valuable for us, as well as the ability to monitor risks for different products and prioritize actions."
>
> Director, Large Biopharma (USA), 2016

4TUNE ENGINEERING
DO IT BETTER


# Are You Prepared for the Industry's Transformation?

**Michael De Felippis, PhD, Eli Lilly & Company, and Morten Munk, NNE Pharmaplan**

Understanding the causes of human diseases and finding life-changing treatments continue to be primary objectives of the pharmaceutical industry. Transforming this knowledge into quality medicines accessible to global patients, however, remains a huge challenge for both industry and regulatory authorities.

For decades, PDA has played a key role in confronting obstacles to progress. PDA is recognized as the premier professional organization promoting and sharing best practices on how to advance scientific and technological innovations across the pharmaceutical industry.

Through its flagship Annual Meeting, PDA provides a venue for obtaining the latest and most comprehensive information on a broad range of topics related to processing, manufacturing and quality control. Even more importantly, the Annual Meeting is a forum for sharing and demonstrating how industry is applying novel approaches to the development and commercialization of pharmaceutical and biopharmaceutical products.

Planning for the *2017 PDA Annual Meeting* is already in high gear. The committee of PDA volunteers entrusted with developing the scientific program has selected "Manufacturing Innovation: The Next Wave of Sterile & Biopharmaceutical Science, Technologies & Processing" as the overarching theme of the conference. In selecting this theme, the committee wanted to ensure an inclusive event that encompasses the wide ranging interests of all PDA members, covering relevant aspects of both the small molecule pharmaceutical and biopharmaceutical industries. Recognizing that the meeting is taking place in Southern California—a region of the country known for its innovation ecosystem and creative "out-of-the-box" thinking, the committee found it valuable to emphasize the crucial importance of novel approaches for bringing products to the market with a keen eye toward future trends in the industry.

The opening plenary session will focus on emerging therapeutic strategies along with a focus on the patient. Inspiring presentations remind everyone of the importance of the industry's work to develop medicines that improve quality of life, and in some cases, may even be lifesaving. Biopharmaceuticals continue to play an ever increasing role as treat-

ment options, and this is why the program includes a plenary session devoted to manufacturing and quality considerations for gene and cell therapies. Additional plenary sessions will emphasize manufacturing science and technology, and feature topics on next generation manufacturing and facilities, application of Big Data for process design and optimization, and accelerating the industry response to healthcare needs.

Concurrent sessions support the conference theme with emphasis on technology, science and processing. These focus areas form the basis of tracks that include topics related to advances in analytical sciences and quality control strategies, developments in patient-centered precision medicine, and next generation manufacturing. Presentations in these sessions will provide a deeper look at advances in these subjects that are shaping our industry now as well as in the future.

From the progress the organizing committee has made to date, there is no doubt that an outstanding program incorporating a diverse spectrum of timely and important topics is taking shape. Mark your calendars now as this will be the one meeting in 2017 not to be missed.

**2017 PDA Annual Meeting and PDA Education courses**

Anaheim, Calif.
April 3–7
www.pdaannualmeeting.org


Vacation season is here! And it is the perfect time to crack open a good book. In honor of this tradition, this issue of the *PDA Letter* includes an expanded "In Print" of recently published PDA literature. In addition, the Editorial Team found out what some PDAers (including recent *PDA Letter* authors) plan to read for fun in the next two months. References and graphics have been removed from the excerpts.

## Environmental Monitoring, Vol. 7

**Edited by Jeanne Moldenhauer**

abridged chapter *"Environmental Monitoring for Sterility Test Isolators"* by Claire Fritz Briglia

Isolators for sterility testing now have a long history of use and have definitely become the gold standard in the industry. The ability to perform the test in a completely closed HEPA filtered environment under positive pressure does undoubtedly reduce the risk of false positives. Isolators are also decontaminated with a vaporous chemical and typically validated with a biological indicator containing $10^6$ *Geobacillus stearothermophilus*. So, why would one need to perform environmental monitoring, if an isolator is so effective in reducing the risk of a false positive?

One reason why a comprehensive EM program is necessary for a sterility testing isolator is because there are notable limitations of the decontamination process. Even though a highly efficacious and validated decontamination cycle is used, it is only a surface process and is not equivalent to "sterilization" or autoclaving. Samples, media, rinse fluids, filters, etc., are all introduced into the isolator prior to testing and can cause contamination unless effectively decontaminated. A properly designed load for sterility testing will limit the amount of contact points but it is simply not possible to completely eliminate them. So, whenever there is a contact point in which the vapor cannot penetrate that surface, there is a risk of contaminating the test. In particular, bottles of media are often packaged in cardboard boxes which can contain bacterial spores. Thus, many users wipe down bottles with a sporicide for added safety factor. As an alternative, double packaged media and rinse fluids that have been terminally sterilized are commercially available.

Vapor concentration is a critical variable of the process. Vapor hydrogen peroxide is the most common method for decontaminating isolators but it is unstable and can readily decompose. As a result, the concentrations could be lower than what was validated and the amount of microbial kill could be variable. There have been cases where water was used in the decontamination system instead of hydrogen peroxide because it was recently serviced and the water was not sufficiently drained. While most production isolators have real-time concentration sensors to show that the cycles are consistent, most sterility isolators do not have this type of monitoring. Performing environmental monitoring before and after the sterility testing session shows that the isolator is in a state of control.

In addition to the issues with the decontamination process, isolators can also provide a false sense of security, and analysts may not use their best aseptic technique. The gloves are the weakest point in any isolator so an environmental monitoring program must include the most sensitive method for detecting contamination on gloves. USP <1208> states that contact plates may not be sensitive enough for isolator applications. As a safety factor, users may wear an additional sterile disposable glove on top of the isolator glove.

### Surface and Air Testing

Similar to a traditional cleanroom, many users will use contact plates and swabs for surface testing in an isolator. Because media residue is a concern, contact plates are only used after testing. All-in-one swabs make sampling easy with a lower risk of contamination compared to a swab that is completely separate from the media. Culture media does need to contain appropriate neutralizers for the chemistry, or chemistries, used for disinfection/decontamination in order to reduce the risk of false negatives. Suppliers should document that their neutralizers are effective. Lastly, culture media should be packaged so that the vapor decontamination process is non-penetrating nor causing false negatives. Per <1208>, isolator users must perform bacteriostasis and fungistasis testing to validate package integrity of all testing items as well as execute growth promotion tests on all environmental monitoring supplies after exposure to a decontamination cycle.

Testing the air is performed by either an active air sampler or passively with settle plates or jars. Studies have demonstrated that passive air sampling is not very efficient in recovering microbes. An active air sampler at 1 CFM (28.3 L/min.) was shown to be 2250 times more efficient

at recovering 1 µm particles than a 9 cm plate. Most commercially available active air samplers have flows of 100 L/min or almost four times of that was used for that study. Active air samplers designed for isolators have integrated sampling heads that can be decontaminated as well as calibrated in place to reduce the risk of contamination. Users who use portable air samplers will need to confirm material compatibility with the decontamination agent as well as include in the load.

### Glove Testing

There are many risks for glove damage from sharp objects due to degradation during the decontamination process. Both physical and microbial testing should be a part of any glove testing program. Pressurizing the glove and sleeve with a commercially available glove tester is easy and sensitive. Other users, however, will simply use concentrated ammonia and ammonia leak detection cloths to look for leaks in both the isolator and the gloves. For microbial testing, some users will immerse the entire glove in a peptone solution and then use filtration and liquid media to check for growth. Another method involves using sterile wipes saturated in phosphate buffer, and then wiping the entire glove before placing in a jar of sterile media.

### Monitoring Outside the Isolator?

USP <1208> states that a sterility isolator does not need to be located in a classified environment but recommends having the isolator in a controlled environment in regards to temperature and humidity as well as user access. It is still best practice to treat the area as an ISO 8 cleanroom and perform cleaning validation and environmental monitoring just as if it was an actual ISO 8 cleanroom. The microbes in a dirty room may eventually get into your sterility isolator.

While isolators are still the best environment for sterility testing, they are far from perfect and false positives can still occur. A comprehensive and validated environmental monitoring program for your sterility isolator is essential for conducting investigations to be regulatory compliant.

## Pharmaceutical Legislation of the European Union, Japan and the United States of America – An Overview

**Edited by Barbara Jentges, PhD**

excerpted from *"Regulatory Bodies"*

### A. Japan

The **Ministry of Health, Labour and Welfare** (MHLW) is the regulatory body responsible for systems closely related to the general welfare of the people. As such, it is responsible for enacting legislation related to pharmaceutical regulatory affairs (Note: veterinary drugs are under the jurisdiction of the Ministry of Agriculture, Forestry and Fisheries).

The MHLW, which regulates many industries in addition to pharmaceuticals, is comprised of many councils, affiliated institutions, local branches, and bureaus. One such bureau is the Pharmaceutical and Food Safety Bureau (PFSB), which is responsible for implementing administrative duties and functions of the MHLW.

"The PFSB enforces the regulations and relief from adverse drug reactions, etc. needed to ensure the safety of pharmaceutical products and food that are essential…for helping to protect…lives and health." Recent work has focused around four policies that will serve to further ensure drug and food safety; two of which relate to the pharmaceutical industry in Japan:

1. *Practical application of effective and safe pharmaceutical/regenerative medicine products, etc.*
   The issue of so-called "drug lag" and "device lag", a situation where drugs/medical devices have been approved in the United States and European countries but cannot be manufactured/sold, etc. in Japan, has almost been resolved through successful efforts to speed up approval, etc.
2. *Sakigake Package Strategy, promoting practical use of innovative drugs, etc.*
   In order to lead the world in facilitating practical use of innovative drugs for life-threatening diseases, a project team within the MHLW compiled the 'Sakigake Package Strategy' in June 2014, and it was also included in the 'Strategy for Rebirth of Japan.'

The Strategy provides that efforts shall be made in taking various measures from clinical research/trials, application reviews, and insurance coverage to global expansion in a consistent manner, including a 'pioneering review designation system' aimed at early approval by giving higher priority to application reviews for innovative drugs, etc."

## Technical Report No. 74: Reprocessing of Biopharmaceuticals

excerpted from *3.0 Reprocessing Considerations*

Reprocessing, or repetition of an existing biopharmaceutical unit operation, requires a well-designed procedure and supportive data to augment the existing manufacturing process validation. Importantly, the supportive data must provide the manufacturer with a high degree of assurance that the drug substance or drug product produced by reprocessing is of comparable quality to a nonreprocessed batch.

A number of scenarios exist under which reprocessing may occur. Scenarios can be generically defined as proactive and reactive.

**Proactive —** The potential need for repro-

cessing is prospectively established through pre-determined criteria and executed according to a validated procedure that has been reviewed by applicable regulatory agencies. The sequence of steps discussed in **Section 3.3** may be used to guide the proactive approach to reprocessing.

**Reactive —** The same categories of data and decisions required for a proactive reprocessing approach apply to this approach except that less time and information may be available for performing assessments. As a result, reactive reprocessing is better suited for steps that are simple and with a low likelihood to affect product quality. The sequence of steps discussed in **Section 3.3** may be used to guide the approach to reactive reprocessing, starting with the design of a reprocessing unit operation **(Section 3.3,** Step 6). Two distinct reactive reprocessing scenarios are described as follows:

**i.** A nonprospectively validated reprocessing unit operation is needed at an in-process hold point. Product can be held for an extended period of time (e.g., frozen storage). During the hold period, a plan can be developed and executed for the validation of a step culminating in the reprocessing of the held intermediate or drug substance.

**ii.** A reprocessing scenario arises during a manufacturing run that must be executed before the reprocessing step is fully validated. If a reprocessing option can be quickly designed and implemented, then it may be performed at risk with the understanding that supportive data must be generated and considered acceptable before batch release.

## Assuring Data Integrity for Life Sciences

**Edited by Siegfried Schmitt**

excerpted from *"Big Data"* by Magdalena Kurpierz

Big data is used in predictive analytics and other advanced methods to extract valuable information from data. Analytics relies on the simultaneous application of statistics, computer programming and operations research to quantify performance. Analytics often favours data visualization to communicate insight. Firms may commonly apply analytics to business data, to describe, predict, and improve business performance. Since analytics can require extensive computation, the algorithms and software used for analytics harness themost currentmethods in computer science, statistics and mathematics. Analytics is the discovery and communication of meaningful patterns in data, especially valuable in areas rich with recorded information. Deriving patterns, trends and associations with the use of big data analytics could help save lives, lower costs and risks as well as improve health care. Decision makers from organisations can make better decisions and gain new opportunities by getting a deeper insight from big data.

Big data initiatives offer the possibility to increase productivity, quality, and flexibility within the life science industry and thus to gain advantages over the competition. Together with data processing and analysing, big data and its real-time availability are identified as new opportunities to bring insight and added value to patients and enable new business opportunities for the life science industry. It could lead to better products with a higher quality at a lower cost, therefore achieving better outcomes in the end.

With a purposeful use of big data analytics companies get helpful insights into the world of consumers. A life science company could, for example, use big data to build customer relationships with a specific focus in mind. The benefits of big data analytics are not limited to the commercial area. Analysing big data ranges across a wide spectrum of topics related to the life science industry.

## PDA's Personal Reading List

***The Last Kingdon,*** Bernard Cornwell—**Richard Johnson,** PDA President

***The Emperor of All Maladies***, Siddhartha Mukherjee—**Rich Levy,** PDA Sr. VP, Scientific and Regulatory Affairs

***Rising Strong,*** Brené Brown — **Jenifer Avenatti,** Baxter, author of "Managing Post-Approval Changes in a Global Environment," January 2016 *PDA Letter*

***Airframe,*** Michael Crichton—**Robert Darius,** Novavax, Vice-Chair of the *PDA Letter* Editorial Committee

***The Screwtape Letters,*** C.S. Lewis —**Enith Morillo,** Complya Consulting, author of "Career Breaks: Paths to Reentry," Nov/Dec 2015 *PDA Letter*

***Prior to the Storm,*** Theodor Fontane—**Falk Klar,** PhD, Senior Director, Training and Education, PDA

***Alexander Hamilton,*** Ron Chernow—**Tricia Vail,** Pall, Chair of the *PDA Letter* Editorial Committee

***The Black Swan,*** Nassim Nicholas Taleb—**Dipti Gulati,** PJI Biotech, author of "Quality Metrics: An Ongoing Journey," April 2016 *PDA Letter*

***Accidental Saints,*** Nadia Bolz-Weber—**Maik Jornitz,** G-Con, former PDA Chair and current *PDA Letter* Editorial Committee member

***The Waters of Eternal Youth***, Donna Leon—**Thomas Peither,** Maas & Peither, author of "Older Pharmaceutical Facilities – What Does FDA Say?" February 2016 *PDA Letter*

***That's the Way the Cookie Crumbles: 62 All-New Commentaries on the Fascinating Chemistry of Everyday Life,*** Joseph A. Schwarcz—**Mirko Gabriele,** Patheon, Technology Transfer Interest Group Coleader and RAQAB member

***The Martian,*** Andy Weir—**Pritesh Patel,** current *PDA Letter* Editorial Committee member

***Workplace Poker,*** Dan Rust—**Praveen Prasanna,** Shire, current *PDA Letter* Editorial Committee member

***As You Wish: Inconceivable Tales from the Making of The Princess Bride,*** Cary Elwes—**Cecilia Turoff,** current *PDA Letter* Editorial Committee member


2016

# Expert Bio/Pharmaceutical Publications and Resources for the Pharmaceutical Manufacturing Industry

1946
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Connecting People, Science and Regulation®

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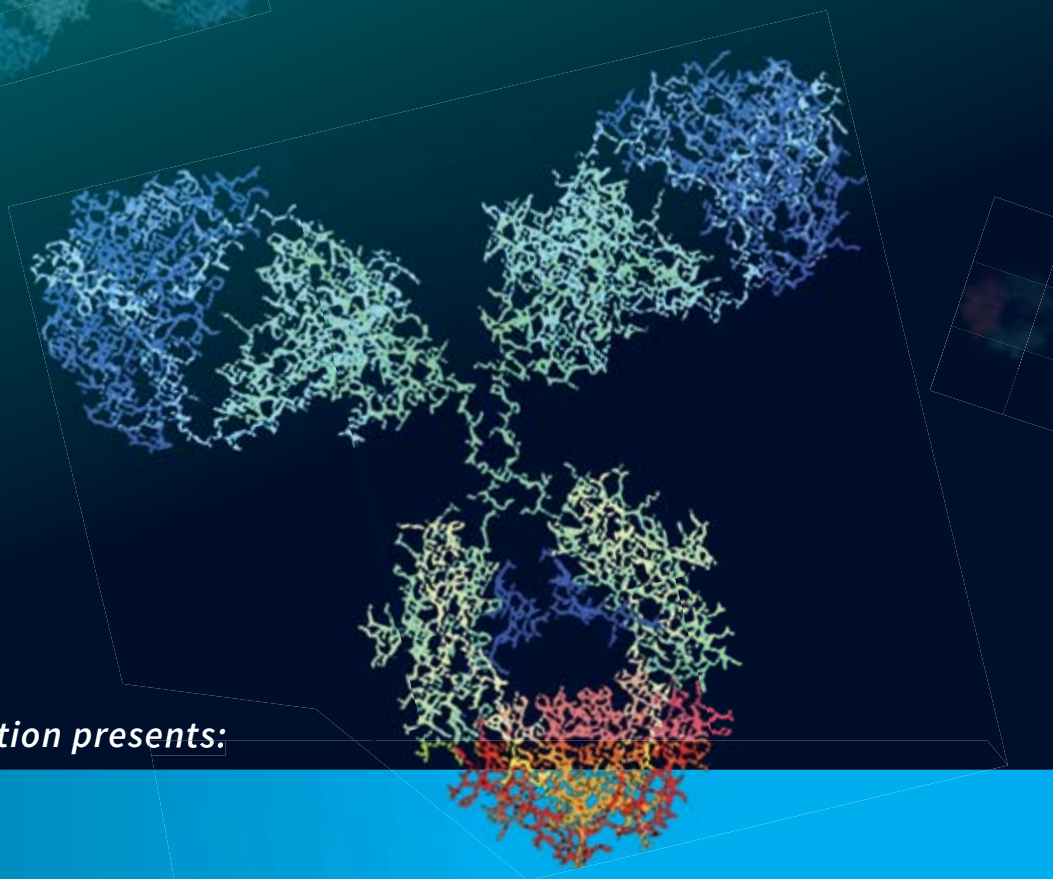

*The Parenteral Drug Association presents:*

## 2016 PDA Europe

# 9th Workshop on Monoclonal Antibodies

## Ensuring mAbs' Quality – Current Considerations for Control Strategy Design

**22 September**
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**22 September**
Elastomers

**22-23 September**
CMC Regulatory Compliance for Biopharmaceuticals

**22-23 September**
Extractables and Leachables

**22-23 September**
Introduction to Aseptic Processing Principles

**22-23 September**
Statistics of Production Monitoring and Capability

**Register by 20 August 2016 and SAVE!**

**20-21 September 2016**

Radisson Blue es. Hotel
**Rome | Italy**

pda.org/EU/MAB2016

# The Future is "Cloudy" for Data Integrity

**Mike Jovanis, Veeva Systems**

Managing the integrity of manufacturing data is becoming ever more challenging, particularly as more and more critical manufacturing functions are outsourced, thus limiting the amount of oversight a pharmaceutical company can provide. Per ICH Q10, "the pharmaceutical company is ultimately responsible to ensure processes are in place to assure the control of outsourced activities and quality of purchased materials" ***(1).*** Further, the U.S. FDA holds "the owner's quality unit ultimately responsible for approving and rejecting drug product manufactured by the contract manufacturer" ***(2).***

Life science companies need to demonstrate control over their data—whether internally or externally generated. FDA officials indicate that "data that are not valid and trustworthy is a sign that an entire operation or facility is out of control and cannot assure the quality of its medicines" ***(3).*** Without accurate data, companies are less equipped to ensure the safety, effectiveness and quality of their products.

## FDA Scrutiny Intensifies

As data integrity issues continue to surface during plant inspections, FDA leaders continue to lead the push for manufacturers to clean up data operations ***(4).*** In fact, standalone, raw data-generating systems, business processes and interfaced business and production control systems that formerly received only cursory reviews, are now under increasing scrutiny ***(5).*** The concern is that these companies' products cannot be trusted due to the absence of credible data. The FDA has subjected many global companies to import alerts, refusing entry of their products into the United States ***(6).***

## Gap Between Systems and Processes

Quality processes now span internal and external parties, however, many supporting systems were designed to operate only within a company's four walls. In addition, many of these applications do not work well together—often existing in silos. Significant, manual overhead is necessary to bridge the gap between all parties and applications in order to stitch together a continuous process—providing many opportunities for data issues.

Having the quality team review the data from manufacturing sites is a great first step. Communication, however, still often occurs via email, or another uncontrolled method in a non-validated environment, which could lead to an observation or warning letter. In fact, according to the FDA's recent draft guidance, "Workflow, such as creation of an electronic master production and control record, is an intended use of a computer system to be checked through validation. If you validate the computer system, but you do not validate it for its intended use, you cannot know if your workflow runs correctly" ***(7).*** As outsourcing grows, there is greater scrutiny of the review of the batch production and control records that support the batch release process—a common concern even without factoring in outsourcing. Companies currently use a combination of email and filesharing sites, making it almost impossible to provide a clear, consolidated audit trail, and to demonstrate chain-of-custody for the controlled data or documents.

## DI Forecast: "Cloudy" Skies Ahead

Using cloud-based technology to orchestrate drug development and manufacturing enables all parties to be incorporated into the process from end-to-end. Every move is controlled and can be overseen. This reduces the risk of data being manipulated or lost amidst fragmented processes and disparate systems.

The cloud gives life science companies the ability to extend data integrity across all parts of the value chain, while at the same time enabling partners to access information they need to provide valuable services. Raw material suppliers, CROs, CMOs, brokers, and distributors can interact simultaneously under very controlled conditions to ensure that accurate, up-to-date information is always available to those that need it—whenever, wherever, or however ***(8).*** ➤

Reviewing information from manufacturing sites helps detect data integrity issues, however, problems are typically more difficult to detect—and the impact greater—near the end of a process. Moving upstream and providing the quality team with direct access to the quality management system allows issues to be detected earlier and accelerates downstream decision-making. The quality team can review in-process deviations and results of the investigation so problems can be resolved proactively and approvals streamlined for improved efficiency. Providing all stakeholders with access to up-to-date, accurate data and content in a single, authoritative system instills greater confidence that operations are being executed with compliance.

As regulators require greater access to manufacturing data, having a solution that directly incorporates all parties into end-to-end processes will be essential to ensuring data quality and integrity.

### There's Only One Direction to Look

The industry must stop looking within, and start looking for solutions elsewhere. The best place to look is up—to the cloud. Cloud solutions that manage quality content and processes bring together all stakeholders on one platform and ensure an auditable trail of all activities with partners. Ultimately, the cloud offers a way to externalize and maintain internal control of quality.

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8. Jordan, K. "Best Practices in Life Sciences for Avoiding Data Integrity & Quality Pitfalls," *Pharmaceutical Online* April 8, 2016. tinyurl.com/hv2fnbw

### About the Author

**Mike Jovanis** is Veeva Systems' Vice President of Vault QualityDocs.

# Keeping Current with Industry Trends and Emerging Technology

**Shawn Kinney, PhD, Berkshire Sterile Manufacturing**

The prefilled syringe is not a new technology. Yet it's at the center of an incredible amount of innovation. This includes new materials, modifications to existing materials, new devices and new connectivity features. Other trends are also impacting prefilled syringes and are almost too numerous to list—individualized medicines, specialized delivery systems, single-use technologies, patient self-administration, greater access to biosimilars, flexible manufacturing systems, etc.

With such a dizzying list of trends and topics to keep up on, how do you stay current? Where do you find the latest information? Where are the thought leaders? Where can you hear from colleagues that have practical experience in many of these topics? How do you quickly get the information you need?

Come to the *2016 PDA Universe of Pre-filled Syringes and Injection Devices*, where industry experts will cover many of these topics. **Markus Bauss,** Managing Director, SHL Connect, SHL Group, will discuss the impact of new "smart" electronic technologies and their implications on patient compliance and the supply chain. **Chris Evans,** Vice President, Research & Innovation, West Pharmaceutical Services, Inc., and **Mike Siemer,** Director of Design & Engineering, Noble, will look at the role of wearable devices in patient training and onboarding. All three of these speakers' companies will also be exhibiting with over 80 other vendors and suppliers in a massive Exhibit Hall where there is something to appeal to everyone. This event is like no other and will provide answers to some of your pressing questions about the latest technological innovations affecting prefilled syringes.

**2016 PDA Universe of Pre-filled Syringes and Injection Devices and PDA Education courses**

Huntington Beach, Calif.
Oct. 17–21
www.pda.org/prefilled2016

**Sometimes** it helps to step back and revisit the past. For 25 years, the *PDA/FDA Joint Regulatory Conference* has served as the defining conference for members of industry to mingle with U.S. FDA regulators in an environment of collaboration, cooperation and support. So, take a step back and revisit some *PDA/FDA Joint Regulatory Conferences* of yesteryear.

# PDA/FDA JOINT REGU

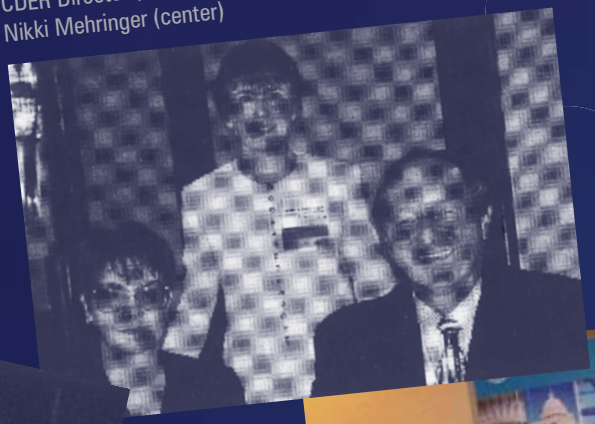
# 2

## ANNIV

## 1991-

The 1992 Organizing Committee, (l-r) Donald Baker, Doris Conrad, Theodore Meltzer, Frederick Gustafson, Committee Chair, Robert Haggerty, and Suzanne Stone

Sharon Smith Holston from the U.S. FDA awards the FDA Commissioner's Special Citation to PDA at the 1995 conference



The 1997 opening plenary featured Janet Woodcock, MD, CDER Director (left) with Kenneth King, PhD (right) and Nikki Mehringer (center)


Opening Plenary Speakers for the 2000 conference included (l-r): PDA Chairman Robert Myers; Deborah Ralston; Amy Scott-Billman; Dr. Joerg Neuhaus; and John Dafoe


The Katrina Relief Fund raised thousands of dollars at the 2005 conference

# ULATORY CONFERENCE

# 5TH

# ERSARY

## -2016

Quality leaders provided insights at the second plenary of the 2012 conference: (l-r) G.K. Raju, Anthony Mire-Sluis, and Greg Guyer


An exhibitor enjoying the 2010 conference

The 2009 conference featured a book signing

Michael Gross (left) and the FDA's Donald Klein (right) offered industry and FDA viewpoints on packaging at the 1999 meeting

The Inspection Trends Interest Group hosted its ever-popular speed-dating exercise at the 2015 conference

# 2016 PDA Upcoming Events

## SAVE THE DATE for PDA's 2016 Events

## JULY

### 28-29

**Moist Heat Sterilization Week**
Bethesda, MD
*pda.org/2016MoistHeatWeek*

## AUGUST

### 2-3

**Understanding Variation and the Metrics of Process Monitoring**
Bethesda, MD
*pda.org/2016Stats*

### 8-9

**2016 PDA-PIC/S Training Course on GMPs for APIs**
San Juan, Puerto Rico
*pda.org/2016Pics*

### 8-12

**Quality Systems for Aseptic Processing**
Bethesda, MD
*pda.org/2016QSAP*

### 15-18

**Quality Week**
Bethesda, MD
*pda.org/2016QualityWeek*

### 22-26

**2016 Aseptic Processing Training Program – Session 4** SOLD OUT
Week 2: September 19-23
Bethesda, MD
*pda.org/2016Aseptic4*

### 24

**PDA New England Chapter 5th Annual Summer Social Event**
Boston, MA
*pda.org/NESummerSocial*

### 30-1

**Environmental Monitoring Course Series**
Bethesda, MD
*pda.org/2EMCourseSeries*

## SEPTEMBER

### 7-8

**Recommended Practices for Manual Aseptic Processes**
Bethesda, MD
*pda.org/2016MAP*

### 12-14

**2016 PDA/FDA Joint Regulatory Conference**
Washington, DC
*pda.org/2016PDAFDA*

### 14-15

**WASHINGTON – 2016 PDA Data Integrity Workshop**
Washington, DC
*pda.org/2016DataEast*

### 15-16

**2016 PDA Regulatory Course Series**
Washington, DC
*pda.org/2016PDACourses*

Denotes Laboratory Courses | Denotes Lecture Courses

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**For an updated PDA calendar of events, please visit:**

# pda.org/calendar

**20-21**
**9th Workshop on Monoclonal Antibodies**
Rome, Italy
*pda.org/EU/MAB2016*

**21**
**PDA New England Chapter Quality Culture Dinner Meeting**
Burlington, MA
*pda.org/2016QualityCulture*

**21-22**
**Quality Metrics and Quality Culture**
Burlington, MA
*pda.org/2016Metrics*

**22**
**Elastomers**
Rome, Italy
*pda.org/EU/Elastomers2016*

**22**
**From Gene to Product – Tailor-made Strategies for High Level Expression of Biologicals**
Rome, Italy
*pda.org/EU/Recombinant2016*

**22-23**
**CMC Regulatory Compliance for Biopharmaceuticals**
Rome, Italy
*pda.org/EU/CMC2016*

**22-23**
**Extractables and Leachables**
Rome, Italy
*pda.org/EU/WSEL*

**22-23**
**Introduction to Aseptic Processing Principles**
Rome, Italy
*pda.org/EU/TCAseptic2016*

**22-23**
**The Metrics of Process Monitoring & Understanding the Risks of Variation**
Rome, Italy
*pda.org/EU/Statistics2016*

**26-30**
**Visual Inspection Week**
Bethesda, MD
*pda.org/2016VisualWeek*

**27-28**
**Pharmaceutical Freeze Drying Technology**
Strasbourg, France
*pda.org/EU/FreezeDrying2016*

**29**
**Application of a Risk-based Approach to Freeze-Drying Processes**
Strasbourg, France
*pda.org/EU/FreezedDryingProcesses2016*

**29-30**
**Development of a Freeze Drying Process**
Strasbourg, France
*pda.org/eu/wsfreezeDrying2016*

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# How to Avoid a Data Integrity Citation

## What Your Company Needs to Know in Today's Regulatory Environment

**Brad Mercer, Mylan, Deborah Autor, Mylan, Zena Kaufman, ZGK Quality Consulting**

One specific topic continues to draw extensive regulatory attention, including numerous citations in U.S. FDA Warning Letters: data integrity. While expectations in this area are based on regulations that have been around for many years, the sheer number of observations (approximately 70% of the citations and warning letters issued in the past three years) should spur every pharmaceutical firm to revisit its approach to this important area.

As pharmaceutical firms and global regulators continue to develop their data integrity approaches and programs, a key component is a risk-based approach that takes into account the intent, scope and impact to patients associated with various data integrity issues. An isolated, unintentional data integrity issue that carries no potential repercussions to patient safety and can be immediately corrected/prevented from future occurrence should have a different level of scrutiny compared to systemic and intentional data falsification by multiple individuals that carry the potential to impact product quality. Consider the spectrum of firms that regulators see: firms ranging from naive, negligent or ignorant in regard to data integrity and lacking formal data integrity plans, to those that have evaluated their systems, equipment and risks and have documented comprehensive remediation plans. The level of scrutiny a firm may expect is likely linked to where it is on this continuum.

In order to ensure patient and product safety, quality systems must be established and maintained to mitigate the potential for data integrity issues to arise. The first steps are to evaluate:

- The flow of data throughout a process, including the equipment, systems and records
- The ability to detect issues through a firm's self-inspections/audits, procedures and the personnel who conduct these audits; and
- The scope and effectiveness of the training program for all employees, including contractors and consultants

Creating procedures and policies that emphasize the expectations and requirements of data integrity will aid employees in making informed decisions. Existing policies and procedures should be assessed to ensure alignment with each other and with current industry standards. Increasing employee knowledge through training and involvement in data integrity evaluations will aid in establishing a quality culture consistent with data integrity. An informed and engaged staff is in the best

position to highlight potential issues to management. To nurture a participatory quality culture dedicated to high quality behaviors, reinforcement mechanisms can be utilized for data integrity concepts/practices. Some examples of reinforcement mechanisms include employee performance plans, employee recognition or financial rewards.

### Detection is Key to Prevention

A firm that is able to detect data integrity issues will be better capable of preventing them in the future. Historically, data integrity checks were rarely built into routine review processes and internal audits, although this is changing. Firms that are not looking for potential issues never see them and, thus, fail to learn how best to prevent them. Regulators worldwide receive specialized training on detecting data integrity issues. Once cited, these regulatory findings become precedents for inspections of other sites within the firm, for contract manufacturing operations, and at other firms. Internal auditors at firms should be trained to detect data integrity issues. This means having a robust understanding of each system and process and where potential issues can occur within each system/process. A systematic review of the detection system and processes, rather than a random review, is required to detect data integrity issues. For instance, a chromatographic management system should highlight for a data reviewer when manual, forced or inhibit integration functions are used. It may be beneficial for firms to hire external specialists knowledgeable in data integrity to aid in detection of potential problems, thereby using these issues as case studies to teach internal auditors a systemic process for detection.

### Article at a Glance

- A firm should be capable of detecting data integrity issues on its own
- There are six common causes of data integrity issues
- A data integrity investigation must drill down to the root cause

**An informed and engaged staff is in the best position to highlight potential issues**

### 6 Common Data Integrity Pitfalls

The following are six of the most common issues behind data integrity breaches at manufacturing sites. Most of these are frequently noted in regulatory inspection reports and subsequent regulatory action letters.

#### 1. Inadequate Process Control

Actions must be taken to prevent possible data integrity issues, both intentional and unintentional. While there always exists potential for human error, systems and documentation processes should be built to minimize the occurrence of unintentional errors through "fail-safe" processes. Manipulation of data must be prevented by implementing system controls or review procedures that ensure detection. To aid in this process, new equipment should be compliant with CFR Part 11/Annex 11, Electronic Records; Electronic Signatures. All legacy GxP equipment should have a risk assessment/gap analysis/remediation plan performed according to these guidelines. Without this evaluation, a firm risks ongoing noncompliance with data integrity issues. A firm with an in-depth assessment system will have controls in place, or at least planned, that minimize the risks.

#### 2. Lack of Process Monitoring

The MHRA guidance issued in 2015 proposes that firms conduct internal data integrity self-inspections. Therefore, data integrity should be built into the compliance program, which includes self-inspections and routine review of data through audit trails. It is important to understand that the firm is also responsible for assuring that associated business partners, suppliers and contract manufacturing organizations are compliant. For contract manufacturing arrangements, this means ensuring that data integrity commitments are included within quality/technical agreements and monitored through external audits. All outsourced work should be closely reviewed for GxP violations, including data integrity issues. When contractors/contingent workers are hired to work on systems internally at a firm, there should be set guidelines stating what they can work on and what kind of training they require. A large portion of this training should be delivered by internal employees who have the appropriate understanding to ensure that contract/contingent workers do not initiate or pepetuate poor data integrity practices.

#### 3. Lack of Training/Oversight

Sufficient manager and supervisor involvement in day-to-day operations is critical to ensure employee focus and comprehension. A quality culture which rewards the raising of issues, questions and discussion should be promoted and encouraged. Management should have a current understanding of industry trends, guidances and requirements, sharing this knowledge with operational staff. An informed staff aware of current industry trends/knowledge will be better able to spot potential data integrity problems. A knowledgeable workforce can be created by providing ongoing data integrity training and fostering a culture of continuous learning.

#### 4. Inadequate Technology

IT departments, technical service departments (process pharmacists), business management and other business support groups often fail to ensure that data integrity requirements are integrated into technologies/processes. Firms may acquire suboptimal technology incapable of meeting requirements for data integrity. They may also acquire technology that is capable, but fail to develop and map its data landscape. Some technology may be too complex for the firm or for the specific use, making it difficult to identify risk. Equipment and system qualification/validation processes must be sufficient to thoroughly evaluate data integrity issues. ➤

### 5. Performance and Business Pressures

In the fast-paced, high demand pharmaceutical industry that operates today, the pressure placed on quality systems through business decisions must be closely monitored. The focus on Key Performance Indicators can drive the wrong quality behavior, so a firm's measurement and monitoring systems must be carefully overseen to avoid unintended consequences. When you drive/reward/penalize Right First Time execution of tasks, for example, it can encourage employees to hide or neglect issues. Organizations are being pushed to be lean, producing more with less, which can lead to time and resource constraints. These can then lead to job complexity and, ultimately, to shortcuts that can impact data quality.

### 6. Absence of a Strong Quality Culture

Site leadership must always be vigilant of the potential for a site to have data integrity issues, ensuring there is no culture of denial and/or neglect. Often, a firm is unaware of a data integrity issue until receiving a regulatory observation. Lack of preparedness may also be caused by naiveté and absence of personal accountability. Insufficent experience and knowledge or little determination to gain the necessary experience and knowledge results in issues. Employees are not always empowered to speak up and are not always engaged with leadership. Leadership must listen and honor all employee concerns, even if they are judged to be inaccurate or trivial. If a concern is ever dismissed or ridiculed, the employee will probably not speak up again, sharing these feelings with fellow peers. Policies and procedures should align and incorporate data integrity within the firm's quality system. Employees should always have these policies and procedures available as a reference for when questions arise. Another key step in creating a culture of data integrity is reinforcement training. This type of training serves to update the corporate knowledge base and establish the firm's ongoing commitment to the issue.

### Analysis from a Firm's Perspective

When a data integrity issue is detected, the equipment, system or process must be evaluated. How many other similar instruments are there? What type of data is in question? Is there actual known impact to data or just the potential for data to be impacted? What are the risks to patients, product quality, and the firm? Once these risks have been determined, they should be ranked using a risk-based approach. This will allow the largest issues (the greatest chances for data corruption, with the biggest potential impact to patient/product safety) to be addressed first. Addressing issues will usually include an investigation for determining impact from all previous occurrences and a documented corrective action/preventive action plan to prevent future occurrences. The discovery of noncompliant equipment/processes may require immediate difficult decisions for organizations (e.g., immediate equipment removal from service versus continued use with a sufficient mitigation/remediation plan). ➤

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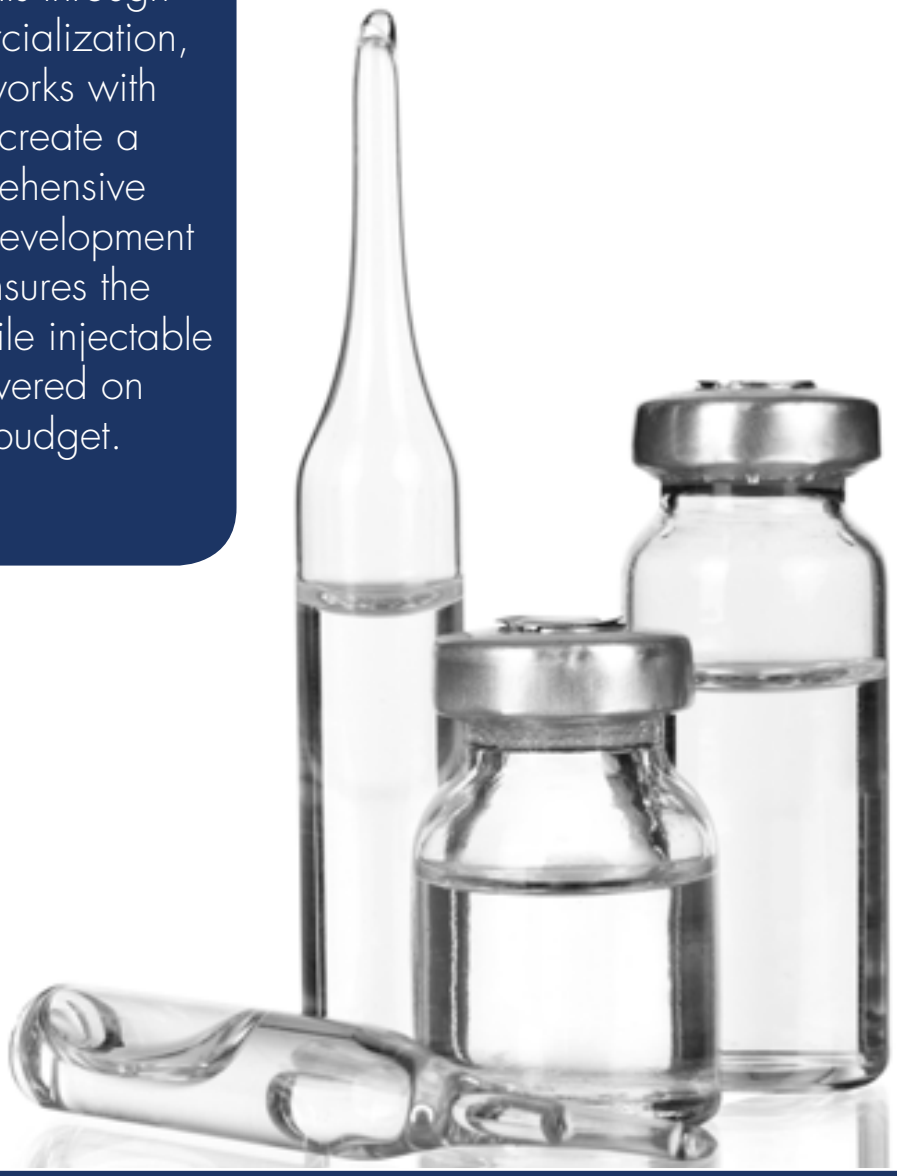

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## Site leadership must always be vigilant

The goal when investigating a data integrity issue is no different than any other investigation—it is vital to drill down to the true root cause. Without a definitive true root cause, the corrective and/or preventative actions may be ineffective and might not reduce the risk of future reoccurrences to an acceptable level. The first step when an issue is found is to immediately put controls in place to contain the issue. The controls may require quarantining data or systems, placing interim controls in a system, or isolating individuals, groups or specific types of users. Data integrity issues can be very difficult to investigate, solve and fix. It is important to determine if the issue was due to malfeasance, lack of knowledge/understanding or systemic process failure. Investigations for systems require input from all the subject matter experts and system and process owners.

A system investigation will utilize a more traditional approach (e.g., factgathering, Fishbone diagrams, 5-Why analysis, etc.). Investigations involving individual mistakes, individual malfeasance, and institutional malfeasance will require an untraditional, modified approach. All of the human factors that drive each specific behavior must be considered and the individuals directly related to the issue must be involved. Once the root cause is determined, corrective/preventative actions must be implemented. These CAPAs should be devised to prevent any future occurrences through additional process controls, process clarifications, revalidation, training and approaches that minimize the possibility of human error. Following completion of CAPAs, it is important to implement appropriate effectiveness checks. If possible, an effectiveness check should be performed immediately after a data integrity CAPA is completed and then again at the appropriate intervals.

### Conclusion

Data integrity is currently trending as the leading cause of health authority citations, warning letters and import bans. While this is not a new topic, it is one with a renewed focus which needs to be taken seriously. The necessary resources to conduct self-inspections, perform investigations, define corrective action/preventive action plans, develop and give robust training programs must be available and dedicated. Overarching is the concept of a quality culture where the integrity of the data of all pharmaceutical processes is highly respected.


**PDA Data Integrity Task Force**

**Anil Sawant,** Merck (Co-chair)

**Maryann Gribbin,** Faith & Royale Consulting Inc. (Co-chair)

**Deborah Autor,** Mylan

**Bob Buhlmann,** Amgen

**Madlene Dole,** Novartis

**Zena Kaufman,** ZGK Quality Consulting

**Brad Mercer,** Mylan

**Siegfried Schmitt,** PAREXEL Consulting

**Ron Tetzlaff,** PAREXEL Consulting

**Denyse Baker,** PDA


At the same time, it is important to recognize that not all data integrity issues are created equal. An important question to ask is whether the firm has taken the necessary steps in advance to prevent and detect data integrity issues, or can otherwise put a fence around a data integrity failure. In a system involving potentially tens of thousands of human beings in a production environment, even at the very best firms, data issues can occur. When an issue does happen, it is important to understand the root cause of the issue, including whether it is related to a lack of process control, process monitoring, training/oversight, adequate technology, control over performance/business pressures, or quality culture. It is also important to assess whether the issue is one individual mistake, individual malfeasance or institutional malfeasance. The answers to these questions, put in the context of the risks presented, suggest appropriate CAPAs and may also be relevant to regulators in deciding the action they should take.

### About the Authors


**Brad Mercer** is a Global Quality Manager at Mylan N.V., where he is responsible for leading and supporting global data integrity and laboratory efforts for the Global Quality Systems team.

**Deborah Autor** is Senior Vice President, Strategic Global Quality and Regulatory Policy at Mylan. She works to advance Mylan's industry-leading efforts to ensure high drug quality standards globally and to expand the world's access to high quality medicine.

**Zena Kaufman** is President of ZGK Quality Consulting.

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# What Recent FDA Warning Letters Can Teach Us

Zena Kaufman, ZGK Consulting

Data integrity emerged as a common theme following an analysis of six recent U.S. FDA Warning Letters. Reviewing the observations cited in these Warning Letters may help firms proactively identify areas of improvement. Firms should use this analysis to assess their own quality systems to determine if the potential for similar issues exists in their own operations, requiring corrective actions. In addition, by reviewing these Warning Letters, firms can learn how to strengthen their own responses to inspectional observations, possibly preventing issuance of a regulatory citation.

## Overview of the Six Warning Letters

The Warning Letters reviewed herein were recently issued (i.e., within the past six to eight months); those not included were Warning Letters issued to compounding facilities or companies with issues that indicated the companies lacked a pharmaceutical quality system in place.

In several cases, a single Warning Letter encompassed more than one site. Of the six Warning Letters, the median length of time between issuance of the 483 and the Warning Letter was 420 days. The shortest time for issuance of a Warning Letter after an inspection was 278 days and the longest was 740 days. The length of time could well be affected by the bundling of multiple sites within a single Warning Letter. For example, a single Warning Letter cited three different sites for a company with time points at 469, 560 and 740 days. This suggests recurring, organizational problems.

The Warning Letters cited many incidents spanning lab controls, reprocessing, facility upkeep, etc. This review looks at three specific data integrity areas:

- Good Documentation Practices
- Computer system controls
- Retesting to obtain passing results/ trial injections deleted

## Good Documentation Practices

Almost all the Warning Letters cited data integrity concerns, particularly failure to adhere to Good Documentation Practices. These observations include: noncontemporaneous data entry in GMP records (e.g., batch records), backdating of information and duplicate records with different information. Frequently, records were found in the trash; unsurprisingly, when these trashed records were compared to official records, discrepancies were found. An inspector also found photocopied labels for final API with information already filled out in advance of the activity in the trash.

At one firm, the investigation reviewed documentation regarding sample prep and incubation. These plates, however, could not be located in the incubator. After questioning the lab personnel, the microbial plate was recreated.

In one example, an unofficial notebook was found noting that a certain microbe was detected in the water system. This information, however, could not be found in any documented investigation or other GMP document.

During one inspection, an FDA inspector referenced the recent guidance on inspection delays and refusals. The firm stored data on a USB thumb drive. When the investigator requested the thumb drive during the inspection, the firm's representative exited with the thumb drive. The investigator was then given a thumb drive 15 minutes later, but could not determine if it was the same thumb drive as requested.

After management had been made aware that there were instances of data falsification and data manipulation, the firm conducted an investigation and determined that none of the deficient and potentially fraudulent data were critical. The firm concluded there was no patient and/or product risk. The firm's investigation was not thorough enough, and the conclusion could not be supported.

In summary, many of these observations reflect the importance of basic good documentation practices. The cGMP data must be accurate, correct, recorded contemporaneously and fully traceable to the raw data record. When issues are discovered, management must conduct thorough investigations.

Ongoing training is essential to prevent these type of issues. Adoption of key documents, such as the PDA Code of Conduct (available on the PDA website at www.pda.org/dataintegrity), can help establish and reinforce a culture of accountability for data integrity. This will be discussed at PDA's upcoming data integrity workshops (for more information, visit www.pda.org/2016data).

## Computer System Controls

Appropriate computer system controls are necessary to assure the validity of electronic data. Lab systems must have adequate controls to prevent and detect compromised data. Where issues are detected, there must be an assessment of the impact to marketed product. Several Warning Letters cited the notable absence of this assessment.

There were also citations for nonunique passwords, or passwords shared between analysts/operators. In one case, a password was shared between four or five individuals to access equipment. Passwords should *never* be shared among staff.

In other instances, audit trails were nonfunctional (e.g., turned off), making it impossible to facilitate traceability of individual data. Firms could not provide a rationale for disabling the audit trail, requiring a response with a timeframe for retrospective review. These reviews

include evaluation criteria and actions taken to address any issues.

One inspection found duplicate records with different information on the records.

Another Warning Letter cited routine retesting of samples without justification, deletion of analytical data, and systemic data manipulation across the facility. Lab analysts had administrator access—this was used to manipulate raw data and test results. The inspection found evidence of manipulation of integration settings to obtain passing results. When the correct integration settings were used, an Out-of-Specification (OOS) result was obtained. By manipulating integration settings, passing results were assured.

In another instance, the system clock was changed and set back so that original data could be reprocessed in order to obtain a passing result. The analyst stated during the inspection that in the event of a failure, the date/time setting was changed and the peak reintegrated to achieve passing results. Once again, the response lacked a review of the impact to marketed product.

Computerized systems must be set up with appropriate controls to assure the integrity of the data. Unique passwords and functional, periodically reviewed audit trails are the cornerstone of a data integrity program. Computer system controls must be included on periodic internal audits. Some of the issues described above are blatant data manipulation. The best defense is ongoing training and an open quality culture where issues can be brought forward freely and the needs of the patient trump the drive to release product. A cornerstone in building a quality culture is to let employees know they are valued and respected. This leads to the empowerment of individuals who do not fear retribution for reporting failing results—instead seeing it as a part of continuous improvement. The openness of a strong compliance function also provides a safe haven for employees to report issues of concern.

### Retesting/Trial Injections Deleted

One firm cited in the Warning Letters retested samples without justification. Seventeen injections were deleted; the missing data were found in a backup folder. The firm stated in response that these were training injections. FDA determined this response to be inadequate.

Where there are concerns with retesting and deletion of injections, it becomes more significant if there are complaints of subpotency, and/or OOS impurity levels. FDA stated that complaint investigations were not able to review all raw data for four lots associated with complaints.

Several Warning Letters cited the use of trial injections and retesting to obtain passing results without justification along with deletion of the analytical data, including overwriting of data.

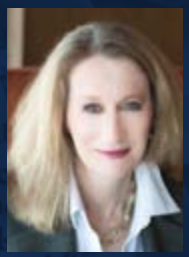
The controls built into the computer systems must not be abridged to allow for retesting of injections and deletion of data. When firms become aware of this, there must be a documented investigation into the impact on marketed product and existing complaint investigations.

### Conclusion

Data integrity continues to be a major focus of the FDA during inspections. Data vital to the quality of the product or the assurance of a state of control of the pharmaceutical quality system must be relied on as true, accurate and traceable. This is the cornerstone of all that pharmaceutical professionals do.

PDA's Data Integrity Task Force is producing a number of documents to assist companies in developing a culture that supports data integrity from the top-down. In addition, the *2016 PDA Data Integrity Workshop* following the *2016 PDA/FDA Joint Regulatory Conference* will offer in-depth presentations and interactive activities designed to help firms improve their data integrity as well as develop effective measures to responding to data issues as they arise.

## About the Author



**Zena Kaufman** is President of ZGK Quality Consulting. She will deliver the presentation, "The Skill of Auditing" in Session A2: Product Quality at 3:45 p.m. on Sept. 12 during the *2016 PDA/FDA Joint Regulatory Conference.*

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# A Line of Sight Approach for Assessing Aseptic Processing Risk

## Part II: The Intervention Risk Evaluation Method

**Hal Baseman, Marsha Hardiman, Walter Henkels and Mike Long, ValSource**

In Part 1 of this article ("A Line of Sight Approach for Assessing Aseptic Processing Risk," June 2016), the authors presented an objective risk management method, known as the Risk Evaluation Method (REM), as a means to improve aseptic processes. In this second installment, the authors offer examples of how REM can be used to evaluate aseptic process interventions. For this case, the method is termed an I-REM or Intervention Risk Evaluation Method. I-REM is a risk assessment method designed to identify, evaluate and rank aseptic process interventions in an objective, simple, reproducible and logical manner using the Line of Sight and Key Word approach. This method uses ranking criteria measureable and objective enough so personnel with varying levels of aseptic process expertise from cleanroom operators to managers can reach similar conclusions on the risk ranking for a given intervention.

The I-REM presented in this case study correlates quantitative data to risk of sterile product contamination as a result of interventions. The examples were initially discussed by the authors in volume 3 of the book *Contamination Control in Healthcare Product Manufacturing* ***(1).*** This installment presents a background for the examples. The third and final installment will provide more illustrative examples.

### Background

The company in the examples below performed aseptic processing and filling of sterile injectable products on multiple lines. Their objective? Find a way to rank or classify aseptic process interventions according to the risk to product sterility assurance. These rankings or classifications could then be used in the overall evaluation of the aseptic process, including design of aseptic process simulation studies. Over the years, 50–60 interventions were identified for the aseptic filling processes. Initial attempts at a ranking method proved to be complex, subjective, potentially inaccurate, and—for those reasons—unsuccessful. An I-REM was developed to simplify the process and make it more objective. The I-REM is based on quantifiable and qualitative measurements and, thus, proved to be significantly more objective than the initial method used.

The objective of the I-REM was to help the company:

1. Determine which interventions should be included in aseptic process simulations and their frequency
2. Make cleanroom personnel aware of the reason for the criticality of interventions, in order to to enable risk communication
3. Decide on proper allocation of resources to reduce or eliminate interventions
4. Improve the aseptic process.

The description, ranking criteria and actions described in the examples below should not be considered as prescriptive standards. Rather, the examples provide a sense of how the method can be designed to provide useful, objective analysis of aseptic processing interventions.

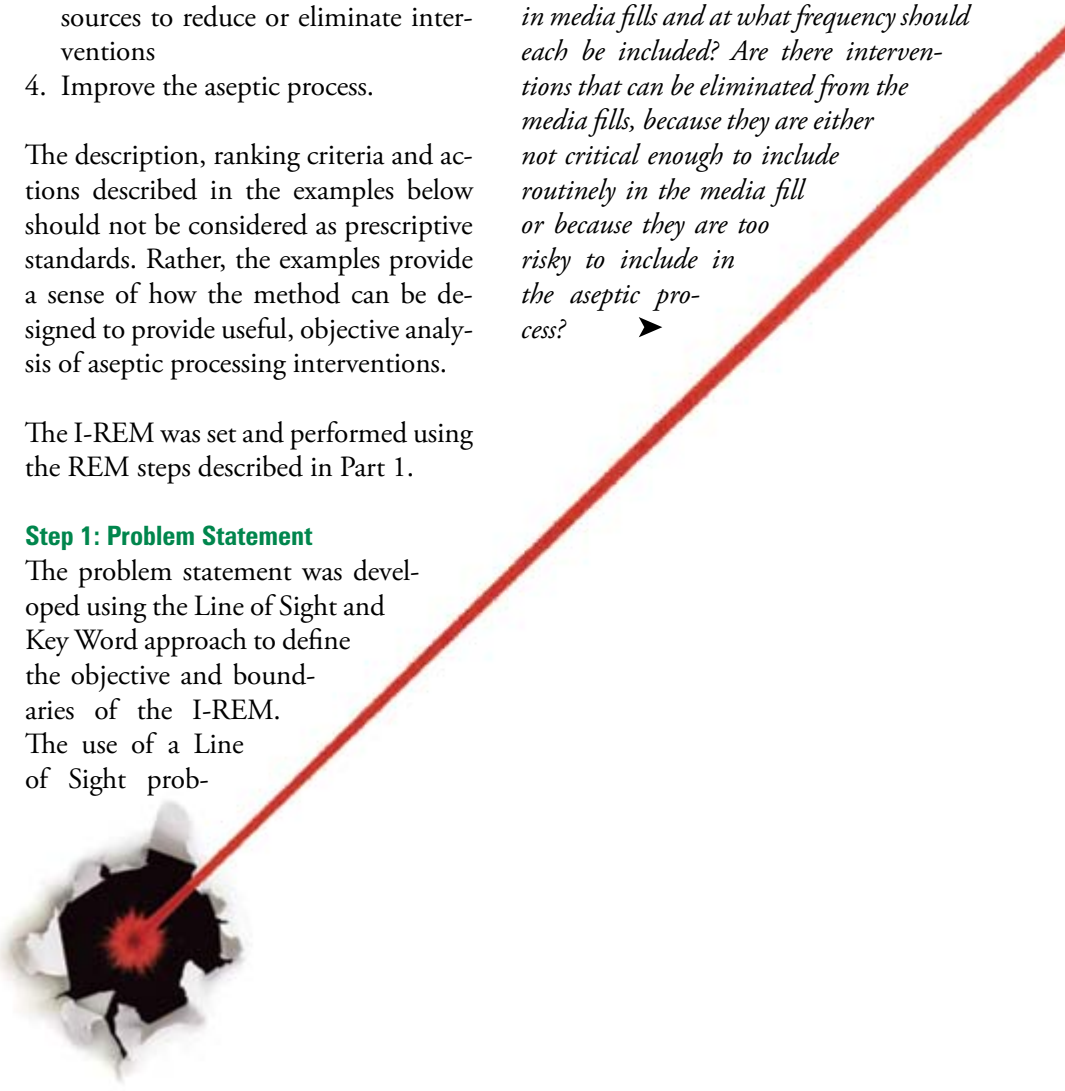
The I-REM was set and performed using the REM steps described in Part 1.

### Step 1: Problem Statement

The problem statement was developed using the Line of Sight and Key Word approach to define the objective and boundaries of the I-REM. The use of a Line of Sight problem statement allows for a clear view of the ultimate objective of the effort. The initial objective of the I-REM involved ranking aseptic process interventions based on the relative risk of loss of product sterility or sterility assurance. It was understood that this ranking would help the stakeholders make better decisions as to which interventions to include, and to what frequency they should be included in media fills. It was reflected in a series of questions:

***Primary risk question:*** *What is the relative risk of loss of sterility or sterility assurance from given aseptic processing interventions?*

***Ancillary risk questions:*** *Which aseptic processing interventions should be included in media fills and at what frequency should each be included? Are there interventions that can be eliminated from the media fills, because they are either not critical enough to include routinely in the media fill or because they are too risky to include in the aseptic process?* ➤



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### Step 2: Team Selection

The I-REM team consisted of subject matter experts with expertise and involvement in addressing the problem statement. This cross-functional team represented multiple departments and levels of authority. The team consisted of site manufacturing and quality unit management, cleanroom operators, mechanics, validation staff, and microbiology personnel. A facilitator helped keep the team focused on the problem statement, manage meeting time and ensure all team members had a chance to provide input. Inclusion of diverse team members was encouraged and blind agreement discouraged. The facilitator helped keep the team productive and focused on the problem statement.

### Step 3: Risk Factor Determination

During a brainstorming session, the team identified the parameters, actions, events, conditions or items affecting the objective or problem. The design of the method focused on factors that can increase or decrease the risk of an intervention. The risk factors used in the I-REM were selected using questions such as: *What makes an intervention risky? What are the measurable factors that contribute to the risk of an intervention?* The team used the Key Word approach, identifying words and factors that had meaning for them. The risk factors were recorded on flip charts during two working sessions. The brainstorming session lasted the better part of a day-and-a-half, resulting in numerous factors. The number of factors was affinity-grouped and reduced in order to simplify the I-REM. Factors were eliminated due to redundancy, lack of differentiation or inability to measure or quantify. In the end, the team selected the following three risk factors:

1. **Duration** of the intervention performed in the critical area
2. **Complexity** of the intervention performed in the critical area; and
3. **Proximity** of the intervention to sterilized product or product contact surfaces

### Step 4: Criteria Setting

Prior to the assessment, the team set the criteria limits, or ranges, used to rank the parameters or elements. These criteria had to be useful, verifiable, measurable and accessible.

**Duration** could be measured by time in minutes that it took to perform the intervention with product or product contact surfaces exposed. Historic media fill observation logs from past years served as the source of the data. Most of the interventions were found to take between one and ten minutes to perform. This "most" level was defined as normal. Therefore, any duration less than normal or less than one minute was considered to be of less concern; any duration above normal, or more than ten minutes, was considered to be of greater concern.

**Complexity** of the intervention was more difficult to determine than duration. What might be complex for one person on the team, was not complex for another. Factors that could define complexity, such as level of training or difficulty in performing the intervention, proved hard to quantify. In the end, the team decided to use the number of steps in the intervention as the criteria for risk ranking, since the number of steps is easy to measure—these could be determined from written procedures—and the objective. The more steps, the more complex the intervention. Again, normality was established as the level by which most of the interventions occurred. Most interventions took between two and five steps to perform. Therefore, any number of steps less than normal, or only one step, was considered to be less complex; any number of steps above five was considered more complex.

**Proximity** proved to be the most difficult factor to measure. At first, the team considered the use of distance from the operator performing the intervention to the exposed product or product contact surface. But almost all interventions were performed at arm's length, therefore, the distance was not enough of a factor to differentiate one intervention from the next And if interventions were performed at arm's length, one could hardly conclude that taller operators presented less risk that shorter ones.

Given proper cleanroom and first air design, however, what became more important than distance was the positioning of the intervention in relation to first air. The rationale? Contamination of the environment surrounding the product or product contact surface posed a risk to the product sterility. Therefore, the criteria were set as follows: if the intervention involved the breaking or disruption of first air using a sterilized component, such as forceps or autoclaved parts, then it was considered to be of midrange risk. If the intervention involved the breaking of first air by a nonsterilized item, such as the operator's sleeve or glove, then it was considered to be of

**Table 1** Risk Factor Ranking Criteria

| Risk Factor Level | Duration | Complexity | Proximity |
|---|---|---|---|
| HIGH | more than ten minutes | More than five steps | Operator breaks first air with nonsterile entity |
| MEDIUM (normal) | Between one and ten minutes | Between two and five steps | Operator breaks first air with sterile entity |
| LOW | Less than one minute | One step | Operator does not break first air |

**Table 2** Two-Stage Risk Assessment Tables

| | Duration | | | |
|---|---|---|---|---|
| | | LOW | MEDIUM | HIGH |
| COMPLEXITY | HIGH | Risk Class 2 | Risk Class 1 | Risk Class 1 |
| | MEDIUM | Risk Class 3 | Risk Class 2 | Risk Class 1 |
| | LOW | Risk Class 3 | Risk Class 3 | Risk Class 2 |

| | Proximity | | | |
|---|---|---|---|---|
| | | LOW | MEDIUM | HIGH |
| RISK CLASS | Risk Class 1 | Medium Risk | High Risk | High Risk |
| | Risk Class 2 | Low Risk | Medium Risk | High Risk |
| | Risk Class 3 | Low Risk | Low Risk | Medium Risk |

relatively increased risk. If the intervention did not occur in the critical area, or disrupt first air, then it was considered lower risk (**Table 1**).

### Step 5: Risk Tool Development

To determine intervention risk, the REM applied a two-stage assessment table method for risk factor evaluation (**Table 2**). The use of two successive risk blocks allowed for simple comparison of three factors. A comparison of the complexity and duration risk factors would yield a risk class where the higher the risk class number, the lower the risk. The risk class was then compared to the third risk factor, proximity, to yield a risk priority level. Because all three factors were weighted equally, i.e., duration was not more important than complexity or proximity and so on, the order in which the factors were combined did not matter.

The team also developed a risk response or action strategy to address the results of the assessment (**Table 3**).

*In the final installment of the article, the authors will present a second set of examples describing the use of the I-REM for assessment of more complex interention risk*

**Table 3** Action Table

| Risk Ranking | Action |
|---|---|
| HIGH | Unacceptable level of risk. Risk should be reduced by reduction of one or more risk factors, taking into account effect of residual risk or unintended consequences of action. Failing that, intervention should be eliminated or deemed improper. In which case, aseptic process might be stopped and line cleared if intervention occurs. If risk cannot be reduced by practical design changes or procedural controls, then it should be recognized that this remains a high risk and efforts should periodically be explored to reduce it. |
| MEDIUM | Actions should be taken to reduce risk to a lower level through reduction of one or more of the risk factors, taking into account effect of residual risk or unintended consequences of action. If risk cannot be practically reduced, it may still be accepted. However, ways to reduce risk should be considered as part of periodic risk review. |
| LOW | Acceptable risk. Not necessary to take any additional actions. |

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## About the Authors


**Hal Baseman** is a Principal at ValSource LLC. He has over 30 years of experience and has held positions in executive management and technical operations at several drug manufacturing and consulting firms.

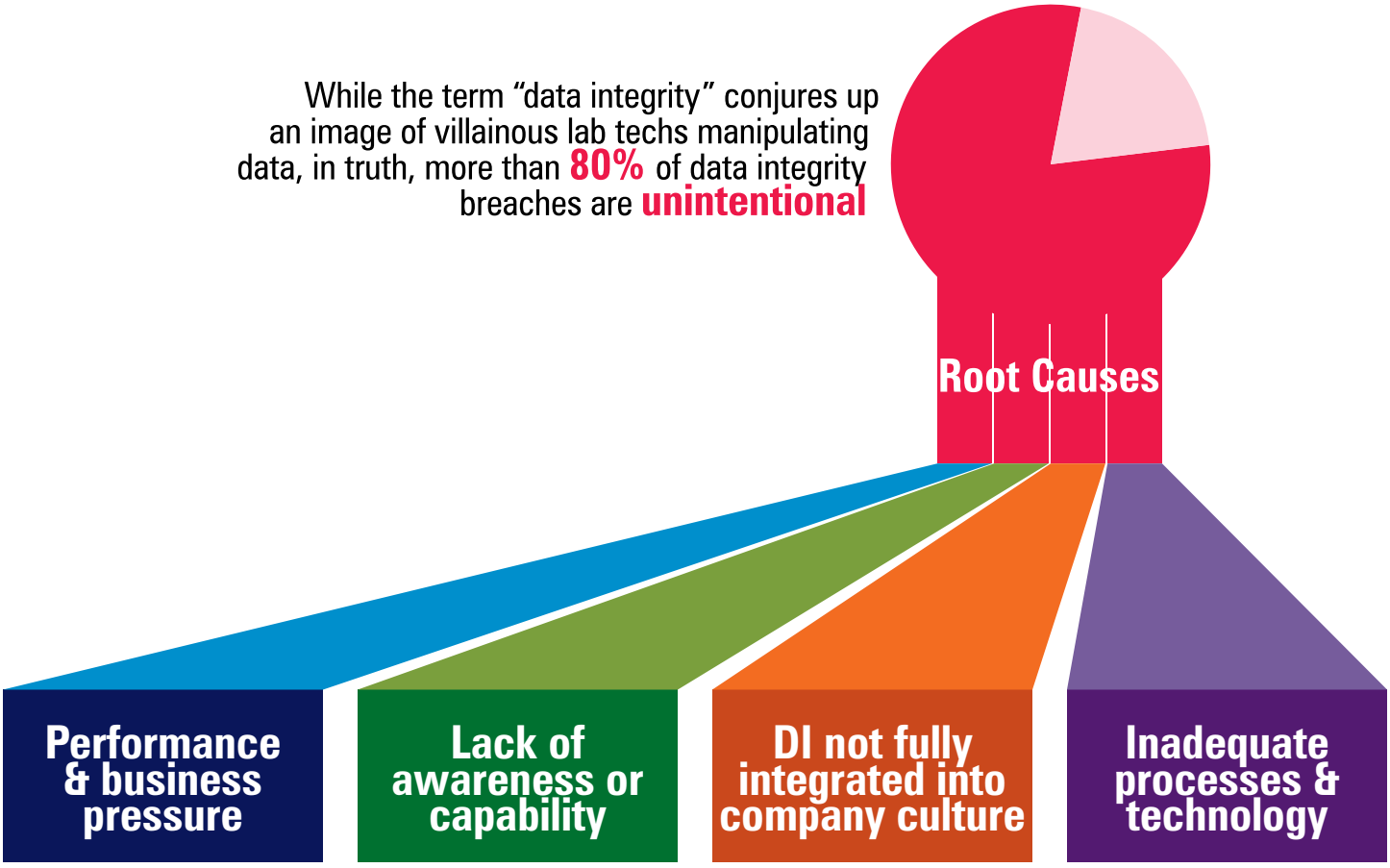
**Marsha Hardiman** has over 18 years of experience in the pharmaceutical and medical device industries with extensive experience in quality and microbiology.

**Walter Henkels** has over 19 years of ongoing experience in the startup, qualification and auditing of aseptic manufacturing facilities and processes.

**Mike Long** has over 20 years of experience in the pharmaceutical and medical device industries. Currently, he is Director Consulting Services at ValSource.

# 4 Ways to Ensure Data Integrity

While the term "data integrity" conjures up an image of villainous lab techs manipulating data, in truth, more than **80%** of data integrity breaches are **unintentional**




## So, how can companies build a culture of data integrity?

- **Educate & communicate**
- **Understand, detect and prevent risks**
- **Define how data integrity is incorporated and assured in the lifecycle**
- **Establish company requirements and a governance structure for data integrity**

Special thanks to PDA's data integrity task force and workshop planning committee as well as the Novartis Data Integrity Team for their assistance with this infographic.

### Source

1. Dole, M. "Data Integrity Overview." Presented at the 2016 PDA Data Integrity Workshop, April 20, London.

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# 2017 PDA Annual Meeting

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snapshot

# Meeting *Preview*

## Interest Group Meeting Schedule

As always, relevant interest groups will meet for the first two days of the *2016 PDA/FDA Joint Regulatory Conference.* Below is a schedule of interest group meetings falling under the Regulatory Affairs and Quality Advisory Board (RAQAB).

| Monday, September 12 | Tuesday, September 13 |
|---|---|
| 5:30 p.m. – 6:45 p.m. | 5:30 p.m. – 6:45 p.m. |
| Regulatory Affairs Interest Group | GMP Links to Pharmacovigilance Interest Group (combined with Visual Inspection of Parenterals Interest Group) |
| Inspection Trends Interest Group | Management of Outsourced Operations Interest Group |
| Quality Risk Management Interest Group | Quality Systems Interest Group |

# Back to the Future

## Ensuring Safe Medicine in the New Millennium

**Joyce Bloomfield**

The past and the future continue to connect and drive innovative change within our industry. Now, more than ever, we're aware of the business value of reliable manufacturing based on preventative systems as well as the risks from using unreliable systems. Not only that, but the U.S. FDA faces its own set of changes as far as its organizational structure and established practices.

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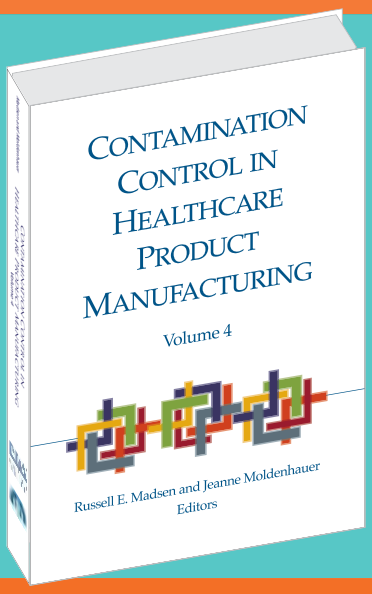


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# Applying QRM to the Change Control Process

**Robert G. Kieffer, PhD, RGK Consulting**

Since the publication of ICH Q9: *Quality Risk Management* in 2005 ***(1),*** there has been much written about the application of risk management to the production process, product development and validation ***(2–5).*** Relatively little has been published about its application to some of production's supporting processes that comprise an important part of the pharmaceutical quality system (PQS). Annex 2 of ICH Q9 outlines the application of Quality Risk Management (QRM) to some of these supporting processes—change management/change control, quality defects, auditing/inspection, documentation, training, calibration/preventive maintenance and periodic review. The use of QRM should result in more effective and more efficient processes.

In 2008, the U.S. FDA's **Kimberly Trautman** said, "A whole host of us still think of risk management as an FMEA…we can't live with that," adding, "We have to integrate that [risk management] more fully for our whole quality system" ***(6).*** In fact, ICH Q9 flat out states that, "QRM should be integrated into existing operations" ***(1).*** The real benefits from QRM arise when it is embedded in all processes, routine activities and the culture of the company. It is a *way of thinking.* The way to start achieving this goal lies in redesigning processes and their accompanying procedures to contain risk analysis as a formal and integral part of the process.

To illustrate the impact of embedding QRM in a company's culture, consider the following example involving change control. The risk analysis takes into account the severity, consequences if a failure occurs, and probability or uncertainty of failure.

## Change Control and QRM

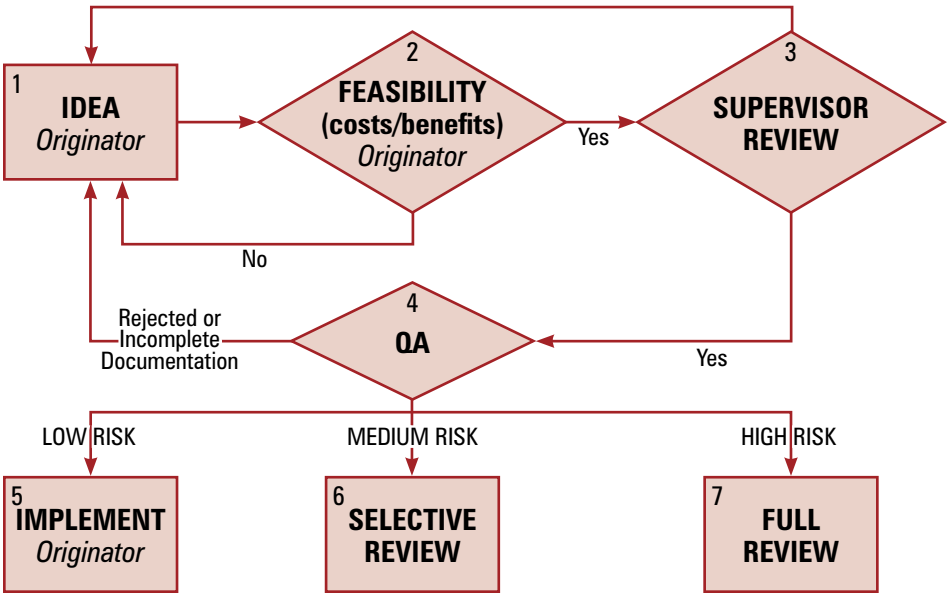
The purpose of this risk analysis is to ensure that changes to critical process parameters do not adversely affect the process and, therefore, product quality. The process itself facilitates change—which is vital to continuous improvement. The seven specific process steps are outlined in **Figure 1.**

There are three risk assessments required for this process, shown by Steps 2, 3 and 4. In Step 2, the originator of the change conducts a risk analysis as well as a cost/benefit analysis. What is the risk that the change will adversely affect the effectiveness and/or efficiency of the process? What is the cost of implementing the change versus its benefit to the manufacturing process? The originator's supervisor repeats the analysis in Step 3. The most important risk analysis, performed by a member of QA, occurs in Step 4. The quality of this analysis depends on several factors:

- Competency of the QA professional
- The quality of the information supplied by the originator; this information should be supplied in a standard format to facilitate its review and understanding and to assure that it is complete
- Knowledge Management, meaning the originator and the QA professional have all the organizational knowledge available pertinent to the process affected by the change; it should be clear what are the critical material attributes (CMAs), the critical process parameters (CPPs) and the critical quality attributes (CQAs) of the product, and this information should be available for the production process, analytical methods, equipment, facilities and critical systems like air and water
- Both the originator and the QA professional should be able to talk to experts in other areas, such as engineering, production, regulatory affairs, quality control, etc.

For Step 5 (low risk changes), the QA professional gives the originator permission to implement the change. There is nothing more to be done. Of course, all is documented in a standard format. For Step 7 (high risk changes), there is the typical team review. The reviewers usually involve QA, QC, production, engineering, regulatory affairs, validation and others if needed. For Step 6 (selective review), the QA professional

**Figure 1** Change Control



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requires review by one or two experts before making a decision. Typically, one would expect that 75–80% of the changes are low risk, 15–20% medium risk and 10–15% high risk.

For training, the inductive method is recommended. This involves taking the last 100 changes and placing them into three categories—high, medium and low risk—under the auspices of a multidisciplinary team, i.e., 75% in low, 15% in medium and 10% in high. This usually involves some discussion and time. It works best if the team members have been thoroughly trained in risk thinking. After this sorting, the team looks at the three categories and describes what all the low risk changes have in common, and similarly for the medium and high risks. This can lead to a description of high, medium and low risk that can be expressed in a procedure. For training new users, the 100 concrete examples along with the procedure are used.

The example of change control is only one example of the application of risk analysis to supporting, nonproduction or nonvalidation processes. Risk analysis can, and should be, applied to all processes. Risk analysis is invaluable in deciding how many checks, signatures and reviews are necessary. It is also particularly useful in setting up sampling plans for environmental monitoring, and materials sampling.

The real benefits of QRM come when risk analysis becomes part of our routine thinking and approach and when it is embedded in the design of all processes. It focuses limited resources, both capital and human, on the most frequent and severe issues, mitigating risk to the lowest possible level given the resources available.

***[Author's Note:*** *The author will teach a course during PDA Education's Quality Week, Aug. 15–19. For more information, visit www.pda.org/2016QualityWeek.]*

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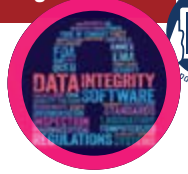
## About the Author


**Robert Kieffer** is a recognized authority on quality management and on quality system design, with over 40 years' experience in the pharmaceutical and medical device, industries.


*Published online first

# Workshop Offers DI Insights from Regulator, Industry

**Rebecca Stauffer, PDA**

Much has been written about data integrity in recent years, as it remains a primary concern of regulators around the globe. Many companies contend that this is a common-sense issue and agree that deliberate acts of fraud are rare among pharmaceutical companies. So the questions remain: Why are regulators, particularly the U.S. FDA, citing data integrity issues in warning letters? And how can industry effectively respond?

MHRA inspector **David Churchward** at PDA's *2016 Data Integrity Workshop* in London this past April, set the stage by asking rhetorically: "When has it ever been okay to have unreliable data?"

Besides expert talks like Churchward's, attendees had the opportunity to break into one of three groups to discuss a fictitious data integrity incident and discuss how they would respond to the scenario.

Churchward's talk provided a short history of the data integrity issue, as well as a look at why MHRA developed its 2015 data integrity guidance—the first ever guidance from a global regulatory body—to explicitly cover the topic. He also illustrated how the guidance could be used to address some of the data integrity failures that MHRA and other regulatory bodies continue to find.

Since 2013, regulators in the EU saw a spike in data integrity findings during inspections, and in 2015 alone, the EU issued 35 "Statements of Noncompliance" that referenced unreliable data as one of the failures. The majority of these, Churchward said, resulted from "bad practice" rather than malfeasance.

While the UK and EU GMPs, promulgated in 1971 and 1989 respectively, are "fit for purpose," Churchward noted they don't adequately cover data handling for the modern scientific enterprise.

"What we also found was that scientific developments did not have quite equivalent data controls. You've seen scientific and technical developments, which have improved the quality and the availability of medicines," he said. "The data controls have not kept up with those advances…we decided what was needed was guidance around how to apply the existing GMPs to modern ways of working."

The MHRA guidance promotes a risk-based approach to managing data. It includes definitions to enable understanding and describes common bad practices and methods of prevention.

Since the release of the guidance, Churchward has seen improvement. Facilities are adopting the guidance and progress is being made, though he sees room for improvement.

"We're still seeing some [issues] around data and metadata review," he explained, "and with segregation of duties and system configuration and also how that impacts validation."

MHRA plans to revise the guidance, Churchward said. These updates will cover GxP applications, so-called "excluded data," data transfer/migration between systems, data processing, electronic signatures and cloud computing.

## Data Integrity Strategies in Action

Following Churchward's talk, industry speakers provided examples of how companies can develop strategies to embed data integrity within a company's quality culture. Two speakers from Novartis showcased that company's data integrity initiative in separate presentations. **Madlene Dole,** Head of Strategic Planning and Operations, Group Quality, described how Novartis realized the need for greater communication and education around the topic. This includes educational posters located in common areas, small group discussions of mini-case studies, and an interactive session led by a facilitator with guided discussions based on participants' experiences.

**Steven Brown,** QA Lead, Novartis Grimsby, provided insight into how to develop a culture of data integrity at a specific manufacturing site. He explained how Novartis' facility in the UK town of Grimsby responded to the company's global push to ensure data integrity. In addition to the communication efforts Dole outlined, the facility includes a dedicated Data Integrity Officer as well as an eCompliance Officer and Site Change Champion.

Following the presentations, participants divided into three groups to discuss hypothetical situations involving data integrity breaches in a hypothetical manufacturing facility, QC lab and clinical trial site. Participants availed the opportunity to discuss and benchmark practices and procedures used during inspections to retrieve, collect into evidence, and review electronic data in a controlled manner. During the readout reports, it became evident there were similarities in how each group would respond and mitigate a breach: avoid over or underreacting, ensure a transparent investigation, develop metrics for data integrity, ensure Senior Leadership support is visible and offer effective training to identify breaches.

The first *2016 PDA Data Integrity Workshop* offered a wealth of information to attendees through both the presentations and workshop exercises. The next three will be held in Washington, D.C. (Sept. 14–15), Berlin (Nov. 8–9) and San Diego (Dec. 7–8).

# Client/CMO Partnership starts with the Quality Agreement

**Astrid McLean, Kite Pharma**

The foundation of a client/contract manufacturing organization (CMO) relationship is a well-written Quality Agreement. The goal is to clearly delineate responsibilities and create open lines of communication between the parties involved. Without this solid foundation, the relationship is off to a rocky start.

The relationship between a client and CMO can be compared to a personal relationship, be it a friendship, marriage or otherwise. It requires hard work and open communication for success. It starts with the Quality Agreement and defining "ways of working" when it comes to day-to-day interactions between the two companies. As with any relationship, numerous challenges and disagreements inevitably will occur. Whereas "hard facts" or metrics are important elements to achieving a successful relationship, it is the "soft skills" that lead to a higher probability of success. The Quality Agreement provides the foundation, but the day-to-day relationship should not be managed through the Quality Agreement.

At the *2016 PDA Outsourcing/CMO Conference,* attendees will hear the latest from the U.S. FDA on the Agency's draft guidance on Quality Agreements. The session will discuss how to establish a robust Quality Agreement providing a solid foundation for the client/CMO partnership. The impact that the guidance will have on how these agreements are created and managed, as well as how to best integrate the concept from the guidance into existing relationships, will be discussed. Additionally, this session will present methods for effective collaboration and what it takes to make the relationship succeed.

Attend the conference to obtain insights, strategies, and tools to discover to what it takes to develop a successful, effective and long-lasting relationship between client and CMO.

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PDA Board Director Anil Sawant

# Assuring Data Integrity

## Our Fundamental Responsibility

Assuring data integrity is a basic GxP principle. Lack of adherence to controls ensuring the integrity of data has always been a concern to both regulators and the industry.

Over the past couple of years, the understanding of what constitutes a breach, or the potential for a breach in assuring data integrity, has evolved, both within the industry and among global regulators. U.S. FDA Warning Letters issued in 2013–2014 to firms in India highlighted examples of data integrity issues due to apparent employee misconduct involving the use of chromatographic data acquisition systems. This has led to the mistaken impression that data integrity is primarily an issue of deliberate misconduct on the part of laboratory personnel at mostly Indian sites. Subsequent FDA Warning Letters, EU-issued Statements of Noncompliance, and WHO Notices of Concern, along with guidances issued by MHRA, WHO (Annex 4), and FDA have helped clear these misconceptions, and shed light on the global nature, broad scope and magnitude of the problem. Lack of data integrity can originate from a system glitch or lack of awareness. Or it can originate from sloppiness. Or it could even be a result of misconduct.

In September 2014, PDA representatives met with FDA to discuss efforts to address the growing concerns about data integrity. Shortly thereafter, the Board of Directors approved a task force to develop a holistic approach to address not just the technical, training and awareness aspects, but also development of a Quality Culture and Code of Conduct. Although fabrication and falsification of data are relatively uncommon, there have been several recent examples where the bond of trust with patients and regulators has been broken. To address this serious menace, in March 2016, PDA released and made freely available its "Elements of a Code of Conduct for Assuring Data Integrity"—a voluntary code that pharmaceutical manufacturers and their suppliers and contractors can adopt. To date, the code has been downloaded close to 2,000 times worldwide. This Code also compliments efforts of PDA's Quality Culture Task Force.

The majority of data integrity issues in our industry appear to be originating from lack of training and awareness. In November 2015, PDA, in collaboration with FDA, conducted data integrity workshops in Hyderabad and Ahmedabad, India, to train local regulators and industry personnel. In April 2016, PDA collaborated with MHRA on a workshop in London (see p. 54 for a summary of this workshop). The next three workshops will be held in Washington, D.C. (Sept. 14–15), Berlin (Nov. 8–9) and San Diego (Dec. 7–8). In addition to the numerous articles and Points to Consider papers on the subject, PDA commissioned the book, *Assuring Data Integrity for Life Sciences,* published earlier this year (for an excerpt, see p. 22). To address the technical and quality system aspect of data integrity, PDA volunteers composed of subject matter experts representing industry and regulatory agencies are working on three data integrity technical reports: laboratories (expected this quarter), manufacturing (expected for the fourth quarter of 2016) and integration with the quality system (projected for early 2017).

Additionally, the FDA's **Karen Takahashi,** Senior Policy Advisor, CDER, will offer the Agency's perspective on data integrity during a breakfast session scheduled for 7:15 a.m., Wednesday, Sept. 14, during the *2016 PDA/FDA Joint Regulatory Conference.*

Assuring data integrity is a fundamental responsibility of pharmaceutical companies, however, this seemingly simple task is becoming increasingly complex as the industry transitions from a paper-based system, to a hybrid paper-electronic system, and finally to a paperless system. PDA volunteers have stepped up their efforts to maintain the bond of trust and uninterrupted supply of medicines our patients deserve. After all, we are in the business of saving and improving lives.

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# A First in Europe; A First and 25th in USA

Who knows what impact Brexit will have on the European Medicines Agency and the broader European Union, if much at all, but the headlines failed to ramp down the buzz surrounding PDA's first European *Annual Meeting*. As stocks and currency crashed and rebounded all around, participants in this inaugural event experienced a number of interesting talks on a variety of industry topics. PDA's entire Board of Directors was on hand to experience the event, which included a lively exhibition hall and PDA Education courses. As for myself, I've returned from the two-day conference with at least six articles planned for future issues.

If you were an attendee, you wouldn't have guessed there was political intrigue during your time in Berlin (unless you were in a large crowd when Iceland beat the U.K. in football). All around the Estrel Hotel were signs of continued rebirth in Berlin as the city continues its reunification. More than 25 years ago, plans were made to reunite the city and the country. Today, tremendous progress has clearly been made (take a simple stroll through any part of the city if you're not certain). But more is to come, as evidenced by the countless number of cranes dotting the skyline in every direction. The Estrel itself is located in a developing neighborhood in the southeastern part of the city known as Neukölln. It was a delightful place, and one I hope PDA returns to for a future PDA Europe *Annual Meeting*.

What is truly remarkable is that PDA is celebrating its own quarter-century milestone with the 25th *PDA/FDA Joint Regulatory Conference* (JRC). Much like PDA Europe's first *Annual Meeting,* the PDA/FDA JRC had humble beginnings. A conference focused solely on regulations was not typical for PDA at the time, so it took a few years for the event to gain traction. Before long, however, the JRC grew and even surpassed the size of the U.S. *Annual Meeting*. Twenty-five years later, as you can see throughout this edition of the Letter, the PDA/FDA JRC remains one of the most important annual events PDA sponsors. This year, FDA officials will delivery nearly 30 presentations. It is truly the one must-attend event we offer.

If you think the EU is the only place with drama, don't forget that this year's PDA/FDA JRC will occur in the heart of the 2016 U.S. presidential election, although I'm not sure Brexit is as controversial as the current U.S. election. Those attending the JRC will hardly know an election is looming once here in Washington, unless they turn on the television and see the steady stream of political ads that are just now starting to hit the airwaves. The JRC has occurred during six previous presidential elections and will, in all likelihood, see many, many more. Let's hope!

Just a week prior to the PDA Europe *Annual Meeting,* PDA sponsored its first conference on biosimilars. This is a topic that will become ever-more important as more come to market with great anticipation over the next few years. The conference was cosponsored with PQRI, and while the numbers for the meeting did not reach expectations, the idea is to hold the meeting again in 2017. Who knows, but maybe both the PDA Europe *Annual Meeting* and the *PDA Biosimilars Conference* will one day celebrate silver anniversaries, too. And if they do, you can read all about them in the *PDA Letter*.

**PDA Letter**

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**PDA Global Headquarters — Bethesda Towers**

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

**PDA Europe — Am Borsigturm 60**

13507 Berlin, Germany
Tel: 49 30 4365508-0 Fax: +49 30 4365508-66
*petzholdt@pda.org*

**PDA Training & Research Institute**

4350 East West Hwy., Suite 600
Bethesda, MD 20814 USA
Tel: +1 (301) 656-5900 Fax: +1 (240) 482-1659
*info-tri@pda.org*

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