People • Science • Regulation

PDA Letter

Volume LI • Issue 9 www.pda.org/pdaletter October 2015

Biosimilar Developers Must Scale Mountains of Data

28

Show Issue

Follow this button to find articles on the Universe of Pre-filled Syringes and Injection Devices

Calling All Active PDA Members – Vote Now!

Online voting is now open for the 2016 PDA Board of Directors Election

PDA members, online voting has opened for the **2016 PDA Board of Directors Election**. Take a moment and vote for your candidates of choice at **pda.org/vote**.

All PDA members in good standing as of **midnight on August 11, 2015 are eligible to vote**. Voting closes at **11:59 p.m. EST on November 15, 2015**. Any votes cast after this date and time will not be accepted.

If you need assistance, please contact PDA at +1 (301) 656-5900 or vote@pda.org.

Thank you for being a valued PDA member and for voting.

Instructions for Voting:

- Go to **www.pda.org/vote**
- Log into the system using your PDA Member ID and last name
- Please read the instructions for each question carefully
- Review the choices for each position then select a candidate for that position
- When you complete your ballot, review your selection and then check the participant consent box and click on the "SUBMIT" button
- You have now completed the voting process
- You can view and print your receipt or just exit the PDA eBallot System

pda.org/vote

The Parenteral Drug Association Presents...

2015 PDA/FDA Vaccines Conference

The New Vaccinology: Global Trends in Development, Manufacturing & Regulation

December 1-2, 2015 | Bethesda, MD

Bethesda North Marriott Hotel and Conference Center

Exhibition: December 1-2 | Courses: December 3-4

Conference Theme: *Focusing on Today's Challenges to Deliver Tomorrow's Vaccines*

The global demand for vaccines that prevent current and emerging infectious diseases is increasing, but vaccine producers are challenged with creating an environment that can accelerate development, licensure and availability of novel vaccine candidates. The *2015 PDA/FDA Vaccines Conference* will address global technical and regulatory challenges and showcase innovative manufacturing approaches and how they are being applied in an effort to effectively deliver new vaccines to the global patient population.

The Conference will simulcast sessions, in real-time, between Bethesda, Maryland and Berlin, Germany and provide a unique opportunity for attendees to engage with world-renowned experts representing industry, regulatory and public health organizations.

Topics include:

- **Lessons Learned from Technology Transfer of Vaccines Quality Control Tests**
- **Challenges and Regulatory Expectations**
- **Impact of the Combination Products Regulations and GMP Guidance on Vaccine Products**
- **Analytical Methods for Vaccines: FDA's Perspective and Overview**
- **Clinical Trials and IRBs in Developing Countries**
- **Using Information Technology-Based Tools to Optimize Yields in Vaccine Production**

Be part of the global discussion about emerging trends in vaccine development and manufacturing. Learn more and register for the *2015 PDA/FDA Vaccines Conference* by visiting pda.org/vaccines2015

PDA Europe will host the *2015 Europe Vaccines Conference* simultaneously, December 1-2 in Berlin, Germany. Six presentations will be simulcast between these two locations, providing you with a truly global perspective on the evolution of the vaccine industry.

Immediately following the Conference, the *2015 PDA Vaccines Course Series* will expand on the material presented with *Current Challenges in Vaccines* (December 3) and *Modern Manufacturing and Trend Monitoring Techniques for Vaccines* (December 4) courses at the Bethesda North Marriott Hotel and Conference Center. Select one or more courses to learn about the complexities and unique challenges in the vaccine field and effective methods for the manufacture of vaccines.

For more information and to register for the *2015 Vaccines Course Series,* visit pda.org/vaccinescourses

PDA Letter

Volume LI • Issue 9 www.pda.org/pdaletter

Cover

Cover Art Illustrated by Katja Yount

Departments

News & Notes

People

Science

Regulation

Voices of PDA

Contents

Features

PDA Letter Offers a New Online Reading Experience

The *PDA Letter* is now at your fingertips 24/7! The next time you turn on your tablet or smartphone device, skip the endless emails and take a few minutes to visit the newly enhanced *PDA Letter* website (www.pda.org/pdaletter).

The new, responsive design accommodates all electronic reading platforms. All content from recent issues is now available online in dynamic HTML, which is much more reader friendly than the flat PDF document that was available previously.

Article are categorized by the three primary PDA areas: People, Science and Regulation for ease of access.

All of our multimedia content (infographics, photos and podcasts) are now available in one central location on the *PDA Letter* website! Plus, our regular columns (Volunteer Spotlight, Tools for Success, Voices of the Board, etc.) are available online as well.

In addition, there's a new online form to contact the *PDA Letter* editorial team with your feedback and to let us know if you're having technical issues.

Future enhancements to the site include real-time publishing, email alerts, videos, online exclusive content, and improved search capabilities.

For those that prefer "offline" reading, the full PDF of each issue going back to 2001 will still be provided.

From its humble beginnings from a typewriter in the 1940s to the new mobile-compatible website, the editorial team behind the *PDA Letter* hopes to continue delivering a product that meets the revelevancy of PDA's members, no matter the format.

Since the site's launch in mid-September there have been over a thousand page views!

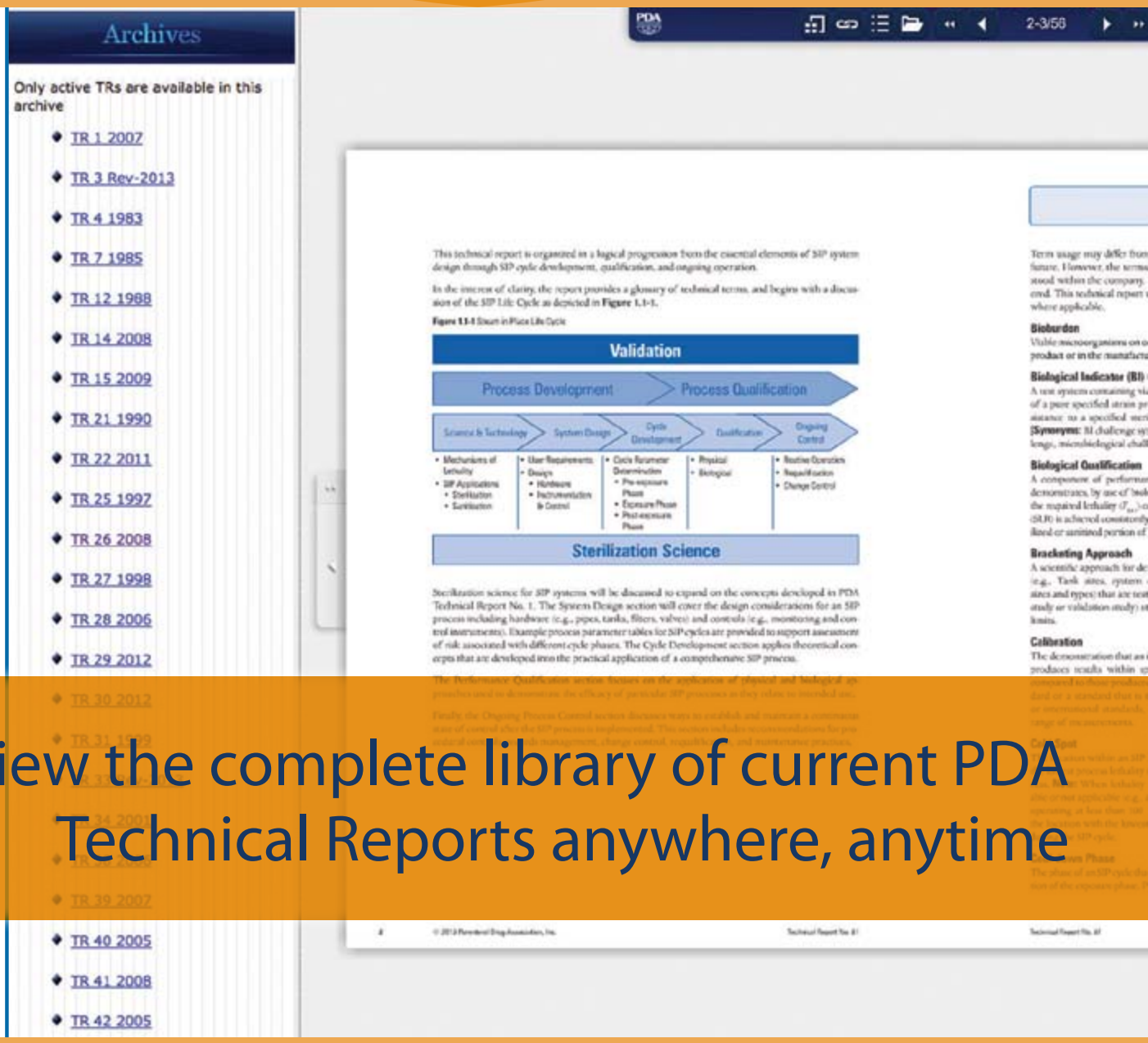
Put Your Touch on the PDA Letter

The redesigned website of the *PDA Letter* would not have been possible without the assistance of the all-volunteer *PDA Letter* Editorial Committee (PLEC). This team of 16 subject matter experts representing various facets of the industry helps set the direction of the *PDA Letter,* including reviewing articles submitted for publication in the Letter, identifying topics of interest for future issues and assisting the editorial team with various initiatives such as readership surveys.

Currently, there are a number of openings for the 2016–2017 term.

For more information about this two-year volunteer commitment, please contact **Rebecca Stauffer** at stauffer@pda.org

PDA's Technical Report Portal



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

For more information and to view PDA's Technical Report Portal please visit:

trarchive.pda.org/t/26426

Licensing options available; contact Janny Chua at chua@pda.org

PDA Vol[illegible]r Spotl[illegible]

Brigitte Reutter-Haerle

- Vice President, Marketing/ Corporate Communications
- *Vetter Pharma International GmbH*
- Member Since | 2005
- Current City | Ravensburg, Germany

Being an active member of PDA has afforded me the opportunity to enhance my skills as a leader

Brigitte finds inspiration in nature

Why did you choose to join PDA?

Honestly, I know of no other organization that offers all that PDA does in regards to cutting-edge discussions and insight on scientific topics, as well as extensive networking opportunities with leading experts in the field. PDA's international community has cultivated an environment of sharing and exchange of valuable information.

How can new members begin volunteering for PDA?

There is no lack of need for newcomers nor lack of work. As someone who has been active in PDA for many years, I suggest that new members begin by participating in a PDA interest group meeting. Also, if a new member is an expert in a particular area, submitting presentations or posters for conferences is a terrific way to get known, meet new people, contribute to the organization, and feel a real sense of reward. **[Editor's Note:** Brigitte will actually be presenting at this year's *Universe of Pre-filled Syringes and Injection Devices* meeting.**]**

What inspired you to choose your current career path?

I find the challenge of developing new delivery devices and their filling for increasingly complex molecules fascinating and inspiring. Vetter is one of the leading companies in manufacturing prefilled drug/delivery systems, and for this reason, has given me the opportunity to interact with many of the leading pharmaceutical and biotech companies and learn about their different drug products. What we do in manufacturing is interesting and challenging, of course, but the role of the department I lead, which requires me to communicate both internally and externally, is also important since it is critical that we inform our audiences why our industry is a key driver in the delivery of quality healthcare.

What are some of the latest tech trends you're seeing?

We expect to see a continued increase in automation in the area of production to minimize human interventions as much as possible. In addition, we are working on processes to increase product quality such as Quality by Design, Process Analytical Technology and serialization systems, to name just a few.

PDA
Parenteral Drug Association

The Parenteral Drug Association presents:

2015 PDA Europe

The Universe of Pre-filled Syringes & Injection Devices

2 Nov | **Pre-Conference Workshops** | *Smart Medication | Innovative Combination Products | Secondary Packaging for Parenterals*

5-6 Nov | **Training Courses** | *Test Methods for Pre-filled Syringe Systems | Development and Manufacturing of a Pre-filled Syringe Elastomers | A Tale of Two Materials: What the Glass vs. Polymer Debate Really Means*

Make sure to be part of the World's largest event on this subject.

3-4 November 2015

Austria Center Vienna
Vienna | Austria

Welcome Party Sponsor: TERUMO

Platinum Sponsors: SHL GROUP, West

Gold Sponsors: BOSCH Invented for life, Insulet, ompi, DATWYLER

Silver Sponsors: MITSUBISHI GAS CHEMICAL, VETTER, OWEN MUMFORD

Media Partner: Drug Development & Delivery, pharmind, PMPS, drugDELIVER

Missouri Valley Chapter Initiates New Student Chapter

Jeff Kisslinger, ProPharma Group

PDA's Missouri Valley Chapter is pleased to announce its newest affiliation, the University of Missouri-St. Louis (UMSL) Student Chapter. The official initiation of the student chapter took place June 12, presided by myself and **Jeffrey Wiegers.** The new chapter has 14 members and is expected to grow over the coming year. **Jeremy Ridenour,** its first President and a PhD student in chemistry stated, "We are really excited to form this student chapter into something that will be mutually beneficial for us and the parent chapter. Having worked in industry for many years and then gone back to school, I can really see how great of an opportunity this is for everyone involved."

The newest student chapter has wasted no time in getting the ball rolling. They recently hosted **Dan Reichert** who spoke at their meeting on "Starting the Career"—a topic that held everyone's attention. **Eldon Henson**, former President of the Missouri Valley Chapter, attended and was pleased. ➤

(l-r) Matthew Queensen, Jeremy Ridenour (President), Matthew Stark, Michael Bengston (Secretary), Ryan Cantwell (treasurer), and Joseph Meisel

"We are excited about the formation of the UMSL Student Chapter," he said. "So far, it appears we are adding value to these students exactly as we had hoped. We look forward to this ongoing collaboration."

The core group of UMSL students realizes the significant value that can be derived from an association with PDA. The students are aggressively networking with their new industry colleagues and plans have been made to expand the chapter to new students arriving in the fall.

Let's all welcome the University of Missouri-St. Louis PDA Student Chapter!

Jeff Wiegers (second from right) hands Jeremy Ridenour (left) his official acceptance letter from PDA with Jeff Kisslinger (right) while Michael Bengston (back) looks on

PDA Who's Who

Eldon Henson, Vice President, Quality Operations, Mallinckrodt Pharmaceuticals

Jeremy Ridenour, Student, University of Missouri-St. Louis

Dan Reichert, Director, Human Resources, Mallinckrodt Pharmaceuticals

Jeffrey Wiegers, Senior Director, Quality and Operations Integration, Mallinckrodt

TOOLS FOR SUCCESS

Brought to you by the PDA Career Center.
Go to www.pda.org/careers for the latest opportunities.

PDA Involvement Results in a Lifetime of Achievement

Rebecca Stauffer, PDA

IN MAY, PDA recognized longtime volunteer and industry consultant, **Dana Morton Guazzo,** PhD, for lifetime achievement at the *2015 PDA Pharmaceutical Packaging Conference.* This served as the culmination of a comprehensive volunteer history with PDA and incredible career progression spanning three decades.

"Clearly, my career would be incomplete without PDA," stated Guazzo.

Over the past 37 years her involvement has included teaching PDA Education courses, presenting at conferences, serving on planning committees for meetings, reviewing articles for the *PDA Journal of Pharmaceutical Science and Technology,* developing technical reports, and other activities.

She joined PDA at the urging of her manager not long after starting her first job in industry with Warner Lambert Co. in the firm's sterile product formulation department. As a newcomer to pharma manufacturing fresh out of the University of Kentucky's College of Pharmacy, "It didn't take long to realize I needed to broaden my education if I wanted to do the kind of research I was interested in," she said. "So, I applied and was accepted to the Rutgers University College of Pharmacy pharmaceutical sciences graduate program."

Guazzo obtained her MS degree in 1984 after years of attending evening and weekend classes and working full-time for Warner Lambert and Schering-Plough. While at Rutgers, her advisor, **Nicholas Lordi,** and her mentor at Schering-Plough, **Thomas Ambrosio,** encouraged her to understand the primary packaging of a parenteral product in order to be a good scientist. Thus, she found a niche in the specialty of parenteral packaging.

After receiving her master's degree, Guazzo then entered into a PhD program, also at Rutgers. Here, PDA came to her aid: She received a grant from PDA to support research on her dissertation, "Quantitative and Mechanistic Measurements of Parenteral Vial Container Closure Integrity."

"The grant was for $15,000," she said. "This amount doesn't seem to like much today, but it allowed me to shift to full-time research, and cut back to part-time employment."

In May, **Roger Asselta** (left) and PDA President **Richard Johnson** (right) presented Dana with her Lifetime Achievement Award at the *2015 PDA Pharmaceutical Packaging Conference*.

Making the Jump to Consulting

She received her PhD in 1988 and her entire doctoral research was published in a series of six articles in the *PDA Journal of Pharmaceutical Science and Technology* ***(1-6)***. For the next decade, she worked in various positions at Johnson & Johnson while continuing to volunteer for PDA. Then, in 2000, she left the company to spend more time with her children.

Initially, she did not plan to become a consultant. Yet her former professional colleagues from PDA continued to contact her for help in resolving packaging-related issues. This led her to create her consulting business, RxPax, LLC, which provides leak testing expertise and education on container-closure issues, resulting in safer products for the market.

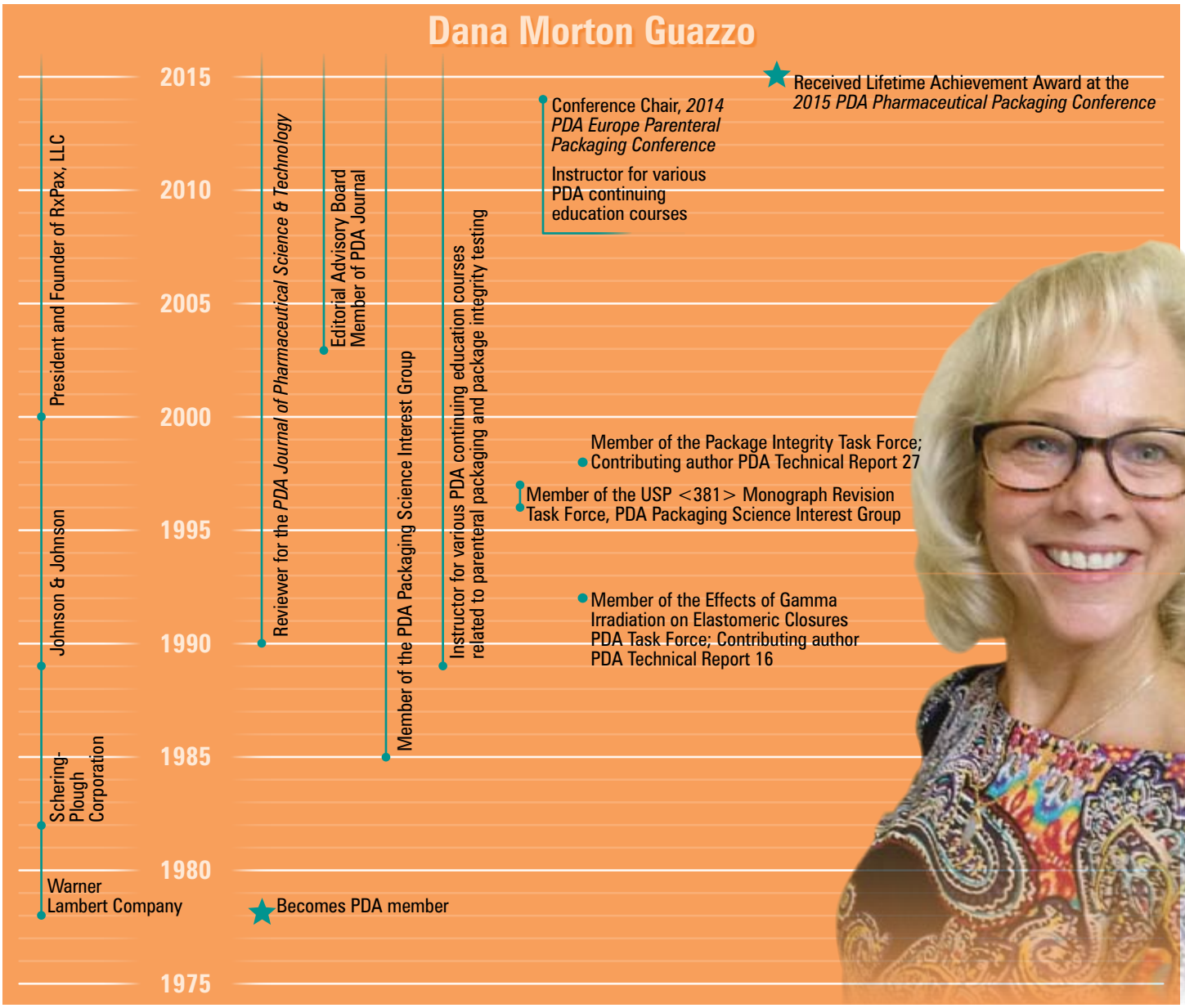
Guazzo noted that her success was in large part due to her involvement as a PDA volunteer.

"PDA helped me be a better consultant in several ways. PDA provided opportunities for networking, continuing education, and publishing, for example," she said. "But these same opportunities would be helpful to anyone, not just consultants. Regardless of whether a person is self-employed or works for big pharma, everyone in the parenteral product world needs these opportunities and support."

She advises anyone considering moving into consulting to consider the following:

"First, before giving answers to your client, ask lots of questions in order to fully understand the background to the problem being posed. Often, you can uncover previously undisclosed information which brings clarity and direction to problem resolution. Second, be willing to tell your clients what you do and don't know. Be brave enough to say you don't have all the answers, but that you are willing to learn and will do your best.

Continued at bottom of page 14



eye on education

Simulated Media Fill Draws Student to Pharma Industry

Reid Nakashima, Azusa Pacific University

My name is **Reid Nakashima,** and I am a senior at Azusa Pacific University, majoring in chemistry. Over the summer, I had the opportunity to intern at PDA's Training and Research Institute (TRI). This internship consisted of two roles: support staff and student. As TRI support, I learned how to write and review SOPs. As a student, I participated in the "Aseptic Processing Training Program," which is an intensive two-week course that combines both lecture and hands-on laboratory training.

Here, I applied aseptic processing concepts and procedures I learned in the classroom to a simulated media fill. These procedures included first air, gowning, environmental monitoring and aseptic technique. I learned how to operate a variety of equipment, such as a fill machine, an autoclave, a dry heat oven and a filter integrity tester. I also became familiar with both viable and nonviable air samplers such as SAS, RCS, R2S, SMA and PMS.

In particular, I enjoyed participating in this simulated media fill because it was all hands-on. I took from this experience the importance of the "first air" concept to maintain sterility throughout the process. First air includes body position in the fill room, the use of tools, and even the way one opens bags to prevent contamination. I am now aware of how parenteral pharmaceuticals are filled and the significance and details of each step involved in making drug products used by millions of patients every day. It amazed me how one wrong move could potentially contaminate the entire fill and lead to the disposal of critical medicines. The reliability required by each sanitizer, machine, and operator was jaw-dropping.

Before this summer, I had no idea what career to pursue. My experience at PDA, however, led to my decision to stay in pharma. Every day, I learned not only the large, critical concepts of aseptic processing, but also the smaller, incremental details associated with it.

At PDA, I was welcomed by some of the friendliest staff, all of whom made me feel as though I was not just an intern, but a part of the PDA family. I would like give a special thanks to the TRI team: **Bob Dana, Stephanie Ko, Kimberly McIntire,** and **Stephanie Grinan.** This was a unique experience I will never forget.

Tools For Success continued from page 13

Lastly, carefully weigh your ability to tolerate the ups and downs of an unpredictable income and work schedule. Having a supportive family who backed me and believed in me made all the difference."

She encourages all PDA members to become more involved and to learn as much as possible through PDA interest groups, publications, education, and events.

"Study the history of the topics you are interested in. Read primary research articles on these topics, going back as far as you can to gain perspective on current approaches and thinking. Sometimes you can rediscover important information that was previously published, but has since been forgotten. Learning history helps to prevent repeated mistakes."

All in all, Guazzo has achieved numerous milestones throughout her career. Yet she recognized that her success lies in the partnerships she's cultivated over the years.

"God blessed me with opportunities to work with so many wonderful people who helped me, encouraged me, and supported my work over the years," She said about her PDA award. "I didn't feel the honor was just for me, but for all those folks, too. I am extremely grateful."

References

1. Morton, D.K. "Container/closure integrity of parenteral vials." *Journal of Pharmaceutical Science and Technology* 41 (1987) 145-158.
2. Morton, D.K., and Lodi, N.G. "Quantitative and mechanistic measurements of container/closure integrity: Viscoelastic measurements of elastomeric closures." *Journal of Pharmaceutical Science and Technology* 42 (1988) 127-141.
3. Morton, D.K., and Lordi, N.G. "Residual seal force measurements of parenteral vials. I. Methodology." *Journal of Pharmaceutical Science and Technology* 42 (1988): 23-29
4. Morton, D.K., and Lordi, N.G. "Residual seal force measurements of parenteral vials. II. Elastomer evaluation." *Journal of Pharmaceutical Science and Technology* 42 (1988): 57-61.
5. Morton, D.K., Lordi, N.G. and Ambrosio, T.J. "Quantitative and mechanistic measurements of container/closure integrity. Leakage quantitation." *Journal of Pharmaceutical Science and Technology* 42 (1989) 88-96.
6. Morton, D.K., et al. "Quantitative and mechanistic measurements of container/closure integrity. Bubble, liquid, and microbial leakage quantitation." *Journal of Pharmaceutical Science and Technology* 42 (1989): 104-108.

The Parenteral Drug Association presents the...

2015 PDA Pharmaceutical Quality Metrics Conference

Quality Metrics in Practice: Accelerating Quality Performance

November 9-10, 2015 | Bethesda, MD

Bethesda North Marriott Hotel and Conference Center

Exhibition: November 9-10 | Course: November 11

Conference Theme: *Operationalizing Quality Metrics: Putting Theory into Practice*

This year's *PDA Pharmaceutical Quality Metrics Conference* advances the conversation regarding successful strategies to implement quality metrics into the pharmaceutical quality systems program. With the release of FDA's Draft Guidance on Quality Metrics, we are one step closer to making metrics a key, universally accepted driver of risk-based decision making and continuous improvement.

There is no better time for a conference dedicated to this important topic!

Learn how to build an efficient and effective quality metric program with limited resources from the experts who have done so. Find out how a metrics program can drive product quality improvements and foster a strong quality culture, while helping to prevent the unintended consequences that can result from too much focus on metrics and foster bad behavior. FDA and industry informatics experts will discuss how to enable a metrics program and assure data accuracy and integrity during the transfer and submission process.

FDA leadership will provide the latest updates on new programs, and industry thought leaders will share their vision of the value of FDA's Metric Program along with best practices for quality metrics.

Hear from noted experts including:

- **Deborah Autor,** Senior Vice President, Strategic Global Quality & Regulatory Policy, *Mylan, Inc.*
- **Jerry Coates,** Director, Risk Modeling, *GlaxoSmithKline*
- **Gerald Heddell,** Director, Inspection Enforcement & Standards Division, *MHRA*
- **Carol Montandon,** Chief Quality Officer, Vice President, Quality & Compliance, *Johnson & Johnson Consumer Inc.*
- **Russell Wesdyk,** Acting Office Director, Office of Surveillance, OPQ, CDER, *FDA*

Be a part of the dialogue for the next frontier for quality metrics! To learn more and register, visit pda.org/metrics2015.

Following the conference, on November 11, PDA will be hosting a course on *The Quality Culture and its Measurement*, taught by a recognized industry expert, who will present his perspective on how to select appropriate metrics to measure quality and determine how best to collect and use the data to improve the Quality System.

To learn more and register, visit pda.org/metricscourse.

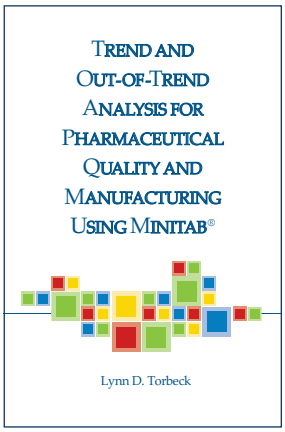
snapshot

In*Print*

Trend and Out-of-Trend Analysis For Pharmaceutical Quality and Manufacturing Using Minitab®

Lynn D. Torbeck

The following is excerpted from the chapter, "Data Presentation," which appears in the PDA/DHI book, Trend and Out-of-Trend Analysis For Pharmaceutical Quality and Manufacturing Using Minitab®, *by Lynn Torbeck, Torbeck and Associates. The book can be purchased at www.pda.org/bookstore.*



OUTLIERS AND OUTLIER MANAGEMENT

Mavericks, rogues, flyers, wild values, spurious response, unrepresentative data and contaminated data are some of the terms that have been used to describe data that are disturbing to the observer.

In fact, Barnett and Lewis (1994), defined outliers as "...observations 'surprisingly far away from the main group'."

Other more formal definitions have been proposed.

> *"In a sample of n observations it is possible for a limited number to be so far separated in value from the remainder that they give rise to the question whether they are not from a different population, or that the sampling technique is at fault. Such values are called outliers. Tests are available to ascertain whether they can be accepted as homogeneous with the rest of the sample."* (Marriott, 1990)

> *"We shall define an outlier in a set of data to be an observation or (subset of observations) which appears to be inconsistent with the remainder of that set of data."* (Barnett and Lewis, 1994)

Historically, the attitude toward outliers has been that they are mistakes that must be corrected or removed. *Ad hoc* and very informal procedures have been used to reject potential outliers.

Continued at bottom of page 26

PDA Journal *Top 10*

PQRI, Particulate Matter in Injectables Still the Top Draw for Journal Readers in August

1. Review

Stephen E. Langille, "Particulate Matter in Injectable Drug Products" May/June 2013

2. PQRI Special Section – *Review*

Diane Paskiet, et al. "The Product Quality Research Institute (PQRI) Leachables and Extractables Working Group Initiatives for Parenteral and Ophthalmic Drug Product (PODP)" September/October 2013

3. PQRI Special Section – *Research*

Dennis Jenke, et al. "Extractables Characterization for Five Materials of Construction Representative of Packaging Systems Used for Parenteral and Ophthalmic Drug Products" September/October 2013

4. PDA Paper

Steve Mendivil, et al. "PARENTERAL DRUG ASSOCIATION POINTS TO CONSIDER: Pharmaceutical Quality Metrics Updated September 2014" September/October 2014

5. Research

Oliver Gordon, et al. "Comparison of Different Calculation Approaches for Defining Microbiological Control Levels Based on Historical Data" May/June 2015

6. PDA Paper

Stan Bukofzer, et al. "Industry Perspective on the Medical Risk of Visible Particles in Injectable Drug Products" January/February 2015

7. Case Study

Thomas Murphy, et al. "Evaluation of PDA Technical Report No 33. Statistical Testing Recommendations for a Rapid Microbiological Method Case Study" July/August 2015

8. Research

Ada Hui, et al. "Kinetic Modeling of Methionine Oxidation in Monoclonal Antibodies from Hydrogen Peroxide Spiking Studies" July/August 2015

9. Letter to the Editor

Perceval Sondag, Raphael Joie, and Harry Yang, "Comment and Completion: Implementation of Parallelism Testing for Four-Parameter Logistic Model in Bioassays" July/August 2015

10. Research

Norhan S. Sheraba, et al. "Quality Control Testing for Tracking Endotoxin-Producing Gram-Negative Bacteria during the Preparation of Polyvalent Snake Antivenom Immunoglobulin" July/August 2015

How Can Companies Meet Demands for Self-Care?

Graham Reynolds, West Pharmaceutical Services, Inc.

Facilitated by advancements in drug delivery systems, new economic realities now drive more and more care into the home environment and out of the physician's office. Those involved in drug development and design must now take into consideration a product's containment and delivery mechanisms in the face of this new reality. Delivery system design is becoming an even more essential part of the drug delivery process, even in the earlier stages of drug development.

With this in mind, how can those involved in drug development employ the collective technical expertise of various scientific and engineering disciplines to meet the changing needs of patients with chronic diseases—who represent a large share of the patient population using prefilled delivery devices for self-injection? There are many potential ways to work within these disciplines, which can be grouped into three general categories.

1. Designing for Affinity

As more patients themselves utilize devices instead of healthcare professionals, it is becoming imperative to design devices that patients not only can use, but want to use **[Editor's Note:** See "Patient Wants Should Drive Prefilled Syringe Design" in the July/August 2015 issue**].** Adherence rates for chronic conditions can be around 50%, so it is critical to find ways to improve patients' ability and desire to maintain an appropriate treatment regimen. The overall patient experience can be improved by a combination of patient-centric device design, effective training and onboarding, and tools and motivation to foster adherence. As the marketplace places more emphasis on "Pay for Performance," these factors become even more important.

Any effective drug delivery system always starts with a suitable container closure system; companies should focus on the scientific, engineering and regulatory considerations of primary packaging for injectable biotech products early in the drug development processes. In addition to focusing on on bringing a safe and effective product to the market, companies must also take the opportunity to differentiate individual products with unique packaging and delivery systems that may help aid patient compliance, and ultimately, treatment outcomes.

While it's optimal to think about delivery systems during the development process, medication adherence can also be engineered into pharmaceutical products that have already cleared regulatory approval. A company might improve and retrofit usability features into manual delivery systems that might not be faring as well on the market as they should. One example of this might be adding ergonomic features for a self-injector to aid patients with dexterity issues.

The overall patient experience can be improved by a combination of patient-centric device design, effective training and onboarding

2. Moving to Autoinjectors

Some patients either don't want to inject themselves with medications in prefilled syringes, or their condition makes it difficult. In some cases as the dose increases, it is difficult to administer the product consistently. Furthermore, some pharmaceuticals—including cutting-edge biologics—might require large volumes of viscous solutions, making a single-dose option either difficult or impossible. This is why many companies have turned to autoinjectors as the delivery solution of choice.

3. Developing Apps for Adherence

Designing a pharmaceutical product with quality packaging that's both convenient and safe but also passes regulatory compliance and clinical testing is a complex and lengthy process. Yet it doesn't take an accomplished industrial engineer or physician to understand the basic idea that a drug doesn't work if the patient doesn't take it.

New formulations such as once-a-month biologic injections take some burdens off of patients administering self-care. But as the time between doses grows, it becomes easier for patients to forget to take it. This leads to the challenge of reminding—and even rewarding—patients for medication compliance.

An important component of prescribing self-medication is effective, multisensory patient training on how and when to use the delivery system. One way to reinforce adherence involves using everyday technology that groups of patients are familiar with, such as smartphone and tablet apps.

For example, an app could record data gathered from an injection event. A physician could use this data to monitor a patient's self-care, serving as a proxy for office visits. The data would also offer a view of compliance over time. While many believe that connected systems are absolutely going to be the norm in the future, for now many pharmaceutical companies are looking for a more simplistic device accessory combination that they can utilize without the whole package (app included) being submitted for approval as a combination product.

Conclusion

New and innovative pharmaceutical delivery systems can optimize the quality of life and outcomes for patients by effectively managing the interrelationship ➤

Securely and confidently protecting the integrity of your cGMP biotechnology materials.

Masy's continuously-monitored biorepository facility securely stores clinical study samples, vaccines, drug compounds, production stock, medical devices, and other biologic products under precisely-controlled temperature and humidity requirements, from controlled room storage through cryogenic freezing, ensuring the integrity of these valuable materials.

You can have confidence that the materials you entrust to us will remain safe, secure, and compliant to your specifications and tolerances until you need access to them again.

Store your critical materials today with Masy BioServices.

Consider off-site, secure, and monitored cGMP biostorage for:

- Mirror banking
- Disaster recovery
- Contingency planning
- Overflow storage
- Transitional storage
- Long-term storage

Masy BioServices

Measurable Quality for Life Sciences

10 Lomar Park | Pepperell, MA 01463

www.masy.com

Validation Services | Calibration Services | cGMP Biostroage | Monitoring | Equipment Rental

of the four primary components: the drug, the primary container, the delivery system and the end user. These systems can help improve the overall value and effectiveness of pharmaceutical delivery systems, and help drive down costs for providers and insurers by keeping patients on their medication plans and avoiding health problems associated with nonadherence. This will require effective partnerships between pharmaceutical and biotech companies and their delivery system partners. **[Editor's Note:** A representative from West will copresent on "Improving Patient Adherence to Self-Injected Therapies," Wednesday, Nov. 4, 11:30 a.m. at the *Universe of Pre-filled Syringes and Injection Devices* meeting in Vienna, Austria**].**

About the Author

As Vice President, Marketing and Communications at West, **Graham Reynolds** leads initiatives to market novel delivery systems and develop strategies for future growth, including the acquisition and development of new technologies. His group is collaborating with HealthPrize Technologies, LLC on a customizable app linked to a drug delivery system that educates and rewards patients for compliant self-care.

Temperature Requirements for Devices

The following blinded, unedited remarks are taken from PDA Connect℠, an online forum that allows PDA members to discuss and share some of the most challenging issues confronting the pharmaceutical industry. The discussions on PDA Connect℠ do not represent the official views of PDA, PDA's Board of Directors or PDA members.

The PDA Letter *will periodically publish selected dialogue from PDA Connect℠. Join at community.pda.org and continue the conversation!*

The following dialogue is from the Combination Products Interest Group forum.

Questioner

Can anyone tell me if these two paragraphs (orange and green) are interpreted as different requirements or optional requirement between multi-use devices and single use devices, orange being for multi-use devices only?

This is from ISO 11608-1 Needle-based injection systems.

10.6 Dry-heat and cold-storage testing — Pre-conditioning

Assembled new NISs without containers or needles are placed in a test chamber for at least 96 h in theatmospheres given in Table 5.

Table 5

Dry heat 70- +/- 2 Cold -40 +/- 3.

System Designations C and D that are manufacturer-filled shall be subjected to pre-conditioning at the acceptable high and low storage temperatures, which shall be stated in the instructions for use.

Respondent

There is an inconsistency regarding the preparation step (orange text) for devices where the drug is integrated, however, the intent was that devices that did not have integrated containers which are assumed to contain drug (which are for the most part reusable) are tested at -40 and 70°C, whereas those where the container is integrated and assumed to contain drug (disposable for the most part) are only tested at the extremes of the temperatures stated on the labeling.

Vaccines Prove Complex but Critical for Global Health Needs

Kirsten Vadheim, PhD, BioCompliance Consulting

Vaccines are a critical aspect of our public health arena and form a specialized, highly diverse niche within the pharmaceutical world. Many vaccines are effectively combination products as they are manufactured into prefilled syringes or other delivery devices. Vaccine antigens are often conjugated with immunogenic proteins or formulated with adjuvants to improve the immune response to the desired antigen. Because adjuvanted vaccines cannot be sterilized, these products must be manufactured using aseptic processing, which considerably adds to the complexity and cost of the production process.

Many of the vaccines that form the backbone of the recommended immunization schedule in the United States rely on decades-old product development programs, manufacturing systems and facilities. Transfer of these manufacturing processes to modern facilities with state-of-the-art equipment represents a significant challenge. Analytical methods have also undergone immense changes over time; it is now possible to detect contaminants and evaluate products in ways not envisioned when these vaccines were initially developed. At the same time, assessing potency of each batch of vaccine remains a complicated and difficult procedure for many products lacking compendial reference standards.

The power of routine immunization programs to improve the health of people from infancy to old age, reduce childhood mortality and raise living standards has been well established in developed countries. Challenges now exist in expanding those benefits to areas of the world that lack a public health safety net. Recent experiences with the Ebola outbreak in West Africa, as well as recurrent outbreaks of MERS, SARS and avian influenza highlight the need to develop rigorous, ethical and effective mechanisms for the creation of safe and effective vaccines for newly emergent diseases in less developed parts of the world.

All these topics and more will be discussed at the *2015 PDA/FDA Vaccine Conference*. An impressive group of international experts present on these issues for two days of vibrant discussion. For the first time, we will link up with PDA's European conference on vaccines, held concurrently in Berlin, sharing presentations and Q&A between the two meetings.

For more information about the U.S. conference, go to www.pda.org/vaccines2015. For the European meeting, go to https://europe.pda.org/vaccines2015. To learn more about PDA Education courses following the U.S. conference, visit www.pda.org/vaccinescourses.

Find Answers to Your Pressing Drug Delivery Questions

Friedrich Haefele, PhD, Boehringer Ingelheim

Prefilled syringes and related products comprise one of our industry's largest niche markets. Autoinjectors, combination products and others have become commonplace.

But as with any advancement in drugs and devices, questions have arisen. What benefits does the systems engineering approach offer for developers? What happens if a raw material change triggers a new plunger rod design? How can a company implement a flexible approach to aseptic processing based on nested containers? These are just a sample of the questions that have arisen in the field.

This year's *Universe of Pre-filled Syringes and Injection Devices* conference in Vienna Nov. 3–4 promises to offer a discussion forum for those who seek answers to these, and other, pressing questions concerning the prefilled syringe market.

For example, in the track, "Novel Formulations Generate New Device Challenges," Osaka University's **Susumu Uchiyama** will talk about the advantages of polymer-based prefillable syringes. Boehringer's **Brian Greven** will look at flexible and modular filling lines in the "Manufacturing/Fill-Finish & Labelling" session, while **Torsten Müller** and **Dana Daneshvari** of Janssen - Cilag will discuss implementing ready-to-use prefilled syringes for large molecules in the new technologies session.

In addition to these invigorating talks, some 140 vendors and manufacturers will showcase their products and services, as well as latest innovations, with equipment displays and live demonstrations.

Learn about sponsor SHL Group's Amber autoinjector that uses Pushclick™ technology, enabling the device to activate simply by pressing against the injection site. Hear from representatives of Insulet Corporation about Omnipod — the only insulin pump featuring wireless technology.

For more information and to register, go to https://europe.pda.org/UPS2015.

New Data Available on LPS and LER Phenomena

James Cooper, PharmD

For the past two years, the topic of low endotoxin recovery (LER) has dominated discussions at various microbiology conferences and literature following concerns raised in 2013 that endotoxin might not be detected with LAL reagent in many monoclonal antibody (mAb) biologics ***(1).*** Widespread studies were initiated to determine if these drug products presented a unique form of inhibition to the BET (Bacterial Endotoxins Test) or if the investigators had misinterpreted their data. Close scrutiny of the first report revealed that the spiking analytes were LPS (lipopolysaccharide) standards rather than native endotoxin.

Two recent publications clarified the so-called LER phenomenon, more correctly defined as LLR, or low LPS recovery ***(2, 3).*** The cause of the interference was traced to excipients in the drug products. Divalent cation chelating buffers in undiluted mAb biologicals, particularly citrate, greatly disperse LPS, such as CSE, and render it nondetectable in the bacterial endotoxins test (BET) and rabbit pyrogen test (RPT). The LPS in native endotoxin, however, is imbedded in cell wall fragments and protected from the dispersing effect of chelating buffers. Positive controls made from preparations of naturally occurring endotoxin (NOE), prepared in the laboratory or taken from natural sources, are recovered in endotoxin hold-time studies. Inoculation of NOE (derived from *Enterobacter cloacae)* and RSE (Endotoxin Reference Standard, an LPS) in a pyrogen test produced compelling results. NOE and RSE in saline were recovered by BET and were pyrogenic in rabbits at zero and 24-hour times. In the presence of a chelating buffer matrix, RSE was BET and RPT negative at 24 hours; in contrast, NOE was fully recovered by BET and pyrogenic both at zero and 24 hours ***(2).*** Valid recovery of NOE verifies that inadvertent endotoxin contamination would be detected when undiluted mAb solutions are suitably prepared for a BET.

Jay Bolden, a Consulting Biologist for Eli Lilly and Company, recently reported that endotoxin was fully recovered over a 60-day period from a mAb product formulated in impure tap water ***(4).*** Such recovery is significant to those who are skeptical about the role of NOE in these hold-time studies. From these reports, we have learned that LPS and endotoxin are not equivalent in their behavior in all milieu and we are reassured that the BET is not limited in specificity.

Since the new data confirms that endotoxin is recoverable from undiluted mAbs, it is unlikely that LER exists. NOE, the seemingly logical analyte for endotoxin hold-time studies, is recovered in chelating buffers ***(2–5).*** Surprisingly, the U.S. FDA declined to accept spiking analytes made from NOE in BLAs; if a biologics producer is unable to conduct studies with LPS, they must use the RPT. The Agency has also asked the industry to find ways to recover LPS controls or use new endotoxin detection methods, seemingly impossible tasks. A reasonable alternative to the FDA position is a protocol that assesses the recovery of LPS and NOE, in parallel, in a biological product. The recovery of NOE or recovery of both indicates that endotoxin would be detected by compendial methods. As with all other types of drugs, there will be unique cases of inhibition that require further study. It is notable that no pyrogenic outbreaks have occurred in the LAL era due to inability to detect endotoxin ***(6).*** A return to the controversial, costly and variable Pyrogen Test is unwarranted and has no value to healthcare.

PDA has established a mechanism for PDA members to resolve controversial issues regarding low LPS and endotoxin recovery in biologicals through its Low Endotoxin Recovery Task Force. More information about the task force's initiatives will be published in upcoming issues of the *PDA Letter.*

PDA wants to hear from you on LER/LLR!

Complete the 2015 PDA Low Endotoxin Recovery (LER) and Hold Study Survey by Nov. 10.

This survey will aid the task force in producing points to consider for developing a standard test method for LER hold studies based on current FDA expectations for BLA submissions. Because of the conflicting opinions on the value of LER hold studies, the task force will be conducting further investigation into the mechanisms behind LER and the true source of any safety concerns, including the validity of measuring LER versus another contaminant.

https://www.surveymonkey.com/r/LowEndotoxinRecovery

References

1. Chen. J., and Vinther, A. "Low Endotoxin Recovery (LER) in Common Biologics Products." Presented at the 2013 PDA Annual Meeting, Orlando, FL, April 2013.
2. Bolden, J. et al., "The use of endotoxin as an analyte in biopharmaceutical product hold time studies." *Pharmacopeial Forum*, 41 (2015).
3. Bolden, J., et al. "Evidence against a bacterial endotoxin masking effect in biologic drug products by *Limulus* amebocyte lysate detection." *PDA Journal of Pharmaceutical Science and Technology* 68 (2014):472-477.
4. Bolden, J. "Low LPS and endotoxin recovery: keeping an eye on the big picture. "Presented at the PMF Bacterial Endotoxins Summit, Iselin, NJ, September 2015.

Continued at bottom of page 35

REMEMBER IN THE OLD DAYS WHEN THE ENDOSAFE®-PTS™ HAD BUTTONS?

INTRODUCING THE ENDOSAFE® NEXGEN-PTS™

Color touch screen. Wi-Fi. Barcode scanning. Password protection. Enhanced reporting.
The features you want, in a tool you need.

Discover the next generation of endotoxin testing at www.criver.com/nexgen-pts.

A PASSION FOR INNOVATION | www.criver.com

charles river

2015 PDA Upcoming Events

SAVE THE DATE for PDA's 2015 Events

OCTOBER

12-16

GSA Schedule Contract GS-02F-113BA

Filtration Week
Bethesda, MD
pda.org/filtration

14
PDA Southern California Chapter Industry Summit & Exhibitor Showcase
Costa Mesa, CA
pda.org/CAsummit

19-21
PDA 10th Annual Global Conference on Pharmaceutical Microbiology
Bethesda, MD
pda.org/microbiology2015

21-23
Validation of Moist Heat Sterilization Processes
Bethesda, MD
pda.org/sterilization

22-23
PDA 10th Annual Global Conference on Pharmaceutical Microbiology Course Series
Bethesda, MD
pda.org/microcourses

26-27
2015 PDA Visual Inspection Forum
Bethesda, MD
pda.org/visual2015

28
PDA Southeast Chapter Annual Fall Conference
Raleigh, NC
pda.org/SEannual

28-29

GSA Schedule Contract GS-02F-113BA

An Introduction to Visual Inspection – Session 2
Bethesda, MD
pda.org/visualcourse

NOVEMBER

2
Secondary Packaging for Parenterals
Vienna, Austria
europe.pda.org/SecondaryPackaging

3-4
The Universe of Pre-filled Syringes and Injection Devices
Vienna, Austria
europe.pda.org/UPS2015

5
Elastomers
Vienna, Austria
pda.org/elastomers

9-10
2015 PDA Pharmaceutical Quality Metrics Conference
Bethesda, MD
pda.org/metrics2015

9-12
Quality Risk Management Week
Bethesda, MD
pda.org/riskmanage

10
PDA Ireland Chapter Particles in Parenterals
Dublin, Ireland
pda.org/IrelandParticles

PDA
Parenteral Drug Association

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

10
PDA Metro Chapter Risk Based Environmental Monitoring & EM Management
Somerset, NJ
pda.org/emmanagement

11
The Quality Culture and its Measurement
Bethesda, MD
pda.org/metricscourse

16-20
GSA Schedule Contract GS-02F-113BA
Quality Systems for Aseptic Processing
Bethesda, MD
pda.org/qualityAP

17-18
Outsourcing/Contract Manufacturing
Copenhagen, Denmark
europe.pda.org/Outsourcing2015

19
Outsourcing, Technology Transfer and CMO – Client Relationship
Copenhagen, Denmark
europe.pda.org/Outsourcing2015

DECEMBER

1-2
PDA Europe Vaccines Conference
Berlin, Germany
europe.pda.org/Vaccines2015

1-2
PDA/FDA Vaccines Conference
Bethesda, MD
pda.org/vaccines2015

3-4
2015 PDA Vaccines Course Series
Bethesda, MD
pda.org/vaccinescourses

7-11
GSA Schedule Contract GS-02F-113BA
Fundamentals of Aseptic Processing – Session 2
Bethesda, MD
pda.org/fap2

PDA CONFERENCE RECORDINGS – Interactive Online Learning

Recordings from PDA's *2015 Drug Delivery Combination Products Workshop* are now available for purchase.

For more information on all PDA conference recordings, please visit pda.org/online-learning

2016 Annual Meeting

Novel Therapies Need Novel Solutions, Flexible GMP

Susan Schniepp, Regulatory Compliance Associates, and Kerry Ingalls, Amgen

It's well known that novel, innovative therapies present unique challenges compared to traditional large-scale GMP manufacturing. The batch sizes are small and the distribution pathways individualized, which presents difficulties in selecting appropriate analytical methods due to the sensitivity to light, heat, shaking and other phenomenon encountered during preparation and distribution.

This leads to the question, how can we adapt the concepts of assay and batch release, sterility testing and the other classic GMP systems to novel therapies?

Well, mark your calendars for March! In the opening plenary session of the *2016 PDA Annual Meeting*, attendees will hear from patients and caregivers on life-saving, innovative treatment options available to today's patients. This session will be followed by a second plenary session that will discuss the manufacturing and supply chain challenges associated with these novel therapies and how these challenges need to be approached on a case-by-case basis. The session features a speaker who will address the complexities associated with collecting and modifying autologous cell therapies to the patient while meeting the time constraints associated with this type of treatment.

In addition, after the opening plenary sessions, conference attendees have the opportunity to attend any of three different concurrent session tracks to further their knowledge and understanding of bioprocessing. These three tracks are: "Advances in Bioprocess Development," "Innovation in Manufacturing Science," and "Lifecycle Management and Continuous Improvement." The sessions in these tracks will drill down into the details of bioprocessing with a combination of theory and practical application.

So don't delay—plan to attend the *2016 PDA Annual Meeting* in San Antonio. For more information, go to www.pdaannualmeeting.org. Information about PDA Education courses following the event will be available on the Annual Meeting website shortly.

InPrint continued from page 16

Outliers are always a concern in the pharmaceutical, biotechnology and medical devices areas, because of the implications for the health and safety of patients who trustingly put their lives in the hands of the doctors, pharmacists and manufacturers.

However, outliers have become an even greater interest and concern for all, since the Barr Case (1993). We need scientifically and statistically sound methods that are defensible to each other, the FDA and in a court of law. The implications of unusual data in practice cannot be evaded.

Outliers have been an issue with practitioners since before 1852 when B. Pierce commented in his paper *Criterion for the rejection of doubtful observations:*

> *"In almost every true series of observations, some are found, which differ so much from the others as to indicate some abnormal source of error not contemplated in the theoretical discussions, and the introduction of which into the investigation can only serve ... to perplex and mislead the inquirer."* (Barnett and Lewis, 1994)

In the past, two extremes have been adopted for outlier management. First, the overly pragmatic advocate, "When in doubt, toss it out." Second, the purist who keeps everything in and will not recognize an outlier unless absolute physical evidence is produced. Both approaches may be counter-productive in actual practice.

Some outliers are scorned and rejected, some are praised and accepted, depending the impact to the observer. Outliers may be an indication of poor measurement, typing errors, uncontrolled events, excessive variability and outright failures. Outliers may be a blessing. True outliers may indicate new positive breakthroughs, patentable ideas and competitive advantages.

Outliers are not good or bad but are valuable information that must be interpreted, managed and used to advantage. Conscience rational decisions must be made to maximize the information gained and minimize the regulatory risks.

SAMSUNG

SAMSUNG BIOLOGICS

Aseptic Fill & Finish at SAMSUNG

Engineered for Quality

CMO LEADERSHIP AWARDS2015

CATEGORIES
- INNOVATION
- REGULATORY
- PRODUCTIVITY

www.samsungbiologics.com

Biosimilar Developers Must Scale Mountains of Data

Powerful Analytics, Strong Science Permit Biosimilars

Rebecca Stauffer and Walter Morris, PDA

On March 6, the U.S. FDA approved Sandoz's filgrastim product, Zarxio, a biosimilar of Amgen's Neupogen. This was a big step for the Agency, and one some feel was long in coming. The same product was approved for marketing in Europe six years earlier (under the name Zarzio). Incidentally, the following year, the Biologics Price Competition and Innovation Act (BPCIA) was signed into law in the United States, which was seen as opening the gateway for biosimilars in the United States.

What took the gatekeepers of the U.S. market so long in letting Zarxio past the gate is the Agency's long history of grappling with how to permit postapproval changes in therapeutic biological product manufacturing. The holdup was distinguishing the product from the process. FDA's website still states:

> *Because, in many cases, there is limited ability to identify the identity of the clinically active component(s) of a complex biological product, such products are often defined by their manufacturing processes. Changes in the manufacturing process, equipment or facilities could result in changes in the biological product itself and sometimes require additional clinical studies to demonstrate the product's safety, identity, purity and potency.* ***(1)***

Article at a Glance

- Analytical methods continue to improve
- Publicly available data ensures easier development roadmap
- Economics of biosimilars different from generic drugs

The idea of comparability was introduced about a decade ago to allow for manufacturing changes. That, and rapidly improving analytical technology, have helped greatly to usher in this new age of generic biologics products.

Sumant Ramachandra, MD, PhD, Research and Development Head of Global Established Pharma, Pfizer, and **Joerg Windisch,** PhD, Chief Science Officer of Global Functions Biopharmaceuticals, Sandoz, discussed the science behind biosimilars with the *PDA Letter* following their talks at the *2015 PDA Annual Meeting.* **[Editor's Note:** The interview with both Ramachandra and Windisch was recorded and available online at www.pda.org/pdaletter**.]**

Advancing Analytical Science

When asked how the Agency's thinking evolved from "the process is the product" to biosimilars, Windisch noted three changes.

"First of all, analytical capability: We can be certain today that if something changes from a molecular perspective of an attribute that it will be seen," he said. "The second thing that changed is our ability to evaluate whether or not that difference is clinically meaningful. So, today with the whole array of biological assays…we have a very good way of gauging what matters and what does not matter. And the third thing, is our ability to optimize and fine tune the process to get rid of any unwanted differences that could result from a scale-up, a new factory and so forth."

With advancement in these areas, "a lot of progress was made and that is why manufacturing changes, including the comparability exercise, are so safe today. And that is also why we can have biosimilars today."

Ramachandra added that "the stringency of our controls"—the analytical tools to actually test the product that comes out the other end—has gone up.

"Any good science experiment is when you try your best to only change one variable at a time, see the result, and change another variable," he said. "If you can change a variable and get a good outcome, for example, everything stays the same. You change a cell line, people say 'Oh, my God, you changed the cell line.' But the reality is it is the product that comes out of the cell line that is most important. So if you can go from a mid-yield cell line to an extraordinarily high-yield cell line... but you don't change a whole lot of parameters along with it, you can actually do a like-to-like experiment and find out how the product is different."

Both scientists predict the analytical methods will only get better, but they discussed how far methods and biologics manufacturing has already come.

"We had roller bottles in the past [and moved] to stainless steel tanks," Ramachandra remarked. "We've moved to disposable-lined manufacturing systems. And we are even going to perfusion-based technology."

But to have a biosimilar, he said, "you have to ensure that there are strong controls so that the certainty you get when you select clones in the laboratory at laboratory scale when you start scaling up stays as close as possible when you get to the commercial manufacturing scale."

He also noted that "there is actually a greater number of tools now where we can interrogate and actually find small differences in glycan structure." Nevertheless, he foresees big improvement in this area. "I think, from an analytical perspective, there will continuously be improvement."

Windisch agreed that methods will continue to improve. "I think we'll continue making progress in learning how different process parameters influence the critical quality attributes. As you go through product after product, especially if you are dealing with monoclonal antibodies (mAbs), you are establishing a knowledge which is like a platform knowledge, because antibodies are kind of similar to each other. You can leverage that knowledge...using bioinformatics systems to have a much more targeted development going forward."

Ramachandra pointed to tumor necrosis factor inhibitor (anti-TNF) products as another example of platform knowledge within a class of therapies.

"I think an example of that is actually across the anti-TNFs. If you look at all the anti-TNF products, they are actually structurally different…they are actually functioning not the same. But if you look at clinical outcomes, there is actually very little difference across these anti-TNFs in terms of clinical effect…. So through that, you can interrogate… the criticality of an attribute that could have an impact in the clinic, whether it's on safety, efficacy or immunogenicity."

Whatever the means a company uses to get to a biosimilar, both scientists agreed that the tools for developing biosimilars exist, but companies have to do it the right way.

"The most important thing any company, if it's Hospira or Sandoz, has to do, is ensure that the quality of the product that comes out the other end is of the highest quality and comparable to the previous one," Windisch said.

Not Your Momma's Generics

Unlike traditional large molecule generic drug development, the foray into biosimilars has "brought to light a level of science that has not been published before," according to Ramachandra.

Firms manufacturing and developing biosimilars have spent an incredible amount of time and research to show that their products are not only of the highest quality but also comparable to the innovator products. This level of research has, in many cases, been released publicly.

And making the data public is critical to the field, he said, "because comparability protocols and changes are typically not published on a routine basis."

In traditional generics, Ramachandra said that the old adage "see one, do one, teach one" applies. "Once you get a lot of experience, you do things just more efficiently, and once you get a ton more experience above that, you can actually teach others to be more efficient.

But that is a different science. "We are not going to see that in biosimilars for a period of time, so that's why we have to depend on biosimilar companies being actually quite public about the rigor of the science."

Ramachandra noted that one can easily get a sense of the roadmap for Sandoz's development process for Zarxio by reviewing the FDA advisory committee process for the product.

Windisch agreed, pointing out that expanded use of bioinformatics systems ties into the development of more biosimilar products. As these products are developed, researchers learn more about how certain parameters influence certain quality attributes. By feeding this information into a bioinformatics system, other researchers do not have to reinvent the wheel when developing the next biosimilar.

"While this was a fairly random process at the beginning, through this learning system, you're having a more targeted way of achieving the similarity that you need," Windisch said.

"We'll continue making progress in learning how different progress parameters influence critical quality attributes in the product. As you go through product after product, this will lead to the platform knowledge."

"We actually have more noise in the system to signal because you can see so many things you have to determine what the true signals are, and I think that's where the bioinformatics actually [comes in]," said Ramachandra.

And that is also why we can have biosimilars today

Not Your Momma's Generics Pricing

It's no question that biosimilars will be priced lower than innovator products on the market. Most estimates suggest that biosimilars will sell for 20-30% less than innovator drugs ***(2).*** Compare this to the drastic differences in price between generic drugs and nongenerics. In 1984, the Drug Price Competition and Patent Term Restoration Act standardized FDA approval procedures for generic drugs. Currently, the vast majority of prescriptions in the United States are now for generics. In 2011, three quarters of the pharmaceuticals covered as part of national healthcare plans in the United Kingdom, Germany, New Zealand and Denmark were generic drugs ***(3).***

Yet biosimilars will probably never reach the low cost ranges of generic drugs because biosimilars are not generics. The development process for a biosimilar is much more advanced than the development process for a generic, particularly when factoring in research required.

An interdisciplinary field that develops methods and software tools for understanding biological data (Wikipedia). Bioinformatics is a central component of the U.S. FDA's Critical Path initiative. FDA recently selected DNAnexus to build "precisionFDA", an open source platform for community sharing of genomic information.

"The more complex the product, the higher the cost is going to be, so if you compare the two things, biosimilar development is actually closer to the development of an original biologic than to the development of a generic," said Windisch. "That being said, they will still help contribute to making biologics significantly more affordable."

He went on to explain that while generics only require a few years to develop, biosimilars generally require eight to ten years of development time, which includes extensive clinical studies. And the cost of this process is usually $100-300 million.

While the question of pricing for biosimilars remains in question, globally, the market for these products is heating up. A recent report indicates that by 2020, the global biosimilars market will reach $35 billion ***(4).***

This is not surprising considering that biosimilar products have been approved outside the United States in many other countries. EMA approved its first biosimilar in 2006. Australia approved its first biosimilars in 2010. In some ways, the FDA is a late arrival on the biosimilar scene as the European Commission published its guideline on biosimilars in 2001.

The Agency, however, has been involved in developing regulations for biosimilars, including three draft guidances issued in February 2012 and a May 2012 public hearing. This spring, FDA finalized three draft guidances on scientific considerations, quality aspects and a Q&A. In August, FDA released a further draft guidance regarding naming standards for biosimilars.

In Windisch's opinion, the European experience reflects what has happened in the United States. "You had the overarching guideline and you had the two general guidelines," he said. "Then as you had more applications coming in, they started issuing more product specific guidelines."

The key to EMA's success, he believes, is that regulatory guidance was not issued based on suspicion. EMA and other Eu-

Continued at top of page 35

ELIMINATE PARTICULATES & FIBERS IN THE CORE.

SYNTHETIC WRITING SUBSTRATE

CleanPrint 10

- Low particulate and non-shedding
- Exceptionally durable
- Tear, abrasion and chemical resistant
- Easy to write on
- Double bagged packaged sterile

CUSTOM DOCUMENTATION

Core2Write

- Logbooks, ID tags, Forms and Labels
- Constructed using CLEANPRINT 10
- Customized specifically per customer
- Individual unique numbering and integrity features
- RFID Technology available

HEPA FILTERED PRINTING SYSTEM

Core2Print

- Print wirelessly into cleanrooms
- Use with pre-sterilized CLEANPRINT 10
- 316L Stainless Steel Construction, can be completely disinfected
- HEPA Filter cabinet
- Sheet fed, high speed digital printer using chemical resistant ink

vai
VELTEK ASSOCIATES, INC.

15 Lee Boulevard
Malvern, PA 19355-1234 USA
(610) 644-8335

www.sterile.com

Tools Available to Reduce Risk During Drug Development

Mark Tunkel, Insight Product Development

The market for combination products continues to grow ever increasingly competitive, especially as innovative therapies and high-volume generic alternatives crowd the marketplace. To achieve success within this new paradigm, combination product manufacturers must get their products to the market quickly and efficiently. At the same time, manufacturers also face substantial lead time required to meet U.S. FDA approval, resulting in intense pressure.

Yet companies that shortcut their design and development process in an attempt to accelerate speed to market, run the very distinct risk of discovering core device functionality issues at a later stage. This not only adds months to the development cycle but can also cause substantial cost overruns. Many drug developers erroneously assume that core-to-function design issues can be mitigated as part of the commercialization process, resulting in a fast-tracked development process that leads to poor outcomes. So how can developers avoid falling into this trap? By leveraging appropriate tools at every step of the development process—from components and subsystems to fully integrated systems design—developers can uncover issues well before commercialization.

Factoring Risk Early on in the Process

As the saying goes, prevention is cheaper than a cure. For this reason, successful companies consider risk mitigation when setting the functional requirements of a product, holistically integrating it into the process early on. This is accomplished by focusing on the most critical, high-risk elements of a potential product and ensuring full operability prior to commercialization. Iterative development—a cyclical process of prototyping, testing and analyzing every technical and user experience element—is a developer's best tool in this area. This approach reveals core issues early on in development, allowing for the time needed to refine product design from concept to initial tooling and production.

By its very nature, iterative development is a nonlinear process that leverages both *theoretical* and *physical* models to vet concepts in tandem with one another throughout the entire design and development cycle. Successful developers leverage each method to continually refine their assumptions instead of relying on one tool to the detriment of the other.

Several tools and methods exist within both models to help companies effectively push risk upstream. It is important to note, however, that no single tool on its own represents a universal solution for every given scenario, When used appropriately for the specific functional requirements of a development program, these tools can effectively confine core functionality issues to the design phase of development.

Just as none of these tools on their own represent a magic bullet to mitigating risk, neither should theoretical analysis or physical prototyping be undertaken independent of each other.

Theory Comes Before Application

After defining functional requirements for a product, the next step toward preventing late-stage core functionality issues involves leveraging theoretical analysis tools. These enable the development team to review assumptions about the initial product concept as well as consider the physical design of the product.

Theoretical Models

In the earliest stage of product development, theoretical models provide developers with a means to prove their design assumptions using analytical sources. These models leverage software simulation, companion engineering math and heuristic usability product design modeling. Multiple optimized iterations ➤

Photo courtesy of Insight Product Development

A CNC machine can be a valuable tool for replicating components during development


Do you know the three ingredients to drug delivery success?
Tailormade drug delivery with reliable performance
The best possible solution for your drug delivery needs is a solution where primary container, medical device and aseptic process form a synthesis. NNE Pharmaplan combines expertise, knowledge and hands-on experience within all three aspects.
That makes us unique. And it enables us to help customers achieve world-class drug delivery solutions which reduce time to market and achieve cost advantages throughout the lifecycle.
www.nnepharmaplan.com
Join us at PDA
– the Universe of Pre-filled Syringes and Injection Devices
Booth 91 and 97-98
3-4 November 2015 in Vienna
nne pharmaplan®
Focused pharma engineering

at the theoretical level can confirm or disprove the expected product performance results of higher fidelity prototypes in later stage development.

User Experience Prototyping

User experience prototyping is another tool deployed early in development. This tool ensures devices meet users' physical, cognitive and emotional needs, and includes workflow projection using storyboards, ergonomic models, and mock device instructions at low fidelity. User interviews and in-field observation vets outputs from this prototyping.

Breadboards

Utilized in tandem with user experience prototyping, breadboards are the earliest physical iteration of product development and design. At the lowest level of design fidelity, using off-the-shelf products or improvised components from string to Legos, breadboards demonstrate high-level functional principles of device components and subsystems, and inform higher fidelity CAD renderings that will ultimately be realized in physical form.

Moving from Theory to Practice

After vetting theoretical design iterations, a number of physical prototyping tools offer developers a means to confirm core product functionality during the design phase of development. Featuring a wide range of fidelity levels, these tools enable developers to work concurrently with theoretical tools.

3-D printing

The fastest growing tool in the developer's prototyping toolbox is 3-D printing. Advancements in material properties have been substantial, resulting in 3-D prototypes that not only represent the intended geometry, but also the intended engineering function of a product, allowing for functional testing. Given the wide range of fidelity available using this tool, prototypes at this stage can also prove user workflow assumptions through observation of in-context usage.

CNC (Computer Numerical Control) Machining

A highly automated tool capable of replicating components at the highest level of fidelity, CNC machine prototyping is a valuable tool in any developer's risk mitigation arsenal. At this stage, proving key functionality through an integrated proof of concept is central to confidently defining design inputs for the final commercialization phase—ultimately producing a final product without core functionality issues. Not only do prototypes at this level of resolution enable the evaluation of core device performance (mechanical, technical and functional) through models that closely mirror full scale production outputs, they also enable manufacturing variability range testing to ensure that any postproduction device performance issues can be confined to issues within the manufacturing process itself—without worrying whether the design will work or not.

So how does the value of this approach translate to a delivery device development program exactly? Well, consider the following example: a hypothetical company enters the market with a novel device; the development team defines the preliminary functional requirements of the product. In an attempt to accelerate the product's entry to the market, the team opts to move quickly from an early design concept that has not undergone the rigors of iterative prototyping using these tools, and proceeds straight to commercialization. Not only is there the distinct chance the company will emerge with substantial volumes of product that does not work reliably, but worse yet, no one can initially attribute the core functionality issues to either product design or the product manufacturing process. Now, the company is in the unfortunate position of incurring significant cost overruns and additional time to rectify the issue. The required remediation to uncover core underlying issues also adds to the product launch timeline.

Successful developers leverage each method to continually refine

By addressing the entire range of development considerations with an appropriate combination of tools, companies can avert costly and time-consuming mistakes as quickly as possible, and emerge from the process with devices poised to effectively compete in the market—on time, and on budget.

About the Author

Mark Tunkel is a partner and director of business development at Insight Product Development. His company will be exhibiting at this year's *Universe of Prefilled Syringes and Injection Devices conference.*

Biosimilar Developers Must Scale Mountains of Data continued from page 30

ropean regulators also worked closely with scientists through various forums, and this led to the realization that product specific guidelines made more sense than receiving a multitude of applications for the same product type.

Zarxio officially entered the U.S. market on Sept. 3 following the culmination of years of work, not only from those involved in its clinical development but the regulators and industry experts worldwide who have collaborated to ensure a smooth passageway for biosimilar development.

And for all involved in biosimilar development, quality and effectiveness remain key. "At the end of the day, the most important thing is what does it mean to the patient," Ramachandra emphasized.

[Editor's Note: PDA will host a conference on biosimilars June 20–21, 2016.**]**

References

1. "Frequently Asked Questions About Therapeutic Biological Products," last modified July 7, 2015. www.fda.gov/Drugs/DevelopmentApprovalProcess/%20HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm113522.htm
2. Grant, Charley. "Big Pharma's Unfamiliar Biosimilar Threat," *The Wall Street Journal*, March 22, 2015. http://www.wsj.com/articles/big-pharmas-unfamiliar-biosimilar-threat-heard-on-the-street-1427053839
3. OECD (2013), "Pharmaceutical generic market share", in *Health at a Glance 2013: OECD Indicators*, OECD Publishing. http://dx.doi.org/10.1787/health_glance-2013-42-en
4. Deshmukh, Roshan. (2014). *Global biosimilars/follow-on-biologics market (types, applications and geography)—Size, Share, Global Trends, Company Profiles, Demand, Insights, Analysis, Research, Report, Opportunities, Segmentation and Forecast, 2013–2020*. Allied Market Research.

About the Experts

Sumant Ramachandra, MD, PhD, brings over 20 years of healthcare experience and strong leadership abilities to his role as Pfizer's Research and Development Head of Global Established Pharma.

Joerg Windisch, PhD, has been working on the development of both, innovative and follow-on biologics for his entire professional career. He joined Sandoz in 1996 as a day one member of the company's biosimilars program.

New Data Available on LPS and LER Phenomena continued from page 22

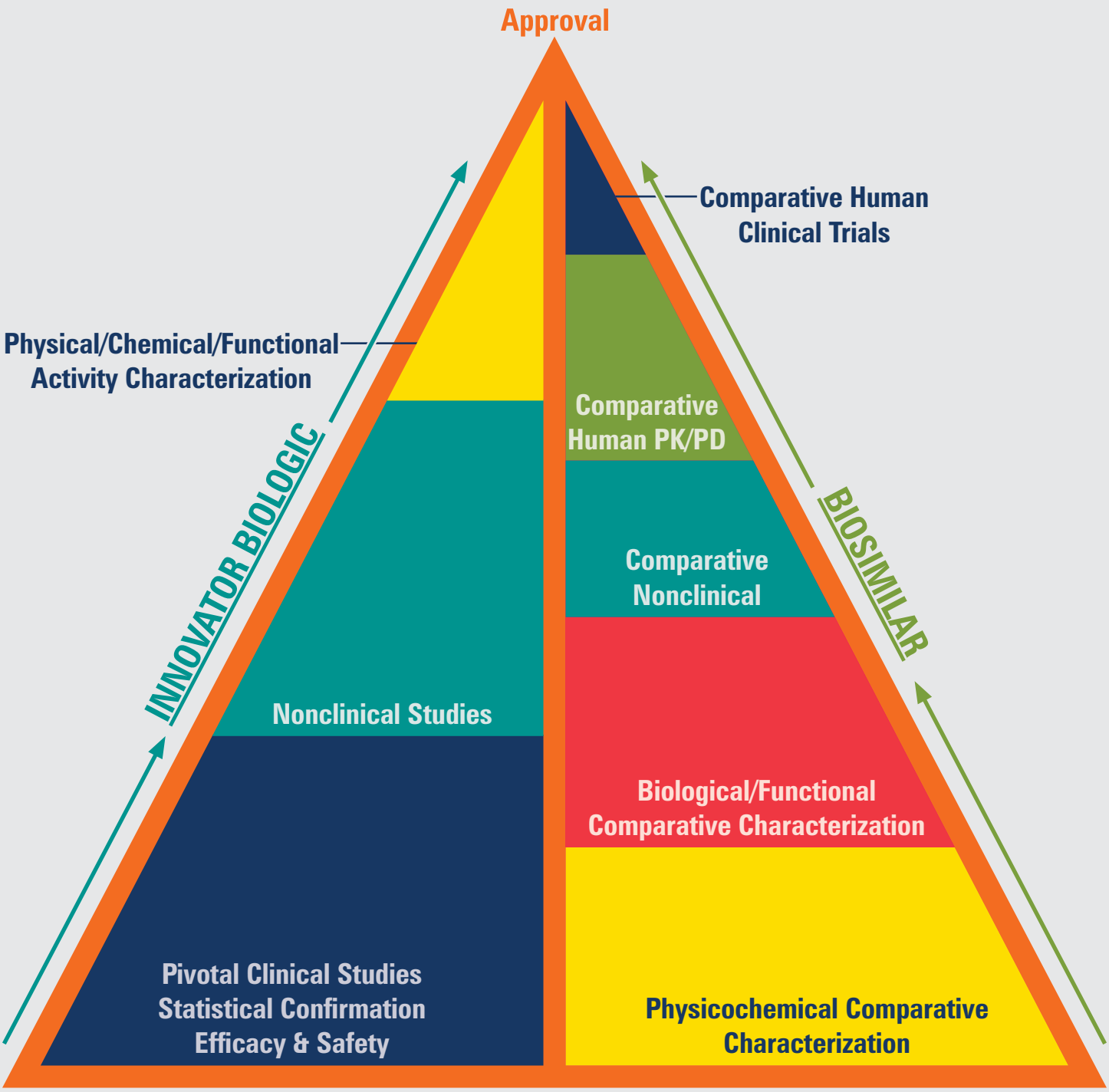
5. Bowers, K., and Lynn, T. "Creation of an in-house naturally occurring endotoxin preparation for use in endotoxin spiking studies and LAL sample hold time analysis." *American Pharmaceutical Review* 14 (2011):92-97.
6. Cooper, J.F." Investigation of endotoxin out-of-specification and unexpected results," in *Microbial Risks and Investigations,* ed. McCullough, K.Z. and Moldenhauer, J ., 563-578. Bethesda, MD: PDA/DHI, 2015.

About the Author

James Cooper, PharmD, is an innovator of the bacterial endotoxins test (BET) for parenteral products. He founded Endosafe Inc. in 1987, an LAL production unit which is now part of Charles River Laboratories. He consults on depyrogenation, BET methods, endotoxin issues and root cause investigations.

Approval Process for Biosimilars vs. Biologics

The processes for evaluating the effectiveness of a biosimilar and a reference biologic can, in some ways, be considered inverses of each other. Still, the review process for both relies on carefully controlled studies and quality data.



Acknowledgment

Special thanks to **John Geigert,** PhD, President, BioPharmaceutical Quality Solutions, for his assistance with this infographic.

REGISTER TODAY

October 15-16, 2015

Puerto Rico Convention Center
San Juan, Puerto Rico

WWW.INTERPHEXPUERTORICO.COM/PDA

1. LATEST INDUSTRY INNOVATION AND TECHNOLOGIES

INTERPHEX Puerto Rico is the place to learn and experience the latest in pharmaceutical, biopharmaceutical and medical device Innovation, Technologies and Knowledge.

2. TWO-DAY TECHNICAL EDUCATION FROM PDA AND INDUNIV

Enhanced Technical Education Program offering educational and training opportunities to increase productivity and improve efficiency.

3. THE PLACE TO BE

Effective and efficient way to solve your development and manufacturing challenges, deliver greater value, drive performance and identify partnering opportunities to meet your production goals and objectives.

4. MORE NETWORKING OPPORTUNITIES

Network with your industry colleagues as you interact with and procure the latest technology under one roof.

INTERPHEX PUERTO RICO

PREMIER SPONSOR: PDA Parenteral Drug Association

CO-LOCATED WITH: MEDICAL DEVICE PUERTO RICO

SHOW SPONSOR: INDUNIV

snapshot

PDA and Dublin Tech Institute to Collaborate on QRM

Kelly Waldron, Genzyme, Emma Ramnarine, Roche-Genentech and Jeffrey Hartman, ConcordiaValSource

PDA's Regulatory and Quality Advisory Board (RAQAB) recently approved a plan for PDA to collaborate with the Dublin Institute of Technology's (DIT) Pharmaceutical Regulatory Science Team to develop methods to advance Quality Risk Management (QRM) implementation throughout the industry.

PDA volunteer and DIT researcher **Kelly Waldron** will lead this initiative. **Emma Ramnarine** and **Jeffrey Hartman,** the coleaders of PDA's QRM Interest Group, will work closely with Waldron as well. This project will employ a variety of research methods and techniques including literature reviews, surveys and benchmarking, along with interviews with industry experts and regulators, to assess the current level of QRM adoption and its perceived value. The outcome and benefits of this research are twofold: identify opportunities for improvement and propose practical solutions to enhance the utility of QRM to achieve meaningful outcomes. This collaboration offers a unique opportunity to further the goals of industry, regulators and patients.

RAQAB Co-chairs **Susan Schniepp** and **Jeffrey Broadfoot** commented on the project, "RAQAB is very excited to collaborate with DIT on QRM research. We believe this partnership has the potential to positively benefit PDA members on this very important topic."

DIT's **Anne Greene** was similarly excited by this project and said, "The mission of the PRST [Pharmaceutical Regulatory Science Team] at DIT is to engage in regulatory science research and development to enable those involved in the manufacture of drug products to meet the expectations of the international pharmaceutical regulatory community and protect public health. QRM was identified in ICH Q10 as one of the primary enablers of pharmaceutical quality systems, yet rigorous inquiry into this area of study has shown to be lacking. Collaboration between PDA and DIT can bridge this gap and accelerate the realization of these goals."

Regulatory authorities stand to gain from this research collaboration as well. Irish regulator **Kevin O'Donnell** noted, "As a GMP inspector, I have the privilege of having access to a lot of risk assessment and QRM work. While we do see some good practices in this area, I think that many current risk assessment and QRM activities do not result in meaningful (or measureable) risk reductions for patients. Serious quality defects and recalls continue to occur at an alarming level. I am very interested in this research and look forward to seeing the benefits it delivers for both industry and regulators alike."

The research effort is expected to span 24 months, with deliverables available to PDA members on a quarterly basis. While all PDA members are encouraged to participate in the research by completing surveys, providing opinions, exploring case studies and benchmarking with others, members of the QRM Interest Group will provide additional input into the research as well. If this interests you, do not hesitate to join the QRM Interest Group. You can do this by updating your member profile at www.pda.org/volunteer or by visiting the interest group's PDA Connect℠ page at community.pda.org.

The first research item, a QRM benchmarking survey, is now open. Please take a moment to participate by completing the survey: https://www.surveymonkey.com/r/PDA-DIT-QRMsurvey. All opinions and perspectives are welcome! The survey closes Dec. 31.

About the Authors

Kelly Waldron has broad experience in various quality functions, including deviations, investigations, CAPA, change control, and microbiology.

Emma Ramnarine is Senior Director, Head of Biologics QC Network at Roche Pharma and is accountable for the biologics QC network strategy.

Jeffrey Hartman has over 30 years of experience in the pharmaceutical industry, supporting API, pharmaceutical and vaccine manufacturing.

PDA Who's Who

Jeffrey Broadfoot, Director, Corporate Quality Compliance, Emergent BioSystems

Anne Greene, Ph.D., Head of the Pharmaceutical Regulatory Science Team, Dublin Institute of Technology

Jeffrey Hartman, Senior Consultant, ConcordiaValSource

Kevin O'Donnell, Health Products Regulatory Authority

Emma Ramnarine, Senior Director, Head of Biologics QC Network, Roche-Genentech

Susan Schniepp, Consultant, Regulatory Compliance Associates

Kelly Waldron, Manager, Global Quality Risk Management, Genzyme

Plan Ahead! Book Your 2016 PDA Exhibit Space and Sponsorships Today!

PDA's wide variety of exhibit and sponsorship options will give your company unsurpassed access to the industry's "movers and shakers." Our Conferences and Workshops draw a large global audience and exhibiting or sponsoring at one of our 2016 events will open new doors for your business, increase your brand's visibility, allow you to showcase new products and services and engage with highly qualified leads.

Find the Conference or Workshop that's right for you, and then schedule a meeting with a member of our Sales team to create the sponsorship and exhibition package that suits your needs.

For Conferences and Workshops located in North America, please contact **David Hall** at hall@pda.org. For Conferences and Workshops located in Europe, please contact **Creixell Espilla-Gilart** at espilla@pda.org.

DATES	EVENT	LOCATION
FEBRUARY 23-24	**Pharmaceutical Microbiology Conference**	Berlin, Germany
MARCH 14-16	**2016 PDA Annual Meeting**	San Antonio, TX
MARCH 16-17	**Preparing for the Next Generation of Regulatory Inspections: A 2016 PDA Manufacturing Science Workshop**	San Antonio, TX
APRIL 12-13	**Parenteral Packaging Conference**	Venice, Italy
APRIL 19-16	**Annex 1 Conference**	San Diego, CA
MAY 2016	**Visual Inspection Interest Group**	Washington, DC
JUNE 20-21	**Biosimilars Conference**	Washington, DC
JUNE 27	**Annex 1 Conference**	Berlin, Germany
JUNE 28-29	**Inaugural PDA Europe Annual Meeting**	Berlin, Germany
SEPTEMBER 12-14	**25th PDA/FDA Joint Regulatory Conference**	Washington, DC
SEPTEMBER 14-15	**Data Integrity Workshop**	Washington, DC
SEPTEMBER 20-21	**9th Workshop on Monoclonal Antibodies**	Europe
SEPTEMBER 27-28	**Pharmaceutical Freeze Drying Technology**	Strasbourg, France
OCTOBER 11-12	**Pharmaceutical Cold & Supply Chain Logistics**	Europe
OCTOBER 17-18	**2016 PDA Universe of Pre-filled Syringes and Injection Devices**	Huntington Beach, CA
OCTOBER 19	**Drug Delivery/Combination Products Interest Group**	Huntington Beach, CA
OCTOBER 24-26	**PDA 11th Annual Global Conference on Pharmaceutical Microbiology**	Washington, DC
OCTOBER 25-26	**Visual Inspection Forum**	Berlin, Germany
OCTOBER 26-27	**Annex 1 Conference**	Washington, DC
NOVEMBER 10-11	**Outsourcing/CMO Conference**	Washington, DC
NOVEMBER 15-16	**Outsourcing & Contract Manufacturing**	Copenhagen, Denmark
DECEMBER 5-7	**Data Integrity Workshop**	West Coast

Subject to Change | **pda.org/calendar**

CURRENT AS OF 10/1/2015

GSA Schedule
Contract GS-02F-113BA

PDA
Parenteral Drug Association

*PDA **Education** – Where Excellence Begins*

Aseptic Processing Training Program

2016 SCHEDULE

SESSION 1
Week 1: January 25 – 29
Week 2: February 22 – 26

SESSION 2
Week 1: April 4 – 8
Week 2: May 2 – 6

SESSION 3
Week 1: June 6 – 10
Week 2: June 27 – July 1

SESSION 4
Week 1: August 22 – 26
Week 2: September 19 – 23

SESSION 5
Week 1: October 17 – 21
Week 2: November 7 – 11

FOR MORE INFORMATION CONTACT:

Kim McIntire, Assistant Manager, Laboratory Operations
Tel: +1 (301) 656-5900 ext. 103
E-mail: mcintire@pda.org

LOCATION:

PDA Training and Research Institute
4350 East West Highway, Suite 150
Bethesda, MD 20814
Tel: +1 (301) 656-5900
Fax: +1 (301) 986-1093

Reserve your seat before our 2016 sessions sell out like they did in 2015. When that happens, there won't be another opportunity to register for our Aseptic Processing Training Program until 2017!

The most comprehensive program in the preparation of sterile parenteral products

This two-week comprehensive training program, taught by 20 industry leading experts in their fields, with more than 300 years of combined experience, will give you and your personnel the training and information needed to properly evaluate and improve your aseptic processes to ensure sterile products. This program provides the perfect balance of hands-on laboratory and lecture training, equipping you with tools and practical experience you can apply immediately on the job.

YOU'LL LEARN HOW TO:

- Evaluate and improve current aseptic processing procedures at your facility
- Correlate basic microbiology concepts and techniques to multiple aspects of aseptic processing
- Evaluate your environmental monitoring program to collect appropriate data, identify and interpret trends
- Develop robust media fill protocols including appropriate interventions, observations and documentation procedures
- And much more!

Register Now For the Course That Fits Your Schedule

pda.org/2016aseptic

Quality Metrics Moves from Theory to Application

Joyce Bloomfield, Merck

Now that the U.S. FDA's draft guidance, *Request for Quality Metrics*, is hot off the press, pharma faces the real challenge of integrating pragmatic programs into manufacturing operations then reporting this quality metrics data to the Agency. Quality metrics are widely used in the industry to monitor processes and quality control; these metrics are often collected and maintained as GMP documents. Companies collect such metrics in order to gain insight into the state of quality at a manufacturing facility so that issues can be anticipated and addressed in a timely fashion.

Quality metrics present a rare opportunity for all segments of the industry to come together with the goal of enhancing quality across the board.

This year's *PDA Pharmaceutical Quality Metrics Conference* will offer an opportunity for both industry and regulatory experts to convene on this important topic. Industry leaders will provide first-hand accounts of how they developed and implemented metrics programs that give insight into the state of quality, how they define, collect and use metrics, and how the data can help influence resource allocation. Take this opportunity to learn best practices and discuss with FDA and industry thought leaders on how to integrate quality metrics into the pharmaceutical quality system. Explore strategies that can be used to implement a robust and complementary system for reporting quality metrics across the supply chain.

For more information about this important conference, please visit www.pda.org/metrics2015. For information about the PDA Education course following the meeting, go to www.pda.org/metricscourse.

Regulatory Briefs

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

North America

New U.S. FDA Commissioner Nominated

The White House announced on Sept. 15 the nomination of **Robert Califf,** MD, for the post of Commissioner of the U.S. FDA. Since January, he has been serving as the Deputy Commissioner for Medical Products and Tobacco at the Agency. Prior to joining FDA, he served as Vice Chancellor of Duke University's School of Medicine and was also a professor of cardiology and medicine at the same school.

If confirmed, he will replace **Margaret Hamburg,** MD, who stepped down in March. **Stephen Ostroff,** MD, has been serving as Acting Commissioner following her departure.

FDA to Review Biosimilars Nomenclature

On Aug. 27, FDA released a draft guidance detailing the Agency's proposal for nonproprietary naming of biologics. Under the Public Health Service Act, biologics must bear a nonproprietary name with an FDA-designated suffix. The Agency believes that shared nonproprietary names are not appropriate for all biologics. To ensure clear identification of biologics for the purposes of pharmacovigilance and to differentiate biologics that are not interchangeable, the Agency proposes that the suffix for biologics comprise four lowercase letters based on the nonproprietary name of the product.

As far as interchangeable products, i.e., biosimilars, the Agency is still considering whether the suffix should be unique or share the same suffix as the reference product.

Comments are due Oct. 27.

FDA Finalizes Rule for Administrative Destruction of Drugs Refused Entry

Effective Oct. 15, FDA now has the authority to destroy any drug valued at $2,500 or less if it has been refused entry into the United States per provisions of the Food and Drug Administration Safety and Innovation Act (FDASIA). This final rule gives the owner of the drug in question the opportunity to receive written notice about the Agency's intent to destroy the drug and to provide testimony to FDA prior to destruction.

FDA hopes this serves as a disincentive for importing adulterated, misbranded or unapproved drugs into the country.

FDA Releases New Search Tool

The FDA's new search tool enables those using the FDA website to search the Agency's growing list of over 3,000 guidance documents quickly and efficiently. This search feature covers the entire FDA space—drugs, devices, biologics, etc. Content is also tagged with metadata based on identified search terms as well.

The search tool can be accessed at www.fda.gov/RegulatoryInformation/Guidances.

FDA Finalizes ICH Q3D Guideline

ICH finalized its Q3D guideline that covers elemental impurities in January. Global regulators identified elemental impurities as an area in need of international harmonization and consensus. This guideline limits metal impurities in drug products and ingredients.

In September, FDA released its final guidance on ICH Q3D. The guidance establishes permitted daily exposures (PDE) for 24 elements according to toxicity data. In addition, the guidance allows for a risk-based approach to assessing the possibility that elemental impurities with allowed PDE will be present in a drug product.

Key Regulatory Dates
Comments Due

October 15 — FDA Finalizes Rule for Administrative Destruction of Drugs Refused Entry

October 27 — FDA to Review Biosimilars Nomenclature

November 24 — Europe Moves Toward GMPs for IMPs

December 31 — Solvent Upgraded Due to Health Concerns

Europe

Europe Moves Toward GMPs for IMPs

In late August, the European Commission released three documents for public consultation on GMPs for investigational medical products (IMPs). One document is a consultation paper that outlines the Commission's views on GMPs for IMPs and the second document covers detailed guidelines in this area. The third details implementation of the proposed GMPs.

Comments are due Nov. 24.

ICH

Solvent Upgraded Due to Health Concerns

The ICH Expert Working Group behind the Q3C Guideline recently revised the PDE for Methyl isobutyl ketone (MIBK). This was listed in Q3C as a Class 3 solvent. Based on new data suggesting MIBK causes carcinogenic health problems in rodents, the Expert Working Group recommends upgrading MIBK to a Class 2 solvent.

Comments are due Dec. 31.

Your Local PDA Connection

Are you curious about the issues unique to your region?

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

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

Gabriele Gori, GSK Vaccines

PDA: Transforming Colleagues into Lifelong Friends

When I decided to attend the PDA conference, *A Day with FDA,* in May 2000 in Verona, Italy, I could not imagine how my participation at this meeting would significantly impact not only my professional life but my social life as well.

At that time, I worked as the Head of Quality for a facility manufacturing sterile medical devices near Milan. I often stayed in the office from 8 a.m. to 8 p.m.—driven by the concept of continuous improvement and the idea that Quality was critical for the safety of our customers and the success of the company.

I knew about PDA for quite some time thanks to reading the invaluable technical reports and reviewing the scientific content of PDA's conferences.

That is why I felt immediately enthused when I met with a small but energetic group of colleagues from other companies at that meeting in 2000. These individuals then shared with me their intentions to create a PDA chapter in Italy.

Despite my busy, and sometimes overwhelming, professional life, I sensed that developing an Italian chapter of PDA would benefit members of the country's pharmaceutical manufacturing industry by creating a forum for open discussion. We could then more easily share state-of-the-art knowledge on manufacturing and control as well as offer more global viewpoints to our Italian colleagues. I felt a strong desire to contribute and realize this vision.

So, a few months later, we organized the first PDA Italy Chapter meeting in Milan, followed by many others. Eventually, in July 2001, we gave it legal status by officially registering it. I still remember the emotion of that day, signing the paperwork with my colleagues and friends, **Stefano Macciò** and **Enzo Baselli,** at the notary!

Since then, I have served several times as Chapter Secretary and then as President. In 2010, I had the honor and privilege to be elected as a member of PDA's Board of Directors, followed by a second three-year term in 2013.

Over the course of my time with PDA, I have served as part of multiple organizing committees, chaired conferences and workshops, and presented and conducted training on aseptic processing and quality systems. Parallel to my PDA involvement, my professional life also grew as I took on more relevant and satisfying roles. More importantly, the large network I have cultivated gives me expanded access to a wealth of collective knowledge and experiences. This helps me address my job's daily challenges. In addition, these interactions and discussions have inspired me to look for novel solutions to problems facing our industry and actively participate in setting new regulatory guidelines.

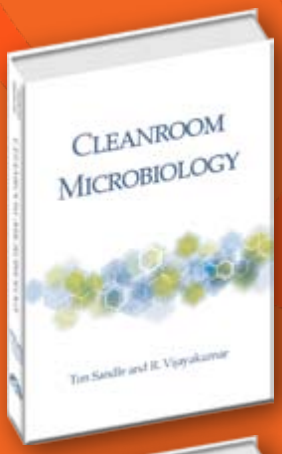
But our relationship goes beyond that of mere colleagues. The camaraderie that we all feel among us anytime we gather together for a conference, task or special event make these occasions enjoyable, and even fun, so I think it is more appropriate to define us all as "friends" rather than "colleagues."

Of course, it has not always been easy, and as anyone involved in organizing these activities or initiatives attests, some weekends and late evenings are necessary to complete various tasks. Looking back, however, it is clear that this was, and still is, very much worth the effort for me, my company, and ultimately, for the patients who use our products.

My recommendation for those who think they are too busy to participate in a PDA workshop, conference, task force or their chapter is to consider all the benefits you can receive from your participation and involvement as well as the satisfaction you receive from actively advancing pharmaceutical knowledge.

Exclusive Publication Bundle

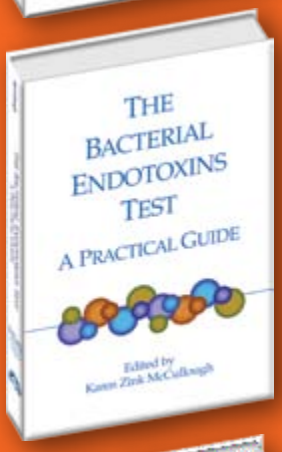
The recent revision to the draft guideline, *European Good Manufacturing Practices Annex 15 for Qualification and Validation*, resulted in considerable changes to the arena of cleaning validation. PDA has assembled a collection of publications to help industry professionals tackle some of the regulatory changes introduced in the revised draft guideline.



Cleanroom Microbiology

By Tim Sandle and R. VijayaKumar
Hardcover: Item #17326

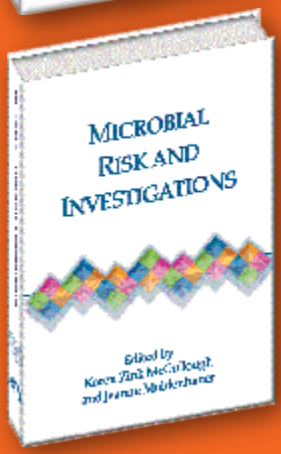
This book is about cleanrooms and controlled environments in relation to the pharmaceutical and healthcare sector. Information is applicable to both sterile and non-sterile pharmaceutical operations with a focus on cleanroom microbiology.



The Bacterial Endotoxins Test: A Practical Guide

Edited by Karen Zink McCullough
Hardcover: Item #17297

This collection of interdependent chapters are part lab manual, part essay, part historical context, part consultant and part plain sage advice that provides a practical and compliant approach to the execution and use of BET.



Microbial Risk and Investigations

Edited by Karen Zink McCullough and Jeanne Moldenhauer
Hardcover: Item #17328

Written by authors with many years of industry experience, this book will provide a wealth of information on microbial investigations and dealing with aberrant data. Many of the chapters include case studies that provide guidance for common situations that may occur at your facility.

Purchase all three publications today and automatically receive 20% off your entire purchase, no campaign code needed! This collection of publications will be a valuable resource as your company implements the revised draft guideline.

*Certain Terms and Conditions May Apply. Discount Shown at Checkout and Applies to Hardcover Copies Only.

Balancing Act: Biosimilars, Science and Public Policy

As we wrapped up the October issue and the cover story on the science of biosimilars, U.S. FDA CDER Director **Janet Woodcock** faced a not-so-friendly round of questions from senators following her progress report to the U.S. Senate's Subcommittee on Primary Health and Retirement Security. This is not the first time Woodcock and other FDA officials bore the brunt of frustrations on Capitol Hill, and it certainly won't be the last.

FDA is often in the unenviable position of trying to satisfy conflicting Congressional goals that frequently shift with changes in the political climate. In the 2000s, the Agency was pressured to back off after years of heavy-handed enforcement. Warnings to the industry slowed during this period. Then heparin happened. Congress, as they are apt to do, blamed the Agency's lax enforcement—not budget cuts and pressure to slow down enforcement. For sure, FDA carries the blame for its own missteps in the affair, but the fact remains, FDA served as a convenient political scapegoat.

Biosimilars are complicated in the United States. For years, biologic innovator companies tried to forestall "generics" in their area. Yet, they also argued for, and received, flexibility from the Agency to enact manufacturing changes based on comparability protocols. As the cover story points out, this opened the door for biosimilars. Competing political goals and constituencies make the process of changing years of policy difficult.

By no means do I wish to defend the U.S. FDA or point the finger at industry and Congress, but the whole situation is complicated, and knowing many FDA officials through their participation in PDA projects, meetings, etc., I suspect they are doing the best they can with the resources they have and the legislation that governs what they can and cannot do.

One thing is for sure, when you come to a PDA meeting like the upcoming 2016 conference on biosimilars, you will see that both the industry and FDA are committed to finding solutions based on science that will benefit patients through safe and effective drugs.

As to the EU's ability to accelerate the biosimilar process, that is laudable. The U.S. FDA should look to what Europe is doing in this space, as the experts interviewed for our cover story urge, and make sure its requirements are not contradictory or unnecessarily different. There is opportunity right now for both sides of the ocean to harmonize their approaches.

I'm sure PDA members will be following the delicate balancing act, or political dance, that currently is going on. Innovators, generic companies, the U.S. FDA, and most of all, the U.S. Congress will be taking whirls on this dance floor for several years to come!

PDA Letter

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

Subscriptions are not available.

PDA Global Headquarters — Bethesda Towers
4350 East West Hwy., Suite 200
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 150
Bethesda, MD 20814 USA
Tel: +1 (301) 656-5900 Fax: +1 (240) 482-1659
info-tri@pda.org

PDA
Parenteral Drug Association

The Parenteral Drug Association presents:

2015 PDA Europe

The Universe of Pre-filled Syringes & Injection Devices

Education Program

Pre-Conference Workshops:

2 Nov Smart Medication
2 Nov Innovative Combination Products
2 Nov Secondary Packaging for Parenterals

Post-Conference Courses:

5 Nov Elastomers
5 Nov Test Methods for Pre-filled Syringe Systems
5-6 Nov Development and Manufacturing of a Pre-filled Syringe
5-6 Nov A Tale of Two Materials: What the Glass vs. Polymer Debate Really Means

For further information please visit our website. **europe.pda.org/UPS2015**

3-4 November | Conference, Exhibition

2-6 November 2015

Austria Center Vienna
Vienna | Austria

The Parenteral Drug Association presents...

2016 PDA Annual Meeting

Achieving Manufacturing Excellence: Current Trends and Future Technologies in Bioprocessing

March 14-16, 2016 | San Antonio, TX

JW Marriott San Antonio Hill Country Resort and Spa

Exhibition: March 14-15 | Post-Workshop: March 16-17 | Courses: March 17-18

Register before January 11, 2016 and save up to $400!

The *2016 PDA Annual Meeting* is the most significant conference to attend to gain the newest and most comprehensive information about innovative biopharmaceutical approaches and the bioprocessing technologies and manufacturing sciences being applied for development and commercialization.

A robust agenda has already been developed to share the latest on these emerging topics. Industry and regulatory leaders will share their experiences, address challenges and provide a platform for engagement and knowledge sharing among conference participants.

Plenary sessions will focus on:

- Accelerating Innovation and Putting the Patient First
- Manufacturing and Supply Considerations to Enable Novel Therapies
- Improving Efficiency and Reducing Manufacturing Cost
- Rapid Product Development
- Ensuring Supply of Medicines and Expanding Access

Three concurrent session tracks, Advances in Bioprocess Development, Innovation in Manufacturing Sciences and Lifecycle Management and Continuous Improvement, will address challenges associated with reliably and efficiently producing and supplying emerging novel therapies to enable patient access globally.

You won't want to miss this important conference. **Save up to $400** when you register before January 11, 2016!

Learn more and register at pda.org/2016annualmeeting.