People • Science • Regulation

PDA Letter

Volume L • Issue 8 www.pda.org/pdaletter September 2014

Will a Shorebird Knot Up Bacterial Endotoxin Assay Supplies?

26

Show Issue

Follow the logo to find articles on the *PDA 9th Annual Global Conference on Pharmaceutical Microbiology*

Calling All Active PDA Members. Vote Now.

Online voting is now open for the 2015 PDA Board of Directors Election

PDA members, online voting has opened for the 2015 **PDA Board of Directors Election**. Take a moment and vote for your candidates of choice.

All PDA members in good standing as of **midnight on August 30, 2014 are eligible to vote**. Voting closes at **11:59 p.m. EST on November 15, 2014**. All votes cast after this date and time will not be accepted.

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

Thank you for being a valued PDA member and voting.

Instructions for Voting:

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

Thank you for your participation in this important election process.

The Parenteral Drug Association presents the...

2014 PDA Drug Delivery Combination Products Workshop

Experiences with Drug Delivery Combination Products

October 8, 2014

HYATT REGENCY HUNTINGTON BEACH RESORT AND SPA
HUNTINGTON BEACH, CALIFORNIA

The *2014 PDA Drug Delivery Combination Products Workshop* will cover the real life experiences of pharmaceutical professionals detailing the challenges they faced during development, approval and manufacturing of their Drug Delivery Combination Products.

Learn which activities succeeded, which resulted in undesirable consequences and lessons learned. Interact with the participants in panel discussions where you will hear what has worked, what will no longer work and what strategies are likely to succeed in the future.

Some of our most notable industry professionals speaking will be coming from companies such as:

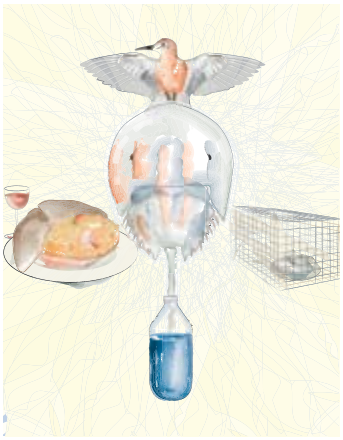
- Amgen, Inc.
- Biogen Idec
- Janssen Research & Development, LLC
- Johnson & Johnson
- And more!

For more information and to register, visit **www.pda.org/drugdelivery2014**

PDA Letter

Volume L • Issue 8 www.pda.org/pdaletter

Cover



Cover Art Illustrated by Katja Yount

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Features

U.S. Gov't Registration for TRI Just Got Easier!

PDA TRI Adds 31 Courses to GSA Schedule

31 PDA Training and Research Institute (TRI) courses are now listed with the U.S. General Services Administration (GSA) under a Federal Supply Schedule contract.

The 31 courses will be included on the GSA Advantage, GSA's online shopping and ordering system (www.gsaadvantage.gov/advantage/main/start_page.do). This will improve the visibility of these PDA TRI courses to federal officials and make it easier for them to participate. Over the years, PDA TRI has conducted numerous training courses specifically designed for officials at the U.S. FDA. In addition, FDA officials have participated in TRI's regular course offerings.

"By adding 31 courses to the GSA Federal Supply Schedule, employees of the U.S. Federal Government will have an easier time participating in the unique, world class training offered by PDA TRI facilities and lecture courses," says PDA President **Richard Johnson.**

The courses are listed under Special Item Numbers (SINs) 874-4: Training Services. They are:

1. An Introduction to the Advanced Molecular Methods for Virus Detection
2. An Introduction to Visual Inspection
3. Aseptic Processing for Senior Management
4. Aseptic Processing Training Program
5. Biosimilars – Understanding the Challenges of Meeting 'Similarity'
6. CMC Regulatory Requirements in Drug Applications
7. Evaluation, Validation and Implementation of Alternative and Rapid Microbiological Testing Methods
8. Filters and Filtration in the Biopharmaceutical Industry – Basics Course
9. Filters and Filtration in the Biopharmaceutical Industry – Basics Course and Advanced Course
10. Filters and Filtration in the Biopharmaceutical Industry – Advanced Course
11. Fundamentals of an Environmental Monitoring Program
12. Fundamentals of Aseptic Processing
13. Fundamentals of Cleaning and Disinfectant Programs for Aseptic Manufacturing Facilities
14. Fundamentals of Lyophilization
15. Fundamentals of Lyophilization and Validation of Lyophilization
16. GMPs for Manufacturers of Sterile and/or Biotechnology Products
17. Implementation of Quality Risk Management for Commercial Pharmaceutical and Biotechnology Manufacturing Operations
18. Implementing Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations: Case Studies in the Manufacturing of Biotechnological Bulk Drug Substances

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Make Your Voice Heard: Vote in the 2014 Board Elections

PDA members have the opportunity to be involved in setting the strategic direction of the Association by electing volunteer leadership for 2015. This year, there is the opportunity to select eight Directors who will take seats on the PDA Board of Directors in an election that ends November 15. Members in good standing can vote online from the PDA website and at conferences that will be held between those dates in the United States and Europe.

Vote Online

You will need your member ID and password.

Voting is open to PDA members in good standing by Aug. 30, 2014.

www.pda.org/vote

U.S. Gov't Registration for TRI Just Got Easier! continued from page 6

19. Implementing Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations: Case Studies in the Packaging and Labeling of Drug Products
20. Implementing Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations: Case Studies in the Manufacturing of Pharmaceutical Drug Products
21. Investigating Microbial Data Deviations
22. Microbiological Quality of Raw Materials and Components
23. Microbiological Risk Assessment of a Pharmaceutical Manufacturing Process
24. Preparation of Virus Spikes Used for Virus Clearance Studies and Virus Filtration
25. Quality Systems for Aseptic Processing
26. Risk-Based Qualification of Sterile Drug Product Manufacturing Systems
27. Single-Use Systems for the Manufacturing of Parenteral Products
28. Validation of Biotechnology-related Cleaning Processes
29. Validation of Dry Heat Processes Used for Depryogenation And Sterilization
30. Validation of Lyophilization
31. Virus Contamination in Biomanufacuring: Risk Mitigation, Preparedness and Response

PDA Volunteer Spotlight

Kim Waters

- Serialisation Business Process Manager
- *GlaxoSmithKline Australia*
- Member Since | 2008
- Current City | Melbourne, Australia

The person who takes our product, is the person who needs it the most

In April, Kim ran a 10K over the Golden Gate Bridge

Who do you admire most within your field?

I am biased but privileged to say I admire **Sir Andrew Witty**, CEO of GSK. He's driving changes and always reminding us of why we come to work—for the person at the end of our supply chain.

What piece of advice has been most helpful throughout your career?

I keep remembering back to what my chemistry lecturer said: "Don't just believe what you are told, find out for yourself." I am not an expert in all areas, so the key is to know from whom and where to seek advice. PDA is a great source.

Where do you see yourself in five years? How about the industry?

The authorities are keeping us on our toes and are asking us to do more. But we should do more, as we need to strive to make the best possible product for our patients. This leads me to serialization. Our industry is being asked to step up and ensure the product we make is getting to our patients. Serialization is one way for us to achieve this.

How can PDA benefit someone who is new to the pharmaceutical industry?

PDA provides online resources and, best of all, gives you a chance to connect to people in your area through local events via chapters.

How can volunteers gain leadership roles at PDA?

PDA offers many opportunities, but the first step is to say, "I want to make a difference." By sharing your knowledge and experience, you are helping our industry.

What are some of your hidden talents?

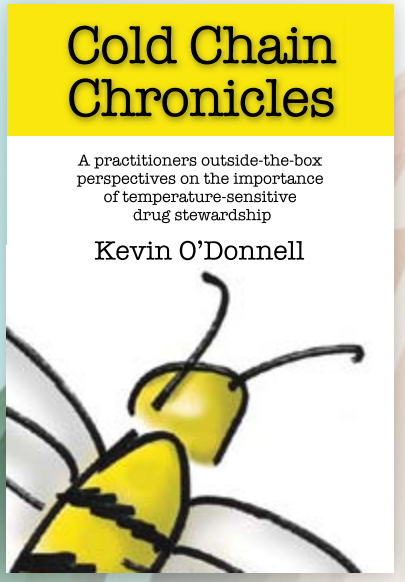
My hidden talents are so well hidden that I haven't found them yet!

What magazines, books or newsletters do you read on a regular basis?

PDA Letter—the only mag worth reading!

AS A MEMBER, YOU'LL SAVE!

New Release at the PDA Bookstore



Item No. 17323

Cold Chain Chronicles:

A practitioners outside-the-box perspectives on the importance of temperature-sensitive drug stewardship

By Kevin O'Donnell

Pre-order your copy by September 15, 2014 and save 15%. Enter Campaign code CCCN during check out.

This book is quite different from the typical prescriptive PDA/DHI "how-to" publication. Noted pharmaceutical cold-chain expert, Kevin O'Donnell, relates a series of engaging stories carefully crafted to elevate awareness, understanding, and criticality of temperature-sensitive drug products throughout the supply chain — not only for the stakeholders involved — but for the consumer in us all. O'Donnell deftly blends his cold-chain storytelling with charm and wit, history and science, and the wisdom of a practitioner's 35 years' experience. These thought-provoking narratives convey to the reader heuristic lessons that underscore the risks involved and the impending need to improve the processes that ensure these fragile pharmaceutical products arrive to their destinations — and to the patients who need them — in a safe, controlled way.

As an added bonus for both new and experienced colleagues, the World Health Organization has granted permission allowing readers to access, either by URL or QR codes available in the book, training videos they have prepared on the subject.

go.pda.org/CCCN

KEVIN O'DONNELL is widely considered one of the principal architects of the modern-day biopharmaceutical cold-chain movement and a champion for the advancement of good distribution and logistics practices for temperature-sensitive drugs. He is Senior Partner at Exelsius Cold Chain Management Consultancy, an international provider of consultative, research and training services to manufacturers, airlines, forwarders and other stakeholders in the life science logistics sector.

Kevin's pioneering efforts are reflected in his various roles within the industry and for his co-authorship of numerous standards and guidance documents including that as a member of the United States Pharmacopeia (USP) Expert Committee on Packaging, Storage and Distribution; temporary advisor and certified mentor to the World Health Organization (WHO); as founding member of the PDA Pharmaceutical Cold-Chain Interest Group and co-author of PDA Technical Report No. 39.

PDA's Japan Chapter Ramps Up Activity in 2014

PDA Japan Chapter Officers

PDA's Japan Chapter has hosted four well-attended, topical events in the spring and summer of 2014, and plans three additional events in the fall and winter.

In May, the Chapter's QAQC Committee hosted a hands-on, experience-based workshop on implementing quality risk management processes for the QC lab. One exercise in this workshop involved applying failure mode and effects analysis techniques to the Karl Fischer titration. An additional workshop was held on the same topic, and participants addressed unanswered questions from the initial workshop.

Also in May, the chapter's Medical Device Committee hosted a two-day *Prefilled Syringe Seminar,* with over 200 people in attendance. This seminar featured leading experts who discussed new manufacturing technology, future challenges concerning prefilled syringes and similar products, quality management solutions for filling and packaging, and ensuring the quality of a broad range of sterile drug and medical device products in the 21st century.

During the summer months of July and August, the Chapter successfully hosted its workshop, *Validation Master Plan to prepare for PIC/S GMP* (which sold out immediately after the invitation) and the Sterile Product GMP Committee's symposium on GMPs.

Moving forward, the Japan Chapter will host its 6th Annual GMP Symposium in the city of Toyama in October. This event will focus primarily on quality risk management (QRM) which is now required in the revised GMP Implementation Guide from the Japanese Ministry of Health, Labour and Welfare. Attendees will learn operational procedures for performing QRM and how to prepare for other requirements from the revised guide. Additionally, Japan's Pharmaceuticals and Medical Devices Agency (PMDA) and Toyama Prefecture Government of Japan, a local affiliate, will introduce their strategy for implementing the provisions.

The Chapter is also excited to hold its 21st Annual Meeting: "Approach to Quality Culture," Dec. 2–3.

And finally, in 2015 the Japan Chapter's API GMP Committee will celebrate its 100th committee meeting by looking at the revision of the API GMP Q&A document set for publication next year.

For more information about Japan Chapter events, please visit www.j-pda.jp.

PDA Who's Who: Japan Chapter Officers

Terada Katsuhide, Chairman

Yoshiaki Hara, General Affairs and Liaison

Akimoto Masahiro, Management Planning

Masashi Imamura, Management Planning,

Saito Izumi, Management Planning

Yukio Hiyama, Auditor

2014年　日本PDA製薬学会はイベント・行事が目白押し

日本PDA製薬学会

日本PDA製薬学会では、以下のように年会を始めとして教育コースや講演会など、多くの行事を行っています。

QAQC委員会では、試験室管理を対象とした品質リスクマネジメントとして体験型のワークショップを5月に実施しました。演習では、カールフィッシャー法による水分測定試験を検討事例としてFMEA法を用いたリスク分析を行いました。なお、本ワークショップは、初回実施の際に参加希望者多数のため、同じ内容で追加開催したものです。

5月ににはメディカルデバイス委員会主催のPrefilled Syringe　Seminarも開催しました。2日間で200名以上の参加者があり、Prefilled Syringeに関する最新の技術と今後の課題と動向、求められる医薬品の品質、充填包装など、市場、製品品質、製造技術などに関して議論されました。

7月から8月にかけては、PIC/S　GMPに向けたバリデーションマスタープランの教育コース（募集直後に満席）と、無菌製品GMP委員会研究報告会も開催されました。

10月には第6回富山県GMP講演会が富山市で開催されます。昨年改訂されたGMP施行通知で必要となった品質リスクマネジメントをメインテーマとする講演会で、参加者は品質リスクマネジメントのやり方、手順書の作成などについて学べます。

開発QA委員会のシンポジウムも10月に開催されます。ここでは治験薬製造を含むCMC開発を対象における品質保証、品質の作り込みについて、及びCMC開発における品質の管理戦略と品質リスクマネジメントについても報告します。

12月2日と3日には日本PDA製薬学会の第21回年会を開催いたします。今年の年会テーマは「クオリティカルチャーとは」です。

2015年には原薬GMP委員会が、100回目の記念定例会を迎えます。現在、原薬GMPのQ&A集改訂を行っており発刊を記念したセミナーが開催されます。セミナーではQ&A集の改訂点を紹介する予定です。

日本PDA製薬学会のホームページhttp://www.j-pda.jp/では、より詳細な情報がご覧になれます。

In Memory of Julius Z. Knapp

John Shabushnig, PhD, Insight Pharma Consulting

The PDA community has lost a good friend and long-time contributor. **Julius Z. Knapp** passed away on July 17, 2014 at the age of 95. He joined PDA in 1972 while working as a biomedical engineer at Schering-Plough Corporation. His pioneering publications on visual inspection in the early 1980s still serve as a guide to many in developing and evaluating this critical process step. During this time, he documented the probabilistic nature of visual inspection and outlined tools to reliably evaluate inspection performance. Retiring from Schering-Plough after 20 years of service, he went on to found Research and Development Associates. Here, for over 30 years, he continued to explore and expand the understanding of visual inspection of injectable products.

Julius was an active member of PDA, attending meetings and publishing his work into his early 90s. During his career, he published over 20 research papers, commentary and reviews in the *PDA Journal of Pharmaceutical Science and Technology* and was a regular speaker at the *PDA Annual Meeting* and *PDA Visual Inspection Forum.* He was awarded PDA's Distinguished Service Award in 2000 and the Gordon Personeus Award for his long-term volunteer service in 2003. In 2006, he was recognized as one of six "Outstanding PDA Scientists" in the celebration of PDA's 60th Anniversary. He received PDA's highest honor, Honorary Membership, in 2008.

He was born in New York City and lived in Somerset, N.J. for most of his life. He served in the U.S. Army Air Corps from 1940 to 1956. Julius was a prolific inventor holding many patents related to visual inspection technology and methods. Many may not know that he also held a patent for colored contact lenses.

He is survived by his wife of 66 years,

Irene; and his son, Dave; and daughter, Lucille; a brother, Phillip; and four grandchildren: Aliana, Travis, Kyra and Sarina. His work touched many in our industry and he will be missed by all.

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Hassana Howe, PDA

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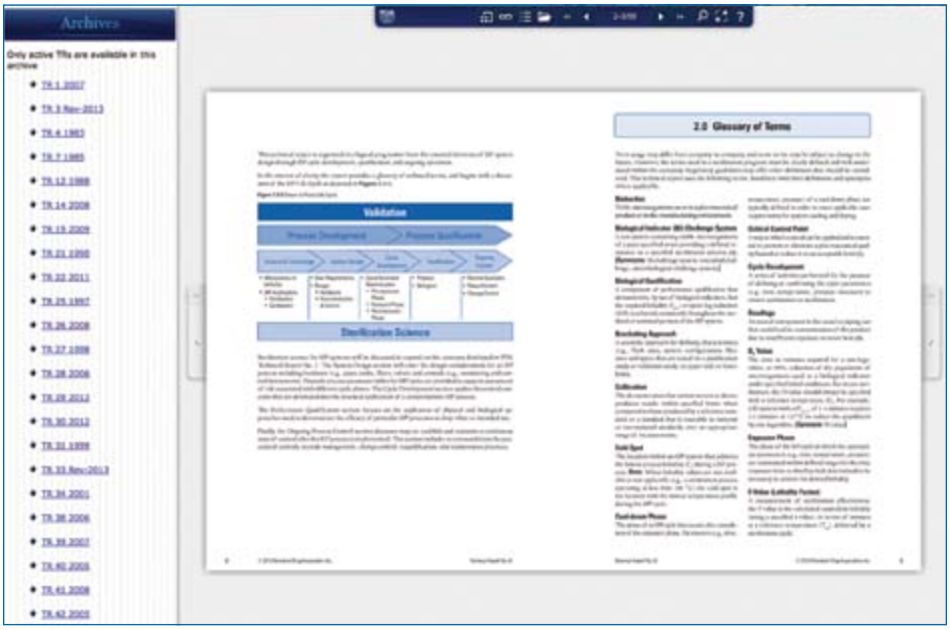

The Parenteral Drug Association presents the...

2014 PDA/FDA Pharmaceutical Quality System (ICH Q10) Workshop on Quality Risk Management

Using Q10 to Make Compliance Synonymous with Quality Performance

November 3-5, 2014

BALTIMORE MARRIOTT WATERFRONT | BALTIMORE, MARYLAND

It's been more than a decade since the ICH Q10 document was completed and in the time since finalization it has helped structure how we all work with quality systems across our industry and within our companies. Expectations have gradually been increasing and QRM and KM are now parts of how we need to operate to sustainable ensure high quality products are produced and the systems and processes are continually improved.

While many companies have implanted efficient QRM processes into their PQS, there are still some opportunities to pursue based on current inspectional finding and drug shortages data.

The FDA and PDA have jointly developed a very comprehensive program for the *2014 PDA/FDA Pharmaceutical Quality System (ICH Q10) Workshop on Quality Risk Management* that will address these issues and looks at how companies have successfully implemented QRM and KM to improve product realization reliability and continually improve their quality performance.

This unique workshop will allow you to learn internationally harmonized quality risk management principles and benefit from actual case studies of practical implementation.

At the workshop, there will be sessions on:

- Quality Risk Management Expectations and Incorporation into National Requirements – Global Regulatory Perspective
- The Four Quality System Elements: Moving from Reactive to Proactive – Case Studies
- Use of QRM in Facility and Process Design
- The Road to Better Risk Identification and Root Cause Analysis The Use of QRM
- QRM in the Drug Lifecycle
- And much more

Visit **www.pda.org/ichq10** for more information.

EXHIBITION: NOVEMBER 3-4 | COURSES: NOVEMBER 6

Networking Dinner

(l-r) Azamolsadat Emami, CinnaGen; Saeed Tafreshi, Intelitec; Behzad Taghipour, CinnaGen

Closing Plenary: Manufacturing in Turkey

(l-r) Fatma Taman, Pharmavision; Dirk Schuster, Groninger; Cem Erdem, Sartorius; Zohre Bazaz, Iran Health Agency

Trainer Christa Jansen-Otten, West Pharmaceutical Services, offers hands-on learning at the "Fill & Finish Operations for Parenterals" training course after the conference.

PDA Europe Sr. Vice President Georg Roessling (right) opens the conference with co-chairs Wenzel Novak, PhD, Groninger (left), and Stephan Roenninger, PhD, Amgen.

Planning committee members and other conference participants pose for a group photo.

The Parenteral Drug Association presents the...

2014 PDA Universe of Pre-filled Syringes and Injection Devices

Improving Patient Outcomes through Innovation

October 6-7, 2014

HYATT REGENCY HUNTINGTON BEACH RESORT AND SPA
HUNTINGTON BEACH, CALIFORNIA

This is the premier conference where industry leaders can meet with colleagues from drug and biologic manufacturing, suppliers, regulatory professionals and academicians from around the globe, who will discuss today's challenges with drug delivery and packaging technologies, formulation development and improving patient outcomes.

Plenary sessions include expert talks from Ernst & Young, connectMeSmart, Amgen, Mylan, the U.S. FDA and the European regulators.

FDA's **Lana Shiu,** MD, Director, Regulatory, Center for Device and Radiological Health, will speak in the third plenary session of the meeting to discuss challenges and pitfalls for marketing applications when prefilled syringes, auto-injectors and combination products are referenced.

Following the conference, the PDA Training and Research Institute will be hosting four courses to complement your learning on October 9-10, 2014.

- Prefilled Syringe User Requirements – *New Course*
- Syringes and Elastomers: Understanding the Effects on Quality and Demonstrating the Production Process, Influences and Needs
- Technical and Regulatory Challenges of Drug Delivery Combination Products – Prefilled Syringes, Autoinjectors and Injection Pens – *New Course*
- Risk Management for Temperature Controlled Distribution

For more information and to register, visit **www.pda.org/prefilled2014**

EXHIBITION: OCTOBER 6-7 | COURSES: OCTOBER 9-10

Using the Lessons of the Past to Build Tomorrow

Richard Levy, PhD, PDA

In the field of pharmaceutical microbiology, I am always reminded of the importance of historical knowledge—that is, learning from the lessons of the past—and staying current in one's field. Both the past and the present should serve as a guide for tomorrow. I always recommend achieving that by routinely reviewing the literature and networking.

Recently, in the *Journal of Industrial Microbiology & Biotechnology* ***(1),*** a familiar topic reappeared and was expanded upon concerning microbial growth in, and recovery from, stressed environments. **Youngbeom Ahn,** et al., wrote the paper, "Evaluation of liquid and solid culture media for the recovery and enrichment of *Burkholderia cenocepacia* from distilled water," and a longtime PDA member and colleague, **David Hussong,** PhD, is one of the coauthors.

As mentioned in the article, *Burkholderia cepacia* complex (BCC) has caused recalls of both sterile and nonsterile pharmaceutical products. The connection to manufacturing is that BCC is one of the most common sources of contamination in aqueous systems. In their research study, the authors confirmed the adaptability/survival of all BCC strains cultured in distilled water for 40 days. This is something that has been shown in the past as well, even with antiseptic solutions—I think back to Anderson, Vess, Panlilio, and Favero's paper, "Prolonged survival of *Pseudomonas cepacia* in commercially manufactured povidone-iodine" ***(2)*** published in 1990—but it's good to see an updated dataset reinforcing previous experiences with these microbes.

Further, on the microbial recovery side, Ahn et. al. demonstrated that diluted TSA and TSB media, as well as R2A and R2AB, demonstrated better recovery efficiency than TSA and TSB for water samples containing small numbers of cells. And, broth me-

Continued at top of page 20

Journal *Preview*

September–October Issue Offers Pharmaceutical Microbiology Content

2014 marks the 50th anniversary of the LAL test. In light of this, two articles in this issue should be of interest to microbiologists. **Jay Bolden,** et al. explore evidence against a bacterial endotoxin masking effect in biologics, and **Anthony Cundell** looks at bacterial endotoxin requirements for dry powder inhalants.

Guest Editorial

Darren Whitman, "Process, People, Perfection: Learning from the Pioneers in Human Performance"

Research

Oliver Gordon, et al., "Comparison of Different Incubation Conditions for Microbiological Environmental Monitoring"

Dennis Jenke, Tage Carlson, "A Compilation of Safety Impact Information for Extractables Associated with Materials Used in Pharmaceutical Packaging, Delivery, Administration, and Manufacturing Systems"

Ina Pahl, et al., "Analysis and Evaluation of Single-Use Bag Extractables for Validation in Biopharmaceutical Applications"

Technology/Application

Jared S. Bee, et al., "Characterization of the Initial Level and Migration of Silicone Oil Lubricant in Empty Prefilled Syringes for Biologics Using Infrared Spectroscopy"

Steven A. Zdravkovic, et al., "A Method Utilizing Ultra-High-Performance Liquid Chromatography with Ultraviolet and Mass Spectrometric Detection for the Analysis of Material Extracts Produced during a Controlled Extraction Study"

Robert A. Schaut, et al., "A New Glass Option for Parenteral Packaging"

Review

Anthony M. Cundell, "Bacterial Endotoxin Requirements for Dry Powder Inhalants and Their Excipients: Are They Critical Quality Attributes?"

Jay S. Bolden, et al., "Evidence Against a Bacterial Endotoxin Masking Effect in Biologic Drug Products by Limulus Amebocyte Lysate Detection"

Kanami Irie, Allison Scott, Norio Hasegawa, "Investigation of the Detection Ability of an Intrinsic Fluorescence-Based Bioaerosol Detection System for Heat-Stressed Bacteria"

Emerging Perspectives on Use of Plant Isolates

David C. Myatt, PhD, bioMérieux

A 2011 *PDA Letter* article ***(1)*** discussed the value of plant isolates in pharma quality, largely concentrating on relevant documents and regulatory activities that encouraged use of plant isolates despite a lack of pharmacopoeial requirements. In addition, the article also looked at the technical merits and practical considerations associated with deploying wild-type strains in addition to reference strains prescribed by various pharmacopoeial chapters. Since then, some level of debate continues to persist. Some favor plant isolate use if species involved are more relevant to their particular contexts and/or these isolates potentially retain some wild attributes (through minimal subculture) that serve to better challenge laboratory media and rapid tests than the pharmacopoeial reference strains. They argue that reference strains have been serially subcultured for decades on rich media in culture collections, and therefore, bear no similarity to organisms that might contaminate products, raw materials or manufacturing environments. Others argue that once an organism has been isolated, its wild attributes are already compromised, and its value as a challenge strain (particularly for growth promotion testing) is impaired by preselection for ability to grow on the media to be challenged.

Nevertheless, authoritative guidance, namely *PDA Technical Report No. 13 (Revised 2014): Fundamentals of an Environmental Monitoring Program* and *Technical Report No. 33 (Revised 2013): Evaluation, Validation and Implementation of Alternative and Rapid Microbiological Methods*, plainly recommend the incorporation of plant isolates in growth promotion testing and validation studies. While these guidance documents do not carry regulatory weight, industry experts' extensive involvement in their development is a compelling indication of the prevailing preference for use of plant isolates.

Plant isolate usage is now commonplace. Currently, many pharma companies maintain extensive batteries of wild-type strains to complement their use of pharmacopoeial reference strains. Several companies offer commercial services to minimally subcultured, standardized preparations of their clients' plant isolates in convenient formats similar to their offerings of pharmacopoeial reference strains. The experiences of these constituencies can build a wider understanding of conventional and best practice in the use of plant isolate strains.

Plant Isolates Complement Pharmacopoeial Reference Strains

One commercial service provider has over three years' experience supplying plant isolates in 13 countries spanning Europe, North America and the Asia/Pacific region. These strains were supplied to the service provider between mid-2010 and end of 2013. Characteristics of the range of strains processed gave some insights into plant isolate selection and usage.

First, 34 different species have been processed. This array comprised 20 Gram positive species. There were only four Gram negative species that might be described as common water organisms and formerly categorized as pseudomonads, and there are ten yeasts and fungal species. The highest frequency species seen were *Micrococcus luteus* (13/34), *Staphylococcus epidermidis* (8/34), *Ralstonia pickettii* (7/34), *Staphylococcus warneri* (5/34), *Stenotrophomonas maltophilia* (4/34) and *Bacillus cereus* (4/34). None of the species received was prescribed in pharmacopoeial methods. This information does not suggest that species prescribed in pharmacopoeial reference are rarely isolated. But it could be inferred that many more relevant species are seen among environmental isolates, and that companies prefer to use these to challenge media and methods. Typical skin flora and water organisms are most prevalent among the isolates, and it could be contended that these are seen as more relevant challenge organisms—at least for growth promotion testing of media used for environmental monitoring, and potentially for rapid microbiological methods.

A further empirical observation concerns the frequently disparate behavior of strains of the same species during their processing to deliver standardized preparations. Colonial morphology, growth rate and survival through lyophilization can vary markedly. This might reflect the survival of unspecified "wild attributes" (mal-

Continued on page 22

Considerations When Moving to Rapid Methods

Claire Fritz Briglia, EMD Millipore

Traditional microbiology testing creates a bottleneck in the release of sterile products which can cause various problems. For example, a vaccine manufacturer needs to release product as quickly as possible during a pandemic. A manufacturer of short-shelf-life radiopharmaceuticals must ship product immediately to avoid scrap costs.

The solution for both types of manufacturers and other companies wanting to avoid the lengthy delay needed for the traditional method is adoption of rapid methods, which have been available since the 1980s.

The U.S. FDA's support of rapid microbiology methods is starting to be recognized, and many companies are investigating various technologies for different applications. The recently revised 21 CFR 610.12 allows manufacturers of biologics to use alternative methods for sterility testing, as long as the new method is fully validated and verified. Some companies are also looking at rapid methods to increase confidence in their overall quality since they can respond faster when a contamination is detected.

Developing a User Requirement Specification

There are quite a few issues to take into account when selecting a technology and application for a rapid method.

Several companies will initially utilize their R&D groups to evaluate new methods for a specific application. Raw materials, water and environmental monitoring represent categories of testing that may be an appropriate first application versus release tests like sterility or mycoplasma. Some may even choose a more specific application such as using rapid only for investigations or perhaps validations.

The application should be well defined at the very beginning of the project and included in a user requirement specification (URS). This document typically includes an objective and a purpose with as much background as possible. The URS should also include a list of "must haves" and "nice to haves." The goal of the URS is to provide as much information as possible so that the expectations are clear to the project team members and potential suppliers. For example, expectations such as "system must be appropriate for filterable volumes over 200 ml" and "system must be able to handle 100 samples per day." One should always ask the question "why?" after each specified requirement along with the cost impact, if necessary.

One of the most obvious requirements that will need to be listed in the URS is the time to result for specific applications; are results needed in hours or days? Many companies have other tests that may hold up release. For example, some companies wait until environmental monitoring plates are read before product release. The entire process for a specific application should be examined closely before deciding on a desired time to result.

A complete financial analysis should also be performed as the URS is being developed. Implementation of a new technology will take a significant amount of resources, and the necessary time, manpower, etc., should be estimated.

Lastly, a project team should be well defined. What areas (i.e., QC, QA, R&D) need to be represented? Unfortunately, when no project team is created and a system is purchased, the rate of success is very low.

Technical Issues to Consider

The risks of false negatives and false positives with various rapid systems needs to be considered. One should first examine the sample preparation and the risks of the analyst contaminating the test. Secondly, if the method is not growth-based, what is the risk of viable but nonculturable cells resulting in a false positive? The supplier or suppliers of the reagents, media and other consumables for the system should also show that their quality systems are superior so that contamination risks are low. Sensitivity of the rapid method may actually be better than the current method. If the product or material has inhibitory properties, however, does the sample preparation allow for neutralization? Does the technology have published papers demonstrating efficacy on environmental isolates that are appropriate to your application? It is a regulatory expectation that one challenge rapid technologies with worst case organisms to show sensitivity. What is the required limit of detection for your application? The user must typically show that the rapid technology has a detection limit equivalent or better than the current method.

Depending on the application, it may be critical to identify the microorganisms in the event of an out-of-specification or a sterility test failure. If the technology is destructive to some of the organisms, how will it be addressed? The supplier should be able to show data on recovery of appropriate organisms.

Another important issue is the complexity of the system. How much training is required and what level of expertise is needed? Rapid technologies that have several steps can be very difficult to validate. If the system is highly automated, service and maintenance need to be readily available in the event of a breakdown. Does the supplier offer on-site service and what is the expected time to have a service technician on-site? Any system with a lot of moving parts will need routine maintenance as well as the availability of spare parts.

Choosing a Supplier

The history of the supplier in the pharmaceutical industry may also be relevant. If special reagents and supplies are required for the rapid system, what is the supplier's ability to consistently supply quality products? An audit of the supplier's manufacturing facility may be worth the time if the application is critical.

The supplier should offer some type of evaluation so that you can check the feasibility of the technology with your

specific application and/or product. It is best to work closely with the supplier in generating an appropriate test plan so that all critical issues are addressed. Reviewing the supplier's own internal validation data before developing the test plan may also be useful.

One of the most critical parts is the regulatory piece. If the rapid system is for a sterility application, how many other companies have received approval to use it? Regulatory agencies will evaluate technologies and often publish their findings.

In the United States, the current guidance for alternative methods is limited, and the compendial chapter for rapid sterility testing is years away from being published. Thus, it is best to have a very detailed strategy and project plan to gain approval.

With all this to consider, obtaining FDA approval should not be daunting if the project is implemented correctly. "New methods are approved and usually on the first review cycle, if validated appropriately and clearly described in the application," said **Jessica Cole,** PhD, Microbiology Reviewer, FDA, at the recent *PDA Aseptic Processing-Sterilization Conference* ***(1).***

While there may not be a rapid technology that meets every need yet, many companies have been successful in implementing and gaining approval. Companies often oppose changing methods because of all that is involved and required. Traditional microbiology methods, however, remain "crude and imprecise" ***(2).***

Regulatory agencies are encouraging companies to improve their methods and their quality. Clinical microbiology has been using rapid testing since the 1980s while the food industry started to embrace it in the '90s. It is definitely time for rapid in the pharma industry.

[Editor's Note: For more information about rapid methods, consider attending session A4: Innovative Technologies: Microbiology Testing Technologies, Oct. 21, 1:15 p.m. at the *PDA 9th Annual Global Conference on Pharmaceutical Microbiology*.**]**

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About the Author

Claire Fritz Briglia is a Technology Specialist for EMD Millipore. She has trained many users in various pharmaceutical microbiology applications for over 15 years.

Using the Lessons of the Past to Build Tomorrow continued from page 16

dia forms were more effective than solid media for recovery of *B. cenocepacia* from distilled water. The authors conclude that their "results may assist in improving detection assays with recovery and enrichment strategies to maximize recovery of these fastidious organisms." Both these papers are worth taking a look at, one for its historical perspective, and the other for some recent data expanding our understanding of microbial growth and recovery in oligotrophic environments typical of pharmaceutical water systems.

So, this all brings me to the networking part which I mentioned in the beginning. I used to split my time between the American Society for Microbiology and PDA. Over time I gravitated toward PDA, so I could focus on pharmaceutical microbiology. We have our *9th Annual Global Conference on Pharmaceutical Microbiology* this October, and there will be several sessions related to the above subjects, in particular biofilms and bioburden control. One session will provide a series of case studies that will take the attendees through the situations and investigations to the root cause and lessons learned, providing insight to processes and practices used for bioburden issue resolution.

For more information about the conference, please visit www.pda.org/microbiology2014. To learn more about PDA TRI courses following the conference, please visit www.pda.org/microcourses2014.

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Endotoxin: 50+ Years of Advancements and Mysteries

Marla Stevens-Riley, PhD, CDER, U.S. FDA

It has been 50 years since the development of the *Limulus* Amebocyte Lysate (LAL) reagent, and the impact of this development has led to the three principal test methods that are used for bacterial endotoxin testing today: gel-clot, turbidmetric and chromogenic. These methods are used for the detection of endotoxins in all facets of pharmaceutical manufacturing, such as water testing, component testing, and most importantly, for release of finished drug product and devices. The impact of this development and its legacy to increasing the quality of drug products and medical devices cannot be emphasized enough.

All Gram-negative bacteria possess a component in the outer wall of their cell membrane called Lipopolysaccharide (LPS), also called endotoxin. Endotoxin elicits a pyrogenic response if it enters the bloodstream. Therefore, the accuracy and reproducibility of the detection of endotoxins in drug products is crucial

More than 50 years of research and development of testing methods for the presence of endotoxins continue to yield both advances and mysteries, thus LAL-based tests are not without controversy. Recently, a phenomenon called Low Endotoxin Recovery (LER) has been described at a number of industry meetings and in research publications. This phenomenon is being observed predominantly with biologic products where there is an inability to recover artificially spiked endotoxins when placed directly into product samples. Secondly, existing LAL-based tests are not compatible with all drug products, forcing pharmaceutical to search for alternative methods.

The need to solve these issues is advancing the field of bacterial endotoxins testing, and opportunities for industry to learn and contribute to the debate are available. This year's *PDA Global Conference on Pharmaceutical Microbiology* will celebrate the 50th anniversary of the development of the LAL test by hosting a keynote address given by **Jack Levin,** MD, one of the researchers responsible for initially characterizing the LAL reaction with endotoxin and the subsequent development of the LAL reagent. Following this address is a session devoted to endotoxin testing issues that will provide both industry and regulatory perspectives. For more information, please visit www.pda.org/microbiology2014.

[Editor's Note: See cover story on page 26 featuring quotes from Levin.**]**

Emerging Perspectives on Use of Plant Isolates continued from page 16

leable physiological or ultrastructural characteristics) in these recently isolated strains that enhance their value as challenge agents.

Case Studies on Plant Isolate Usage

Senior microbiologists at six global pharma and device companies agreed to be surveyed about their plant isolate usage. All requested anonymity. Nevertheless, their contributions and insights are acknowledged and greatly appreciated.

Regarding reasons for introducing use of plant isolates, most responses reflected the perception that it is now a regulatory requirement implied by guidance documents. Although, one response focused on convenience (of commercially prepared preparations) and the associated relief from lab errors in preparation of controls, and another focused on the value of plant isolates firstly for validation studies, and secondly for routine growth promotion testing of media.

Concerning the number of plant isolate strains routinely used, two or more was most common. It was apparent from a couple of comments that different strains were used for different applications. Selection of plant isolate strains was generally related to highest frequency of isolation from environmental monitoring, and annual reviews of the strains and frequency of isolation were most common (5/6 cases reviewed annually, with one claiming a 2–3 year review interval). Several comments also alluded to choice of strains from incidents of product contamination, and two implied efforts to include representative strains of different types of organisms.

When asked about regulatory clarity, two respondents clearly thought there is none; otherwise, most believe it is now well understood that plant isolate usage is recommended despite lack of explicit criteria. Regarding commentary from regulatory auditors, several companies reported no auditor comments at all, while two reported "complimentary" or "good feedback." In the latter, the usage included both method and disinfectant validation.

Lastly, in relation to perceived value of incorporating plant isolates in testing, responses referenced benefits including thoroughness of testing, confidence in test results, and relevance of strains to the local facility. Further, in relation to commercially prepared plant isolate strains, one commentator noted the advantages of repeatability of testing and reduced risk of invalid tests with the consequent costs to repeat testing.

Conclusions

Despite a modest level of residual concern about the value of plant isolates, there now seems to be general acceptance, at least among many global companies and those operating in developed markets (perhaps the most regulated markets), that use of plant isolates represents best practice and adds value to microbiology testing. The rationale for this appears to relate to increasing confidence in plant isolate use in testing plus risk aversion practices; this can be associated with the relevance of plant isolates to the local manufacturing context (environment, raw materials, etc.).

There is a strong perception that regulators expect use of plant isolates despite the lack of a definitive requirement and clear guidance. But many companies select two (or more) of their high frequency isolates based on annual review of environmental monitoring data. Some also seek to include strains representative of a diversity of organism types. Different plant isolates strains seem to be selected for different testing applications, and larger numbers of plant isolate strains appear to be used for validation studies than for routine growth promotion testing of media.

There appears to be no relation between common plant isolate species and those prescribed by pharmacopoeial methods, thus questioning the relevance of prescribed strains. That is not to say that pharmacopoeial reference strains are irrelevant, but it certainly seems to be widely held that plant isolate strains are a pertinent complement to pharmacopoeial reference strains for growth promotion testing and validation studies.

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About the Author

David Myatt has over 25 years' experience in diagnostic and industrial microbiology, having held senior roles in quality management, marketing and commercial leadership.

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16-17
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Brussels, Belgium
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16-17
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18
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18
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18-19
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23
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24-25
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29-30
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1
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1-2
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6-7
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6-8
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8
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9
Strategies for Reducing Human Error Non-Conformances
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9-10
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16-17
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20
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6-7
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6-7
PDA Workshop on Endotoxins and Pyrogens in Parenterals Manufacturing
Berlin, Germany
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6-7
Utilization of Statistical Methods for Pharmaceutical Production Manufacturing
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12-13
Recommended Practices for Manual Aseptic Processes-Lab
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17-21
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Will a Shorebird Knot Up Bacterial Endotoxin Assay Supplies?

Walter Morris, PDA

The remarkable red knot shorebird has one of the longest migrations of any bird—over 9,000 miles from the southern tip of South America to the Arctic. That's 18,000 miles round trip. A long annual journey made possible by its many stops on South American and North American Atlantic shores.

The last stop on its northern return to its Arctic breeding grounds along the coasts of Delaware, New Jersey and New York is perhaps the most pivotal, for there these birds fill up on enough fuel to power them north to their summer mating grounds. The food, eggs. Horseshoe crab eggs. And thus, the migratory pattern of this little shorebird is inextricably linked to the lives of fish farmers, fishermen and users of intravenous pharmaceutical products and medical devices worldwide.

Countless numbers of patients rely on intravenous pharmaceutical and medical device products to manage illnesses, cure and prevent disease and to maintain their health. These products must be tested to assure no harmful bacteria are present. The ubiquitous test is the *Limulus* amebocyte lysate (LAL) method. Of course, LAL is extracted from another remarkable creature, and one of the most distinctive ones found in the Atlantic Ocean, *Limulus polyphemus*—the horseshoe crab.

Most patients have no idea when they receive an injection or a medical device that a horseshoe crab (*Limulus*) had to be bled in order for a testing lab to conduct the LAL pyrogen test. The crab's blood cells (amebocytes) contain the active components of the reagent. The process for producing the reagent utilizes lysed blood cells (lysate).

Are the health needs of countless patients at loggerheads with the existence of this little bird?

LAL, A Disruptive Technology

Prior to the 1970s, labs tested for pyrogens in products by injecting rabbits. Switching over to LAL was not only the humane thing to do, it was easier, faster and cheaper.

LAL testing was pioneered at the Marine Biological Laboratory in Woods Hole, Mass. by **Dr. Jack Levin,** a hematologist at The Johns Hopkins University, who had a particular interest in human blood platelets. Professor **Frederik Bang**, MD, also of Hopkins, was at the Marine Biological Laboratory studying horseshoe crabs and called on the the hematology department to send an expert to help explain why the crabs' blood clotted.

"Joining Dr. Bang was one of the smartest professional decisions I ever made in my life," Dr. Levin told the *PDA Letter.*

"In studying the coagulation [of the blood of the horseshoe crab], I quickly discovered that I could not stop the blood from clotting using the usual anticoagulants," he continued. "This caused a great limitation in what I could initially do. One day, in desperation, I considered that endotoxin was triggering clotting. I prepared glassware which was endotoxin free, and discovered I could stop coagulation from occurring, and that was an enormously important clue that in fact bacterial endotoxin was capable of clotting *Limulus* blood."

Thus, a truly superior test was created. By switching over to it, healthcare companies of all stripes gained a new public image, as rabbit and other kinds of animal testing were growing unpopular.

LAL testing involved an animal of little public interest; it did not require the killing of horseshoe crabs nor the breeding of them in controlled environments. Crabs chosen for bleeding were removed from the water, bled and then returned to their habitat. When handled correctly and promptly returned to their habitat, horseshoe crabs never die for LAL purposes. Dr. Levin said that in all his years of bleeding crabs, his work never resulted in a death.

The development and spread of LAL testing is a remarkable and almost unprecedented example of a new technology creating sweeping changes in both the public view and the bottom line of multiple industries in such a short period of time.

Alternative Tests Emerge

The success of this test, however, relies on an easily accessible supply of horseshoe crabs. Not a problem in the 1970s, but by the 1990s, increasing demand for

Article at a Glance

- LAL test dominated industry following its development
- Environmental concerns plus greater demand prove a potential threat
- Alternate assay tests are available but have limitations

these ancient animals from healthcare and commercial fishing, along with environmental damage and warming seas, meant the horseshoe crab was no longer as readily available.

In fact, *Limulus polyphemus* is the only one of four species of horseshoe crab—the only species in North America—not currently threatened. Populations of the three Asian species—*Carcinoscorpius rotundicauda*, *Tachypleus gigas* and *Tachypleus tridentatus*—have declined rapidly. *Limulus polyphemus,* however, is under threat, too. And there are no horseshoe crabs elsewhere. Not on European, Australian or African coasts. The type of amebocyte lysate (AL) used depends on the source blood, so besides LAL, there is CAL and TAL.

Finally, the greatest possible threat to LAL supplies is not overharvesting or ecological disaster. Rather, it is the red knot shorebird.

Dr. Levin was honored with special recognition to the industry by PDA at the 2014 PDA Awards Dinner, and will speak at the *PDA 9th Annual Global Conference on Pharmaceutical Microbiology* in Bethesda, Md., October 21, 2014.

Remarkably, Dr. Levin never profited from his work, as he never patented the discovery. He noted that he worked in a "totally different era of biomedical research in an academic institution. I know it sounds naive now, but none of us gave any consideration to commercial applications, patents or anything else like that… There wasn't even an office at the Johns Hopkins University at that time which dealt with patent development for the work of faculty." Moreover, he added, it woujld have been "considered extremely bad form and academically unattractive for people like ourselves who were doing basic research to be involved in any way with commercial development."

To learn more, visit www.pda.org/microbiology2014.

Understanding the threat to these creatures, particularly those in Asia, National University of Singapore Professor **Jeak Ling Ding,** with an eye to the dangerously dwindling populations of the Asian species, decided to explore the possibility of developing a completely environmentally friendly alternative to pyrogen testing.

Dr. Ding also believed that a more consistent test could be created rather than the one that relies on LAL. She noted in a conversation with the *PDA Letter* that there are "batch-to-batch variations in sensitivity and specificity of pyrogen detection." These variations occur, she explained, as a result of habitat and seasonal changes.

"Furthermore, LAL/TAL contains Factor G, which is sensitive to fungal toxins, resulting in the activation of the coagulation cascade," said Dr. Ding. This can result in "a false positive test result for pyrogen."

Following many years of "fundamental research on the basic biochemistry and molecular biology of endotoxin-activated coagulation cascade reactions in horseshoe crab amoebocyte lysate by many researchers including our own," Dr. Ding and her team had "a good understanding on how Factor C—the first enzyme in the cascade—is the target of endotoxin."

Based on the research, CAL was chosen for genetic engineering because it is the most potent endotoxin-sensitive lysate, as a result of its microbe-rich estuarine habitat.

After nearly two decades, however, recombinant Factor C (rFC) and other LAL alternatives have not caught on.

Lonza, which markets PyroGene™, an rFC pyrogen test has seen sales increase recently, but nowhere near enough to suggest LAL is out of favor.

Lonza Walkersville's **Allen Burgenson,** who is the President of the PDA Capital Area Chapter, recently discussed LAL testing, the stresses on horseshoe crab populations and the alternative test PyroGene™ with the *PDA Letter.*

Hear more from the *PDA Letter's* interview with Dr. Levin and Lonza's Allen Burgenson in the August *PDA Letter* Podcast. Visit www.pda.org/pdaletter to listen to the podcast.

One reason for the slow uptake of PyroGene™, he said, is because it is not a compendial test. "It's not yet found in the United States Pharmacopoeia, the European Pharmacopoeia, or the Japanese Pharmacopoeia," said Burgenson.

Alternative tests are acceptable, however, and the U.S. FDA went so far as to specifically name rFC and the monocyte activation type pyrogen test as acceptable alternatives to USP <85> BET Testing in a 2012 Q&A guidance ***(1),*** as long as their use is validated per USP <1225>.

Burgenson noted that once a firm validated the test for a few of its products, it can "write a comparability protocol and submit it to the FDA." Application of the test to additional products "instead of being a prior approval submission the way the first couple would have been, they become a CBE-30, with changes being effective in 30 days once the protocol is approved by FDA."

While other suppliers of LAL like Charles River Laboratories International ***(2)*** do not agree with environmental/preservation arguments for moving away from LAL, Lonza—which incidentally holds an exclusive license with the developers of rFC—believes there are ethical reasons to switch to alternative tests.

Burgenson explained: "The horseshoe crab is obviously a live animal, and in Europe, there is a mandate to remove animals from the manufacturing and testing process wherever possible."

Threatened LAL Supplies

In addition, he cited potential threats to Atlantic horseshoe crab populations beyond overfishing by the fishing and food industries, the damage from which seems to have reversed in recent years.

"Right now, we seem to have reached a point of stability. There was a point several years ago where the population was severely impacted by overfishing, and the Atlantic States Marine Fisheries Commission had to restrict that and to increase the population. And it looks like the population is recovering," Burgenson said. However, "as you saw with Superstorm Sandy when it came ashore in New Jersey and Delaware, the beaches where the horseshoe crabs spawn were really torn up, so Mother Nature can have a severe impact, especially with storms such as that on the breeding grounds—spawning grounds—so the horseshoe crabs can't get to shore to spawn, [and] that can severely impact the population of horseshoe crabs in that area."

And demand for LAL could outpace the supply, Burgenson predicts. "Well, as the pharmaceutical industry grows, it increases the greater demand on the supply of LAL....For every two products that make it to market, 98 don't. But you still have to test all of those products as they are being developed and put through the submission pipeline. So, there's a lot of products that never make it to market that still need to be tested. So, as that demand increases, supply of LAL or the population of horseshoe crabs is stationary. The population is not increasing in great numbers."

Finally, the greatest possible threat to LAL supplies is not overharvesting or ecological disaster. Rather, it is the red knot shorebird.

Burgenson has followed the plight of the shorebird closely, and even appeared on a recent American Public Media Marketplace segment to discuss it ***(3).***

"Right now the red knot is threatened, and it is being proposed to be put on the Endangered Species List. This bird flies all the way from Tierra del Fuego at the very tip of South America all the way to the Arctic every year to breed, and there is a stopover in the Delaware Bay region where they gorge themselves on horseshoe crab eggs. Horseshoe crabs spawning and the arrival of these birds happens simultaneously—while, it actually happens up and down the East Coast—and once the birds get heavy enough to continue their journey to the Arctic, they'll fly and go up to the Arctic for breeding."

If listed as a "threatened species" under the U.S. Endangered Species Act, "the whole objective is to try to reduce any stress on the horseshoe crab population to keep those birds healthy and existing," said Burgenson.

Dr. Levin, who does not consider the alternative methods to be as useful or effective as LAL, believes the horseshoe crab conservationists finally have a powerful ally in their efforts to stop harvesting for bait—the National Audubon Society. It remains to be seen, however, what impact such listing would have on harvesting for LAL purposes, since the crabs are left relatively unharmed.

The public comment period on the proposal to list the red knot as an endangered species was reopened in April 2014 and closed in June. A decision could be made by September. It is unclear as of now how the decision will impact horseshoe crab harvesting, if at all.

While the red knot's potential status as a threatened species might not impact the ability of LAL suppliers to bleed horseshoe crabs, it does serve as a cautionary note to healthcare companies that rely on living creatures for critical materials. With environmental strains, growing demand for food (animal and human), and the desire to preserve species, companies must vigilantly monitor supplies and have backup plans in case supplies are disrupted.

In the case of LAL, alternative methods are available.

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Continued at bottom of page 36

Proposed USP Chapter on Nonsterile Bioburden Long Overdue But Clarification Still Needed

Karen Ginsbury, PCI Consulting

USP's microbiology-related chapters continue to evolve and a new one is wending its way through the pharmacopoeial pathway. The new chapter, with a focus on nonsterile products, is unique and much needed.

In 2013, the U.S. Pharmacopeial Convention (USP) published a draft general chapter on bioburden control of nonsterile products ***(1).*** A work of this nature, providing industry with some background and recommendations for strategies to control the environment in which nonsterile products are produced, is long overdue. Typically, companies have directed the majority of their resources to risk management of sterile—particularly aseptic—processing operations. Nonsterile manufacturing environments and processes tended to evolve from current practices rather than from a rigorous assessment of process and product requirements to control the introduction and propagation of microbes.

The USP has developed several general chapters in the area of microbiology over recent years, some with greater success and others with less. Chapter <1117>, Best Microbiology Laboratory Practices, is—together with the WHO Annex 2 on microbiological laboratories—one of the major resources for recommendations on appropriate practices in running a microbiology laboratory within a pharmaceutical company. On the other hand, <Chapter 1116>, Microbiological Evaluation of Clean Rooms and Other Controlled Environments (updated in 2012) came on top of the U.S. FDA's aseptic processing guide (now somewhat outdated at ten years of age), EU's Annex 1 on Manufacture of Sterile Products, plus PIC/S and ISO cleanroom guidances, seemingly superfluous at this point in time. The 2012 revision of this chapter to "Microbiological Control and Monitoring of Aseptic Processing Environment" added to the overall body of knowledge on cleanroom management with recommendations for monitoring microbial recovery rates rather than just looking at day-by-day numbers. This was a useful addition to the overall cleanroom management approach although other issues with the chapter's content remain.

The proposed <1115> chapter on nonsterile products can undoubtedly provide valuable recommendations for industry regarding a microbial control strategy for products which have a defined bioburden requirement (microbial limit) but are not required to be sterile. In order to provide this value, the chapter needs to emphasize the challenge in maintaining a stated microbial limit, as opposed to maintaining sterility, which is an absolute state and maintained for as long as the package is integral. What the draft chapter fails to do—and, in fact to a large extent, creates the opposite impression—is illustrate the uniqueness of this challenge. Microbes are distinct in their phenomenal ability to survive under minimal nutrient conditions (e.g., to lay dormant and to proliferate at astounding rates). The chapter tells the reader it is inevitable that there will be pathogens in the production environment. The chapter, however, does not clarify that under appropriate circumstances, one of those pathogens could double itself every twenty minutes, resulting in 16 million (under ideal conditions) within an eight hour shift.

There are three major issues with the draft as published in *Pharmacopeial Forum*:

1. The chapter exclusively warns against "excessive microbial controls" for nonsterile products as costly without added benefit. It neglects to mention the reverse scenario regarding the dangers of inadequate controls and the harm this could cause. The chapter gives the sole consideration for microbial control as "patient safety," whereas in fact, the product itself, in addition to the process, may require microbial controls. Implementation of risk management over the past few years has shown clearly that when the sole focus is patient safety, processes and products continue to fail. If the intention is prevention, rather than detection and correction (which is far more wasteful and results in drug shortages), controls required to ensure appropriate processing conditions are essential. For example, some processes are inherently more susceptible to contamination (those using moist environments and temperatures convivial to microbial proliferation) than others, and therefore, require tighter controls. An initial read of the draft leaves the impression that very few measures are actually justified for nonsterile products. It seems unlikely that this is the message which the authors intended to convey.
2. The chapter fails to consider the professional background of the reader, which is especially critical in the case of nonsterile products, where there may not even be a microbiologist on the company payroll. There is no ➤

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explanation of the nature of the risks posed by microbes with respect to their unusual capacity for entry, survival and proliferation under minimal nutrient conditions. Without this background, and in light of the exhortations against "excessive controls" plus extensive, repeated statements about how human bodies can serve as incubators for microbes and that pathogens are always present in the production environment, a naïve reader might come to the conclusion that microbial risks posed by nonsterile products are negligible, thinking "we really should not be diverting resources to fix this minor issue."

3. The draft muddles the concept of risk management due to the manner in which it is written. For example, the chapter provides a list of product types with the (potential) risk, from high to low, that they pose for microbial contamination. There is no rationale for the grouping, which appears to contradict earlier statements such as:

   "nonsterile products are administered to regions of the human body that are rich in microbial flora and have physical or immunological barriers to infection. Examples include the oral cavity, skin, nasopharynx, vagina, and rectum, which harbor a high and diverse viable microbial population."

4. Why then are vaginal suppositories higher on the list than topicals and aqueous oral liquids? Surely, risk management requires each company to perform their own assessment of their products and processes, looking at diverse factors and failure modes along with categorizing the risk based on identified controls. This is not addressed anywhere in the proposed chapter and there is a real danger that nonmicrobiologists may apply the recommendations blindly with little or no understanding of the underlying risks.

The draft chapter states that:

> *"When formulators evaluate the susceptibility of nonsterile pharmaceutical products to microbial hazards, considerations include whether the active ingredient has inherent antimicrobial activity, the microbiological content of excipients, inclusion of antimicrobial preservatives in the formulation, and water activity."*

Undoubtedly, before considering if the active has inherent antimicrobial activity, it would be prudent to look at whether the active, excipients or product formulation and production process have inherent ability to support and promote microbial proliferation.

In conclusion, the proposed chapter could, and should, be a valuable addition to the body of knowledge for manufacture and control of nonsterile products. Chapter <1115> should provide useful material for companies developing, maintaining and improving a microbial control strategy for these products. In order to achieve this goal, caution is needed in both the background material provided, the manner in which it is presented and the way in which risk management is described and approached. Consideration should be given to the readership, many of whom will not be experienced microbiologists. Some basic microbiological background is warranted, regarding the nature of microbial proliferation and the challenges in maintaining a defined bioburden as opposed to asepsis/sterility which is an absolute.

[Editor's Note: There will be a session focused on objectionable organisms in nonsterile drugs at the *PDA 9th Annual Global Conference on Pharmaceutical Microbiology,* Monday, Oct. 20 at 1:15 p.m. In addition, Plenary Session 5 will cover microbiology-centric USP updates at 8:15 a.m. Oct. 22.**]**

Reference

1. Bioburden Control of Nonsterile Drug Substances and Products. *Pharmacopeial Forum* 39 (2013)

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. She has designed, implemented and maintained company-wide compliance systems which have passed Israeli Ministry of Health, U.S. FDA and European inspections, working with both small start-ups and large pharma.

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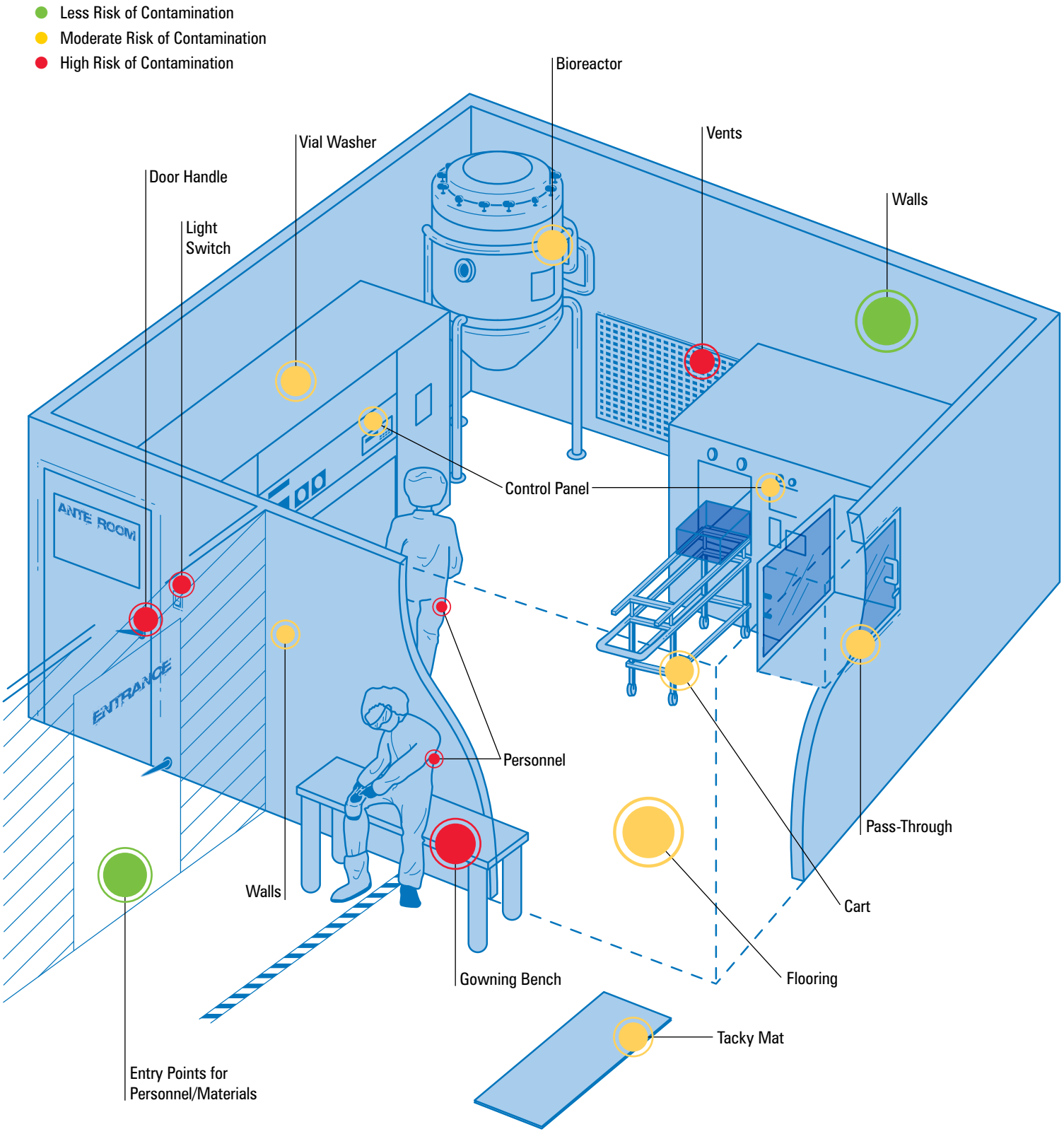

Special thanks to **Tricia Griffiths,** Pall Life Sciences, and other PDA members and staff (Science and Regulatory Affairs/TRI) for their assistance with this infographic.

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snapshot

Quality Culture Survey to Guide PDA Metrics Conference

Cylia Chen-Ooi, Amgen

In early 2013, the U.S. FDA began soliciting input from industry on establishing a set of quality metrics. These metrics would assist in the evaluation of product manufacturing quality with the aim of preventing drug shortage issues. The Agency also proposed that quality metrics be used in the risk-based inspectional model to supplement current inputs.

Until now, the focus has centered heavily on compliance metrics such as product complaint rate, OOS, and others. Several speakers at the *2013 PDA Pharmaceutical Quality Metrics Conference* in December acknowledged that quality culture may be one of the most critical factors in determining a company's quality. A company's quality culture defines the organizational value system that results in an environment conducive to continual improvement in quality. It is also the foundation in ensuring consistent quality performance. Any set of compliance metrics will only assure quality if it is supported by a strong quality culture that permeates throughout the organization.

[Editor's Note: See p. 32 of the February *PDA Letter* for a transcript from a portion of the breakout session readout that covered quality culture.**]**

Recognizing its importance is easy, but defining and measuring quality culture is a challenging one. This fall, PDA will begin an initiative to publish a Quality Culture Survey, gathering data from the industry to help grasp the topic of quality culture. The goal of the survey is to explore what the attributes of a quality culture are, and which ones are measurable with minimum subjectivity.

PDA's efforts on quality metrics, including the survey, will also be presented at a breakfast session at the *2014 PDA/FDA Joint Regulatory Conference*.

Your participation in the survey is highly encouraged as findings from the Quality Culture Survey will be a key subject of discussion at the upcoming *2014 PDA Pharmaceutical Quality Metrics Conference* in December. The conference will be co-chaired with FDA again this year and a number of key FDA leaders will be presenting and participating in panel discussions.

We look forward to your participation in the Quality Culture Survey. Watch for an email from PDA with a link to the survey around early September.

Will a Shorebird Knot Up Bacterial Endotoxin Assay Supplies? continued from page 28

About the Experts

Allen Burgenson is the Regulatory Affairs Manager for Lonza Walkersville Inc. He holds a MS in Biotechnology Management from the University of Maryland, and serves on the Horseshoe Crab Advisory Panel of the Atlantic States Marine Fisheries Commission.

Dr. Jack Levin has been a member of the faculty of the University of California School of Medicine in San Francisco since 1982. Previously, he was Professor of Medicine at The Johns Hopkins Univ. School of Medicine, Baltimore, Md.

Jeak Ling Ding, PhD, is a professor of biological sciences at the National University of Singapore. Her research interests focus on innate immunity and pathogen surveillance strategies. She received her doctorate from the Royal Postgraduate Medical School in London.

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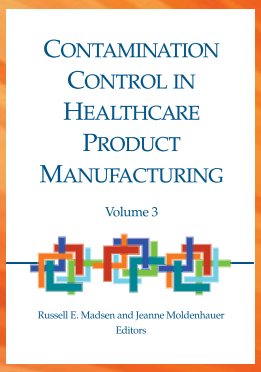

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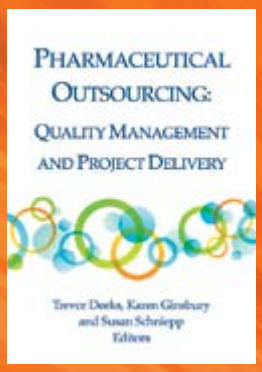

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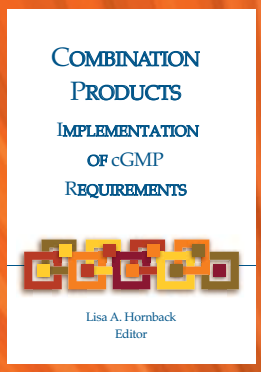

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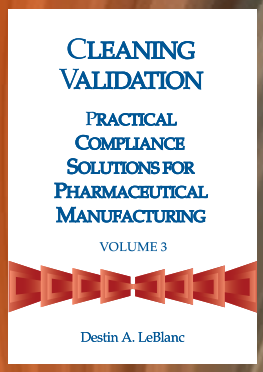

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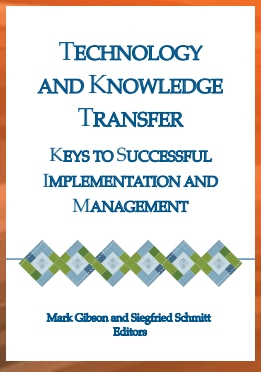

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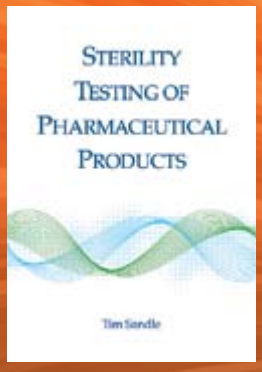

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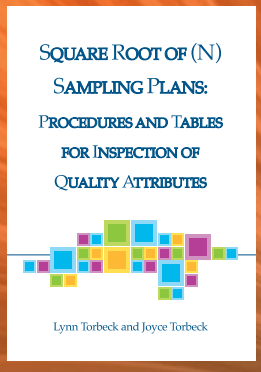

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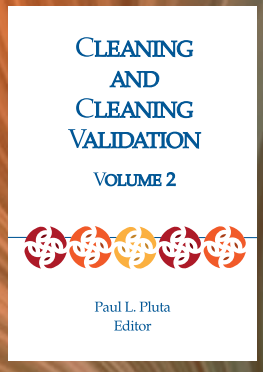

Item No. 17298

New Rule, Guidance Impact Development of Drug Delivery

Olivia Henderson, Biogen Idec

Just over a year ago, the U.S. FDA issued two important publications that affect the combination product development space: the final rule on cGMPs for combination products and the guidance, *Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products.* This final guidance provides the requirements for developing combination drug delivery products.

In addition to increased expectations from regulators, the cost of developing new drugs has greatly increased over the years. As pharmaceutical scientists, we all need to be concerned with optimizing our efforts to bring new drugs to our patients and to minimize these costs while developing safe, effective products which are valued by our patients.

By the time we are ready to put the drug into a device/combination product, much of the uncertainty around drug development has been reduced to a manageable level. Many groups are finding, however, that integrating the device development with the drug development early can provide some important benefits. At this point we still need to implement the device/combination product aspect of a drug product in a time and cost-efficient manner to get this product to market and to patients as efficiently as possible. Understanding the implications of the final rule on GMPs for Combination Products (21 CFR Part 4a) will be instrumental in an effective combination product development program.

Those attending the *2014 PDA Drug Delivery Combination Products Workshop* scheduled for Oct. 8 will be treated to discussions on the impact of new guidance on change control, risk management, and the use of common technologies for drug delivery device development. The speakers in this workshop will use best practice approaches to help illustrate how combination products can be developed efficiently using several avenues. drug/device combination products.

For more information, please visit www.pda.org/drugdelivery2014.

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www.pda.org/disinfection
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Management of Aseptic Processing

October 6-8 | Bethesda, Maryland
www.pda.org/apmanagement
Arms managers with the tools they need to make informed business decisions related to aseptically produced products, including selection of aseptic processing technologies, and sourcing decisions.

2014 Universe of Prefilled Syringes and Injection Devices Course Series

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- Prefilled Syringe User Requirements – *New Course* (October 9)
- Syringes and Elastomers: Understanding the Effects on Quality and Demonstrating the Production Process, Influences and Needs (October 9)
- Technical and Regulatory Challenges of Drug Delivery Combination Products – Prefilled Syringes, Autoinjectors and Injection Pens – *New Course* (October 9)
- Risk Management for Temperature Controlled Distribution (October 10)

Strategies for Reducing Human Error Non-conformances

October 9 | Bethesda, Maryland
www.pda.org/humanerror2014
This interactive course will explore the reasons behind frequent and persistent human errors in the pharmaceutical industry, and then discuss strategies for reducing this ever-present metric.

2014 Aseptic Processing Training Program

October 13-17 and November 3-7, 2014 | Bethesda, Maryland
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PDA 9th Annual Global Conference on Pharmaceutical Microbiology Course Series

October 23-24 | Bethesda, Maryland
www.pda.org/microcourses2014
Immediately following the PDA 9th Annual Global Conference on Pharmaceutical Microbiology, the PDA Training and Research Institute will be hosting four courses to complement your learning.

- Regulatory Aspects of Microbiology in a Non-Sterile Environment – *New Course* (October 23)
- A Risk-Based Approach to Global Environmental Compliance – *New Course* (October 23)

PDA 9th Annual Global Conference on Pharmaceutical Microbiology Course Series *(continued)*

- Exclusion of Objectionable Microorganisms from Pharmaceutical and OTC Drug Products, Consumer Health Products, Medical Devices and Cosmetics – *New Course* (October 24)
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Quality Metrics: The Next Frontier

Steven Mendivil, Amgen, Neil Stiber, PhD, U.S. FDA, and Russell Wesdyk, FDA

In 2013, the U.S. FDA announced its intent to collect quality metrics. This collection is in conjunction with the Food and Drug Administration Safety and Innovation Act (FDASIA), which authorized the Agency to obtain drug manufacturing records in lieu of, or in advance of, an inspection. Last year's *PDA Pharmaceutical Quality Metrics Conference* laid the foundation for PDA's "Points to Consider" paper that shared the current thinking of PDA's membership about quality metrics with FDA.

The 2013 conference highlighted various metrics that are valuable in assessing site and product quality; but, did not focus on quality culture or systems. The importance of these factors has been acknowledged in a number of articles and studies. From an FDA perspective these factors are important additions that promote the creation of the "balanced scorecard" called for by many stakeholders.

This year's conference will be different because we aim to move beyond conventional discussions about the concepts of quality culture and quality system maturity. We expect that the interactions at this conference will increase understanding about specific attributes that can be measured objectively. The outcome of these presentations and collaborative breakout sessions will support a revision to PDA's "Points to Consider" paper. The updated version will present new insights and highlight metrics that may better indicate site and product quality.

For the second year, PDA's Quality Metrics Conference is co-chaired by FDA and industry. It will again bring together key FDA and private sector quality leaders. The plenary presentations will provide updates on where FDA is going, what industry has learned about quality culture and quality system maturity, and how these may be integrated into a new set of metrics for consideration by industry and FDA.

In addition, attendees will hear about a FDA project to modernize drug inspection protocols by emphasizing manufacturing quality. This new inspection protocol will yield semiquantitative assessments on the state of quality at inspected facilities. While continuing to document observed deficiencies during inspections, the new inspection protocol will also identify practices that exceed basic compliance.

Please mark your calendars and make plans to attend this year's *PDA Pharmaceutical Quality Metrics Conference* in December. For more information, please visit www.pda.org/metrics2014. For information about the PDA TRI course following the conference, please visit www.pda.org/metricscourse.

Seeking Additional Clarification on Analytical Methods

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

May 20, 2014

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

Reference: FDA Guidance for Industry Analytical Procedures and Methods Validation for Drugs and Biologics

Docket [FDA-2014-D-0103]

Dear Sir/Madam,

PDA recognizes and appreciates that FDA has incorporated many elements of PDA Technical Report 57 Analytical Method Validation and Transfer for Biotechnology Products in this draft guidance, including the concepts for method comparability, the concepts for "pre-determined and justified", and the approach to significant digits. PDA also recognizes the alignment with other existing standards such as USP <1224> and applauds the agency for moving towards greater harmonization.

PDA's attached comments are focused on additional clarification that we believe will strengthen the document such as: when and how to apply the concepts of equivalence, non-inferiority, or superiority in comparison models; a clear statement of FDA's intention to treat analytical methods previously approved in a marketing authorization (i.e. NDA, BLA, ANDA) in a similar manner to compendial methods when evaluating new and post approval change submissions; and inclusion of methods from pharmacopeia, other than USP, which are recognized by FDA (e.g. JP, EP) per MAPP 5310.7.

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 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

PDA Commenting Task Force

Susan Schniepp, Allery Laboratories (Chair)
Stephan Krause, PhD, MedImmune
Jeffrey Broadfoot, Emergent BioSolutions
Barbara Jentges, PhD, PhACT GmbH

[Editor's Note: see story on page 48 of the July/August issue for a comparison between the U.S. FDA guidance and PDA Technical Report No. 57.**]**

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Gabriele Gori, Novartis

PDA Working to Harmonize Sterile Manufacturing

PDA has almost seventy years of focus and leadership in the best practices for sterile pharmaceutical manufacturing. PDA leadership remains focused on promoting science-based guidance, and driving greater international harmonization. PDA has commented on many of the major regulatory guidances on this subject over the years, and continues to do so, as the technology changes.

For example, the current version of Annex 1 of the European GMPs regulating the manufacturing of sterile products has been effective since March 2009 (provisions on capping of vials have been effective since March 2010). During the past five years the pharmaceutical industry has faced several challenges in the interpretation and implementation of the new requirements, and in the new interpretation of already existing predicated rules. In addition to this, while some of the new requirements moved toward more harmonized regulations (e.g., media simulations, cleanroom classifications, etc.), significant differences, such as integrity testing of sterilizing filters prior to use, nonviable particle monitoring, and cleanliness requirements for capping of vials remain with respect to other regions of the world. This impacts both the costs of the manufacturing and control of medicines, affecting competition with manufacturing sites outside the European Union that lack similar constraints.

In addition to this, the current Annex 1 does not take into consideration risk management elements and tools, to the extent recommended in Parts I and III of the EU GMPs/ICH Q9, nor the implementation of new technologies. Recently, EMA (through the GMP/GDP Inspectors Working Group) consulted with PIC/S to review and clarify some requirements of Annex 1. This may lead to revision of this document, issuance of additional clarification notes ("Q&A's") or revision of the PIC/S interpretation document (Technical Interpretation of Revised Annex 1 to PIC/S GMP Guide – PI032-2). A revision of Annex 1 would also be required following the revision of the referenced EN ISO 14644-X series for the classification of cleanrooms/clean air devices. We are aware that other regulatory agencies are considering updating their guidances on sterile manufacturing. Therefore, PDA is also prioritizing updates for several of our related technical reports.

PDA has set up a task force of subject matter experts aimed at developing a Point to Consider document which will provide recommendations on specific areas that may benefit from clarification, or that should be updated to reflect current state-of-the-art practices, leading to common understanding and implementation.

The document is planned to encompass (but is not limited to) the following key topics:

- People
- Cleanroom design, qualification and monitoring
- Equipment design and operation
- Sanitization and decontamination
- Sterilization processes
- Process Simulation
- Fill finish

The proposed solutions will focus on ensuring product quality and patient safety while supporting increased harmonization with other relevant regulations concerning the manufacturing of sterile medicines.

Stay tuned for more updates on these activities. As always, PDA's Mission is 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.

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The Intersection of Mainstream and Pharma News

Rarely does a niche publication like the *PDA Letter* have an opportunity to cover a mainstream news story, but we've had several opportunities over the last decade with various supply chain scares (heparin, in particular), drug shortages, and the compounding incident. In this issue, we tread on ground probably never covered before in PDA's magazine: wildlife conservation. But the story of the red knot is a compelling one, and the fact that the U.S. government will decide sometime this year on whether to list it as a threatened species couldn't have intersected any better with the recognition of **Dr. Jack Levin** and the 50th anniversary of the discovery of LAL testing. In addition, the red bird has become an important cause for PDA Capital Area Chapter President **Allen Burgenson,** who participated not only in our story, but in an American Public Media Marketplace story.

Our intent is not to scare people away from LAL or support alternative methods. In fact, we made it clear in the cover story that other companies don't agree that LAL is at all a threat to horseshoe crab populations and by extension, the red knot shorebird. In addition, we quote Dr. Levin who does not believe the alternative methods are as good as LAL.

Readers can listen to expanded portions of the interviews with Dr. Levin and Allen Burgenson in the August *PDA Letter* podcast.

I'm expecting the cover story might create a buzz, so I look forward to reader feedback. One of the hardest things to do as the editor of the Letter is to stir our readers up enough to send us notes. So, if you feel our article was too one-sided, too sensational, or just right (as we think it is), send us a note.

The issue includes more information on BET and other issues pertaining to microbiology, all of which nicely sets the stage for October's *PDA Global Conference on Microbiology*. Dr. Levin, who helped kick off PDA's year by speaking at the Annual Meeting, will help us close it by speaking at the Micro Conference. He promised to mention the shorebird, but most of his talk is about the science of BET and LAL. But who knows, maybe Allen Burgenson will show up with a newly "threatened" red knot on his shoulder!

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