People • Science • Regulation

PDA Letter

Volume LII • Issue 8 www.pda.org/pdaletter September 2016

Heads or Tails

Statistical Methods for Interpreting Multiple Biological Indicator Results

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11th Annual PDA Global Conference on Pharmaceutical Microbiology

Universe of Pre-filled Syringes and Injection Devices

Calling All Active PDA Members – Vote Now!

Online voting is now open for the 2017 PDA Board of Directors Election

PDA members, online voting has opened for the **2017 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 25, 2016 are eligible to vote**. Voting closes at **11:59 p.m. EST on November 16, 2016**. 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 **pda.org/vote**
- Log into the system using your PDA Member number 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 the...

SAN DIEGO, CA –
2016 PDA Data Integrity Workshop

December 7-8, 2016 | San Diego, CA

Manchester Grand Hyatt

Exhibition: December 7-8 | Courses: December 9
#2016Data

Register before September 26 and save up to $400

An In-depth, Multi-faceted Approach to Prevention, Detection and Mitigation of Data Integrity Issues

Data integrity is a major issue facing the bio/pharmaceutical industry. To help companies identify and understand underlying causes of data integrity problems and how to resolve them, PDA is offering the *2016 Data Integrity Workshop*. The final installment of this Workshop will take place in San Diego, CA.

Through plenary, breakout and breakfast sessions, industry and regulatory experts will explore the multiple facets of data integrity, including quality culture, human behavior, training needs and technology requirements.

Gain insight on these important topics:

- **Clinical Data:** A case study will be presented to illustrate the potential implications of data integrity violations at a clinical study site and showcase appropriate actions to determine the root cause and prevent future errors.
- **Diagnosis & Detection:** Forensic auditing will be discussed as a method for detecting and diagnosing data integrity issues within a quality control chemistry lab.
- **Remediation:** Examples will be provided to illustrate how to achieve a sustainable response to data integrity issues through pragmatic and implementable solutions.

This unique format is ideal for promoting a holistic understanding of the challenges in this area; strategies for tackling these challenges will be provided.

To learn more and register for this Workshop, please visit pda.org/2016DataWest.

Immediately following the Workshop, PDA Education will host the *2016 Data Integrity Workshop Course Series*, which offers two continuing education courses on *Investigating Microbial Data Deviations and CMC Regulatory Requirements in Drug Applications*.

To learn more and register for the Course Series, please visit pda.org/2016DataCourses.

PDA Letter

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Cover Illustration by Katja Yount

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Features

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

An Election Worthy of Your Vote

No missing emails. No walls. No bull.

Vote for PDA's next volunteer leaders and help shape the strategic direction of an organization that always reaches across the aisles and oceans to connect people, science and regulation. Voting opens Sept. 6 and closes at 11:59 p.m. on Nov. 16.

Members in good standing as of Aug. 25, 2016 can vote online at the PDA website (www.pda.org/vote) and at conferences held between Sept. 12 and Nov. 16 in the United States and Europe. For information about the candidates, visit www.pda.org/election. This election is "yuuuuge!"

Vote Online

You will need your member ID and password.

www.pda.org/vote

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

Director Candidates

Barbara M. Allen, PhD

Joyce E. Bloomfield

Véronique Davoust, PharmD

Ghada Haddad

Stephan O. Krause, PhD

Marty R. Nealey

Morten Munk

Brent Watkins

The Parenteral Drug Association presents...

ARLINGTON, VA –

2016 PDA Workshop: Current Challenges in Aseptic Processing, Potential Changes in EMA/PIC/S Annex 1 Revision

Addressing the Unanswered Questions of How to Use Risk- and Science-Based Approaches to Meet Global Health Authority Expectations and Improve Aseptic Processing

October 26-27, 2016 | Arlington, VA

Hyatt Regency Crystal City
Exhibition: October 26
#2016Annex

Workshop Theme: ***Points to Consider in Modern Aseptic Manufacturing – with Special Reference to the On-going Revision of the European GMPs for Sterile Medicines***

The last installment of the *2016 PDA Workshop: Current Challenges in Aseptic Processing, Potential Changes in EMA/PIC/S Annex 1 Revision* will take place in Arlington, VA, **Oct. 26-27**.

Presentations by industry and regulatory experts will showcase the use of critical thinking to better understand the aseptic process and associated risks of contamination, and how to develop optimal process control strategies. Several presentations will reference the *PDA Points to Consider for Aseptic Manufacturing Part 1 and Part 2* series to highlight consensus-based best practices for improving sterile healthcare products.

Designed to inform and promote energized discussion, this interactive Workshop is a unique opportunity to engage with peers, industry leaders and experts on a wide range of topics related to aseptic processing.

For more information and to register, please visit pda.org/2016Annex1East.

PDA Ed. Offering FDA Sterilization and Media Fills Training

PDA will offer five specialized PDA Education courses for officials in the U.S. FDA's Center for Drug Evaluation and Research (CDER), commencing in September and running through early 2017. These lecture courses will take place at FDA's White Oak Campus in Silver Spring, Md.

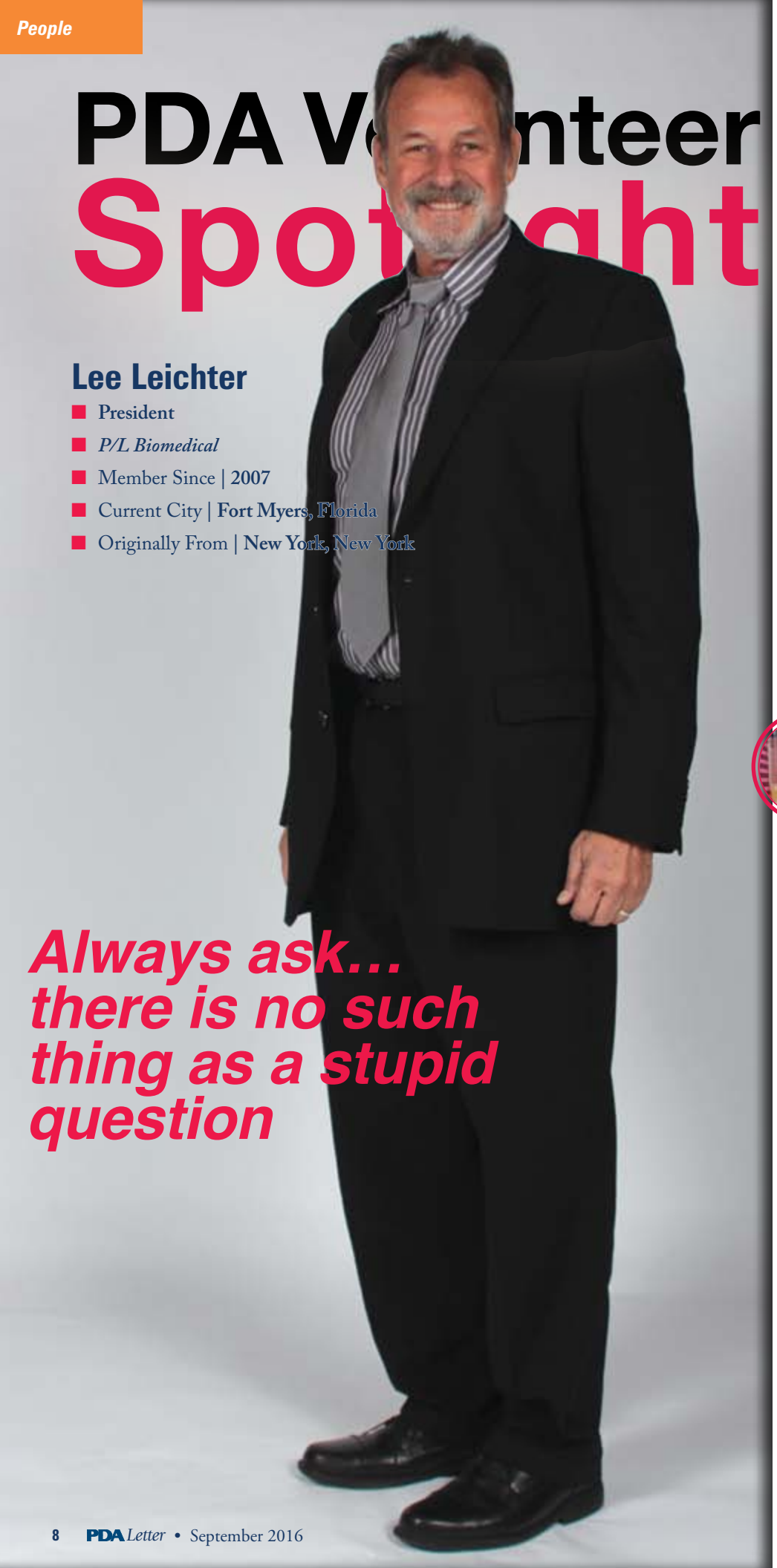
Topics covered in this series of courses include sterilization, sterile filtration, and media fills. The courses will be taught by faculty comprised of leading industry experts, representing such companies as Eli Lilly, Baxter, etc.

PDA has a long history of providing expert training to regulators worldwide. FDA has regularly participated in specialized courses on aseptic processing techniques and sterilization since PDA opened the Training and Research Institute (TRI) in 1997. PDA has also conducted inspectorate training with European regulators, and in recent years, has partnered with PIC/S to provide regulatory training on topics like data integrity. In addition, PDA has provided specialized training sessions for regulators from Russia, Italy, Ireland, and Kazakhstan.

Below is the schedule of courses, including instructor information. For more information about other PDA Education courses, please visit www.pda.org/courses.

Topic	Instructor(s)	Date and Time
Basics of Steam Sterilization	Mike Sadowski, Director, R&D Sterility Assurance, Baxter International Inc.	September 9, 2016 8 a.m. – 12 p.m.
Advanced Steam Sterilization	Mike Sadowski, Director, R&D Sterility Assurance, Baxter International Inc.	October 7, 2016 9 a.m. – 1 p.m.
Media Fills	Harold Baseman, Chief Operating Officer and Principal, ValSource LLC	November 8, 2016 9 a.m. – 1 p.m.
Container Closure Systems and Integrity Testing	Lei Li, PhD, Sr. Consultant Engineer, Delivery and Device R&D, Eli Lilly and Company	January 10, 2017 8 a.m. – 12 p.m.
Sterilizing Filtration	Maik Jornitz, President, G-CON Manufacturing Inc. Wayne Garafola, Field Applications Specialist - Filtration Technologies, Sartorius Stedim North America Inc.	February 7, 2017 9 a.m. – 1 p.m.

PDA Volunteer Spotlight



Lee Leichter

- President
- *P/L Biomedical*
- Member Since | 2007
- Current City | Fort Myers, Florida
- Originally From | New York, New York

Always ask… there is no such thing as a stupid question

What was it like leading the team responsible for PDA's comments on the U.S. FDA's combination products guidance?

It was difficult and rewarding. It was challenging to gain consensus from the many talented individuals, each with a different perspective and opinion. It was rewarding in that, through the hard work of the team, I believe we were able to offer important comments and some very creative suggestions to provide FDA with all the information they need to understand the industries' concerns and help achieve the goal of a clear, consistent, and helpful guidance.

What have you gained from chairing the *2016 PDA Drug Delivery Combination Products Workshop*?

The satisfaction of helping pull together a program, presented by talented and knowledgeable professionals, that provides valuable, usable information to allow more people to be successful with combination products. I also always gain new perspectives and learn from these types of experiences.

What upcoming PDA conferences are you looking forward to?

The *Universe of Prefilled Syringes and Injection Devices* because I can get together with over 800 of my closest personal friends.

Where do you see combination products in the next five years?

I see companies taking a more holistic role in treating their patients. This will include providing the simplest, most intuitive, and least invasive treatments and devices, then combining these with support that encompasses the company, the patient, their caregiver(s) and social networks in a connected web of care.

Then again, when I started 20 years ago, I thought that combination products would only be a "thing" for five years or so, so what do I know!

What was your least favorite subject in school?

In high school it was English. I loved science and math. It took 50 years for me to realize the importance of clear, succinct, and understandable communication, and that if you cannot communicate, it does not matter what you know or how smart you are.

Who inspires you?

My Wife! She is my muse, my partner, my confidante.

The Parenteral Drug Association presents the...

11th Annual PDA Global Conference on Pharmaceutical Microbiology

Advancing Quality and Safety through Sound Science

October 24-26, 2016 | Arlington, VA

Hyatt Regency Crystal City

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

#2016Micro

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

The *11th Annual PDA Global Conference on Pharmaceutical Microbiology* continues a long tradition of exploring the latest developments in pharmaceutical manufacturing and regulation. This year, industry, academia and regulatory experts will present on pharmaceutical microbiology "hot topics" such as:

- The Challenges for Developing a Zika Vaccine
- Solutions for Overcoming Testing Challenges with Fungal and Bacterial Spores in Disinfectant Coupon Studies
- Lessons Learned in Microbial Data Integrity Management from a Manufacturer's Perspective
- Development of an Effective Microbial Control Strategy in a Biomanufacturing Facility
- FDA Perspective on Endotoxin Testing and LER

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

Extend your educational experience when you attend the *11th Annual PDA Global Conference on Pharmaceutical Microbiology Course Series*, **Oct. 27-28**. PDA Education will offer four courses on important pharmaceutical microbiology topics.

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

chapter update

PDA's Southern California Chapter Gives Back

Stephanie Powers-Kurtz, Veltek Associates, Inc.

It's well known that PDA's chapters offer a multitude of conferences and evening presentations designed to fill minds hungry for knowledge. But did you know that some chapters are also working to keep actual physical hunger at bay in our communities?

On May 5, the philanthropy arm of PDA's Southern California Chapter spent the day distributing food donations to local charities in the San Diego area. Chapter leaders **Randy George** (President-Elect), **Ileana Ayala** (Secretary), and **Stephanie Powers-Kurtz** (Treasurer) began the day by picking up food from the Hyatt Regency at Mission Bay.

The first stop was Mama's Kitchen, a community-driven organization that provides nutrition support to men, women, and children affected by AIDS or cancer and vulner-

Randy George (far left) and Ileana Ayala (inside the van) showcase the chapter's food donations

Ileana Ayala (far left) and Stephanie Powers-Kurtz (far right) pose with representatives of the Salvation Army

able to hunger. Next, the three dropped off food at Father Joe's Villages—San Diego's largest homeless services provider. Services offered include housing aid, employment assistance, and a health center. Father Joe's prepares up to 3,000 meals and provides a continuum of care every day to nearly 1,500 individuals from infants to senior citizens.

Lastly, the three chapter leaders delivered food to the Salvation Army of San Diego.

Overall, the chapter delivered 115 dozen granola bars, 50 personal lunches consisting of sandwiches, pasta salad, vegetable chips, cookies, and apples, and 700 bottles of water!

All three charities were extremely appreciative of the donations. It was such a great and rewarding day to spend time with fellow chapter members, gathered for a wonderful cause. In addition to the joy of giving back, the chapter leaders also enjoyed getting to know each other on a more personal level.

Ileana Ayala (center) and Stephanie Powers-Kurtz (second from right) stand with representatives from Father Joe's Villages

The chapter looks forward to participating in more events like this! For more information about the chapter's philanthropy activities, contact Chapter Treasurer Stephanie Powers-Kurtz at spowerskurtz@sterile.com or (610) 608-4142.

PDA Who's Who

Ileana Ayala, U.S. Business Developer, Pharma-Bio Serv US

Randy George, Area Director, Rescop Inc.

Stephanie Powers-Kurtz, Southwest Territory Sales Manager, Veltek Associates, Inc.

Workshop: Business Opportunities India
(l-r) Joerg Strassburger, Go East; Yvonne Metzger, BVMW; Sushil Khanna, University Calcutta

Session 1: Continuous Manufacturing & Flexible Facilities
(l-r) Eric Meier, Novartis; Jochen Strube, Clausthal University of Technology

Opening Plenary
(l-r) Martin VanTrieste, PDA Chair; John Johnson, NSF Health Sciences; Thomas Friedli, University of St. Gallen; Jean-Louis Robert, EMA; Paul Hargreaves, PIC/S

Session 4A: Modern Analytical Techniques
(l-r) Cenk Undey, Amgen; Ryan Smith, SightMachine; David Brueckner, Roche

Session 3: Regulatory Track
Kevin O'Donnell, HPRA, Ireland

Session 3: Big Data Processing/Industry 4.0
(l-r) Francisco Herrador, Altran; Toni Manzano, BigFinite

Session 4: Drug Administration
Markus Bauss, SHL Connect

Closing Plenary
Morten Munk, NNE Pharmaplan

Attendees chat with one of the exhibitors during a refreshment break

Ompi was one of the exhibitors at the meeting (Ompi will also be exhibiting at Booth 211 at the upcoming 2016 PDA Universe of Pre-filled Syringes and Injection Devices)

Rich Levy, PDA (left) chats with Madlene Dole (center) and John Shabushnig (right) in front of the Afton Scientific exhibit

PDA Board Secretary Jette Christensen enjoys coffee with attendees in the Exhibit Hall

+ ATMPs and Viral Safety of ATMPs June 6–8 | Berlin, Germany

The Future of ATMPs: Trends & Developments (ATMP conference)
(l-r) Phil Bassett, Adaptimmune; Tony Hitchcock,Cobra Biologics; Clive Glover, GE Healthcare; Manuel Corrondo, IEBT

Session 2: Human-derived Raw Materials (Viral Safety of ATMPs)
Katharina Schallmoser, Paracelsus Medical University; Salvador Grancha, Grifols

eye on education

Training Critical to Safety of Sterilized Filters

Maik Jornitz, G-Con Manufacturing

Since aseptic processing is now prevalent within the biopharmaceutical industry, regulators and industry alike are now focusing on the last barrier to sterile effluent: sterilized grade filters. Used in many applications, sterilized membrane filters play a critical role as a point-of-use filter before the filling process.

These filters require appropriate process validation to verify they perform as specified, e.g., not retaining microbial contaminants and/or avoiding release of leachables or particulates. Process validation for these filters needs specific attention and knowledge.

For example, the retention capabilities of a filter depend on a multitude of parameters. These can be influenced by the fluid, process conditions, filter membrane material, and microorganisms. The process validation lead must understand this jigsaw puzzle of possibilities in order determine the appropriate tests for analyzing retention and filtrate sterilization.

In addition, a filter should not leach chemical components into the product; tests and methods are available to analyze for this possibility. Likewise, the filter membrane should not absorb components from the fluid, preservatives, or target protein. Thus, evaluating and choosing an optimal filter or filter combination requires analyzing a multitude of key factors. Determining the right filter material as well as the appropriate filter size is critical to preventing nasty surprises following validation.

After a filter has been selected, the day-to-day routine of using the filter involves the critical elements of handling, steam sterilization, and integrity testing. If anything in this routine goes wrong and a filter fails the integrity test, the end user must figure out what happened, determine the next appropriate steps, and collect the necessary information to understand why the filter failed.

Mos failures occur due to wetting problems but incorrect handling or detrimental process operations can also cause filter failures. Steps can be taken to determine if there is a wetting issue or if the filter is truly incompatible with the process.

All of the steps listed above emphasize the critical importance of filtration to the aseptic process. Yet there is no "Filtration 101" course offered by any university; much of the industry's filtration knowledge is gained through on-the-job training which has its limitations. In many instances, inexperience and lack of knowledge can result in inappropriate installation, sterilization, and filter use.

The PDA Education course, "Filtration Processes in the Pharmaceutical and Biopharmaceutical Industry," offered at PDA's Training and Research Institute (TRI), provides an opportunity for those involved in filtration to expand their knowledge and gain the hands-on experience that's usually only available through many years of filtration work. This is an opportunity to learn practical information and even make mistakes. While filtration failures and mistakes can be disastrous in a plant, they serve as a mere learning point within the confines of this course.

Join your industry colleagues this October and build up your knowledge of filtration.

Filtration Processes in the Pharmaceutical and Biopharmaceutical Industry

Bethesda, Md.
Oct. 3–7
www.pda.org/2016filtration

PDA
Parenteral Drug Association

The Parenteral Drug Association presents:

2016 PDA Europe

Outsourcing & Contract Manufacturing

14 November
Risk-based Approach for Prevention and Management of Drug Shortages

15-16 November
Conference, Exhibition

17 November
Quality by Design for Biopharmaceuticals

17-18 November
– Root Cause Investigation
– Basics of Successful Auditing

Register by 15 Oct 2016 and SAVE!

15-16 November 2016

Olivia Balmes Hotel

Barcelona | Spain

pda.org/EU/Outsourcing2016

PDA's LER Task Force Holds its First Workshop

Dayue Chen, Eli Lilly and Co., Friedrich von Wintzingerode, Roche Diagnostics GmbH, Josh Eaton, PDA, Patricia Hughes, U.S. FDA, Jack Levin, MD, University of California San Francisco

Since it was first reported by Chen and Vinther in 2013 ***(1),*** the phenomenon known as low endotoxin recovery (LER) has been broadly observed in certain matrices commonly used for biologic formulations and certain therapeutic proteins. These observations have generated concerns that a pharmaceutical product contaminated with endotoxin may go undetected by the compendial USP <85>/EP 2.6.14./JP 4.01 bacterial endotoxin test (BET). In response to these reports, the U.S. FDA's Center for Drug Evaluation and Research (CDER) recently began asking companies to conduct endotoxin spike/hold recovery studies to determine whether a given biological product is affected by LER ***(2–4).*** As a result, numerous spike/hold recovery studies have been carried out by many individual firms hoping to ameliorate FDA's concern. These studies, however, have often produced confounding and sometimes contradictory results with regard to the cause, biochemical mechanism, and biological relevance of the LER phenomenon, likely due to variations in study designs, experimental procedures, and/or type of endotoxin used. Clearly, there is a mutual interest and desire for the industry and FDA to work together to develop a science-based and data-driven strategy in dealing with the LER phenomenon.

Recognizing the significance and complex nature of the LER issue, PDA's Biotechnology Advisory Board (BioAB) sanctioned the LER Task Force in early 2015. This Task Force is composed of subject matter experts from academia, FDA, the biopharmaceutical industry, and reagent-supplier/testing companies. Many of the firms that have submitted LER data to the FDA are represented on the PDA LER Task Force, ensuring broad representation. The Task Force, however, will continue to reach out to maximize industrial participation.

The task force has three specific goals:
1. Investigate the root cause of LER
2. Standardize the experimental protocols for spike/hold recovery studies
3. Identify the potential safety impact of the LER phenomenon

As part of the effort to achieve these goals, the Task Force sponsored the first workshop exclusively dedicated to LER in March 2016 in San Antonio, coinciding with the *2016 PDA Annual Meeting.* To facilitate the discussion, a questionnaire was sent out prior to the workshop to individual participating firms to collect specific information relevant to the LER phenomenon and spike/hold recovery studies. This approach proved to be highly valuable and effective since such details/specifics were usually not included or shared in conventional meetings.

Once at the two-and-one-half day workshop, attendees heard 11 presentations on endotoxin spike/hold recovery studies. Approximately two hours were allocated for each speaker, divided roughly between a 45 minute oral presentation and in-depth Q&A discussion. Highlights extracted from the workshop are summarized below.

Lack of Standardized LER Protocol Complicates BLA Review

Due to the lack of a standardized protocol, individual companies perform spike/hold recovery studies differently as reflected by the information provided to the FDA. This sometimes complicates the BLA review process by the agency and highlights the urgent need to establish a harmonized procedure for spike/hold recovery studies.

Although there was extensive discussion of how spike/hold recovery studies should be executed with regard to temperatures in the context of GMP manufacturing conditions, the issue remains unresolved at this time. It has been observed that different compendial bacterial endotoxin testing (BET) methods—kinetic turbidimetric assay (KTA), kinetic chromogenic assay (KCA), and gel clot assay (GCA)—may have different susceptibility to LER. FDA will accept change to another compendial method that does not show LER, provided that the results are consistent and reproducible. Change to a noncompendial method will even be accepted if adequate method validation data and relevant information are provided.

Several firms presented data from spike/hold recovery studies using both purified lipopolysaccharide (LPS) and in-house prepared natural occurring endotoxin (NOE). In some studies, LER was observed only when LPS was the spiking analyte, but not with NOE. In other studies, no difference was seen between LPS and NOE with regard to LER. In one study, it was shown that NOE prepared from different bacterial species exhibited a great degree of variability in recovery when spiked into a drug product formulated in a phosphate and PS80 matrix. The same study also reported that reference standard endotoxin had substantially slower

rate of activity loss than control standard endotoxin in the drug product matrix. The exact bases for such confounding and even contradictory results remain unknown and the debate of using LPS versus NOE in spike/hold recovery studies is likely to continue for the foreseeable future.

Different Strokes for Different LERs

Data shared at the workshop showed that LER could be triggered by very different factors. Multiple companies reported that therapeutic products themselves could potentially cause LER. Although the combination of chelator/PS80 often leads to LER, it is not always the case, suggesting the involvement of other unknown elements or synergistic effects of individual components.

Participants also discussed that the role of surfactants (e.g., PS80) in LER is significantly less profound than chelators (e.g., citrate). One participant reported that LER observed in a DP formulated with citrate and PS80 could be overcome by the addition of divalent Mg++ prior to testing, suggesting that LER is readily reversible. A similar approach, however, did not result in successful rescue of recovery in other companies. The data and experimental details of these studies will be collected and analyzed in order to better understand the cause for the apparent discrepancy.

In addition, the Task Force learned that LER could be overcome by a "de-masking" process using proprietary reagents. However, the effectiveness of de-masking appears to be product/formulation dependent.

Finally, it was shown that LPS recovery can also be influenced by sampling scheme and vortex time ***(5).***

Recommendations

Based on the data and experience shared at the workshop, the group has proposed several recommendations with the objective of ensuring the relevance of the spike/hold recovery studies and harmonizing the experimental procedure as much as possible:

1. If there is no LER observed in the final DP, it is not essential to perform the spike/hold recovery studies with the prior process intermediates such as drug substance (DS).

2. Spike/hold and recovery studies should be carried out in a manner representative of the corresponding QC BET testing with regard to materials, containers, and experimental procedures.

3. LER is defined as the endotoxin activity falling below 50% of the spiked amount at two consecutive time points; and

4. Sampling repeatedly from a single spiked container should be avoided. Instead, reverse assay (spiking independently on different days and testing all the spiked samples on the same day) or multiple-aliquot approach (dispensing the spiked material into individual containers and testing individual containers on different days) is strongly recommended.

Workshop Moves Debate Forward

The LER phenomenon has generated much discussion and debate in almost every microbiology conference and workshop during the last three years. Experimental results and data presented at this workshop indicate that while considerable progress has been made during this period, fundamental questions concerning the LER phenomenon remain unanswered.

All individual members of the PDA LER Task Force are committed to work together to advance our understanding of the LER phenomenon.

The LER Task Force currently has four subgroups with each working on a different aspect of the LER phenomenon. Subgroup 1 is focused on providing a clear guidance for spike/hold recovery studies. Subgroup 2 is working on understanding the underlying mechanism of the LER phenomenon and evaluating whether it is possible to develop a procedure/method ➤

to produce an endotoxin standard for spike/hold recovery studies. Subgroup 3 is concentrating on assessing the potential safety risk of the LER phenomenon by careful evaluation of the available data. And finally, Subgroup 4 is devoting all its efforts to providing clear definitions for terms relevant to the LER phenomenon using the USP *Pharmacopeial Forum* (PF) as a starting point.

There is no doubt that more research and investigation are needed in order to better understand the LER phenomenon, elucidate its underlying mechanism, and determine its potential clinical significance. The LER Task Force is confident, however, that the group's specific goals will be achieved by working together as a team and adhering to data-driven/science-based principles.

[Editor's Note: Learn more about the Task Force's workshop in session "A2: Challenges in Endotoxin Recovery," Oct. 24, 1:30 p.m. at PDA's pharmaceutical microbiology conference."**]**

The task force acknowledges the following individuals for sharing their information and data at the workshop: ***Mazukazu Tsuchiya,*** *Charles River;* ***John Dubczak,*** *Charles River;* ***Jay Bolden,*** *Eli Lilly;* ***Stefan Ishak,*** *Sandoz;* ***Johannes Reich,*** *Hyglos;* ***Phil Villari,*** *Merck Sharp & Dohme;* ***Cheryl Platco,*** *Merck;* ***Anders Thorn,*** *Novo Nordisk;* ***Chris Knutsen,*** *BMS;* ***Ned Mozier,*** *Pfizer; and* ***Karen McCullough;*** *MMI Associates***.**

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Still Room for Improvement in Glass Packaging

Analysis of a New Type of Glass Composition with Existing Glass Types

Bettine Boltres, Stephan Tratzky, Christof Kass, Rainer Eichholz, Peter Nass, Schott AG

As more and more newly developed drugs prove quite sensitive toward changes in their chemical environment, regulatory agencies have started focusing more on drug-container interactions. These interactions vary, depending significantly on the composition of the primary packaging material, the conversion process, and the drug product.

The contribution of the liquid drug formulation to this interaction is, apart from its chemical nature, its pH value. **Figure 1** shows the basic chemical reaction between a borosilicate glass and a liquid with acidic (pH <7) and alkaline (pH > 7) pH values. In the lower pH range, there is an ion exchange taking place, exchanging ions like sodium, potassium, calcium, etc., from the glass into the solution. On the other hand, at higher pH values, a constant erosion of the whole glass surface occurs. The chemical nature of the drug solution determines whether it is an ion exchange or rather an erosion that is occurring ***(1).***

Figure 1 Borosilicate Glass Interaction with Acidic and Alkaline pH Values

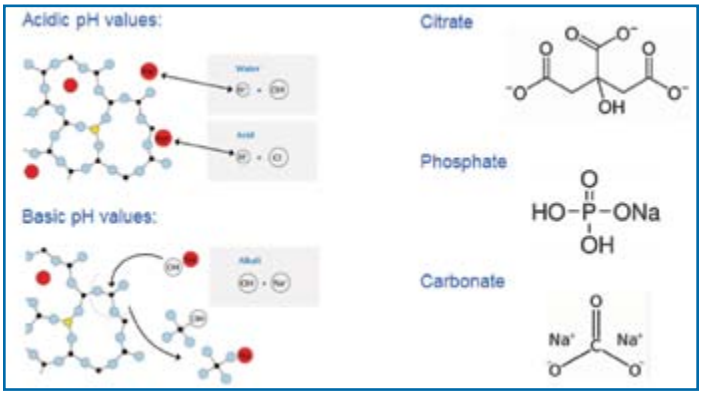


Figure 1 shows glass interactions with water or an acidic solution (left side upper schematic) resulting in an ion exchange; an alkaline solution with erosion (left side lower schematic); and the different chemical nature of buffer solutions leading to different reaction mechanisms with the glass packaging material (right side).

The suitability of a glass as a primary packaging material can be evaluated parallel to performing accelerated ageing studies (e.g., for six, 12, or 18 months at 40°C) by monitoring the amount of leachables and extractables. Glass lends itself to such tests because of the limited number of components used in fabrication and the composition is known and publicly available.

To what extent the various elements are released from the glass, however, is dependent on different factors. The glass matrix is a quite complicated interplay between the oxides that are used. This interplay defines the strength of the silicate network and the chemical and physical properties. Minor compositional changes can have a significant impact on the chemical and physical properties.

Below is an analysis of a new glass composition (borosilicate Type I, according to current USP and the European Pharmacopeia ***(2–3).*** Evidence suggests it offers greater chemical stability and a lower total accelerated leachable level due to an optimized interplay between the elements.

For this study, globally supplied glass tubing for pharmaceutical applications was chosen for comparison with the new glass composition. **Table 1** shows the composition of the glass types used. Glass A is the newly developed glass, whereas Glass B represents a commonly used borosilicate glass that has been used for over a century. Glasses C and D are comparative neutral borosilicate glass compositions currently used for pharmaceutical applications. All glasses were characterized by using X-ray fluorescence spectroscopy.

The team responsible for the study chose an extraction study with one hour autoclaving at 121°C, since autoclaving is a standard terminal sterilization method used in parenteral packaging processing. Furthermore, it is a very aggressive procedure on glass, quickly ➤

Table 1 Composition of Glass Types

Elements	Glass A	Glass B	Glass C	Glass D
SiO_2	73	75	72	72
B_2O_3	11.0	10.5	10.5	11.4
Al_2O_3	6.9	5.4	7.1	6.8
Na_2O	7.3	7.1	6.3	6.7
K_2O	0.5	< 0.01	1.9	2.0
Li_2O	< 0.01	< 0.01	< 0.01	< 0.01
BaO, CaO, MgO, SrO	0.5	1.5	2.0	1.0

revealing the chemical stability of the inner glass surface. The concentration of extractables is important because it can enhance possible interactions with the drug. If the drug is sensitive toward any changes in its environment, the amount of extractables should be kept as low as possible.

Figure 2 shows the results of the extraction study. Visible silicon forms the biggest part of the extracted elements as it represents the major component of the glasses. Glass A appears to offer the lowest amount of total extractables in the solution, followed by Glass B. Glasses C and D exhibit the highest amount. Glass D releases four times the higher amount of silicon into the solution than Glass A, indicating a strong glass attack by the water.

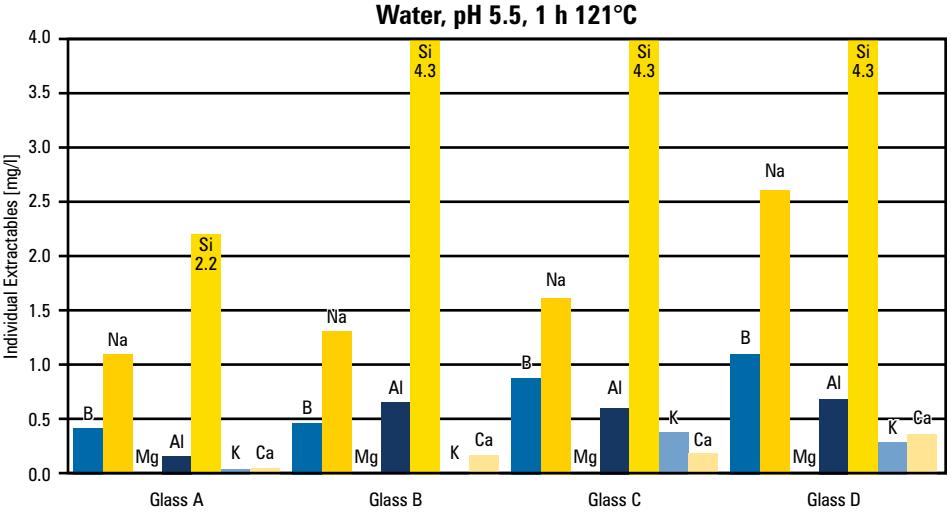
The development of biopharmaceuticals has increased steadily in the past years. Because these molecules are much more chemically complex, they possess a significantly higher amount of interaction sites with their environment. Often times they are very sensitive to a change in their chemical environment which is why the possibility of interactions with primary packaging material should be kept as low as possible.

It could be shown that with minor compositional changes in the glass the chemical stability of the same can be improved measurably. As the interactions depend on a variety of factors, the compatibility needs to be tested on an individual basis with the specific drug formulation.

The new glass composition analyzed suggests it offers a greater degree of protection compared to traditional glass compositions. Further studies should shed more light on its capability to provide low interactions with product.

[Editor's Note: This is an abridged version of an article in Vol. 70, issue 4 of the *PDA Journal of Pharmaceutical Science and Technology*. It was also presented at the PDA *Parenteral Packaging* meeting in April.**]**

Figure 2 Extraction Results on an Individual Basis of Glasses A, B, C, and D



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Heads or Tails

Statistical Methods for Interpreting Multiple Biological Indicator Results

Donald Eddington, PhD, Eddington and Bond Associates, Inc.

One of the main advantages of using an isolator for an aseptic processing application is that it creates a physical separation between the operator and the aseptic workspace. Another main advantage is that an isolator can be completely sealed before aseptic work begins, allowing for the exposed interior surfaces within to be biodecontaminated, typically, via hydrogen peroxide vapor or mist.

When isolators were first introduced in the pharmaceutical industry, the validation of the biodecontamination process was largely patterned after methodology used for steam sterilizer validation. Biological indicators (BIs), typically containing over one million microbes per sample, were used to challenge the biodecontamination process. BIs for use with isolators were most often prepared with spores of *Geobacillus stearothermophilus*, because this organism is known to be very resistant to the hydrogen peroxide decontamination process, and by coincidence, the same organism is used for steam sterilization validation. The typical validation approach involved distributing numerous BIs within the interior space and load items of a system, including in worst case locations where kill is expected to challenging. Complete kill of the BIs was usually expected for process qualification to be considered successful.

Isolator operators, however, sometimes experienced difficulties with an occasional posi-

Article at a Glance

- ★ Multiple biological indicators are frequently used for isolator validations
- ★ Most Probable Number calculation frequently used for estimating log reduction
- ★ Binomial distribution calculations can also be used to interpret results

tive BI result during the initial qualification or annual requalification. Following such occurrences, maintenance procedures, such as cleaning the vaporizer or injection needles, were conducted on the hydrogen peroxide vapor generator. If the next decontamination cycle obtained complete kill of the BIs, the maintenance procedure was indicated as the corrective action.

Rogues One Reason for Positive Results

Over time, isolator operators began to realize that these occasional BI issues were not caused by maintenance issues. Instead, they started to suspect that some lots contained a very low percentage of "rogue" BI's—individual samples with very high resistance compared to the rest of batch. Rogues can be caused by large clumps of spores, debris, scratches on the surface of the carrier substrate, etc. These samples may be more prone to have some spores survive a hydrogen peroxide decontamination process that relies on direct surface contact than similarly prepared samples exposed to a more penetrating process like steam sterilization.

One must recognize that not all positive BIs that occur during qualifications are rogues. When positive BIs occur, an investigation must be made to make sure the decontamination cycle conformed to the expected cycle parameters, SOPs were followed, etc. If the investigation does not reveal a probable cause, a rationale is required for interpreting the occurrence of an occasional positive BI. PDA Technical Report No. 51 ***(1),*** describes the situation thusly: "Current industrial experience indicates that occasional positive BIs occur even in well-defined cycles. Such rogue results may not be indicative of a failed cycle. Appropriate statistical methods may be used to support the acceptance of such rogue results in both primary validation and revalidation programs." Statistical methods used to interpret BI results require more than one sample per location.

Isolator operators, however, sometimes experienced difficulties with an occasional positive BI result

PIC/S recommendations on isolators ***(2)*** describe the limitations of using single BIs for validation: "If there is only one BI in each position, and only growth/no growth is established, then the number of survivors is unknown and the size of the possible variation in the process cannot be estimated." The document describes approaches using single or duplicate BIs in each location. The surviving number of spores on exposed BIs can be estimated using serial dilutions and counting colonies on media plates, or statistical interpretation of growth/no growth of aliquots of broth. This approach is labor intensive and may not be practical when large numbers of locations are being tested. The PIC/S document goes on to describe the approach that has become common place today: "Another possibility is to place three or more BIs at each position in the isolator and put them individually into broth for incubation. If there are any positive broths, the proportion of positive to negative can be used to estimate the number of survivors and thus the log reduction."

Microbiologists Must Do the Math

The Most Probable Number (MPN) calculation can be used as the basis for estimating the log reduction of spores obtained when using multiple BIs for validation. This method is probably the most familiar one to microbiologists, as the calculation is also used to estimate the initial population of organisms in a sample analyzed by serial dilution techniques. The MPN calculation has different uses in various fields of applied microbiology. This method is alluded to in the previous quotation from the PIC/S guide ***(2).*** The method uses the 1933 Halvorson-Zieglar equation ***(3).*** The equation estimates the most probable number of surviving organisms when multiple BIs are used and a mixture of positive and negative results is obtained.

$$MPN = \ln(n/r)$$

Where:
MPN = Most Probable Number of surviving organisms
n = number of replicate BIs at each discrete test location
r = number of growth negative BIs at each test location

The MPN calculation can then be used for estimating Spore Log Reduction (SLR).

$$SLR = \log(N_0) - \log(MPN)$$

Where:
SLR = Spore Log Reduction
$\mathbf{N_0}$ = Initial spore population of the non-exposed BIs

An example follows for the results from triplicate BIs with an initial population of 2×10^6 that have results of one growth positive sample and two growth negative samples:

$$SLR = \log(2 \times 10^6) - \log(\ln 3/2) = 6.69$$

The probability of obtaining cumulative results from series of individual tests with yes/no outcomes is characterized by a binomial distribution. A well-known example of a yes/no outcome is a coin toss which has a 50% chance of yielding a "heads" result and a 50% chance of yielding a "tails" result. The possible outcomes of three coin tosses in a row are: 3 heads, 1 tail and 2 heads, 2 tails and 1 head, or 3 tails. The probabilities of these results occurring are shown in **Table 1.**

The application of a binomial distribution to the fractional results of triplicate BIs is only slightly more complicated; the odds of getting positive or negative BI results are not 50–50 because of the natural variability from sample to sample. As the average number of surviving spores approach zero during a lethality ➤

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14-15
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15-16
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19
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20-21
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21-22
Quality Metrics and Quality Culture
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21
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21
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22
Elastomers
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22
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22-23
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27-28
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29
Application of a Risk-based Approach to Freeze-Drying Processes
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29-30
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3-7
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5-6
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11-12
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13

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13-14

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14

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Table 1 Possible Outcomes of Three Coin Tosses

Total Results	Possible Outcome	Probability Calculation	Probability	Total Probability
3 Heads	H H H	0.5 × 0.5 × 0.5	12.5 %	12.5 %
1 Tails, 2 Heads	T H H	0.5 × 0.5 × 0.5	12.5 %	37.5 %
	H T H	0.5 × 0.5 × 0.5	12.5 %	
	H H T	0.5 × 0.5 × 0.5	12.5 %	
2 Tails, 1 Heads	T T H	0.5 × 0.5 × 0.5	12.5 %	37.5 %
	T H T	0.5 × 0.5 × 0.5	12.5 %	
	H T T	0.5 × 0.5 × 0.5	12.5 %	
3 Tails	T T T	0.5 × 0.5 × 0.5	12.5 %	12.5 %
				100 %

Table 2 Possible Outcomes of Three 2×10^6 BIs Exposed to a 6-log Decontamination Process

Total Results	Possible Outcome	Probability Calculation	Probability	Total Probability
3 Negatives	- - -	0.135 × 0.135 × 0.135	0.25 %	0.25 %
1 Positive, 2 Negatives	+ - -	0.865 × 0.135 × 0.135	1.58 %	4.74 %
	- + -	0.135 × 0.865 × 0.135	1.58 %	
	- - +	0.135 × 0.135 × 0.865	1.58 %	
2 Positives, 1 Negative	+ + -	0.865 × 0.865 × 0.135	10.12 %	30.36 %
	+ - +	0.865 × 0.135 × 0.865	10.12 %	
	- + +	0.135 × 0.865 × 0.865	10.12 %	
3 Positives	+ + +	0.865 × 0.865 × 0.865	64.65 %	64.65 %
				100 %

process, the number of spores on individual samples approach a Poisson Distribution ***(4),*** which is used to describe probability when the average outcome of an event can be calculated and the results of individual events don't influence each other. In this case, the "event" is exposing a BI to a lethal process and the result is the number of viable spores surviving. The average number of surviving viable spores on a BI exposed to a lethal process can be calculated as follows:

$$m = 10^{(\log N_0 - t/D)}$$

Where:

m = Average number of surviving spores after exposure time

$\mathbf{N_0}$ = Initial spore population of the non-exposed BIs

t = exposure time

D = D-value

The average number of surviving spores on a BI with an initial population of 2×10^6 that is exposed to a 6-log decontamination process (t/D=6) is calculated as follows:

$$m = 10^{(\log(2{,}000{,}000)-6)} = 2$$

The probability that various quantities of spores will survive in BI individual samples can be estimated based on the Poisson model when the overall average is known ***(4).*** The general formula is as follows:

$$P(a) = \frac{m^a}{a!} e^{-m}$$

Where:

P(a) = The Poisson probability that of the quantity of microorganisms exists in a given sample

a = The number of organisms in a specific sample

If complete kill of an individual BI sample is obtained, no spores survived and a=0, in which case the formula simplifies to:

$$P(0) = e^{-m}$$

The probability of obtaining complete kill of a BI that is exposed to a lethality process that yields an average of two surviving spores is calculated as follows:

$$P(0) = e^{-2} = 0.135$$

For this example, a BI with an initial spore population 2×10^6 exposed to a 6-log decontamination process has a 13.5% chance of having a growth negative result and an 86.5% change of having a growth positive result. With these "odds" established, the probability of obtaining the results from triplicate exposed BIs can now be calculated *exactly* in the same way as the coin toss example. A summary is shown in **Table 2**.

The probability that a 6-log decontamination process will produce growth negative results on triplicate 2×10^6 BIs exposed at the same location is only 0.25%. In other words, the probability that the process yielded a greater than 6-log spore reduction is 99.75%. Similarly, if the results produced one growth positive result and 2 growth negative results the probability that the process yielded a greater than 6-log spore reduction is 95.26%. Typically, the acceptance criteria used in validation protocols allow for a small percentage of locations to yield single growth positive results when using triplicate BIs.

Conclusion

Currently, many different strategies are used when implementing BIs to validate the decontamination process. It is advis-

Typically, the acceptance criteria used in validation protocols allow for a small percentage of locations to yield single growth positive results

able that those companies continuing to use single BIs for validation with the expectation of 100% negative growth results allow for a contingent follow-up test using multiple BIs when an occasional growth positive result is noted. More than three BIs per location can be used during a follow-up test, depending upon the physical space available. The MPN calculation and probabilities based on binomial distribution can be used to defend occasional positive BI results when multiple BIs are used. Using BIs with initial spore populations that are slightly greater than the targeted log reduction being validated adds rigor to the statistics involved.

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About the Author

Donald Eddington, PhD, is a Technical Consultant with Eddington and Bond Associates, Inc. He has over 25 years of experience with isolators, biodecontamination and biological indicators. He is also a coinstructor for the upcoming PDA Education "Isolator Technology" course Oct. 25–26.

A QbD Approach to Mitigating Risk in Prefilled Syringes

Fran DeGrazio, West Pharmaceutical Services

Over the past several years, we have seen a steady shift in the pharmaceutical industry toward an even more patient-centric approach to the development of prefilled components. Nearly every aspect of the industry—from drug discovery to regulatory guidance, trial design to drug delivery system—is focused on developing new approaches to put patients first. The impact of this shift can be seen in the types of many new drugs proliferating the pipeline—namely cutting-edge biologics used to treat chronic conditions such as multiple sclerosis and other autoimmune diseases. These innovative treatments offer new hope to patients with these conditions. Biologics can also help acute conditions, such as certain types of cancer, become chronic yet manageable conditions as they can often target specific components of a disease in ways never before thought possible.

With this new hope, however, comes new considerations for biopharmaceutical companies and their manufacturing partners with regard to drug delivery and risk mitigation. Since most biologics under development are manufactured as injectables, drug makers are increasingly exploring the use of prefillable syringe and self-injection systems for administration. The potential for improved patient experience only further drives this approach. After all, self-injection systems offer patients newfound freedom to self-manage their conditions outside traditional healthcare settings.

But advanced biologics often have very specialized needs around containment and delivery. Many are highly viscous, often requiring larger containment systems and slow dosing of large volumes of the drug product over time. Additionally, biologics can have sensitive chemical compositions which could potentially interact with traditional materials used for packaging and delivery systems. Thus, demands on packaging components are changing; it is now essential to package these new biologics using high-quality components that ensure the quality, safety, and efficacy of the product.

In this new era of treatment, the application of Quality by Design (QbD) principles to the development and manufacture of biologics has been widely adopted within the biopharmaceutical industry, driven and supported by regulatory guidance such as the ICH Q8, Q9 and Q10 guidelines. A QbD approach delivers improved, data-driven output that provides manufacturers with superior product and process understanding, minimizes risk, emphasizes patient-critical quality requirements, and enhances drug product effectiveness in an industry where patient-centricity is paramount and quality must be factored in from the very beginning. Adopting these same QbD principles in the design and manufacturing of packaging components provides a drug package designed to meet these same stringent needs.

Greater Emphasis on Quality

Driven by concerns for patient safety, regulatory bodies around the world are asking drug and packaging manufacturers to build quality into their products from beginning to end to ensure consistent quality throughout a drug product's lifecycle in order to minimize risks to the drug and the patient. As an example, for injectable drug products, mitigating particulates caused by delamination or other drug/container interaction issues is crucial. If small particles in the drug ➤

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Prefilled Drug Development is Not a Journey to Travel Alone

Christina Braden-Moore, BD

Drug and device development are complex undertakings on their own. When combined, the complexity of bringing prefilled product to market is amplified. There are many factors to consider during the development of a prefilled drug product, from drug interactions and stability with the primary device and its components to flawless integration of the primary device with a secondary device. In many cases, the suppliers of the drug, components, primary devices and secondary devices are different. Therefore, coordination amongst all players is essential to ensuring that the final combination product is safe and effective while being delivered to the market as quickly as possible.

For years, companies have successfully leveraged strategic collaborations for drug discovery and development. Now, with the growing adoption of prefilled, ready-to-administer drug product, companies should collaborate more with suppliers. These alliances allow for coupling expertise on the drug with knowledge of the intricate nature of drug delivery and device development. Although a plethora of actions lead to a successful launch, key success factors include the following:

- Early collaboration to define the critical attributes and requirements of the final combination product (Target Product Profile) with engagement as early as Phase II of drug development
- Management of a holistic product development roadmap inclusive of alignment on the intersection of critical drug and device development milestones with clearly defined roles and responsibilities across all contributors
- Establishment of clearly defined rules of engagement and communication forums for all parties

Millions of people around the globe rely on prefilled drug product to save or improve their lives. As these drugs become more complex, the need to rapidly access expertise and align with a variety of partners will become more critical for successful commercialization. At the *2016 Universe of Prefilled Syringes and Injection Devices* conference and exhibition, learn how others have optimized the journey of drug device development through effective partnerships across the supplier continuum through case studies, posters, and networking.

product are unknowingly injected into the patient, there is potential for significant adverse reactions. Depending on a number of factors, including the nature of the particulate, particle size and shape, and patient population, a contaminated injectable product has the potential to result in inflammation, allergic reactions or blocked vessels, which may cause damage to tissues and organs and may even be life threatening ***(1).*** When particles are found in an injectable drug, it can be a race against time to determine the source of the particles, the extent of the issue, and the impact of the defect. The defective product also needs to be removed from the market, impacting the supply of the drug. **[Editor's Note:** For more information about particulate matter, see the *PDA Letter* Infographic on p. 32.**]**

Particles in drug products can come from many sources: extrinsic (from outside the process), intrinsic (from within the process) and even inherent (as part of the drug formulation) ***(2).*** In some cases, the primary containment and delivery system and its components can be a source of particulates because of chemical interaction between the drug and its primary containment system, functional characteristics of the packaging system during the rigors of processing, storage and distribution, or other factors.

With many sensitive biologics arriving on the market as combination products, regulators are scrutinzing the compatibility of packaging components with injectable drugs and their delivery systems. These regulatory requirements are challenging drugmakers to look for consistent, reliable, high-quality packaging components that meet GMP standards as well as the high expectations of end users.

Data-Driven Approach to Risk Mitigation

The scientific, risk mitigation-based QbD approach is fast becoming an essential strategy for bringing high-quality biologics to market quickly and efficiently while also addressing potential quality concerns. High-quality components designed using QbD principles can enhance the performance of drug delivery systems and protect sensitive drug products with exceptional cleanliness and barrier properties, while helping ensure patient safety and product efficacy.

The QbD approach promotes a holistic understanding of the drug product, its integrated delivery system and the manufacturing process. When designing and developing a packaging or delivery system component using QbD principles, manufacturers define desired product performance goals and identify Critical Quality Attributes (CQAs) of the drug delivery system. The product and process are then designed to meet those attributes, potentially improving understanding of how material attributes and process parameters impact CQAs, mitigating variability. From this knowledge, a company can continually monitor and update its processes to ensure consistent product quality and reduce the risk of issues that could result in patient harm.

Employing QbD in Component Design

One packaging component that is particularly essential to understand and assess during the QbD process is the prefillable syringe plunger. Plungers (also called pistons and stoppers) are important elements in injectable drug delivery because they can serve as the primary seal for container/closure integrity—helping to maintain the purity of drugs during shelf life—and function to transfer contents of the barrel and deliver drugs to the patient. Plungers are typically made from butyl rubber and can be coated with a fluoropolymer film that can increase lubricity and serve as a barrier between the drug and the elastomer, reducing the potential for extractables to become leachables.

As industry demands for higher quality components have evolved, there is a growing need for plungers developed using QbD processes. The design and manufacturing of high-quality plungers should follow a development lifecycle program that uses a Quality Target Product Profile (QTPP) and associated CQAs to assure control of the force required to dislodge the plunger from its resting posi-

tion (breakloose force), the force required to move the plunger through the barrel (glide force), and dimensional accuracy of the component and ultimately functionality in the final system. Preliminary development studies using Finite Element Analysis (FEA) modeling, a computer-based method of simulating/analyzing the behavior of engineering structures and components, should also be conducted, as well as testing of multiple design concepts to confirm the modeling and final product performance verification with glass barrels from multiple suppliers to meet the QTPP and CQA objectives.

The Benefits of a QbD Approach

By applying a data-driven, QbD approach to the design and development of plungers and other prefillable syringe components, packaging manufacturers can gain a thorough understanding of both the product and the process. This, in turn, offers multiple benefits for end users and manufacturers:

Advanced biologics often have very specialized needs around containment and delivery

- **Improved Functionality:** Using QbD principles can help to optimize breakloose and glide forces—aspects that are very important to ensure delivery system functionality and improve the consistency and rate of injections
- **Risk Mitigation:** The use of clean, high-quality components can lower the risk of particulates and leachables, helping to reduce patient risk and ensure the drug and its packaging meet strict standards for quality set by regulatory agencies
- **Manufacturing Efficiency:** Employing a QbD approach in the manufacturing process can help facilitate more efficient process control by significantly reducing variation from part to part, supporting a reliable supply of drug products
- **Patient Confidence:** A self-injection system needs to function consistently and reliably in order for patients to have confidence that it will work; QbD-designed components can enable safe, effective and reliable self-administration, taking into account larger dose volumes common with biologic therapies

By enabling science-based, data-driven decisions, adhering to QbD principles in the design and manufacture of drug packaging components ensures that critical specification for defects, visible/sub-visible particulates, and extractables are consistently met. The knowledge gained throughout the QbD process can also be used to enable continuous improvement in manufacturing and design for future pharmaceutical products.

Continued on page 43

Visible Particulate Matter in Injectable Drug Products

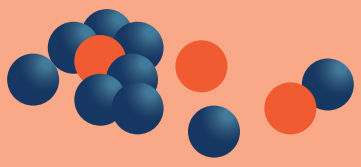
100% of all injectable drug products must be inspected for visible particulate matter

Examples of Visible Particulate Matter Sources

Skin/Hair

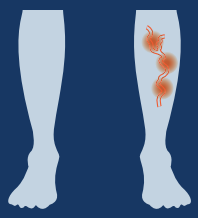
Rust/Metal

Glass

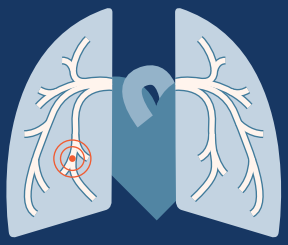


Polymers

Some of the Possible Clinical Effects



Phlebitis



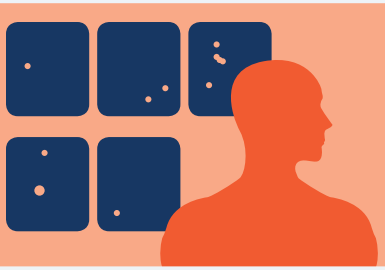
Pulmonary Dysfunction

Infarction

Death

Nearly **190 million L** of intravenous fluids are administered annually

That's almost **5 L** per patient

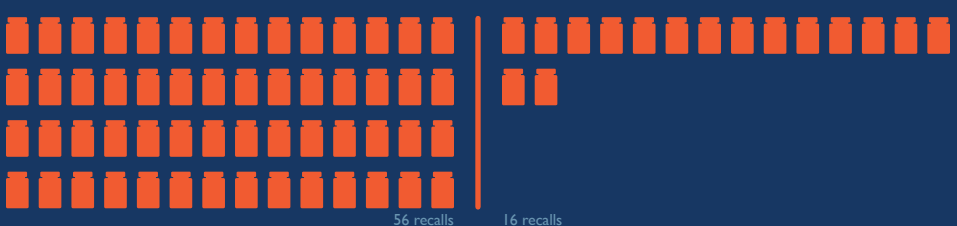


Interested in learning more about visible particulate matter? Attend PDA's Visual Inspection Forum!

www.pda.org/EU/VisualInspection2016

But is the Problem is Getting Better?

Recalls due to Visible Particulates in the United States



Sources

1. Langille, S. "Particulate Matter in Injectable Drug Products." *PDA Journal of Pharmaceutical Science and Technology* 67 (2013) 186–200.
2. Archive for Recalls, Market Withdrawals & Safety Alerts, U.S. FDA, Accessed July 18, 2016 www.fda.gov/Safety/Recalls/ArchiveRecalls/default.htm

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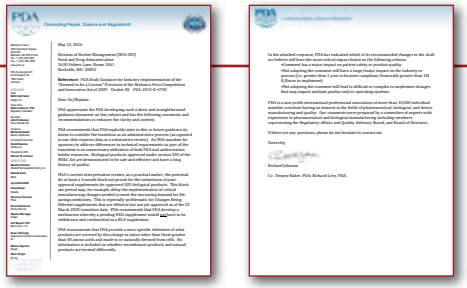
Clarification Sought on Biologics Licensing Guidance

For the comments grid, visit www.pda.org/regulatorycomments



May 23, 2016

Division of Docket Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Reference: FDA Draft Guidance for Industry Implementation of the "Deemed to be a License"
Provision of the Biologics Price Competition and Innovation Act of 2009 Docket ID: FDA-2015-D-4750

Dear Sir/Madam:

PDA appreciates the FDA developing such a short and straightforward guidance document on this subject and has the following comments and recommendations to enhance the clarity and content.

PDA recommends that FDA explicitly state in this or future guidance its intent to consider the transition as an administrative process (as opposed to one that requires data or a substantive review). An FDA mandate for sponsors to address differences in technical requirements as part of the transition is an unnecessary utilization of both FDA and authorization holder resources. Biological products approved under section 505 of the FD&C Act are demonstrated to be safe and effective and have a long history of quality.

FDA's current interpretation creates, as a practical matter, the potential for at least a 6 month black out period for the submission of postapproval supplements for approved 505 biological products. This black out period may, for example, delay the implementation of critical manufacturing changes needed to meet the increasing demand for life savings medicines. This is especially problematic for Changes Being Effected supplements that are effective but not yet approved as of the 23 March 2020 transition date. PDA recommends that FDA develop a mechanism whereby a pending NDA supplement would not have to be withdrawn and resubmitted as a BLA supplement.

PDA recommends that FDA provide a more specific definition of what products are covered by this change in status other than those greater than 40 amino acids and made in or naturally derived from cells. No information is included on whether recombinant products and natural products are treated differently.

In the attached response, PDA has indicated which of its recommended changes to the draft we believe will have the most critical impact based on the following criteria:

- Comment has a major impact on patient safety or product quality
- Not adopting the comment will have a large/major impact on the industry or process (i.e. greater than 1 year to become compliant; financially greater than 1M $/Euros to implement)
- Not adopting the comment will lead to difficult or complex to implement changes that may impact multiple quality and/or operating systems.

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by a committee of experts with experience in pharmaceutical and biological manufacturing including members representing the Regulatory Affairs and Quality Advisory Board, and Board of Directors.

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

Sincerely,
Richard Johnson
Cc: Denyse Baker, PDA; Richard Levy, PDA.

PDA Commenting Task Force

Robert Porter, ValSource (Lead)

Rebecca Devine, Regulatory Consultant

Stephan Krause, PhD, AstraZeneca Biologics

Tia Bush, Amgen

John Dougherty, Eli Lilly and Company

Allison Kennington, Eli Lilly and Company

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And, on **Oct. 20-21**, PDA's Education Department will hold three courses complementing what you have learned.

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Outsourcing: Ensuring a Successful Relationship

Aligning Expectations of Contract Giver and Contract Acceptor

Firelli Alonso, PhD, Pfizer, Siegfried Schmitt, PhD, PAREXEL, and Katherine Brandt, Afton Scientific

Outsourcing has become a standard practice for both the smallest biotech companies and the largest pharmaceutical firms. Outside partners perform vital processes due to their experience, speed, cost, and quality. Outsourced activities range from development and validation services, API manufacture, fill/finish, etc.

To ensure success, Contract Giver expectations need to be strongly aligned with those of the Contract Acceptor. There is plenty of risk to realizing a project, but it is not insurmountable. A mutual understanding of these risks by both the Contract Giver and the Contract Acceptor is a prerequisite for developing an appropriately sized, compliant development and manufacturing program.

As the industry pursues lower volume, more complex products, such as cytotoxic products, orphan drugs, and cell/gene therapies, knowledgeable, experienced partners with flexible manufacturing space become even more crucial. The right Contract Acceptor can fill its client's other needs such as flexible scheduling, serialization, adaptability to intricate projects, and the capability to manufacture for the global market.

Not surprisingly, managing this resource is a big challenge for Contract Givers. As difficult as it is to find a partner with the needed capabilities for a product, an even greater challenge is finding a partner with the right company culture—particularly, quality culture.

To explore further the challenges of creating a lasting partnership between Contract Givers and Contract Acceptors, consider attending PDA's *Outsourcing & Contract Manufacturing* conference in Barcelona. In addition to presentations from speakers with experience on both sides of the Contact Giver/Acceptor line, attendees can submit questions for discussion via the conference website. The conference is designed to be interactive so those on both sides can learn about what works well as well as how to identify potential pitfalls.

Outsourcing & Contract Manufacturing
Barcelona, Spain
Nov. 15–16
www.pda.org/EU/Outsourcing2016

Pharma Supply Chain Faces New GDPs, Reg Requirements

Rafik H. Bishara, PhD, and Erik van Asselt, PhD, MSD

Recent changes to the EU Good Distribution Practices guideline offer continued opportunities for learning, implementing, and establishing best practices. Manufacturers and their supply chain partners must continue to improve their quality systems for meeting the challenges of ensuring a secure temperature-controlled supply chain. The industry continues to face new and evolving trials as novel medicines and vaccines require more attention to temperature, humidity, vibration, drop, and security issues during their handling, storage, and distribution through the supply chain.

Some of the factors that need to be addressed include: the security of cargo while in storage or under transportation, lane qualification, Track and Trace, serialization, the EU Falsified Medicines Directive, and more.

These topics will be shared, discussed and debated at the 2016 *Pharmaceutical Cold & Supply Chain Logistics* conference in Amsterdam this October. Expect attendance by representatives from manufacturers, European regulators, WHO experts, and many supply chain partners/vendors.

In addition, attendees have an opportunity to visit Schiphol Airport the day before the meeting to view the facilities of World Freight Services, Envirotainer, and DHL's Life Science Competence Center as well as participate in the onsite workshop "Pharma by Road" to discuss the minimal requirements for temperature-controlled trucking.

2016 Pharmaceutical Cold & Supply Chain Logistics
Amsterdam
Oct. 10–12
www.pda.org/EU/ColdChain2016

A Comparison of Microbial Environmental Limits

A Case Study of Existing Regulatory Action Limits versus USP Recommended Recovery Limits

Raphael Bar, BR Consulting

The new paradigm of microbial monitoring of aseptic processing environments, suggested in USP <1116> ***(1),*** continues to raise interest. Yet questions persist regarding its implementation and usefulness compared to existing regulatory limits ***(2).***

The EU GMP Annex 1 ***(3)*** and the U.S. FDA's 2004 guidance on sterile processing ***(4)*** impose maximal limits of microbial contamination that vary between 1 to 200 cfu in an environmental monitoring sample recorded in a classified environment. These limits—taken to be action limits—are 1, 5, 10, 25, 50, 100, or 200 cfu in the EU guide while those in the FDA guide are 1, 3, 5, 7, 10, 50, or 100 cfu. This implies that all environmental monitoring samples, particularly in Grade B, C, and D rooms, may be contaminated. But they are acceptable as long as the corresponding regulatory action limits are not breached. This approach is totally different from the one suggested in USP <1116>, which limits the proportion of contaminated samples. The USP chapter calls for monitoring the proportion of observed contaminated samples from all tested samples, irrespective of the underlying probability or data distribution. The cumulative contamination rate can be calculated as the number of all contaminated samples obtained until a given time divided by the total number of samples tested until a given time then multiplied by 100%.

Contamination Recovery Rate (CRR) is essentially a cumulative metric, and as more data are collected, it is updated through recalculation with additional data. USP recommends retabulating data (i.e., recalculating CRR) on a monthly basis. A CRR value becomes meaningful at reflecting the contamination level of a controlled environment when it involves a significant number of independent samples, e.g., at least a few hundred samples in Grade A or B environments. Examples of CRR calculations are currently available ***(5–7).***

The USP limits refer to the ISO classification and span CRR of 1–10%. For example, for ISO 8 (taken here as equivalent to Grade D), 90% of tested samples must not show even a single colony, while nonsterile materials and equipment are handled in this environment. One may indeed wonder how these limits were set. The lower the limit, the cleaner the environment should be, resulting in higher costs for maintaining a higher level of cleanliness. Again, one may justly wonder if these extra costs are warranted. *PDA Technical Report No. 13* ***(8)*** even states that the USP limits for ISO 7 and 8 may not be achievable. So, how realistic is it to expect these limits? The following is an attempt to provide a preliminary answer by calculating the actual CRR values recorded over the course of a year in a single small pharmaceutical company which manufactures a sterile drug product aseptically under EU GMP. This analysis includes a comparative examination of the existing regulatory and USP limits for Grade A and Grade B–D rooms.

Recall that the relationship between ISO classes and EU A–D Grades is not straightforward and depends on whether the classified room is in a state of operation or at rest ***(8).*** For the sake of simplicity, Grade A will be considered here as equivalent to ISO 5, and Grade C and D to ISO 7 and 8 respectively.

Comparison of Limits for Grade A Rooms

Both the EU and U.S. regulatory and USP limits for these classified rooms are all numerically expressed as 1. Dimensional units, however, make a big difference between the two: the first are expressed as numbers of counts (1 cfu) and the second as a percentage number (1%). Within the regulatory limits, there is yet another subtle difference: the EU limit is "less than 1 cfu" while the FDA limit is "equal to 1 cfu."

Since a microbial count can be 1, 2, 3 etc.…, one would first interpret the existing EU regulatory limit of "<1 cfu" as implying a discrete test result that is below 1 count, meaning in fact 0 cfu. A footnote under the tabulated limits in the EU guide, however, states that these limits "are average values." Since an average value can be less than 1 cfu, this footnote allows, in principle, some contaminated samples among noncontaminated ones. The FDA guide does not allow averaging and expects each individual test result to comply with the regulatory limit. But since this limit is expressed as "equal to 1 cfu," again, some contaminated samples are allowed in principle. So, it appears that both the EU and FDA guides convey a message that some contamination is inevitable in real life.

Considering the USP limit, recall that it is a cumulative percentage of contaminated samples from all tested samples. The limit of "less than 1%" implies that it could be 0.9%, 0.8%, etc. It is clear that some contamination is allowed and cases of recurrent contamination events may take place and yet be formally in line with the USP limit. As a theoretical example, a Grade A/ISO 5 room monitored by testing 700 samples during a year can have a single contaminated sample every two months, and by the end of the year, the CRR, based on six contaminations per year, would be:

CRR = 6×100/700 = 0.85%

This limit does not exceed the 1% limit and apparently, the regulatory limit is not breached.

As a side note, one may wonder if the USP rules of rounding numbers also ap-

ply to the reportable CRR result. It is usually expected to obtain a reportable result with the same number of decimal digits as in the acceptance criterion. According to these rules, calculated CRR values of 0.5% and 0.4% would be rounded to 1% and 0%. In the above example, three and four contaminated samples from the 700 tested samples would lead to 0% and 1%. Thus, three contaminated samples would be acceptable in this example but four would not. Since <1116> is an informational chapter, however, the rounding procedure may not be applicable.

A review of the EU and FDA guidance documents, as well as the USP chapter, shows that zero contamination is not always possible in real life. Yet one should strive to obtain it. All three sources express the common expectation that contamination should be a rare event in Class100/ISO5/Grade A rooms, and in this sense, they are essentially equivalent in their approach to the expected contamination level in these classified rooms. *Is this true also for the other classified rooms?*

Case Study of CRR for Grade B–D Rooms

Environmental monitoring microbial data collected weekly in a small company that manufactures an aseptic product under EU GMP were used to calculate the percentage of CRR from all samples tested at several Grade B, C, or D sites throughout one whole year. The settling and contact samples consisted each of a couple of TSA and SDA plates and a location showing either one or two contaminated plates is considered one sample and one contamination event. Upon examining three sets of samples tested during one year in rooms graded D, 69.4 to 76.0% of the settling plates, 55.1 to 92.1% of the plates of active air samples, and 2.0–16.0% of contact plates were contaminated at levels below the corresponding regulatory action limits of 100, 200 and 50 cfu per plate. Thus, the observed actual contamination levels largely surpassed the USP limit of 10%.

Similarly, upon examining three to six sets of samples tested during one year in rooms graded C, 33.3 to 88.3% of the settling plates, 19.6 to 60.8% of the plates of active air samples, and 0 to 10.4% of contact plates were contaminated at levels below the corresponding regulatory action limits of 50, 100, and 25 cfu per plate. If Grade B is taken to be equivalent to ISO 7 which requires a USP CRR limit of 5%, then one annual set of setting plates from three sampling locations had 12.2% contaminations, and two annual sets of active air samples out of three exhibited 22.2 and 27.8% of contaminated samples—all without breaching the corresponding regulatory limits of 5 and 10 cfu/plate. Of course, these results would not comply with the USP limit of 5%. ➤

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The IsoBag™ eases your environmental monitoring set-up by:

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It is clear that *the suggested USP limits of CRR are more stringent than the regulatory limits for Grade B–D rooms* as compliance with the regulatory limits of these classified environments appears to be easier to achieve. Yet, the CRR concept seems to be a useful general metric of the quality of the monitoring process. It is simple to understand, easy to communicate, and can be used as a supplementary metric to routine EM data charting against the regulatory limits, particularly for Grade A and B rooms ***(7).***

Conclusion

The requirements for both the USP recovery rates and the regulatory limits for Grade A rooms are judged to be more or less equivalent. As far as the other classified rooms, it appears that the USP recovery rates for Grade C and D rooms are significantly more stringent than the corresponding regulatory action limits, and mildly more stringent for Grade B rooms. Additional real data from more companies would be desirable to further corroborate this conclusion.

[Editor's Note: Hear the author speak on this topic at PDA's pharmaceutical microbiology conference" He is also teaching a course on it after the meeting.**]**

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8. Moldenhauer, J. et al. *PDA Technical Report No. 13 (Revised): Fundamentals of an Environmental Monitoring Program.*

About the Author

Raphael (Raphy) Bar, PhD, is presently a pharmaceutical consultant for the pharma and biopharma industries.

A QbD Approach to Mitigating Risk in Prefilled Syringes continued from page 31

Conclusion

Now more than ever, employing a QbD approach to component design and manufacturing brings patient well-being and the needs of drug manufacturers to the forefront. Patient safety needs and expanding regulatory expectations are spurring increased focus on the quality attributes of the components used to package and contain injectable drugs—and rightly so. Drug packaging components play a vital—but often overlooked—role in drug safety and efficacy. They are a critical part of integrated combination products and are essential to ensuring delivery systems are safe, intuitive and easy to use.

Growing use of biologics and the trend toward self-administration means manufacturers need to select components carrying a high level of reliability, consistency and compatibility with sophisticated drug products and delivery systems over the course of their lifecycle. It can be difficult, however, to know which component is the best quality fit for a particular drug product.

There are new component offerings on the market designed to address the need for high-quality packaging solutions, including components designed using QbD principles to provide high reliability for break loose and glide force, dimensional accuracy and consistency, subvisible and visible particulate control, and low parts per million (ppm) defect attributes.

Yet timing is everything. Drug packaging and delivery partners should build quality into the development and manufacturing process from the very beginning. This not only helps ensure that high quality standards are met, but also allows the pharmaceutical industry to reach its ultimate goal: delivering safe, effective medications to the patients who depend on them.

[Editor's Note: West will exhibit at the 2016 PDA *Universe of Prefilled Syringes & Injection Devices*.**]**

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1. Langille., S.E. "Particulate Matter in Injectable Drug Products." *PDA Journal of Pharmaceutical Science and Technology* 67 (2013): 186-200.
2. Shabushnig, J.G. "Visible Particles: Regulatory and Compendial Requirements." Presentation at the PDA Ireland Chapter Visual Inspection Seminar, June 2014.

About the Author

Fran DeGrazio has been in the pharmaceutical packaging industry for over 30 years with extensive expertise in the area of delivery of injectable drug products, such as vial/closure combinations, prefillable syringe systems and injectable combination products.

Jette Christensen, NovoNordisk A/S

Microbiology: A Critical Focus Area for Strategic Plan

Are you interested in microbiology and related topics? Well, continue to stay tuned. For many years, microbiology has been a key focus for PDA. And it will remain a critical focus as PDA looks ahead to 2020 and beyond.

I've always been involved in PDA's microbiology activities. When I first joined PDA, I immediately joined the Microbiology/Environmental Monitoring Interest Group. The first PDA Education course I ever attended covered isolators. And my first experience on a technical report team was for the revision of *PDA Technical Report No. 13: Fundamentals of an Environmental Monitoring Program*. In addition, I served on the planning committee for PDA's first *Global Conference on Pharmaceutical Microbiology* in the United States in 2005. As you can see, throughout my years as a PDA member, microbiology and related topics have been core areas of focus for me.

But microbiology remains a critical focus area for PDA as well, reflected in the PDA 2020 Strategic Plan. First, PDA intends to maintain a focus on pharmaceutical/biopharmaceutical manufacturing core competencies, including aseptic and sterile processing, manufacturing procedures and technologies, and analytical techniques and technologies. And PDA also plans to "ensure that current and upcoming technical and scientific topics within PDA's core competencies will be addressed in a timely and high-quality manner, through the activities of PDA volunteer groups, Interest Groups, Education, Conferences and Publications."

So, what ongoing initiatives connect microbiology to PDA's strategic plan for 2020?

Well, PDA will continue regular activities in this area, such as:

- Microbiology/Environmental Monitoring Interest Group meetings at the *PDA Annual Meeting* and *PDA/FDA Joint Regulatory Conference* in the United States
- Annual microbiology conferences in both Europe and the United States
- Articles on microbiology in the *PDA Journal of Pharmaceutical Science and Technology* and the *PDA Letter*
- PDA Education courses in microbiology
- PDA technical reports covering microbiological topics

In addition, PDA has also started new initiatives with a strong emphasis on microbiology. If you haven't already, I encourage you to read our two-part *Points to Consider on Aseptic Processing* as well as attend the related *2016 PDA Workshop: Current Challenges in Aseptic Processing* next month in either Dublin (Oct. 5–6) or Arlington, Va. (Oct. 26–27). These workshops will address regulatory and technological changes in the areas of environmental monitoring/control and media fills.

PDA's aging facility initiative also touches on microbiology. As mentioned by Board member **Susan Schniepp** in the February *PDA Letter*, PDA's Aging Facilities Task Force identified "analytics" as one of three core areas of assessment for aging facilities. Naturally, this includes microbiological analysis of a facility and its equipment. At this time, the question of how to address analytics of aging facilities still needs to be resolved but, undoubtedly, the answer will include rapid methods for microbiological analysis in some form or another.

So, as you can see, the area of microbiology is well anchored in PDA's 2020 Strategic Plan. Looking beyond 2020, microbiology will also certainly remain a core area for PDA in the coming decades. The future is always uncertain but I can say that 50 years from now, PDA will continue to serve as a source of exciting microbiology-related initiatives!

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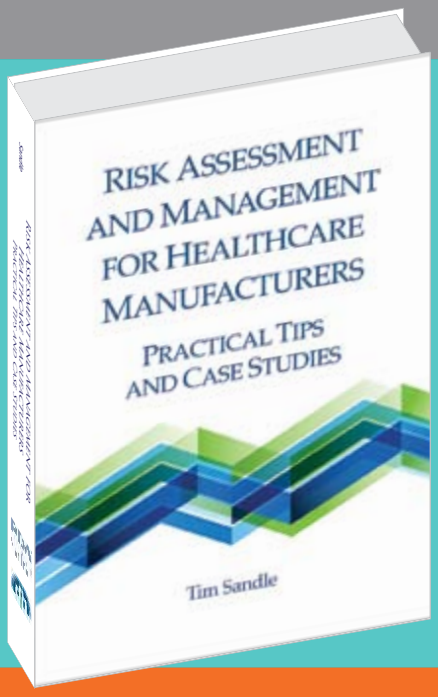

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BY: TIM SANDLE

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Avoidance of hazards and assessment of risk have long been part of the manufacture of pharmaceuticals and healthcare products. Tim Sandle's newest book, *Risk Assessment and Management for Healthcare Manufacturers*, incorporates regulatory perspectives, scientific methods and practical examples to describe approaches to problem solving when assessing, managing and reviewing risks.

The book is divided into four sections that present a formal approach to risk. Sections focus on risk assessment and hazards; common risk assessment tools and problem-solving approaches; 'soft skills' that help in conducting risk assessments; and case studies exploring the problems and events that occur with pharmaceuticals and healthcare, against which the reader can consider real-life problems. The wide range of topics covered includes risk considerations for aging pharmaceutical facilities, application of quality risk management to cleanroom design and process incident investigation.

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editor's message

Dog Days of Summer End, Busy PDA Season Begins

It may be August as I write this but I can already feel the changes in the air. It's getting slightly cooler, the leaves are a smidgen less green and already pumpkin-flavored products are hitting the store shelves. In other words, fall (my favorite time of year) is almost upon us!

The season brings with it many changes. But it also brings PDA's line of fall conferences. In fact, two of PDA's biggest fall conferences occur this October—the *Universe of Pre-filled Syringes & Injection Devices* and the *11th Annual PDA Global Conference on Pharmaceutical Microbiology.* I'm looking forward to meeting new colleagues and running into old associates at these two meetings. Perhaps I'll even get a chance to talk to you as well!

This issue includes a number of microbiology and prefilled syringe articles to whet your appetite for these meetings. Our cover story by **Donald Eddington** explores the use of statistics to determine biological indicators, and the second feature from **Fran DeGrazio** delves into the use of QbD methodology during development of prefilled syringe products. On p. 39, **Raphael Bar** compares USP's recommended microbial recovery limits with the standard regulatory limits. And in our Volunteer Spotlight, **Lee Leichter** offers his insights on combination products.

PDA Europe is also offering a compelling slate of conferences this fall. The *Visual Inspection Forum* in Berlin Oct. 25–26 is one. **Stephen Langille** of the U.S. FDA will provide a regulatory update at the meeting. His 2013 article in the *PDA Journal of Pharmaceutical Science and Technology* serves as the inspiration for the *PDA Letter* Infographic on page 32. Since the publication of his article, it has consistently been in the list of Top 10 most-read PDA Journal articles each month (in fact, it was the second most-read article this July).

This fall is also an extra exciting for our U.S. readers as it is the year of a presidential election, and this one is proving exceptionally lively (I'll leave it at that). But this is also the season for PDA's board elections. I encourage all of you to take some time to review this year's slate (see p. 6) and vote for your preferred candidates. Keep in mind, this election is open to eligible PDA members across the globe, not just in the United States.

It's an exciting time to be a PDA member this fall. And for those of you unable to attend the microbiology and prefilled syringe conferences, don't sweat. I'm confidant both meetings will offer enough intriguing content to generate future *PDA Letter* articles and multimedia content.

— **Rebecca Stauffer,** filling in for **Walter Morris** this issue.

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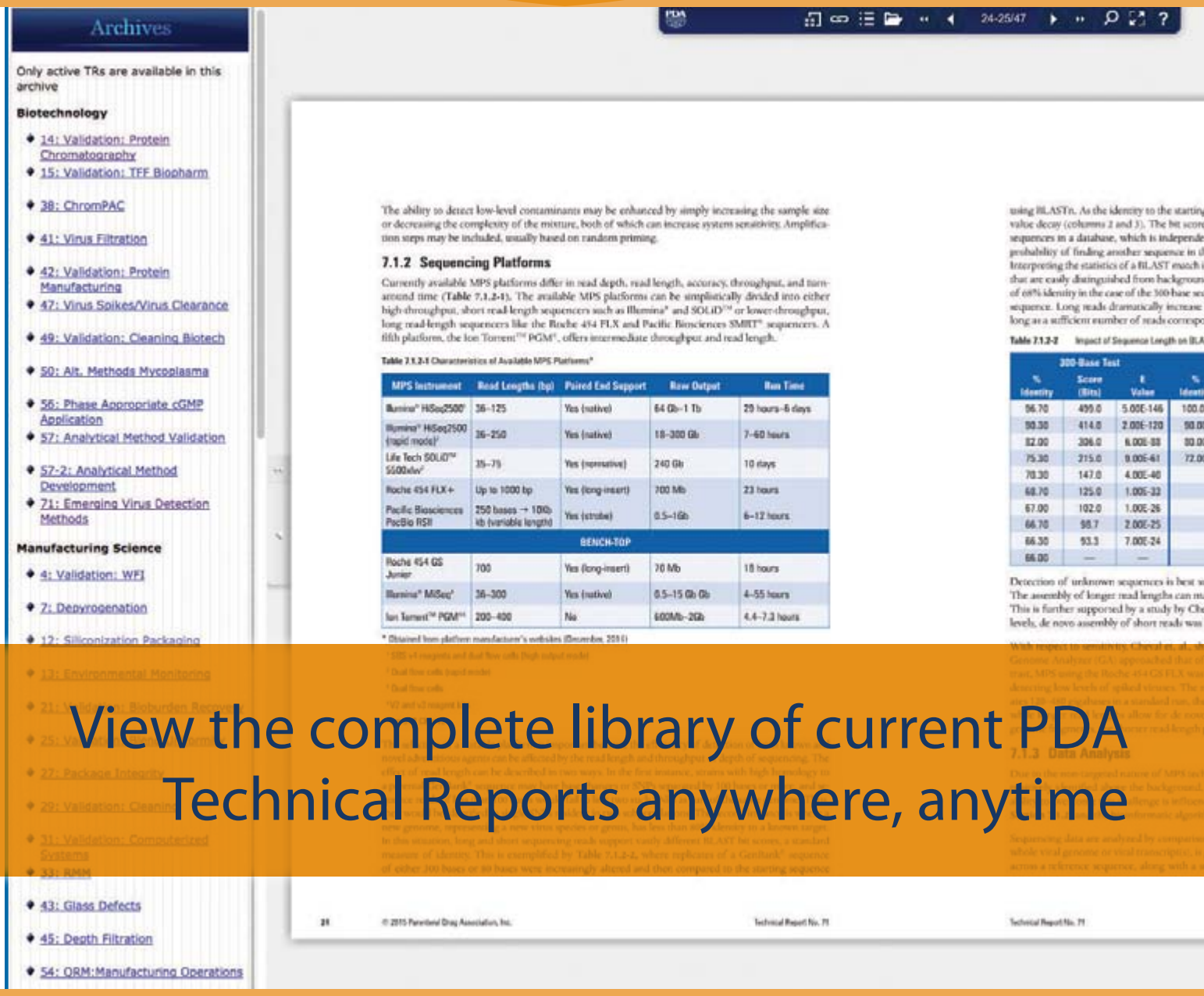

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