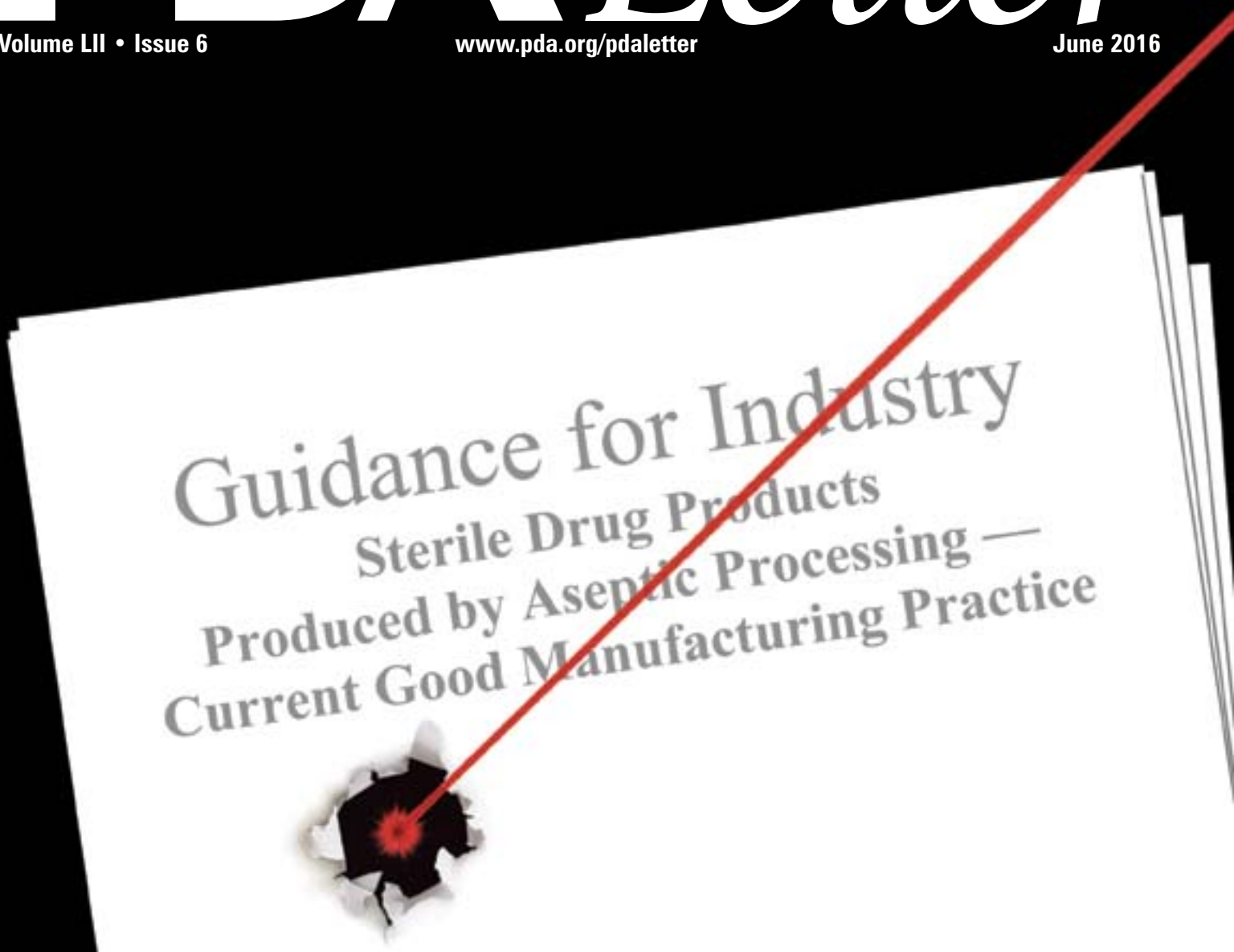
People • Science • Regulation

PDA Letter

Volume LII • Issue 6 www.pda.org/pdaletter June 2016



A Line of Sight for Assessing Aseptic Processing Risk 22

The Parenteral Drug Association presents the...

2016 **PDA/FDA** Joint Regulatory Conference

Celebrating 25 Years of Shaping Global Regulatory Strategy

September 12-14, 2016 | Washington, DC

Renaissance Washington, DC Downtown Hotel

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

Now in its 25th year, the *PDA/FDA Joint Regulatory Conference* will again give you unparalleled access to FDA regulators and industry experts who will enhance your understanding of the implications, expectations and requirements of new regulatory programs. Hear updates on current efforts impacting the development of global regulatory strategies and gain practical solutions and advice for the regulatory issues facing today's pharmaceutical industry.

Plenary sessions will focus on current factors affecting the industry, including:

- Patient Perspectives
- Center Updates
- How to Achieve Compliance
- Quality Assurance
- Compliance Updates

This year's breakout sessions address *Product Quality, Science and Innovation and Lifecycle Management (Regulatory Challenges and Opportunities)*. Breakfast sessions will cover "hot topics" in the industry, including human factors, cybersecurity and updates from CDER/OPQ.

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

Immediately following the Conference, Sept. 14-15, PDA will host the *2016 PDA Data Integrity Workshop*. At this Workshop, regulatory and industry experts will discuss strategies on how to address the prevention and detection of, response to and learning from data integrity issues.

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

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

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

#2016pdafda

Register before July 1 and save up to $600!

The Parenteral Drug Association Education Department presents...

Quality Week

August 15-18, 2016 | Bethesda, MD

PDA Training and Research Institute

If improving quality is important to you and your company, you simply cannot afford to miss *PDA's Quality Week*.

COURSE OFFERINGS INCLUDE:

- **Application of Quality Risk Management to Non-Production Processes in the Pharmaceutical Quality System** (Aug. 15) NEW COURSE
  In this course, models of various supporting processes that integrate quality risk management into their design will be presented.
- **Role of the Quality Professional in the 21st Century** (Aug.16-17)
  In this course, the traditional role of the quality unit will be contrasted with what the modern role of the quality professional should be. The role of senior management and production management as it relates to the responsibilities of the quality unit will also be discussed.
- **Quality Metrics – Performance Indicators** (Aug. 18)
  The instructor will present his perspective on selecting the appropriate quality metrics, determining how best to collect the data and how to use the data to improve the quality system.

Discounts apply if you register for more than one course!

Learn more and register at pda.org/2016QualityWeek

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Denotes Lecture Course

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

PDA Letter

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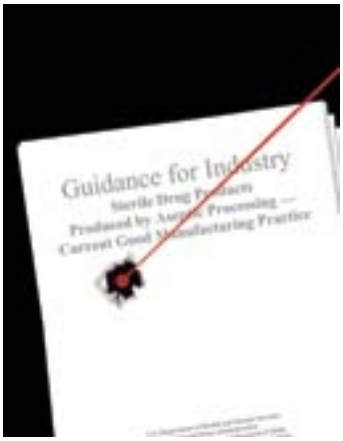
Cover



Cover Art Illustrated by Katja Yount

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

PDA's Mission

To develop scientifically sound, practical technical information and resources to advance science and regulation for the pharmaceutical and biopharmaceutical industry through the expertise of our global membership

PDA's Vision

To be the foremost global provider of science, technology, and regulatory information and education for the pharmaceutical and biopharmaceutical community

PDA® Parenteral Drug Association

Connecting People, Science and Regulation®

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PDA Receives 1st Johnson & Johnson Kilmer Award

Participating in the first *Kilmer Conference* in over 13 years, PDA received the first Kilmer Award given to an organization in recognition of the Association's long-standing leadership in the science of sterility assurance.

Richard Johnson, President of PDA, accepted this award on behalf of the Association, with these words:

"Thank you for this honor. PDA is celebrating our 70TH anniversary of connecting people, science and regulation. Over this period, products that our members have produced have impacted the lives of hundreds of billions of patients all over the world. Our first meetings focused on sterility assurance were before most of us were born.

"I am humbled when I think about the leaders upon whose shoulders we stand: **[Frederick] Carleton, [Gordon] Personeus, [Frederick] Simon, [Irving] Pflug,** and more recent leaders like **[James] Akers** and **[James] Agalloco, [Theodore] Meltzer** and **[Russell] Madsen,** and current contributors like **[Maik] Jornitz, [Harold] Baseman, [Martin] VanTrieste, [Michael] Sadowski** and **[Gabriele] Gori,** and the many others who have contributed to this legacy. On their behalf, I am proud to accept this honor."

Johnson & Johnson brought back the landmark Kilmer Conference on sterility assurance and sterilization this May after a 13-year hiatus. Johnson & Johnson hosted eight Kilmer Conferences between 1976–2003 for invited sterility assurance professionals from industry, academia and regulatory authorities. These conferences take their name from **Fred Kilmer,** who was a pioneer in the pharmaceutical industry and director of Johnson & Johnson's scientific laboratory from 1889–1934.

Foster Relationships with Key Decision Makers as an Exhibitor or Supporter of a PDA Signature Event.

For 25 years, the *PDA/FDA Joint Regulatory Conference* has been recognized as the premier forum to hear from and interact with regulators, thus drawing a large audience of key decision makers from manufacturing operations, compliance, quality, regulatory and engineering. Take advantage of this opportunity to gain visibility and build your company's brand by becoming a supporter of and/or exhibitor at the *2016 PDA/FDA Joint Regulatory Conference*.

Multiple refreshment breaks and evening social events in the exhibit area provide ample time to connect with this desired audience of industry leaders. Customizable and comprehensive packages are available to help you better position your product and/or service offerings.

To learn more, please visit pda.org/2016pdafda or contact David Hall, Vice President, Sales, at +1 (240) 688-4405 or hall@pda.org.

The Parenteral Drug Association presents...

2016 **PDA/FDA** Joint Regulatory Conference

Aligning Manufacturing Goals with Patient Needs through Successful Innovation and Compliance

September 12-14, 2016 | Washington, DC

Renaissance Washington, DC Downtown Hotel

EXHIBITION: SEPTEMBER 12-13

#2016PDAFDA

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PDA Members have FREE online access to members-only publications such as the *PDA Letter* and *PDA Journal*, as well as industry-leading Technical Reports, which are PDA's peer-reviewed global consensus documents and one of PDA's most popular benefits.

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PDA Launches Quality Culture Assessment Pilot

Representatives of two pharma companies participated in a pilot program for PDA's Quality Culture Assessment Tool. Members of PDA's Quality Culture Maturity Task Force met with six auditors for an "assessor training session." The auditors were introduced to the assessment tool and learned how to apply it to simulated manufacturing case studies. The purpose of the pilot is to work with assessors from up to 20 different pharmaceutical companies to refine the assessment tool.

The assessment tool is intended to help companies advance their overall quality culture maturity by identifying attributes that are strengths as well as others that are ready for improvement.

"PDA is developing this tool for assessing quality culture maturity within a manufacturing site so that companies can perform internal assessments of their own operations as well as audits of their suppliers and contract manufacturers," said PDA President **Richard Johnson.** "The pilot is an important step in developing the Quality Culture Assessment Tool to ensure that it is optimized for wider industry use."

During the pilot, the task force developing the tool will be assessing:

- Reproducibility—is the tool objective and verifiable?
- Differentiability—can the tool differentiate sites?
- User-friendliness
- Training effectiveness

Using the tool, assessors will look at various aspects of a manufacturing site to determine how mature the quality culture is. These attributes of quality culture include: leadership commitment, communication & collaboration, employee ownership, continuous improvement, and technical excellence.

Complementing the tool is a survey that companies will use to gather broad input on quality culture behaviors. PDA will conduct an analysis of the maturity attribute data collected by the assessors and behavior data from the surveys at each site to look for correlations similar to what was found in the PDA Quality Culture Maturity Survey of 2015 (an analysis of which was published in the PDA Journal of Pharmaceutical Science and Technology). Each participating site will receive a copy of the analysis of their individual results.

PDA Volunteer Spotlight

Amelia Mutere

- Head, Global Quality Inspection Management
- *F. Hoffmann-La Roche Ltd*
- Member Since | 2008
- Current City | Basel, Switzerland
- Originally From | San Francisco, California

I have a very large network of colleagues that I can reach out to across the globe

This month, Amelia plans to hike Peru's Inca Trail

You lead the Supply Chain Management Interest Group. How does one become an Interest Group Leader?

Get involved with a PDA interest group and sign up to participate on PDA Connect℠. I can only add: participate, participate, participate! Try to attend the in-person interest group meetings held during PDA conferences—this is your opportunity to meet people in the industry face-to-face.

PDA Connect℠ is a wonderful tool for members to ask questions, receive very quick feedback and initiate discussions.

What do you have planned for the Supply Chain Interest Group in the near future?

We plan to hold a face-to-face meeting in September at the *2016 PDA/FDA Joint Regulatory Conference.* Additionally, we plan to survey interest group members this year using PDA Connect℠.

What current pharmaceutical topic interests you?

I am very interested in emerging markets and new requirements from global regulators. We have heard that Russia will now require onsite inspections prior to approval in their market. Since January 2016, all foreign manufacturers have to be inspected by Russian authorities.

China is also very active, recently issuing a new 2015 pharmacopeia and conducting overseas inspections.

What do you expect from the industry in the next five years?

I hope to see PIC/S come into maturity with greater more alignment among its members and emerging markets.

I also hope to see the various pharmacopeias align with each other.

What do you plan to do when you retire?

When I retire, I will continue to volunteer for PDA and help train the next generation. Also, I plan to climb Mount Kilimanjaro and go to base camp at Mount Everest.

The Parenteral Drug Association Education Department presents...

Understanding Variation and the Metrics of Process Monitoring

August 2-3, 2016 | Bethesda, MD
PDA Training and Research Institute

Learn to Effectively Apply Statistics in Your Real-World Setting

The *Understanding Variation and the Metrics of Process Monitoring* course will help you identify and use statistical process monitoring methods to validate, calibrate, maintain, troubleshoot and prioritize.

This course will convey the appropriate use of statistical methods at a level, and in a way, that can easily be understood. Hands-on experience using a syringe filler will generate data to measure, quantify and compare sources of variation. The various methods will be described, typical applications will be identified, and pros and cons of each method will be examined. Examples of each method will be described to show how they can be used in a real-world setting.

Taught by industry expert **Jason Orloff,** Principal Statistical Consultant, *PharmStat,* this course will show you how to:

- Apply the most appropriate statistical tool based on the case at hand
- Cite the regulatory references relevant to understanding, controlling and reducing process variation
- Calculate the probability of OOS within a single lot and series of lots for reporting

This course will utilize *PDA Technical Report No. 59, Utilization of Statistical Methods for Production Monitoring* as a resource and attendees will receive a complimentary electronic copy of this Technical Report.

Learn more and register at pda.org/2016Stats

PDA is accredited by ACPE and offers continuing education for professional engineers.

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chapter update

NE Chapter Explores Technology Transfer in a "Modern Age"

Enith Morillo, Complya Consulting Group

As more companies rely on CMOs in an evolving landscape, technology transfer has assumed a key role. So it was no surprise that over 100 professionals attended the PDA New England Chapter's January dinner meeting, "Technology Transfer in the Modern Age." This highly popular and successful event, hosted by **Eric Forrand** and led by Chapter President **Jonathan Morse,** featured three Shire representatives discussing aspects of technology transfer.

Paul Gauthier opened the proceedings with a look at the basics of technology transfer, touching on its definition according to ICH Q10 and the importance of using a project management approach that clearly defines milestones, decision key points, responsibilities, and most importantly, communication.

(l-r) Jonathan Morse, Paul Gauthier, Catherine Bannish, Praveen Prasanna and Eric Forrand

2016 PDA Europe Conference, Exhibition

Pharmaceutical Cold & Supply Chain Logistics

10 October
Interest Group Meeting Pharmaceutical Cold Chain

11-12 October
Conference, Exhibition

13-14 October
Good Cold Chain Practices

11-12 October 2016

Novotel Amsterdam Schiphol Airport | **Amsterdan | The Netherlands**

The Parenteral Drug Association presents the...

WASHINGTON, DC –

2016 PDA Data Integrity Workshop

September 14-15, 2016 | Washington, DC

Renaissance Washington, DC Downtown Hotel

Exhibition: September 14-15

#2016Data

The *2016 PDA Data Integrity Workshop*, offered three times in three global locations, will explore the multiple facets of data integrity, such as quality culture, human behavior, training needs and technology requirements.

Gain a broad perspective on cause and effect and common factors involved in data integrity issues, and benefit from round table discussions and case studies addressing implementable, best practices for preventing, detecting, mitigating and remediating data integrity issues.

Submit a poster abstract for presentation at one of the *2016 PDA Data Integrity Workshops!* Abstracts on data integrity issues and industry standards and best practices are highly appreciated.

Register before August 2 and save up to $200

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

To explore all dates and locations for this important workshop, please visit pda.org/2016data

Next, **Praveen Prasanna** emphasized how technology transfer has shifted from a focus on "parameters-focused" to an "attributes-focused" endeavor. Creating a control strategy that is more holistic instead of the traditional unit-by-unit operation is fundamental, he explained, since this shift brings about a heavy reliance on external partners.

Thus, finding the right partners is critical for a successful technology transfer, according to **Catherine Bannish.** Finding the right CMO requires forming a robust set of selection criteria centered on capabilities, quality and partnership. While capabilities can be straight forward, quality and partnership take time to build. Technology transfer is highly dependent on process understanding and knowledge transfer, she said, noting the value of the batches often produced prior to production (i.e., engineering runs) for test purposes. Whether an opportunity to train operators, troubleshoot unexpected process challenges (i.e., "hit the hopper with a mallet so the material flows!"), or test batch record documentation, the benefits of engineering runs far outweigh the drawbacks in cost and time.

The panel wrapped up the session with a few examples of technology transfer project timelines and budgets.

The chapter thanks Eric Forrand for hosting this event and looks forward to more successful meetings for the rest of the year.

PDA Who's Who

Catherine Bannish, External Drug Product Manufacturing Lead, Shire

Eric Forrand, Quality Systems Lead, Shire

Paul Gauthier, Director of Due Diligence, Integration and Alliance Management, Shire

Enith Morillo, Quality Assurance Consultant, Complya Consulting Group

Jonathan Morse, President, Complya Consulting Group

Praveen Prasanna, Associate Director & Principal Engineer of Drug Product Manufacturing Sciences and Technology, Shire

2016 PDA Europe Parenteral Packaging

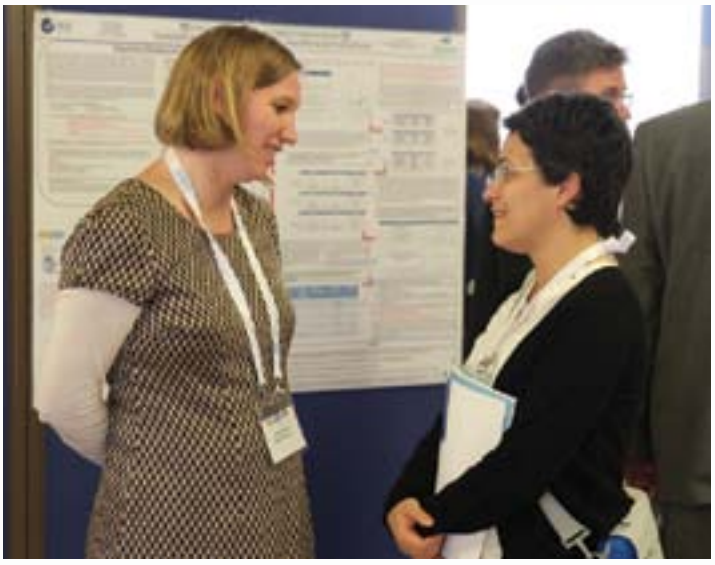
Session 1: Regulatory Update
(l-r) Renaud Janssen, Datwyler; Donald Klein, U.S. FDA; Conference Chair Joerg Zuercher, Bayer

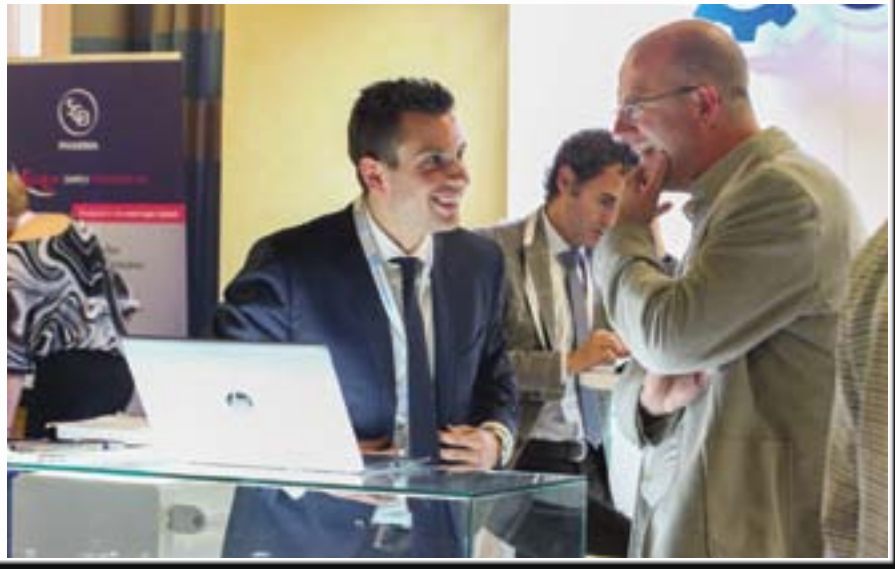
Session 2: Internal Glass Surface Metallic Inclusions
Nicola Favaro, Stazione Sperimentale Vetro

Session 2: How to Reduce the Delamination Risk: A Converter Perspective
Daniele Zuccato, OMPI

Ronald Iacocca, Eli Lilly, presents "Mechanical Modeling of Parenteral Packaging" in Session 2

Donald Klein from the U.S. FDA presents a U.S. regulatory perspective to attendees





Opening Plenary Speakers
(l-r) Hal Baseman, ValSource; Thomas Arista, U.S. FDA; Gabriele Gori, GSK Vaccines

P2: Physical Environment and Environmental Monitoring
(l-r) Edward Tidswell, PhD, Merck; Marsha Hardiman, ValSource; Richard Johnson, PDA

P3: Personnel & Material Transfer
(l-r) Richard Johnson, PDA; Carol Lampe, Former Senior Consultant; Edward Tidswell, PhD, Merck

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6 Careless Mistakes to Avoid On Your Resume

Don Goodman, About Jobs

THINK YOU KNOW

all there is to know about resume writing, and have yours ready to go? Take another look to see if you've made these six careless mistakes. When you're anxious to apply for a job you think you're the perfect match for, you may overlook some basic things.

1 You forget to update your contact information

When it comes time to update the resume, the first thing most job seekers think about is adding details on the last job they held and any new skills gained, but they forget about basic details like contact information. Make sure your resume includes a phone number and email address you regularly check. If you've moved, make sure to include your current address or city and state.

2 You don't provide enough details on your last job

Your resume may have gotten you to your last job, but it's going to need updating to get you a new job. Think about major successes and accomplishments from your last job and highlight them on your resume so employers can see what you're capable of. If you've been promoted, outline that on the resume. It helps employers to see you have something of value to offer, and that you've continued to advance in your profession.

3 You don't update your skills or remove old certifications

Each new job experience provides you with new skills, so make sure they're added to your resume. And if you have dated information like certifications for certain programs listed, check that it's still relevant to include, otherwise it'll just look like you have outdated skillsets.

4 You use abbreviations and acronyms only you may know

If you're going to use abbreviations, make sure they are popular enough that the HR person will understand it. Every organization is different, so what may have been common lingo at your old job may not apply with other employers. Many employers are using applicant tracking systems to help filter through resumes and they will search for keywords. You want your resume to include the popular terminology that will be searched, so don't just stick with abbreviations and acronyms—spell it out, too.

5 You don't remove irrelevant jobs

If you already have a resume in place to work with, that can help save you a lot of time. The problem arises when jobseekers add to the resume, but forget to remove irrelevant jobs. Employers are typically looking to see your last 10–15 years of experience, so anything before that can essentially be taken out for most professions.

6 You name your resume file inappropriately

If you're sending your resume as an attachment, make sure it has a file document name like "JohnSmith-WebDeveloper.doc." Unfortunately many job seekers send out their resume document without considering the file name like: JohnSmith2009 (leading employers to question if that was the last time you updated your resume); JohnSmith-ABC Company (revealing the name of another employer you've applied to); or JhnSmiht (showing how careless you are that you can't even spell your name correctly). You want the hiring manager receiving your resume to be able to identify you from other applicants, so present a recognizable and professional file name for your resume.

It's the things that seem obvious that get most people in trouble on the resume. Make sure you're not making any of these careless mistakes!

Continued at middle of page 19

snapshot

PDA Releases Part 2 of its Aseptic Processing PtC

Jahanvi (Janie) Miller, PDA

PDA is proactively addressing industry concerns with the EMA's revision of Annex 1 with its two-part *Points to Consider for Aseptic Processing*

The two parts of the *Points to Consider for Aseptic Processing* encompass over 100 points related to aseptic processing. Part 1 (published in 2015) overs: physical environment, environmental monitoring, cleanroom personnel and behavior, material transfer, filter integrity testing and water for injection preparation. Part 2 (May 2016) includes additional information on some of those topics and delves into aseptic process simulation and validation, modern blow/fill/seal technology, RABS and isolators, cleaning, disinfection and sterilization and critical utilities. Keep in mind that these two documents are not standards or regulatory requirements; they are consensus-based best practice guidance documents developed by subject matter experts comprised of PDA volunteers. The goal of these PtC documents, in particular, is to support harmonization of technical and regulatory language and offer a scientific and risk-based perspective on aseptic processing.

The topics within Parts 1 and 2 are organized into categories. Each begins with a problem statement in the form of a question, representing issues or points for clarification. Recommendations from the PDA task force behind the document are presented as an answer to the problem statement. The rationale and reference for each recommendation then follows.

PDA also issued the book, *Global Sterile Manufacturing Regulatory Guidance Comparison,* in February of this year (https://store.pda.org/ProductCatalog/Product.aspx?ID=3085). This book provides an easy-to-follow comparison of the various regulation and guidance on sterile drug manufacturing and related aseptic processes. PDA's *Points to Consider for Aseptic Processing* documents are currently available at the PDA Bookstore (www.pda.org/bookstore).

Points to Consider in the Manufacturing of Sterile Products Revision Task Force

Hal Baseman, Valsource, Co-chair
Gabriele Gori, GSK Vaccines, Co-chair
Masahiro Akimoto, Otsuka
Marc Besson, Sanofi
Jette Christensen, Novo Nordisk
Veronique Davoust, Pfizer
Vincent O'Shaughnessy, Amgen
Phil DeSantis, Consultant
Richard Johnson, PDA
William Miele, Pfizer
Janie Miller, PDA
Rainer Newman, Consultant
Michael Sadowski, Baxter
Edward Tidswell, PhD, Baxter

PDA Immediate Past Chair Hal Baseman Challenges Industry to Innovate

Walter Morris, PDA

Hal Baseman, COO and Principal, ValSource and Immediate Past Chair, PDA, opened PDA's two-day workshop on current challenges in aseptic processing with a challenge to younger attendees to question "why and why not" in regard to the way their companies manufacture sterile drug products.

The workshop is the first in a series of four that PDA is sponsoring in 2016 to generate information on current practices in aseptic operations as part of its efforts to prepare comments on EMA's revision to its GMP guidance for sterile drug products, Annex 1.

"Aseptic processing really hasn't materially changed all that much in 38 years," observed Baseman. "I really would like to see you, a young group of people moving this industry forward."

A number of leading experts then followed Baseman on the podium, discussing various aspects of good aseptic processing practices and PDA's 2015 *Points to Consider for Aseptic Processing.* **Thomas Arista,** a U.S. FDA national expert investigator in pharmaceutical and biotechnology, headlined these discussions, providing a regulatory perspective on the topic.

Continued at bottom of page 19

PDA Course, Technical Reports Trigger Success for Takeda

Converting a Dedicated, Cytotoxic IMP Manufacturing Line to Multipurpose

Karen Ginsbury, PCI Pharma

PDA's educational courses not only can have great impact on one's career, they can prompt an entire company to change the way it does business. The former happens all the time, and is well documented in the *PDA Letter* and other PDA materials, but the latter happens too and makes a compelling case for participation in PDA events. This is a story about the largest Japanese pharmaceutical company and its decision to institute a transformational change in its manufacturing operations at one site following a PDA course which introduced the firm to PDA's technical reports on risk management.

Takeda's **Tsutomu Ota,** Manager, Global IMP GMP Quality Assurance Dept., CMC Center, explained to a rapt audience at the *2016 PDA Annual Meeting* how PDA's 2014 course on multipurpose facilities served as the catalyst for Takeda to consider a previously unthinkable measure: conversion of a cytotoxic product dedicated manufacturing line to multipurpose.

The story begins in August 2013. At that time, the company's Osaka facility began production of a parenteral, investigational medicinal product (IMP) on Line A. The facility was designed for high containment, capable of processing API with Occupational Exposure Levels (OELs) of ≥0.01µg/m^3 using closed systems for formulation and filling with C/SIP. The facility was originally designed to serve as a dedicated facility for the manufacture of cytotoxic IMP.

Then, in March 2014, Ota attended the PDA Education course in Lyons, France, "Dedicated or Shared Facilities? A Risk Based Approach." This course integrated ICH Q9 principles on Quality Risk Management (QRM) with PDA's QRM-oriented technical reports to provide a practical case study on implementing revisions to EU GMP Chapters 3 and 5 (at the time the revisions in question were merely proposed but have since been finalized). These revisions focused on provisions for prevention of cross-contamination within premises and production, as well as EMA's guideline on setting health-based exposure limits for use in risk identification for the manufacturing of different medicinal products in shared facilities.

Points specifically addressed in the course included:

- Facility design
- Decision making based on risk assessment
- HVAC design
- Airlocks and clean/dirty corridors
- Other technical and organizational measures

The intimate forum of the course allowed the participants and the instructor to grapple with real life issues. During one such discussion, Ota asked if, in the instructor's opinion, it would be possible for Takeda to use its current dedicated manufacturing line for multiproduct. After all, the company was also introducing single-use technology in place of shared formulation equipment.

The instructor responded cautiously. Without actually seeing the line, the facility or the quality system, it was impossible to say, but, if the line existed inside an isolator (containment) with closed systems and there was no shared product contact surface, then it likely could be done.

Spurred by this discussion, Takeda made an internal decision in June 2014 to move from dedicated to multipurpose and initiated a facility assessment/gap analysis, inviting the PDA instructor to visit the Osaka site and perform the assessment. The instructor spent three days on the site, reviewed the process flow map and the types of IMPs the company wanted to process on the line. ➤

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NOVATEK INTERNATIONAL

Between July and October 2014, the company conducted an intensive risk assessment to identify potential weaknesses and build a set of agreed upon preconditions *required* to be in place to consider such a proposition. These discussions resulted in the following six preconditions.

1. **Takeda Commitment and Policy to Prevent Cross-Contamination:** In other words, this was not a slap-dash opportunity to relax preexisting policy. Company culture was one of the prime reasons for all parties agreeing that this was a feasible project. Takeda will never consider cross-contamination to be acceptable in spite of the fact that IMPs are only used by clinical trial subjects for a short time.

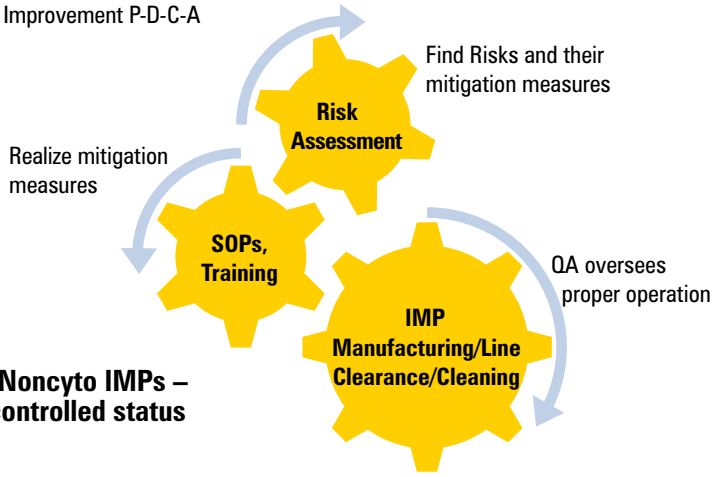
2. **No Sensitizing Products to be Produced in the Shared Facility:** One week spare (based on facility usage) for clean-up; cleaning verification testing before next IMP manufactured.

3. **Controls Over the IMPs Processed on the Line**

4. **Validated Analytical Methods with Sufficient Sensitivity to Meet Detailed Criteria for Residue Testing of Either Permitted Daily Exposure (PDE) or Threshold of Toxicological Concern (TTC):** It was interesting to note that in several cases the residue level for noncytotoxic phase 1 IMPs is far lower than for cytotoxic products because there is less data available and therefore additional safety factors are needed.

5. **Lyophilization Chamber Excluded:** In other words, only nonlyophilized products used since the lyophilizer is considered product contact (although no direct contact).

Figure 1 Continual Improvement P-D-C-A



Manufacturing Noncyto IMPs – How we keep controlled status

6. **Contingency Plans for Spills and Disasters Such as Equipment Malfunction and Increased QA Oversight**

QP Accepts Transformation

A team of 20 people performed the risk assessment which involved brainstorming potential failure modes. It took three initial days, along with additional out-of-team work, followed by a two-day session with the team. Half of the team brainstormed failure modes for the 6Ms (man, machine, materials, methods, measurements and miscellaneous), and the other half the process flow (weighing, formulation, filtration, etc.) to ensure nothing was omitted.

After the initial brainstorming, which identified over 100 potential failure modes, existing controls and means of detection were added to the FMEA. The single-use system was then qualified. For any existing controls identified as inadequate, redesign or additional control measures were implemented.

In October 2014, the team pulled Takeda's Qualified Person (QP)—the individual who performs the batch releases— into the project. The QP accepted the idea, provided it was subject to audit. In March 2015, Takeda successfully passed the onsite QP audit—only one year after the PDA course in Lyons—and started manufacturing noncytotoxic IMP on the previously dedicated cytotoxic line.

Now that the new line is in place, Takeda culture does not allow the company to sit back and relax. **Figure 1** shows the proactive measures the company will continue to implement in a Plan-Do-Check-Act cycle of improvement and control requiring nonstop vigilance, monitoring and action when warranted.

Takeda found that it is possible to switch a dedicated line to multiproduct. After all, the EU GMP revisions were developed precisely for this purpose. There is, however, a caveat—without preconditions that specifically *include* company culture, implementing a measure of this kind can be disastrous. Takeda has shown that it is possible to maintain a quality culture while switching to a mutlipurpose line, resulting in phenomenal cost savings and no adverse impact on quality.

About the Author

Karen Ginsbury is President and CEO of PCI, Pharmaceutical Consulting Israel Ltd., a company which provides services to the pharmaceutical, biotech and allied industries.

Microbial Control to Ensure Product, Patient Safety

Ed Balkovic, PhD, Sanofi

Microbiology is a critical component of the pharma industry, particularly management of microbial risk and prevention of microbial contamination. To ensure a high level of control, it is critical for microbiologists to identify current trends in the field (including new technologies), digest new advances in rapid microbiological methods and updates in endotoxin testing, understand the challenges posed by mold and spore contamination, and remain aware of all relevant regulatory and pharmacopeial expectations.

Despite it's importance, however, microbial control methods remain rooted, in many cases, in 20th century technologies. As innovative therapeutic products and facilities expand, the need for new forms of microbial control also will grow.

Therefore, the program planning committee for the *11th Annual Global Conference on Pharmaceutical Microbiology* would like to invite those interested to attend this year's conference, the theme of which is "Microbial Control: Key to Product Quality and Patient Safety." A breakout session on "Contamination Control" will highlight novel efforts at improving contamination control by engaging operators on the manufacturing floor. This session will also explore efforts to control contamination during disruption of a controlled environment, and finally, will feature a case study covering responses to contamination in a cell culture manufacturing operation.

Curious what the U.S. FDA thinks about the current state of microbial control? On the final day of the conference, there will be an opportunity to hear from an invited FDA representative on the current state of microbiology operations. The concluding session will then feature the annual "Ask the Regulators" roundtable composed of reviewers, compliance experts, and field investigators. Here, attendees will be free to ask the regulators their most burning questions on microbial control and other micro-related topics.

All-in-all, the organizers of the conference hope attendees leave with increased knowledge in many areas of microbiology, including managing microbial risk and the dynamics of microbial contamination

11th Annual Global Conference on Pharmaceutical Microbiology and PDA Education courses

Arlington, Va.
Oct. 24–28
www.pda.org/2016micro

Tools for Success continued from page 15

[This article was originally published at CAREEREALISM.com]

About the Author

Don Goodman is a triple-certified, nationally recognized Expert Resume Writer, Career Management Coach and Job Search Strategist.

PDA Immediate Past Chair Hal Baseman Challenges Industry to Innovate continued from page 16

The goal of the workshop series is to generate information on current best practices via breakout discussions and a survey that will be taken at each location. The next two-day workshop takes place in Berlin, May 31–June 1.

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To offer you the most flexibility, this interactive Workshop will be presented multiple times in different locations in 2016.
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Is Silicone Oil-Based Lubrication Still State-of-the-Art?

Christian Helbig, SCHOTT

Silicone oil-based lubrication is the current industry standard for today's prefilled syringes. Yet, it represents a complex system with limitations. In particular, two main limitations stand out:

- Impact on syringe functionality, particularly those in combination with devices such as autoinjectors due to improper distribution and/or silicone migration during shelf-life
- Potential impact on drug stability, i.e., the interaction of silicone oil with sensitive biopharmaceuticals

While silicone oil-based systems have improved over time through improvements such as the introduction of uniform distribution that reduces the total quantity or new methods needed to assess distribution at suppliers, the industry is also in the process of advancing innovative approaches to substitute—or even completely eliminate—the lubricant in both glass and polymer prefilled syringe systems.

Where can you find the latest update on these new advancements? This year's *Universe of Pre-filled Syringes and Injection Devices* conference and exhibition will be the place to learn about the latest in these advancements. The University of Colorado's **John Carpenter,** PhD, will discuss silicone oil induced protein aggregation and immunogenicity, while Eli Lilly's **John Ayres,** MD, a longtime PDA volunteer, will explore the immunogencity affects of this protein aggregation.

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Combo Products Put Control in the Hands of Patients

Diane Paskiet, West Pharmaceutical Services

As healthcare rapidly moves from the clinical setting to home, the demand for innovative drug/device combination products continues to rise. The value and benefit of today's medicines will need to show evidence of safety, efficacy and quality, as well as demonstrate patient adherence, and provide confidence to healthcare practitioners and proof of value to payers. How will an effective drug product be realized if the delivery is not optimal and patients do not comply? What constitutes a comprehensive understanding of the factors influencing drug delivery from the perspective of patients and healthcare providers?

Human factors will guide the development of drug delivery combination products by indicating optimal use. Each drug or biologic product has a unique set of requirements that will impact the type of device and features needed for delivering safe and effective medicines. Biologic products in particular bring new challenges to device development due to the large size of the molecules, increased viscosity, stability, rate of delivery, and injection volume. Overall design factors will include a range of hazards related to material compatibility, mechanical failure, dispensing errors, and user interfaces. A strategy for a unified development approach that can identify and mitigate risks based on the viewpoints of multiple stakeholders will advance drug delivery/device development and commercialization.

Discover the latest scientific and technical advancements in patient-centric drug delivery at the *2016 PDA Drug Delivery Combination Product Workshop*. Experts from across the drug-delivery device development spectrum will join together to discuss related topics such as human factors, risk management, and engineered drug delivery. Experiences from Janssen, Biogen, Eli Lilly and Sanofi Pasteur will be shared. Design verification, technology transfer, change management and new technologies will be among the topics addressed.

2016 PDA Drug Delivery Combination Product Workshop

Huntington Beach, Calif.
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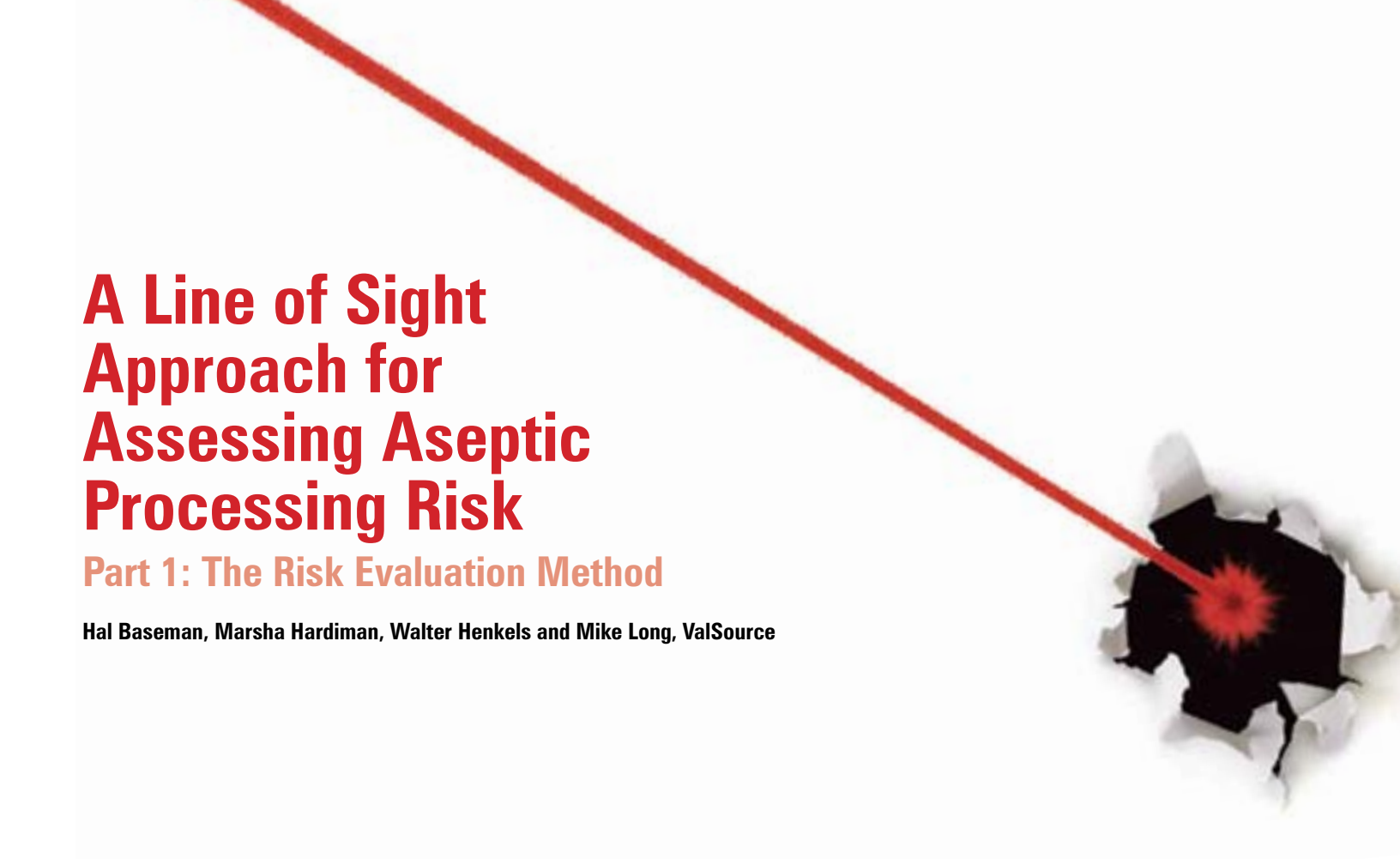
A Line of Sight Approach for Assessing Aseptic Processing Risk

Part 1: The Risk Evaluation Method

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



Aseptic processing of sterile drug products can and should be improved. The same challenges, problems and issues seem to appear, reappear, or never really disappear from year to year. These problems persist despite more awareness of the issues due to increased training, conference sessions on the topic, guidance documents, quality system management approaches and metrics. Each year, regulatory audit observations, 483s, and warning letters continue to cite the same problems and issues over and over. Admittedly, aseptic processing is challenging, and there are obstacles to improvement, but it is the job of those working in this area to resolve these challenges.

Numerous documents stress the need for science and risk-based decision making in aseptic process design and performance. These include *PDA Technical Report No. 22* ***(1),*** *PDA Technical Report No. 44* ***(2),*** *PDA Points to Consider for Aseptic Processing* (Parts 1 and 2) ***(3–4),*** as well as the U.S. FDA aseptic processing guidance and the planned revision to EU's Annex 1. As stated in Part 1 of the *PDA Points to Consider for Aseptic Processing*, decisions based on product risk can, and should, be used to improve aseptic process. Risk assessments should provide the information needed to make informed decisions throughout the process lifecycle. The objective is not merely to identify risk but to improve the process. Yet, the industry still struggles with developing effective risk assessment methods for aseptic processing.

Aseptic process risk assessments have some unique challenges. The severity of sterility-related issues, primarily the loss of sterility, is high and certainly worthy of consideration. Yet, the causes of aseptic process failures, which are directly correlated with the loss of sterility, are relatively rare; hence, very low occurrence rates are noted. Detection of process failures is not always reliable, and the correlation between what we can detect and the desired or undesired outcome may not be quantifiable. An issue with many aseptic processing risk assessments is the lack of objectivity. Since it is not easy to measure or quantify people or environmental risk factors, risk assessments tend to be subjective and therefore of limited benefit. This subjectivity comes from the lack of data that can be correlated to sterility or aseptic process failure. For example, interventions can add microbiological contamination to the environment. However, we may not know when, or to what extent, those interventions can result in a level of contamination necessary to contaminate the product. In common practice, boundaries and limits are set, then the results are observed. Too often this leads to approaches based largely on the assessor's experience and bias rather than science. An objective method for considering the correlation and evaluation of risk to aseptic processes is needed to facilitate process improvement.

Article at a Glance

- Aseptic Processing is a subjective process
- Line of Sight approach to risk management drives all actions
- Risk Evaluation Method is an 8-step process

Objective Defines the Method

The Risk Evaluation Method or REM described in this article was initially developed to satisfy a need for an objective, simple, and more accurate method to rank aseptic process interventions, in order to better plan media fills ***(5).*** This first article will present the basic objective and steps for the REM. Subsequent articles will explore its specific use for aseptic process improvement.

For the aseptic processing REM to be effective and useful, it should be:

Objective: Objectivity reduces the potential for bias. Bias leads to disagreement, loss of confidence in the method, and risk assessments without benefit. Objectivity is achieved if different people with similar knowledge about the process and access to information are able to use the REM and conclude a similar risk rating. For example, if the Quality lead and the line mechanic use the REM, they should obtain similar rankings. For this to happen, meaningful, measurable data or information must be available and accessible. It may be that different people have different perspectives and varying levels of knowledge. This knowledge becomes valuable input into setting the ranking criteria. Once the criteria are set, the evaluation of information should be objective.

Simple: Simplicity allows for the use of the REM by a larger group. This leads to better acceptance of the REM outcome. The REM should be performed by the people engaged in the process itself. The REM should not be burdensome to use. The people using the method should be able to explain the basis of the method and be able to perform the assessment.

Robust: A robust method is one that is applicable to most relevant applications or processes. It also avoids the need for multiple or changing methods which may add confusion, bias and complexity.

Logical: The REM must be based on sound science in order to be viewed as truly objective, to gain user acceptance of results and convince regulators that the method and its results are credible.

The REM relies on two principles to achieve effectiveness. It uses a *Line of Sight* approach. Line of Sight focuses and links actions to the overall objective of the assessment. That objective is defined and stated in a problem statement. The use of a problem statement linked to the objective assures that all actions are directly beneficial and useful to accomplishing the objective and that actions of little value are omitted.

For this to work, the definition of the objective as reflected in the problem statement must be well thought out. For example, is the objective of the environmental monitoring program to find particles, achieve a particle free environment, meet regulatory requirements, ➤

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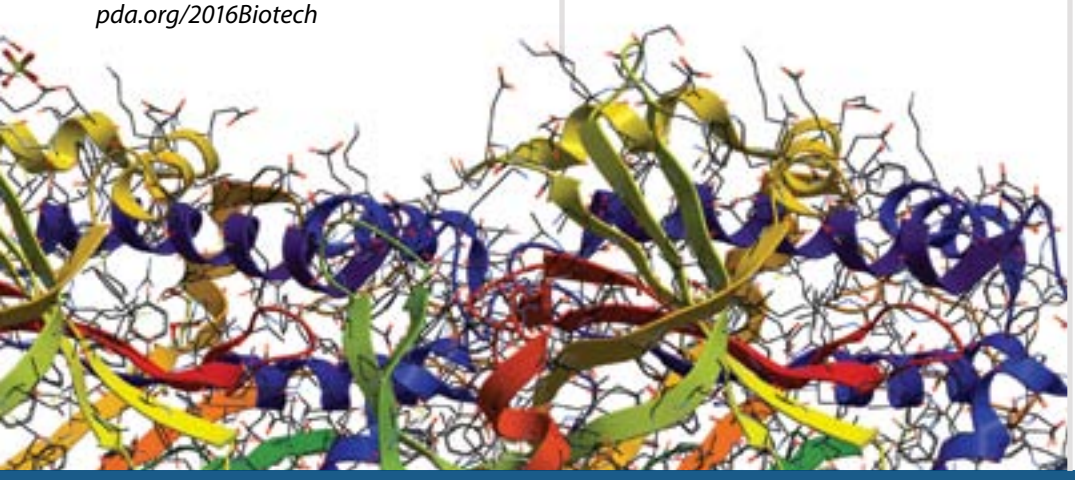

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30-1

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or achieve an environment suitable for aseptic processing? Is the objective of the aseptic process simulation to qualify the operators, the interventions or the aseptic process? As the objective varies, so will the focus and use of the assessment.

The second principle is the use of a *Key Word* approach, a tactic in which those assessing process risk identify the words and values most relevant and meaningful to them. Rather than use general terms or risk tables, the participants decide which words best describe or assess their situation and tie these to risk scales.

Aseptic processes may seem similar throughout the industry, but companies have unique cultures and individuals have different backgrounds, biases, perspectives, and experience. Trying to match one set of criteria to all aseptic processes would prove difficult. The Key Word approach applies the company's and the involved individuals' knowledge to the problem at hand. Also, by asking the involved individuals to select the risk criteria, it better assures ownership, respect and use of the method. It reduces the chance of the model becoming a checklist exercise.

Because the Key Word approach encourages individual assertion of criteria and factors, one company/process may not be completely applicable to other companies/processes. The tempatation to to develop a one-size-fits-all template should be resisted, as it is the process of developing the factors and criteria for the assessment which is most valuable in ensuring its effectiveness.

While not necessarily an exhaustive list, those factors should fit the four basic requirements of the REM—objectivity, simplicity, robustness and logic. All of the elements should be objectively measured. No one factor alone fully defines risk. It is the combination of the factors that presents risk.

Taking these principles into consideration, the REM comprises eight steps:

It is important to resist the temptation to develop a one size fits all template

Step 1 Problem Statement

The team develops a problem statement that defines the objective and boundaries of the REM. This helps the team stay focused. The objective should be meaningful to those performing and analyzing the assessment and should not be broad beyond reasonable usefulness, yet it should not be too narrow as to be limiting.

Step 2 Team Selection

The REM team should consist of subject matter experts in the field defined by the problem statement. They should represent multiple departments and levels of authority. The team does not have to include all affected stakeholders. In this phase, the objective is to define risk elements and criteria, rather than inform stakeholders. Team size is important. While it should include all relevant stakeholders, large groups can stifle participation. It should include diverse participation, thus reducing the risk of bias or preconceived outcome. A facilitator may be of benefit.

Step 3 Risk Factors Determination

The team identifies the parameters, actions, events, conditions or items that affect the objective or problem. These should have measurable criteria. The data for those criteria should be accessible and understandable by anyone doing the assessment. Brainstorming may be used to select risk elements.

Step 4 Criteria Setting

The criteria, limits or ranges used to rank the parameters or elements should be set by the team prior to the assessment. The criteria should be meaningful, logical, attainable, useful, verifiable and measurable. The data should be accessible. Rules should be set for accepting levels of risk. For instance, are high levels of risk acceptable or must steps be taken to reduce those risks? Are less-than-low levels of risk accepted without attempts to further reduce them?

Step 5 Assessment Tool Development

The team should choose a tool that evaluates the parameters and meets the objective, both from a product quality and process performance perspective. One-size-fit-all tools may not work for all applications. Customizing a tool or model for a particular use may be useful.

Step 6 Risk Evaluation

The team performs the assessment and obtains the risk rankings. The meeting in which the evaluation is performed should have a duration target to help keep things on track. All should have a voice at the meeting.

Step 7 Mitigation Actions

The team or additional stakeholders should determine, evaluate and implement actions and steps based on the ranking in an effort to improve the process and/or meet the objective, considering the rules set out in Step 4. Remember that the purpose of the evaluation is to improve the process, not merely identify risk. Where actions or steps are to be taken, consideration should be given to the addition of risk from any unintended consequences of the action or change.

Step 8 Review

Follow up on actions to confirm that they a) were implemented properly, b) were effective, and c) did not add any unintended consequences or additional risk. Communicate results to ➤

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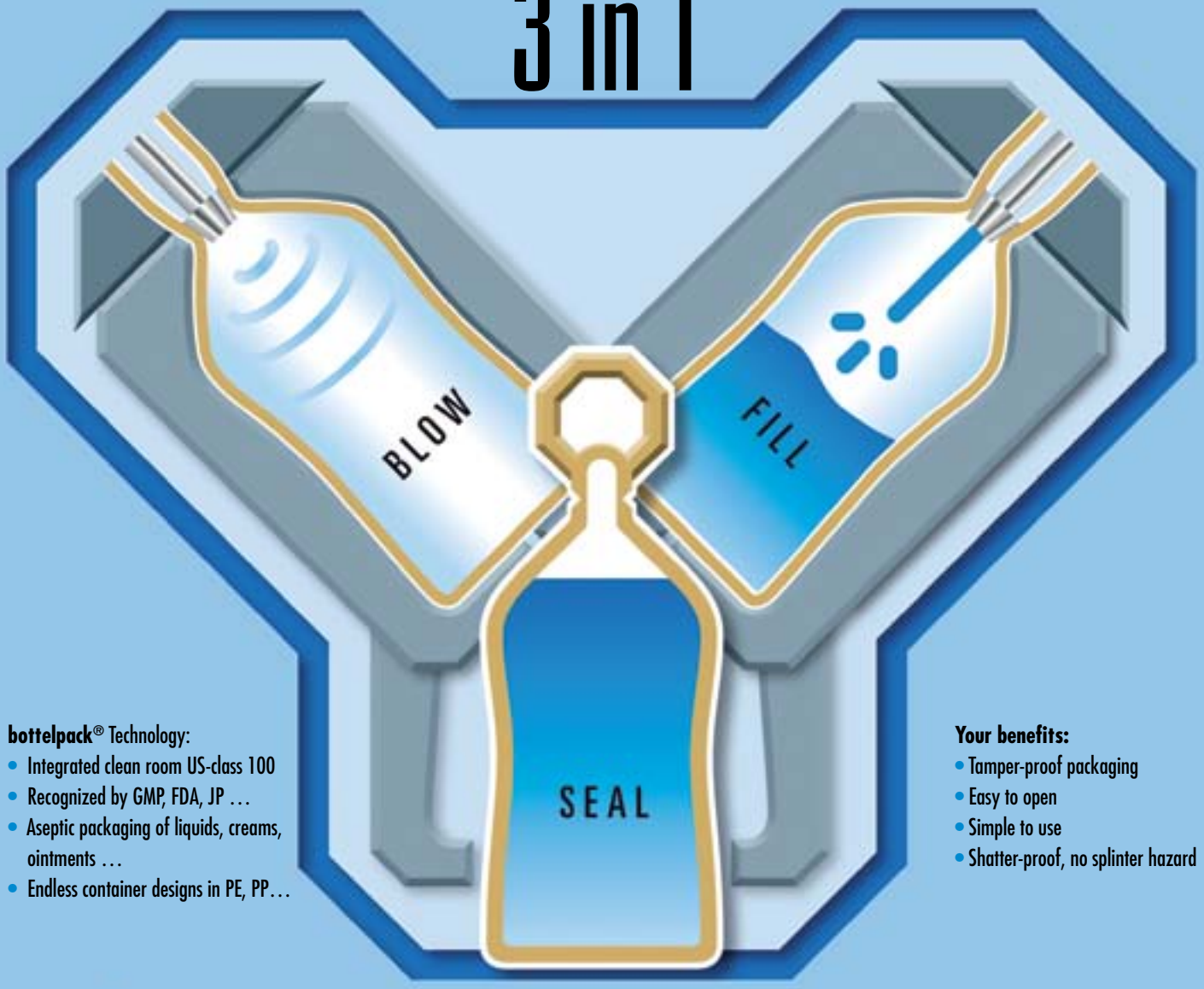

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affected departments. Perform periodic review of the REM to confirm accuracy and effectiveness of results.

Now, that a case for aseptic process improvement has been made and the REM introduced, Parts II and III of this article series will show how the method is used to improve aseptic process interventions and cleanroom environmental monitoring through examples and case studies.

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About the Authors

Hal Baseman is a Principal at ValSource LLC. He has over 30 years of experience and has held positions in executive management and technical operations at several drug manufacturing and consulting firms. In addition, he has been a long-time PDA Education instructor for the "Aseptic Processing Training Program."

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Mike Long has over 20 years of experience in the pharmaceutical and medical device industries. Currently, he is part of the management team at Concordia ValSource.

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7 Steps for a Reproducible Cycle Development Plan

Stefan Kleinmann PhD, Matthias Scheu, Christian Fecht, METALL+PLASTIC

Decontamination cycle development takes place between the completed operational qualification and the subsequent process validation. It also determines the parameters for a successful, effective and repeatable decontamination process that complies with the requirements of both regulatory agencies and end users. The PIC/S guide for isolators states that an isolator decontamination cycle using a minimum 6-log spore reduction is often applied ***(1)***. During routine operation, pharmaceutical isolators and material transfer chambers use decontamination cycles to yield a theoretical 10- to 12-log spore reduction for additional safety.

Decontamination cycle development is conducted on each isolator using a structured, comprehensive strategy. The supplier prepares a cycle development plan and approves it together with the customer. The majority of biological indicator (BI) locations are defined based on the rationale when creating the plan (see Step 4). Additional BI locations can be defined prior to the start of the cycle development process. Errors can be avoided in advance and potential critical points can be recognized early and corrected using a structured approach.

Below is a 7-step plan for a reproducible cycle development plan.

Step 1 Determine the Maximum Injection Rate and Duration of Dehumidification

The maximum H_2O_2 injection rate (in grams per minute) is determined during the first step of cycle development. This avoids condensation by the hydrogen peroxide in the decontamination air supply piping.

The time required to reach a selected humidity set point is determined using the built-in humidity sensor. Additional humidity sensors are distributed on the isolator baseplate to verify the readings of the built-in sensor. The dehumidified air can absorb more vaporized hydrogen peroxide in the injection phase. The initial part of the cycle development process determines parameters that define the starting conditions and enables reproducibility in all subsequent decontamination cycles.

Step 2 Temperature and Gas Distribution Study

The next step benchmarks the isolator temperature distribution using thermocouples. Gas distribution is analyzed using chemical indicators (CIs). During normal operations, it is desirable for the temperature on the interior surfaces of the isolator to be as uniform as possible. Temperature distribution data may identify potential problematic areas which will need to be challenged with BIs. It is important to control the room pressure, temperature and humidity at the set point that will be used during normal operation to ensure meaningful isolator temperature distribution. The isolator's operation may also affect the air balance of the room.

In the isolator, the surface temperatures are important during the decontamination process. "Hot spots" and "cold spots" can significantly affect the process. Hot surfaces can have a lower kill rate of BIs because the resulting saturation of the humidity and H_2O_2 vapor is lower due to the higher temperature. The inactivation of spores on BIs is most efficient near the saturation limit where condensation begins forming. "Hot spots" can have a complete absence of condensation.

A contrary effect can be observed with "cold spots." The colder temperature surfaces have increased condensation compared to warmer places. This condensation increases the spore inactivation rate in those cold areas; however, the accumulation of excessive liquid hydrogen peroxide reduces chemical availability in the other areas. Heavy accumulations of liquid hydrogen peroxide should also be avoided because it can increase aeration time and cause long-term damage to some surfaces.

Step 3 Preliminary Lethality Study

An important step in cycle development is the preliminary lethality study **(Figure 1)**. A number of BIs are placed in the isolator along with a ➤

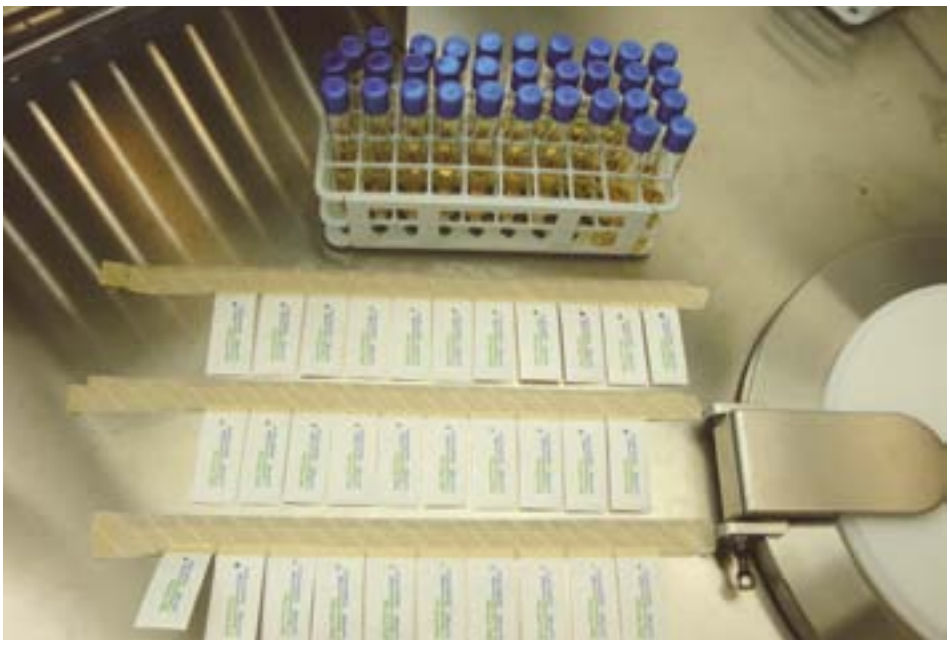

Figure 1 Preliminary Lethality Study

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corresponding number of media tubes on a location that is easily accessible. Starting at the beginning of the injection phase, BIs are transferred into the media tubes at specified time intervals. When the cycle is complete, the media tubes are transferred to an incubator. The D-value of the BIs can be estimated using the Limited Spearman Karber Method (LSKM) as described in ISO 11138 ***(2).*** The D-value can be defined as the time necessary to achieve a 90% reduction of the test organism under analysis with specified exposure conditions. The study benchmarks the resistance (D-value) of the BI lot during exposure in the customer's isolator used for validation. This information can be very valuable during future revalidations. This study also determines the initial exposure time for the worst case location lethality studies.

Step 4 Worst Case Lethality Study

BIs and CIs are both used for the worst case lethality study **(Figures 2 and 3).** CIs provide qualitative information about chemical distribution in geometric positions in the isolator. A mean system D-value can be estimated for each location tested with BIs using the selected time interval. Three BIs should be used at each location to support statistical interpretations.

In this step, the BI locations are selected on the isolator configuration. The U.S. FDA guidance document on aseptic manufacturing recommends including BI locations in areas difficult for the vapor to reach ***(3)***. All initial BI locations are chosen for the first study. A high speed filling line isolator may use 200–300 initial BI locations, while a small four-glove isolator may use 40–50 locations. The rationale for the BI location selection is based on the following criteria:

- **Geometric:** Locations chosen to improve overall geometric coverage of the isolator
- **Difficult:** Different materials or areas where air flow is substantially blocked by equipment or supplies
- **Critical:** Locations with direct or indirect product contact such as feeder, stopper bowls, areas or objects which require frequent operator intervention, such as environmental monitoring stations, areas near to the filling process, etc.

The first worst case lethality study cycle is conducted using the injection parameters determined in the preliminary lethality study. All BI locations are used in the first study. For all further studies, the total injection time is extended by a uniform time interval. Locations that have complete BI inactivation are removed from the subsequent studies. These incremental studies are continued until complete BI inactivation is achieved at all locations. The location where the last growth occurred is considered to be the worst case location with respect to the lethality. A proven 6-log spore reduction is demonstrated at this worst case location. A mean system D-value can be estimated for the worst-case location. This D-value can be used to estimate the desired spore reduction cycle (10- or 12-log) to be used for routine production.

Figure 2 Worst-Case Lethality Study BI/CI Locations

Figure 3 Worst Case Lethality Study BI Locations

Step 5 Aeration Study

This step involves a study to determine the duration of the aeration phase for subsequent routine operation. The aeration phase is selected so that the isolator's H_2O_2 residual concentration is below the limit set by the end users. Catalyst technology creates the possibility of reaching low residual levels in the isolator after a short aeration time. Usually, isolators are aerated down to H_2O_2 residual concentration of less than 1.0 or 0.5 ppm. For products that are sensitive to oxidation, H_2O_2 residual concentrations of less than 0.1 or 0.05 ppm can be achieved.

Step 6 Process Validation

Following successful cycle development, the teams involved validate the decontamination and aeration processes with three successful validation runs. The worst case location(s) and a selection of the geometric, difficult, critical and worst case BI locations are used for validation of the decontamination process. As a conservative approach, a cycle with reduced injection time is often used. PDA *Technical Report No. 34: Design and Validation of Isolator Systems*

Continued at bottom of page 37

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Source

1. PDA Technical Report No. 30 (Revised 2012): Parametric Release of Pharmaceutical and Medical Device Products Terminally Sterilized by Moist Heat

PDA thanks **Michele Creech**, Grifols, for her assistance with this infographic as well as Baxter's **Michael Sadowski** for his contributions.

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And, on October 20-21, PDA's Education Department will hold two courses complementing what you have learned:

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- *Essential Elements of Extractables and Leachables: From Material Extraction to Final Report* (October 21)

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snapshot

2016 PDA Annual Meeting

Chinese Monographs on Excipients Much Stricter

Rebecca Stauffer, PDA

What will bring together three PDA interest groups—Management of Outsourced Operations, Supply Chain Management and Pharmacopeial—in one sitting? A major rewrite of the Chinese Pharmacopoeia excipient standards that has far-reaching implications for pharmaceutical companies doing business in China will, for one. All three interest groups conducted a joint-session at the *2016 PDA Annual Meeting* in San Antonio.

The revisions, according to **Susan Schniepp,** Consultant, Regulatory Compliance Associates and coleader of the Management of Outsourced Operations Interest Group, "are really going to affect global companies, suppliers and their ability to market products in China."

Lisa Milano, Head, PQS Document Process, Genentech Roche, said, "The expectation is that if the Chinese Pharmacopoeia's specification is tighter, this is the requirement." The Chinese Pharmacopoeia does allow for another test method, but only if the method is equivalent. Roche was not aware of the changes until a Chinese FDA inspection of its Shanghai facility. The Chinese regulators explained that "excipients in drug products imported to China/manufactured in China need to meet the Chinese Pharmacopoeia regardless of the filing."

These changes come at a time when the Chinese government is looking at requiring foreign companies to adhere to other, more stringent standards.

Janeen Skutnik-Wilkinson, Staff Associate, Compliance and Standards at Biogen and coleader of the Pharmacopeial Interest Group, noted that "the head of the Chinese government and the head of the CFDA made a formal announcement that they intend, on purpose, to have stricter standards than anywhere else in the world....Some of what we are encountering here is a direct result of that position."

Roche plans to comply with the new excipient standards as it has no intention of ceasing operations in China. The company's drug product, drug substance and general methods will be compared with the Pharmacopoeia, based on internal filings, and equivalency studies will be conducted. Gaps will be discussed to determine if methods and limits need to be added to the specifications. The company will also require its suppliers and CMO/outsourcing partners to adhere to the 2015 Chinese Pharmacopeia.

"Our initial effort will be in the QC assessment of the additional monographs, including method equivalency testing," Milano explained. "Further effort may only be required if the China Pharmacopoeia has tighter specifications or additional tests are required."

She then pointed, as an example, to the excipient assessment for sodium chloride. Here, the Chinese Pharmacopeia requirements are stricter for heavy metals, arsenic and potassium.

Yet Roche does foresee certain challenges. Their suppliers have not yet confirmed if they can meet the specifications—a situation compounded by the fact that an official translation of the pharmacopoeia is not expected to be available until this month. A retrospective review of test results taken from random excipients had several tests that failed the new specifications. This means there is a risk to the supply chain if the Chinese Pharmacopoeia specifications are adopted without guarantees from excipient suppliers. And water for injection (WFI) is site-dependent, meaning every site will have to create separate strategies to defend their own specifications.

The company created a project plan to address these challenges. First, the company intends to gather supplier information for all affected excipients. Next, provide these suppliers with translations of all relevant 2015 Chinese Pharmacopeia monographs. And finally, ensure all products imported to China comply with the 2015 monographs through supplier feedback, QC gap assessments, inclusion of the Chinese Pharmacopeia in local release specifications, and strategies for determining whether additional testing is required.

While Roche has developed a strategy to address the 2015 Chinese Pharmacopeia's more stringent requirements, Milano explained that her department is interested in how other companies that export product to China are handling these changes. The leaders of the Pharmacopeial, Supply Chain Management and Management of Outsourced Operations Interest Groups are also interested and encourage further discussion on this topic on PDA Connect℠ (community.pda.org).

About the Expert

Lisa Milano is head of Genentech's Pharmaceutical Quality System Document Process.

Measuring the State of Quality Assurance in 2016

Maria Guazzaroni Jacobs, PhD, Pfizer, Inc.

As a discipline, Quality Assurance (QA) has evolved over the last century. QA, Quality Control (QC), and continual improvement philosophies were developed in the 1920s with later additions from the work of luminaries such as Demig, Juran, Crosby and Taguchi. Since the 1970s, substantial advances in thinking and methodologies have proliferated to the present.

But what is the business value of reliable manufacturing based on preventive systems? What about the customer benefit? And what are the risks and outcomes relating to unreliable systems?

Answers to these questions can be found on the last day of the upcoming *2016 PDA/FDA Joint Regulatory Conference*, which will feature the session, "Quality Assurance in the Year 2016, and Beyond." Moderated by **Rick Friedman,** U.S. FDA, CDER Deputy Director, Science and Regulatory Policy in the Office of Manufacturing Quality, this session will feature both regulatory and industry speakers, offering their perspectives on the evolution of QA and its current challenges and future opportunities.

In addition to QA, attendees will also learn about ongoing international collaborations, how to effectively handle post-inspection activities (e.g., responding to 483s), how to identify key performance indicators for measuring quality, what industry is doing to combat falsified medicines, and other topics of high importance in our industry.

As usual, the conference has a very large regulatory presence, especially from the FDA. In one plenary session, representatives from the FDA Centers (CDER, CBER, CDRH, CVM, ORA, and Office of Health Informatics) will provide updates about their Centers and share their vision for the future. Another session will cover compliance, and attendees will learn about FDA's current and future compliance and enforcement strategies and actions to secure the safety and quality of the nation's drug supply.

Industry experts and regulators will convene for this seminal event in Washington, D.C. Make your reservations now!

2016 PDA/FDA Joint Regulatory Conference and PDA Education courses

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www.pda.org/pdafda2016

7 Steps for a Reproducible Cycle Development Plan continued from page 33

for the Manufacturing and Testing of Healthcare Products recommends 5–10 BI locations per cubic meter of the isolator volume for process validation and revalidation ***(4)***. Triplicate BIs are most often used at each location.

A cycle with a slightly extended decontamination time is often used for the aeration process validation for extra conservatism. The residual concentration is usually verified manually using H_2O_2 sampling tubes or external sensors at the end of the aeration process.

Step 7 Regular Revalidation

Single replicate tests to revalidate both the decontamination and aeration process are recommended annually, or if there are plans to change the load configuration.

Conclusion

Cycle development of H_2O_2 decontamination and aeration processes uses a structured approach to identify suitable process parameters for routine production. It is also important to develop parameters for process validation and revalidation. It

Continued at bottom of page 38

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Nurturing the CMO Partnership Lifecycle is Crucial

Jeff Hargroves, ProPharma Group

Choosing the right contract manufacturing organization (CMO) is critical to the success of your company. Choosing the wrong CMO can put your product and your company at risk.

Our industry is using CMOs at an increasing rate. Contract manufacturing and laboratory organizations are a vital part of the modern drug supply chain landscape. Thoughtful and proactive management of this relationship's lifecycle is crucial to the long-term success of our drug supply. How do you simultaneously consider the business and financial aspects of this relationship, contemplate the intricacies of a complex technology transfer process, ensure a continuous commitment to quality and understand and manage regulatory risks?

At the *2016 PDA Outsourcing/CMO Conference*, you can learn from experienced speakers representing drug companies, contract manufacturing and laboratory organizations, and service providers on how to effectively select the right CMO for your organization and maintain this intricate relationship. This conference brings together industry experts to share their experiences, insights and best practices.

Conference sessions will cover:

- Identification and selection of a CMO—when and how to determine best fit
- How quality metrics should be handled with a CMO and the U.S. FDA quality metrics draft guidance
- Best practices for Quality Agreements
- Effective auditing of a CMO—due diligence before hiring, routine audits, PAI mock audits
- Technology Transfer—How to transfer your products and methods correctly and efficiently

Attend this conference to learn the strategies, tactics and tools to identify and select the right CMO and how to construct the quality agreements and partnership approach to ensure a long-lasting and successful relationship for all.

2016 PDA Outsourcing/CMO Conference and PDA Education courses

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Nov. 2–4
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7 Steps for a Reproducible Cycle Development Plan continued from page 37

is advantageous for the customer to perform the decontamination cycle development and process validation together with the isolator supplier, who knows the system, critical components and the potential worst-case locations in the isolator. In addition, plans and reports are from a single source, making links between cycle development, process validation and revalidation transparent and easy to understand. This ensures that the decontamination process is robust, safe and reproducible, and complies with the applicable regulatory requirements.

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Recommended Resources

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About the Authors

Stefan Kleinmann, PhD, is the Chief Executive Officer at METALL + PLASTIC GmbH, and has served in this position since February 2014.

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Christian Fecht is a Qualification Engineer at METALL + PLASTIC GmbH. In addition, he works in the laboratory and is responsible for analytical determination of hydrogen peroxide as well as checking of material resistance.

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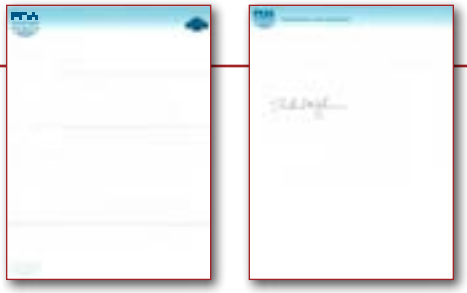
PDA Shares Concerns about IDP Storage General Chapters

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



March 29, 2016

Desmond Hunt
United States Pharmacopeia
2601 Twinbrook Pkwy,
Rockville, MD 20852
Reference: USP General Chapter Prospectus Documents:
Storage and Transportation of IDPs
Metal Packaging Components and their Materials of Construction

Dear Dr. Hunt:

PDA appreciates that the USP has listened to the feedback of its stakeholders, and has put in place this General Chapter Prospectus pilot process for early input into general chapters. General chapters have such broad reaching impact. This new process will enhance the knowledge base of the Expert Committees, and will hopefully result in chapters with broader industry consensus and buy-in.

With respect specifically to the Prospectus on Storage and Transportation of Investigational Drug Products, PDA believes the creation of this general chapter is superfluous and will cause confusion ultimately resulting in delay in bringing new therapies to the market. This is contrary to ICH Q10 whose first objective is to achieve product realization.

PDA has a concern that USP general chapters cannot be written, revised, and implemented to keep pace with the rate of change in industry and innovation. Creating general chapters such as these runs the risk of inhibiting new practices and product types. Therefore discussions on investigational drug products are best kept between regulators and the companies developing the products.

Clinical Trial Materials are controlled by the regulatory agencies and the companies; covered under GMPs and standards developed by ICH; and do not fit under the remit of the USP. WHO already has regulatory guidance in place to address these issues as do other major regulatory agencies around the globe (e.g. Annex 13 of the EU GMPs). USP's proposed chapter could be misinterpreted as a binding requirement regarding storage and transportation practices. Such requirements do not belong in a pharmacopoeia. Whereas PDA believes that in the case of the Prospectus on Metal Packaging Components and their Materials of Construction, this fits well within the primary remit of the USP, to develop monographs that ensure safe drugs and supports the development of this general chapter.

PDA would be happy to elaborate further through participation in a teleconference, if such is scheduled, or to set up a meeting discuss this further.

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 manufacturing and pharmacopeia publications including members representing our Board of Directors and our Regulatory Affairs and Quality Advisory Board.

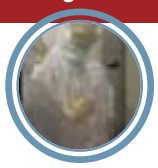
If there are any questions, please do not hesitate to contact me.

Sincerely,
Richard Johnson
President, PDA

CC: Jaap Venema, USP; Richard Levy, PDA; Denyse Baker, PDA

PDA Commenting Task Force

Janeen Skutnik Wilkinson, Biogen (Lead)
Karen Ginsbury, PCI Pharma
Susan Schniepp, Regulatory Compliance Associates



Aseptic Processing Practices Discussed at Lively Workshop

Walter Morris, PDA

PDA gained valuable insight into aseptic processing practices from attendees representing a number of companies at the *2016 PDA Workshop: Present Challenges in Aseptic Processing, Potential Changes in EMA/PIC/S Annex 1 Revision,* April 19–20, in San Diego, Ca.

The workshop was designed to solicit input from industry for use by PDA's Aseptic Processing Task Force, which has revised PDA's 2003 Points to Consider in Aseptic Processing and is now gathering information on the state of the art in aseptic processing via surveys and workshops. The group will comment on the EU revision to Annex 1 when it is released for comment.

The San Diego workshop represented the task force's initial effort to collect information. Workshop attendees represented a wide variety of companies. Participants answered survey questions distributed at the outset of the workshop and participated in two lively sessions where they broke into small round-table groups to discuss topics covered in the Points to Consider document.

Task force members then summarized the discussions in the workshop's final session. They found that not every practice aligned with PDA's Points to Consider. That was expected, according to **Hal Baseman,** PDA Immediate Past Chair and member of the task force, pointing out that the task force felt that if participants in the exercise had said they were already doing everything listed in the PtC, then "the PtC wouldn't have much value because you are already doing it."

The task force agreed that the survey and questions discussed and addressed in San Diego were valuable and would carry over to the next three scheduled workshops. The discussions are summarized in the following box.

At the end of the workshop, Baseman concluded that it featured "pretty good engagement in all the groups and pretty good discussion."

The workshop will be repeated three more times:
Berlin (May 31–June 1)
Dublin (October 5–6)
Arlington, Va. (October 26–27)

Roundtable 1 Summary Report

Discussion Question 1: What do you do if there are EM excursions in Grade A filling area—and why? Would the excursion trigger automatic batch rejection? If so, then what is the reason for rejection? Or would there be an investigation to determine batch disposition? If so, then what would be the criteria for batch acceptance?

- Good alignment/consensus within the teams
- Does not trigger automatic rejection of batch—but you have to prove that it is acceptable!
- The following would lead to rejection: Organism on a critical surface; presence of some microorganisms [considered] more objectionable than others (use Bad Bug Book from [U.S.]FDA as a reference for bad microorganisms)

"Responses well aligned with PtC proposal"

Discussion Question 2: What is the objective of monitoring EM of 5.0 um or greater particulate? What are the challenges to doing so? What is the result of this type of EM indicate? Are there other ways to meet the same objective?

- Good consensus within the teams
- When peaks [are] noted [they are] always easily correlated to specific events (e.g., glass breakage, product droplets, etc.)
- One case where monitoring of 5 um or greater identified [an] issue after shutdown earlier than by monitoring 0.5 um particulate
- Value of monitoring only when looking at trends (same as for 0.5 um or greater particles)

"Good alignment with PtC proposal"

Discussion Question 3: PUPSIT (Pre–Use, Post Sterilization Integrity Test)—Should you perform a PUPSIT? What are the benefits? What are the risks? What are the elements of a risk assessment to be considered?

- Very good alignment within the teams
- It is not common practice, according to the participants' feedback
- When done, it is done to comply with EU regs rather than scientific rationale
- PROS: prevent rejection of batch, if lack of integrity detected before use (but mitigated by pre-use, pre-sterilization test)
- CONS: high risk for product contamination not easily detected downstream

"Apparent alignment with PtC proposal"

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2016 PDA Workshop: Current Challenges in Aseptic Processing, Potential Changes in EMA/PIC/S Annex 1 Revision: October 26-27

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Immediately after the Conference, on Oct. 26-27, PDA will host the *2016 PDA Workshop: Current Challenges in Aseptic Processing, Potential Changes in EMA/PIC/S Annex 1 Revision*, to discuss science- and risk-based approaches that support modern aseptic processing and control strategies and to explore critical topics that may be addressed in the revised EU GMP Annex 1 guidance.

For additional information and to register for this Workshop, please visit pda.org/2016Annex1east

Interested in obtaining new skills or expanding your knowledge on pharmaceutical microbiology? Consider extending your stay and attending one of the four continuing education courses offered as part of the *11th Annual PDA Global Conference on Pharmaceutical Microbiology Course Series*.

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

Discussion Question 4: What incubation temperatures are scientifically appropriate for environmental monitoring samples? Should one temperature range be used? Two temperatures? If so, which sequence? What is the scientific rationale?

- Various approaches reported by the participants
- 20–25° C followed by 30–35°C because: USP 61 (for non-sterile), FDA guidance, better for finding fungi
- 30–35°C only because: based on recovery study
- 20–25°C only because: based on recovery study (temp similar to manufacturing area), similar recovery to higher temps
- 30–35°C followed by 20–25°C to better recover Staph
- Different approaches for the incubation time
- Apparently, no clear scientific rationale for the selection of the incubation temperatures

Roundtable 2 Summary Report

Discussion Question 1: What are the temperature ranges and conditions for incubation of media fill units and what is the rationale for such conditions? Do you use multiple temperatures and why? How would one determine the right temperature and conditions? Should this be done for EM sampling as well?

- Most doing low to high—seven and seven. Most [are] doing two temperatures. In one group there was an even split on one vs. two temperatures. Based mostly on regulatory expectations, [it's] not a problem doing the two.
- Based on indicator and plant flora. Not sure what to do without plant flora info.
- [Only one temperature because of] inadequate incubator space
- Different than EM because media would dry out

"Might not be in PtC alignment"

Discussion Question 2: Consider the following hypothetical (yet not atypical) procedure regarding the outcome of the APS. Under what circumstances would a contaminated unit be accepted in the media fill?

- PASS: In an initial validation, zero positive units or a maximum of 1 contaminated unit (in a series of at least 3 consecutive runs). In a routine requalification (1 run), the criteria should be zero positive units.
- FAIL: In an initial validation, more than 1 positive units or 1 positive unit. In a routine requalification (1 run), 1 or more positive units.

- Intitial – one positive in one of three media fills. Investigation would drive to 1–3 media fills depending on outcome of investigation.
- Investigation needed—might result in not repeat a media fill—more than 10,000 units. 1–3 media fills.
- Tough to find the smoking gun: Past history for personnel; Small batches a factor; Look at waste bags. Not always sure if that was contaminated; Nonintegral unit; Non-aseptic cause (outside the aseptic process); Non-procedure; Cracked vial after the inspection …Turned cloudy.

"Aligned with spirit/theme of PtC"

Discussion Question 3: Should non-integral media fill units and/or units which are otherwise procedurally deemed "rejected" units (during routine operations), be incubated and evaluated as part of the media fill study? What are the criteria for excluding a unit? What about start-up units? What type of documentation is necessary to assure that the units excluded are identical to the production process?

- Do not incubate any non-integral units.
- Split on incubating integral rejects, half did not. Two groups—none incubated integral rejects.
- If it was positive, not much done with info.
- Procedural rejects, non-integral units.
- Some incubate start up flush and some did not. When not [it was because they were] following procedure. Some flush to trough—not incubation… Some do incubate waste bags.
- Documentation – accountability records, reject forms, batch record.
- Segregating and then incubating – FIO for QC. A positive did not affect media fill results.
- Tracking integrity based on media fill reject type criteria, saving low fills, consider auto-reject equipment.
- Secondary 'referee' inspection for interal vs. Non-integral.
- Final inspection—finds non-integral units—FIO (for informaiton only)
- Discussed contaminated non-integral units, post-inspection/incubation—split on effect on passing or failing media fill—investigation needed.

"Pretty much aligns with PtC"

Discussion Question 4: What is the appropriate duration of an aseptic process simulation run? How should process simulation address multiple shifts and campaign production runs? What are the elements of a risk assessment?

- Full duration because of not wanting to be challenged by regulators, some did start and stop
- 10-day campaign—10-day media fills off and on
- Cover all interventions in three or four days
- 24 hours at the end of the campaign. 5,000 units
- Cover multiple shifts at end of campaign
- Majority leaning towards full duration, operator fatigue, env. contamination/conditions, piggy back, shedding machines
- Isolator might matter
- Water fill and media fills
- Doing the worst or most risky or frequent interventions

"Not really aligned with PtC"

Masahiro Akimoto, Otsuka Pharmaceutical Factory Inc.

PDA Continues to Facilitate Sharing of Knowledge in Sterile Product Manufacturing

Exciting regulatory and technological changes are coming for the sterile product manufacturing industry. Revisions to EU Annex 1 and PIC/S Annex 1, along with EMA's recently issued draft document, *Guideline on the sterilization of the medical product, active substance, excipient and primary container,* not only introduce advancements in manufacturing technologies, they also signal a move for companies to embrace quality risk management (QRM) and knowledge management into their quality systems to ensure patient safety throughout the quality lifecycle. For example, with advancements in automation, operators can potentially have less direct contact with sterile products than with previous technology, which furthers patient safety. Implementing these new systems, however, requires changes to risk management and environmental monitoring protocols.

As the industry expands their knowledge of these systems and associated risks, a platform would be useful to share experiences and lessons learned from current and past experiences. PDA provides members with opportunities to facilitate this sharing of knowledge.

For 2016, PDA has strategically planned a series of workshops on Annex 1. The first workshop was held in April in San Diego. Upcoming workshops will take place in Germany, Ireland and the United States. These workshops will draw from PDA's recently revised *Points to Consider on Aseptic Processing*.

Also, PDA Education regularly offers courses focused on essential manufacturing technologies, GMP controls and QRM at its Training and Research Institute (TRI) in Bethesda, Md. Upcoming courses of interest include "Fundamentals of an Environmental Monitoring Program (August 30–31), and "Establishment of a Risk-Based Environmental Monitoring Program (September 1)."

PDA is the leading global facilitator of science, technology and regulatory information. Since 1946, PDA has created awareness of important issues facing the pharmaceutical and biopharmaceutical community, providing membership with opportunities to share knowledge and lessons learned for innovative improvement. For 70 years, PDA members have worked together to continuously advance the industry. As the field of aseptic processing advances, PDA will continue to offer opportunities for members to network and seek solutions to the challenges of the present and of the future.

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PDA's Bread and Butter on Display

Quality metrics, quality culture, drug shortages, post-approval changes, and data integrity are just a sampling of the issues and problem areas PDA members face as they continue to manufacture safe and effective medicines of the highest quality. But we should never forget that at its core, PDA was founded to advance the science and technology of sterile and aseptic manufacturing. For 70 years, that's been the Association's bread and butter, and remains so today. The first half of 2016 has only reinforced that fact.

And what a first half it has been! PDA's activities in sterile/aseptic processing got off to a bang with the publication of *Global Sterile Manufacturing Regulatory Guidance Comparison,* a first-of-its-kind comparison of U.S., EU, PIC/S and WHO GMPs for sterile products. The publication includes access to a spreadsheet that companies can use to compare the regulations and track "gaps"in their processes. This publication was an immediate hit with members and broke download records within its first month of availability. PDA's Global Sterile Task Force, which includes *PDA Letter* Editorial Committee member **Robert Darius,** deserves all the credit for their careful and thorough work on this comparison.

Things really got moving in April with the first of four PDA workshops on challenges in aseptic processing in beautiful San Diego (see articles on p. 16 and p. 41). By the time you're reading this, the second workshop will have taken place in Berlin.

The task force behind the workshops also published the second part of the PDA *Points to Consider for Aseptic Processing.* The first part published in 2015, and Part 2 expands on topics covered in Part 1 and addresses new topics. Both are available for download at the PDA Bookstore (www.pda.org/bookstore), and members still have an opportunity to download Part 2 for free as part of their member benefits.

With all this activity, it is no wonder PDA was recognized at the renewed Kilmer Conference on sterility assurance and sterilization in May for leadership in contributing to the science of sterility assurance (see "News & Notes", p. 6). The honor was received by PDA President **Richard Johnson,** who represented PDA at the first Kilmer Conference held since 2003.

Later this year, members can expect to see PDA comment on the revision to the EU's Annex 1 and complete a survey on aseptic processing practices.

PDA is the "Parenteral" Drug Association for a reason, and 2016 has shown why!

PDA Letter

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

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.

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