People • Science • Regulation

PDA Letter

Volume LI • Issue 8 www.pda.org/pdaletter September 2015

10th Annual Global Conference on Pharmaceutical Microbiology

Science Driving New State-of-the-Art Practices for Microbial Control

Calling All Active PDA Members – Vote Now!

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

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

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

If you need assistance 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 for voting.

Instructions for Voting:

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

Thank you for your participation in this important election process.

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PDA Letter

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

Cover

Cover Art Illustrated by Katja Yount

Departments

News & Notes

People

Science

Regulation

Voices of PDA

Contents

Features

PDA Members, It's Time to Rock the Vote!

As a PDA member you have the opportunity to be involved in setting the strategic direction of the Association by electing volunteer leadership for 2016. This year, there are three open Officer seats (Chair-Elect, Treasurer, and Secretary) and four open Director positions. Elections are open until Nov. 15; members in good standing as of Aug. 11, 2015 can vote online at www.pda.org/vote or at conferences held before Nov. 15 in the United States and Europe.

Officer Candidates

Rebecca Devine, PhD (Chair-Elect)

Michael Sadowski (Treasurer)

Jette Christensen (Secretary)

Director Candidates

Eric Drapé

Zena Kaufman

Marty Nealey

G.K. Raju, PhD

Dr. -Ing. Stephan Rönninger

Anil Sawant, PhD

Susan Schniepp

Melissa Seymour

To learn more about the candidates and to vote, go to www.pda.org/vote.

PDA Approved as Course Provider for NJ, NC Engineers

Engineers in New Jersey and North Carolina can now attend PDA Education courses for continuing professional competency (CPC) credits. PDA worked with both the New Jersey Board of Professional Engineers and Land Surveyors and the North Carolina Board of Examiners for Engineers and Surveyors. Both bodies approved PDA as a course provider for engineers in those states.

"This latest accreditation further demonstrates the value and quality of PDA's professional education offerings," said PDA President **Richard Johnson.** "Our lecture courses and hands-on professional training at the Training and Research Institute (TRI) in Bethesda, Md. are taught by leading experts in the pharmaceutical industry."

PDA will continue to reach out to state boards of engineering as part of a greater initiative for engineers to receive CPC credits for PDA Education courses.

PDA Education already is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education. In 2014, 31 PDA Education courses were listed with the U.S. General Services Administration (GSA).

PDA Education: Where Exellence Begins!

For information visit www.pda.org/courses

PDA Volunteer Spotlight

Jim Polarine

- Technology Service Manager
- *STERIS*
- Member Since | 2011
- Current City | St. Louis, Missouri
- Originally From | Troy, Illinois

I seem to learn something new every day in the industry

As a child, Jim wanted to be a storm chaser

What were your first PDA activities and how did they help you professionally?

Since my early days, I have attended and participated in local and national PDA events. These allowed me to network and share my industry knowledge and experiences with other PDA experts. Gradually, I became more involved with the Biotechnology Interest Group, the Environmental Monitoring Interest Group and the task force on cleaning and disinfection, along with other task forces.

Which PDA conference/course is your favorite? Why?

I always really enjoy the *PDA Global Conference on Pharmaceutical Microbiology* and view it as an opportunity to connect with peers and colleagues in the industry. I have seen some excellent presentations at these conferences. For example, at the 2008 micro conference, I really enjoyed **Thomas Arista's** keynote address comparing production of the Boeing 787 to troubleshooting cleanroom contamination issues.

[Editor's Note: Jim will be speaking on mold contamination at this year's microbiology conference in October.**]**

What is the greatest benefit of being a PDA member?

As a PDA member, I benefit from interacting with my peers and colleagues in the industry. I also enjoy reading the *PDA Letter, PDA Journal of Pharmaceutical Science and Technology* and the latest PDA/DHI technical books.

What is an issue or trend in the industry you think more people should be talking about?

I think one area of interest is bringing cleanrooms online after worst case events. There is also a trend and expectation in the cleanroom industry to complete disinfectant validation on coupon with facility isolates. Many end users in the industry are taking a look at older disinfectant testing validation studies and repeating the testing due to various issues such as controls and log reductions.

The Parenteral Drug Association Presents...

2015 PDA Visual Inspection Forum

October 26-27, 2015 | Bethesda, MD

Bethesda North Marriott Hotel and Conference Center

Exhibition: October 26-27 | Course: October 28-29

The leading meeting and exhibition dedicated to quality assurance of injectable products

The industry has seen an increase in particle-related recalls and heightened scrutiny of visual inspection processes during regulatory inspection. The *2015 PDA Visual Inspection Forum* will feature new developments in the field of visual inspection and present current perspectives on critical aspects of visual inspection to help industry professionals develop a robust and compliant inspection process.

Leading regulatory and industry experts will share lessons learned and best practices on topics of visual inspection, including:

- **Regulatory Compendial Issues,** providing an update on current USP activities, specifically chapters <1790> and <790> as well as the FDA/CDER perspective on visual inspection.
- **Challenging or Difficult to Inspect Products,** presenting inspection strategies for opaque containers, suspensions and freeze-dried formulations that cannot be easily inspected in a conventional light booth using manual inspection.
- **Case Studies,** featuring two plenary sessions showcasing special aspects of the manual and automated inspection process, risk assessment and manual and automated data.
- **Packaging Materials/ Container Closure Integrity/Leak Testing,** discussing defects in packaging materials and strategies employed to detect and control them. Various automated drug and biologic inspection methods will also be covered, with an emphasis on precision defect recognition, minimization of false positive reject rates and use of the generated data to improve upstream processing.

To learn more and register please visit, pda.org/visual2015

Engage with suppliers of inspection systems and services at the industry's largest exhibition of commercial inspection hardware, including the latest automated inspection machines and other visual inspection technologies.

Are you new to the field of Visual Inspection? PDA's Education course, *An Introduction to Visual Inspection*, taking place October 28-29 immediately following the Forum, is the course to attend to learn the fundamentals of visual inspection and their application to injectable products. This laboratory course will provide you with the unique opportunity to practice inspection skills under close guidance of experienced faculty.

Learn more and register at pda.org/visualcourse

chapter update

Australia Chapter Tours New CSL Facility in Melbourne

Kim Waters, GSK Australia

The PDA Australia Chapter toured CSL Behring's new facility in Melbourne on May 26. The state-of-the-art plant is dedicated to the manufacturing and packaging of Privigen (intravenous immunoglobulin).

Justin Daly opened the tour by sharing CSL's expansion plans for the site. **George Barlas** then showed a presentation on the manufacturing process and equipment. The video showing CIP of the filter press was very impressive. The other manufacturing equipment shown was also state-of-the-art.

Carlo Volpe followed with a presentation on the bottle cleaning and filling process-

(l-r) John Montalto, George Barlas, Carlo Volpe, and Anastasios Xidias

PDA Who's Who

George Barlas, Bulk Manufacturing Manager, CSL Behring

Justin Daly, VP of Manufacturing, CSL Behring

John Montalto, Manager, QRM, Quality Processes and Training, CSL Behring

Carlo Volpe, Filling / Finishing Manager, CSL Behring

Anastasios Xidias, Manufacturing Manager, CSL Behring

es. He showed attendees his office, which is known as the "fishbowl" due to its windows offering a 180-view of operations.

The chapter thanks Barlas and Volpe as well as **John Montalto** and **Anastasios Xidias** for organizing the event.

Are Your Documents Secure?

Jahanvi (Janie) Miller, PDA

A client places a confidential document outlining financial terms on a cloud-based storage platform. An employee inadvertently emails everyone in the company criticism of a recent initiative. A co-worker's network password is written in large text on a visible Post-it note. Spreadsheets listing employees' salary information are left on a printer for all to see.

In today's electronic-centric work environments, information—even confidential, proprietary information—is easily available 24/7. Even someone who rarely watches the news can easily remember news reports about organizations criticized due to thoughtlessly sent e-mails and other forms of electronic communication. Yet, for many, awareness of the security of the stored data on an organization's server is often an oversight. This easily accessible data could potentially be used against an organization in a legal action.

As part of internal PDA staff development, **Nancy Singer,** President of Compliance-Alliance and a former U.S. FDA prosecutor, presented a session on good documentation practices. The lessons learned by PDA staff regarding securing documentation and data can also be applied by those employed in other organizations or companies.

Singer began the presentation asking if anyone had ever seen or experienced:

1. Individuals submitting opinions on issues for which they did not have responsibility and authority
2. Post-it notes on documents
3. Assumed expectations of privacy when sending e-mails through an organization's e-mail system

She then asked those present to form small groups, analyze improperly written documents, and revise them to reflect the writer's true intent. The staff also participated in a high-energy discussion on identifying land mines within electronic communications and how to actively avoid them. After participating, the staff came away with the following insight: "Documents are like diamonds. They are very precious, and they last forever."

About the Expert

As president of Compliance-Alliance, **Nancy Singer** works closely with manufacturers of drugs and devices to ensure adherence on the latest FDA requirements.

2015 PDA Single Use Systems Workshop | June 23–24 | Bethesda, Md.

P5: Points to Consider for Single Use Systems (SUS) Implementation Part I
(l-r) Duncan Low, PhD, Amgen; Robert Repetto, Pfizer; Mark Petrich, PhD, Merck

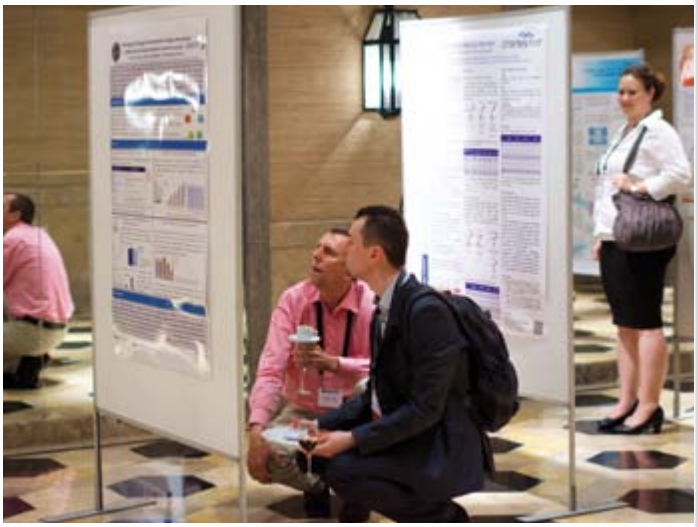
P4: Implementation and Deployment
(l-r) Jeffrey Carter, PhD, GE Healthcare; Eric Langer, BioPlan Associates; Stephen Brown, PhD, BE Vaccines SAS; Patricio Massera, CMC Biologics

P1: The Challenges and Needs for SUS Practices
(l-r) Tor Gråberg, Swedish Medical Products Agency; Robert Repetto, Pfizer

P3: Supply and Quality Concerns
(l-r) Sally Kline, PhD, Amgen; Magali Barbaroux, PhD, Sartorius; Duncan Low, PhD, Amgen; Helene Pora, PhD, Pall Life Sciences

P8: Ask the Regulators Panel Discussion
(l-r) Robert Repetto, Pfizer; Jeffrey Carter, PhD, GE Healthcare; Tor Gråberg, Swedish Medical Products Agency; Duncan Low, PhD, Amgen; Jerold Martin, JMartin Consulting; Christopher Smalley, PhD, Merck

Georg Roessling (center) shakes hands with Adam Inche (left) and Martin Wisher, representatives of networking event sponsor BioReliance



Attendees took the time to check out an extensive exhibition of poster presenters

Session 3: Safety of Starting & Raw Materials
(l-r) Martin Wisher, BioReliance; Dayue Chen, PhD, Eli Lilly; Thomas Kreil, PhD, Baxter BioSciences

Taking Aseptic Processing Education to a Higher Level

Rebecca Stauffer, PDA

When you think of PDA Education's Training and Research Institute, you think of the "Aseptic Processing Training Program." One of TRI's first programs when it was a fledgling training center at the UMBC campus near Baltimore, the two-week program has become an industry standard in training. Consequently, the course sells out every year, as it has done once again this year.

The *PDA Letter* reached out to one of the course's lead instructors and PDA Chair **Hal Baseman** to find out why it is such a "hot" course. He also discussed a TRI course on quality systems for aseptic processing.

PDA Letter: How will your course, "Quality Systems for Aseptic Processing," address changing requirements, such as quality metrics?

Baseman: An underlining focus of the "Quality Systems for Aseptic Processing" course is risk- and science-based decisionmaking, process design, validation and problemsolving. The objective is to educate participants on not only how to develop an effective quality system, but the reasoning behind the use of these methods. For quality metrics to be effective, they must be logical indicators of manufacturing performance. This is particularly important in aseptic processing, where the correlation between what we can measure and the desired outcome is not always easy to determine. Selection and implementation of effective aseptic processing quality metrics depends on a good understanding of those aseptic processes, including areas of variability and their relationship to process control strategies. In addition, it is important to be aware of recent quality metrics trends and regulatory agency expectations. The course will be a valuable forum for discussions on these trends and their impact of aseptic processing.

PDA Letter: Will it address any new technologies in the aseptic processing space? If so, will there be a hands-on component?

Baseman: As with all of the PDA aseptic processing courses, the instructors strive to keep up to date with industry and regulatory trends. New and innovative technologies are an important means to mitigate risk and improve aseptic processes. The "Quality Systems for Aseptic Processing" course presents up-to-date tools for making risk- and science-based decisions on design, selection, and validation, including innovative approaches to environmental monitoring, advanced airflow design and analysis, automated inspection systems, and aseptic process technology. The course is further designed to include several hands-on demonstrations and participation sessions in areas of particular interest in aseptic processing control strategy development, such as environmental monitoring sampling, sterile filtration, airflow analysis, visual inspection and risk assessment.

PDA Letter: How has the "Aseptic Processing Training Program" changed over the years?

Baseman: For well over a decade, the "Aseptic Processing Training Program" two-week course has been one of the most successful, effective and comprehensive educational programs in the industry. In recent years, the course has expanded into a series of courses to include separate sessions focusing on fundamentals, quality systems and management. This allows students to choose which area best meets their needs. The "Fundamentals" course provides a solid background for those who require a basic understanding of aseptic processing. The "Quality Systems" course provides the background needed to develop systems and approaches for effective process control decisionmaking. The "Management" course is designed for mangers and aspiring managers. It focuses on the elements of aseptic processing needed to make sound business and technical decisions in a complex global environment.

PDA Letter: How would this course benefit someone who has some years of experience in aseptic processing?

Much of the thinking in pharmaceutical manufacturing and aseptic processing in particular is changing. It is important to keep up with changes, trends and expectations. The objective of "Aseptic Processing Training Program" courses is to instruct students on how to perform an aseptic processing-related task effectively with better understanding of why these tasks are important. It is that focus on the *why* that makes these courses such an effective training method.

It is also important to interface and network with peers sharing ideas and experiences. PDA Education courses provide such an opportunity. Much of the learning experience occurs from questions, discussions and exchanges on topics. As with any dynamic subject, many times it is these interactive episodes that help explore and develop what will become new industry trends.

PDA's Who's Who

Hal Baseman, COO, ValSource

In addition to those courses in the "Aseptic Processing Training Program," he will also teach the "Quality Systems for Aseptic Processing," course Nov. 16–20 at TRI in Bethesda, Md. For more information about the course, please visit www.pda.org/qualityAP.

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snapshot

Journal *Preview*

Find Out the Results of PDA's Quality Culture Survey in the September–October Issue

Find out the results of PDA's quality culture survey in the September–October issue of the *PDA Journal of Pharmaceutical Science and Technology.* This issue also features editorials from the BioPhorum Operations Group (BPOG).

Review

Stephan O. Krause, "PCMO L01—Setting Specifications for Biological Investigational Medicinal Products"

Technology/Application

Kim Li, Yasser Nashed-Samuel, et. al., "Creating a Holistic Extractables and Leachables (E&L) Program for Biotechnology Products"

Carles Parés, et. al., "Manufacturing of Plasma-Derived Medicinal Products: Qualification Process of Plasma Suppliers"

PDA Paper

Pritesh Patel, et. al., "Quality Culture Survey Report"

BPOG Special Section – Editorial

Darren Whitman, "Introduction to BioPhorum Operations Group (BPOG) Special Section Editorials"

David Bain, et. al., "Overview of Best Practices for Biopharmaceutical Technology Transfers"

David Bain, et. al., "Strategies for Maximizing Successful Drug Substance Technology Transfer using Engineering, Shake-down and Wet test runs"

Gerry McAuley, Amy Wilson, Michael Moedler, "Changing the Performance Paradigm in Pharma / Biotech: Integrating Human Performance in Global Organizations"

Continuous Manufacturing Reaching its Tipping Point

Hal Baseman, ValSource

The other day, I asked a friend why our industry had not moved from batch to continuous manufacturing processes as other industries had. What would it take to reach that tipping point where enough momentum had been built to ensure widespread implementation? His conclusion was mixed. In some areas we have reached the tipping point, but in others progress is still needed.

From a business and quality standpoint, we are there. Continuous manufacturing processes that are correctly designed with appropriate monitoring and controls that adjust processes in real time results in a more consistent product produced at a higher rate. Regulators also see the value in pursuing it. U.S. FDA CDER Director **Janet Woodcock,** MD, spoke in support of continuous manufacturing processes for pharmaceuticals at a congressional hearing April 30 on a provision in the proposed 21st Century Cures Act, which would provide grants to academia and nonprofits to recommend improvements to the process of continuous manufacturing of drugs and biological products.

Continuous manufacturing and efficient implementation of postapproval changes will be discussed at the *2015 PDA Manufacturing Science Workshop*. This workshop will present the thoughts of experts, colleagues, and global regulators presenting ideas, case studies, new FDA guidances, and ICH Q12 initiatives.

Workshop presenters include: **Sau L. Lee,** PhD, Associate Director, Office of Pharmaceutical Science, CDER, FDA; **Salvatore Mascia,** PhD, CEO, Continuus Pharmaceuticals; **Moheb Nasr**, Vice President, CMC Strategy, GlaxoSmithKline; **Lawrence Yu,** PhD, Acting Director, Office of Pharmaceutical Science, CDER, FDA.

For more information, please visit www.pda.org/manufacturing2015.

2 CHEERS

2 COINS IN A FOUNTAIN

2 FRENCH HENS

2 LITTLE PIGS

GOLDILOCKS AND THE 2 BEARS

2 SHEETS TO THE WIND

2 TIMES A LADY

2 PIECE SUIT

2 STOOGES

2 BLIND MICE

2 WISE MEN

2 RING CIRCUS

2 POINT LANDING

2'S A CROWD

2 DIMENSIONAL

2 MUSKETEERS

2 DOG NIGHT

2 CARD MONTE

2 LEAF CLOVER

2 TENORS

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Help us welcome the newest member of our team at the **10th Annual PDA Microbiology Conference**, and learn more at **www.criver.com/emd.**

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Yes, You Can Design a Successful Visual Inspection Program

John Ayres, MD, Eli Lilly and Company

How do we assess the adequacy of parenteral product inspection? The answer might not be as simple as you think. Many factors determine the acceptability of the visual inspection process:

- The training and skill of those performing the inspection
- The relevant criteria utilized in an effective inspection program
- The timing of inspection processes or inspector training
- The location of the inspection process
- The decision to build a process that incorporates a clinical risk assessment into the accept/reject paradigm
- The building of programs that successfully integrate all elements

Advances in technology have enabled a remarkable ability to assess the contents of parenteral vessels with increasing sensitivity. Nondestructive technology allows us to confirm the adequacy of container closure. Enhanced orthogonal techniques and tools permit a better understanding of the characteristics of extraneous materials. A fuller understanding of the potential clinical implications of product defects aids in the appropriate resourcing of critical inspection functions.

Visual inspection of injectables has become one of the most dynamic functions in pharmaceutical manufacturing. Staying attuned to the changes in regulatory and compendial requirements, inspection process capability, advances in inspection-related technology and the impact on the ultimate recipient—the patient—is essential to address the question: *Are* our programs built to meet the litmus test of quality and capability?

The years ahead will continue to provide interesting challenges and opportunities. The *2015 PDA Visual Inspection Forum* provides an unparalleled opportunity to participate in in-depth discussions of new technologies, hear the thoughts and insights of regulators and engage with recognized industry leaders in visual inspection programs.

For more information, visit www.pda.org/visualinspection2015. And to learn more about the PDA Education course following the event, visit www.pda.org/visualcourse.

Micro's Past and Present Drives its Future State

Renee Blosser, U.S. FDA

What can past lessons and present solutions tell us about the future of pharmaceutical microbiology?

Large-scale outbreaks such as the Ebola virus have created public health challenges on a global scale. In the current world of antibiotic resistance, microbiologists are tasked with developing new treatments for resistant infections.

PDA is excited to announce the *10th Annual Global Conference on Pharmaceutical Microbiology.* It's been a busy ten years with many changes in the field of parenteral manufacturing. Join us for an exciting conference where we will explore current topics in microbiology, including those encountered every day in the laboratory as well as global topics with large-scale impact on public health. The conference will open with two exciting talks on the challenges faced during the Ebola epidemic, regulatory agencies' roles in the development of novel treatments and vaccines, and global efforts to fight the disease. The second keynote address will explore the potential of Arctic microbes as a next generation source of antibiotics. Other presentations will explore innovative technologies, risk assessments, workforce development, and a variety of other topics.

Other popular sessions will return, including "Urban Myths" and "Emerging Leaders." The final day of the conference will focus on standards and regulation. A CDER representative will give a presentation on the structure and function for microbiology in the newly reorganized Office of Pharmaceutical Quality (OPQ). A second talk will focus on current updates from PIC/S. The conference will close with the "Ask the Experts" panel discussion giving attendees an opportunity to pose questions directly to U.S. FDA and industry personnel with expertise in manufacturing issues.

To learn more about this signature PDA event, visit www.pda.org/microbiology2015. For information about PDA courses, following the conference, go to www.pda.org/microcourses.

Science Driving New State-of-the-Art Practices for Microbial Control

Rebecca Stauffer, PDA

While microbial contamination control in pharmaceutical manufacturing is at a level needed to ensure safe products, most would not characterize it as "state-of-the-art." An outsider taking a stroll through most pharmaceutical operations might question why 21st century products produced primarily with 21st century technologies are monitored using 19th and 20th century microbial tests. It is fair to say that this is one area where the science and its practical applications have left the industry far behind.

Nowhere is this contrast more stark than in the control of biofilms and bioburden and in sterility testing. Those who have been involved in pharmaceutical microbiology over the past two decades understand that the sterility test has its limitations—in fact, many consider it useless—yet it is still the most widely used control test within the industry. With respect to bioburden control, current approaches are based on a 30-year-old scientific understanding of bioburden, at least until very recently.

Microbiologists can now expect to access an increasing number of new tools for contamination control. To ensure successful control, however, these approaches will need to be utilized within a framework that accounts for knowledge passed down between generations of microbiologists. Current, mainstay technologies need to be fully understood even as new technology gradually becomes available.

Edward Tidswell, PhD, Director, Quality, Baxter Healthcare; **Mark Pasmore,** PhD, Manager, Sterility Assurance Research Center, Baxter HealthCare; and **Cheryl Platco,** Principal Scientist, Merck Research Laboratories, spoke to the *PDA Letter* about where the pharmaceutical industry stands on state-of-the-art microbial control. All three will present at the upcoming *PDA 10th Annual Global Conference on Pharmaceutical Microbiology* in October ***(1–3).***

Logic-Driven System for Global Control

Baxter Healthcare is a large global firm with approximately 40,000 employees spread across 71 facilities in over 25 countries. The company found that an extensive global supply chain, differing regulatory standards and a growing portfolio of diverse, innovative products presented challenges to ensure the microbial

Article at a Glance

- Global firm utilizes "self-correcting" system for micro control
- New document outlines steps for biofilm and bioburden control
- Microbiologists still need a holistic understanding of existing test methods

control needed to manufacture product at its highest quality. This led to the development of a systems-based microbial control strategy.

Tidswell described this approach as a "self-detecting and self-correcting system." He characterized it as a systematic, logic-driven process that controls microbial risks during the product lifecycle, and relies on understanding the individual components of the system through each other rather than in isolation.

Baxter's system is holistic. Real-time risk assessments and data trigger certain specifications that result in review and evaluation of risk (pFMEA, traffic flow, etc.) (**Figure 1**). Baxter's real-time risk assessments occur on a frequent, periodic basis and involve subject matter experts (usually microbiologists) interacting directly with those on the manufacturing floor. Traditionally, risk assessments are performed only on an ad hoc basis with little to no direct involvement with those on the manufacturing floor.

Real-time risk assessments then lead to a control scheme that documents the controls, monitoring and logic, and then generates a Quality Plan that specifies the schedule of required improvements.

"We've got all these well-evolved elements that contribute," he said. "We've got these parts that are really, really good. We've got some well-established tools and very sophisticated parts to it...each part of these elements in this system have to work and keep together almost like pieces of a jigsaw, so you don't have to keep going back and reinventing the wheel."

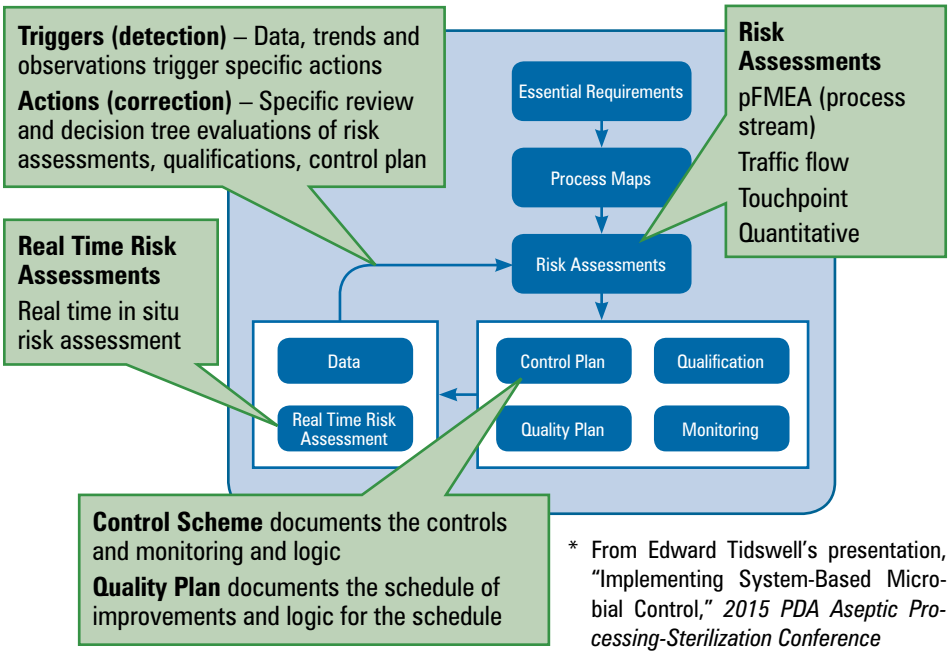
Tidswell's team designed the system in such a way that it could be viewed, in a sense, as an "automated" system.

"It certainly has the aspect of running independently," he explained. "If you put these parts together, then the reliance upon human beings or subject matter experts remembering or relying upon trigger systems to do something is removed. It almost becomes an automated process and it drives continuous improvement."

Still, one could argue that these individual elements are characteristics of a company with an overall good quality system. But Tidswell said that he has not seen many firms that take a true systematic approach to it.

"Systems-based takes a sort of different perspective because systems-based microbial control instills automatically," he said.

Figure 1 System-based Microbial Control – Environmental Control



* From Edward Tidswell's presentation, "Implementing System-Based Microbial Control," *2015 PDA Aseptic Processing-Sterilization Conference*

"Continuous improvement is not a singular project or program. It's not a business venture or a business ideal. It is ingrained in what you do and how you behave as an organization. And that's part of your system. I don't think many organizations build that into true genuine systems that are self-identifying and self-correcting."

Further, he emphasized that it's "far better to have a system that you plug in everywhere that automatically self-detects and automatically self-corrects. I think companies with strong quality cultures do have elements of this, but I don't believe it's put into a true system. It's a slow process as well. When you implement a system, the scientists and engineers want things to be perfect like a well-oiled engine from the start. Systems-based allows you to turn that motor over and start it without having it perfect."

New Tool for Bioburden, Biofilm Control

The management of bioburden and biofilm within a facility is key to ensuring effective microbial control. Recalls and plant shutdowns have resulted from failure to control persistent bioburden and biofilm contamination. Until recently, however, pharmaceutical microbiologists and engineers lacked an authoritative document outlining control considerations for bioburden and biofilms.

PDA *Technical Report No. 69: Bioburden and Biofilm Management in Pharmaceutical Operations* is a groundbreaking document that not only provides an overview of the science of bioburden and biofilm management but also offers steps for remediation and approaches for microbial control in this area. This includes a guideline for an overall microbial control strategy and recommendations for a sound, scientifically based program to detect and characterize bioburden and biofilms.

Mark Pasmore, who participated on the technical report team, feels that TR-69 is overdue. In his opinion, there has been a lack of communication in the industry regarding how to effectively handle bioburden and biofilms—particularly the

latter which present challenges due to being surface-adhered and notoriously difficult to inactivate with disinfectants and sanitizers.

"Part of it is that education piece—letting the community know about biofilms, getting not just the microbiologists, but the entire pharmaceutical community, up to speed on what they are has been a slow time coming," he said. "I think the other part of it is... some groups feel that if they haven't noticed a problem, there isn't a problem."

Pasmore added: "I think there has been, unintentionally, a little bit of a denial that this is truly an issue, and I think there is a little bit of that aspect of companies not wanting to air their dirty laundry when they've had an issue."

But now companies are looking more extensively into biofilm and bioburden. Some are even exploring automation of sampling. The ideal would be to remove human involvement in isolators and solution lines entirely as human contact increases contamination risk. Pasmore pointed out that cleanrooms in the silicon wafer industry are completely automated. These cleanrooms have "taken the human component out of there because the cost of having a single microbial contamination in those systems can cause millions of dollars of material to be scrapped. Those systems have become highly automated, highly functional and because of that, have very minimal bioburden issues."

At this time, both industry and regulatory agencies have been slow in embracing automation. At the same time, there is a critical need for enhanced solutions to detect biofilm instead of just measuring biobuden.

"Enhancing our detection of biofilms certainly will benefit down the road," Pasmore said. "That said, right now, there is no ideal system for biofilm detection. There is no great means to be able to readily detect biofilms."

Tidswell described this approach as a "self-detecting and self-correcting system"

He hopes that TR-69 leads industry to encourage academia and vendors to research new methods for biofilm detection. Pasmore sees rapid methods becoming an important technology, especially as these methods become more sensitive.

Awareness of LAL Intricacies Needed

Microbiologists now have expanded tools and methods to ensure microbial control along with greater knowledge of the variable nature of microorganisms. But while new technologies and processes offer innovative solutions for the future of control, some microbiologists worry that newer generations of microbiologists fail to understand the intricacies of standard tests used at present—even old standbys like the LAL assay.

Microbiologist Cheryl Platco views the latter as a factor in the controversy surrounding Low Endotoxin Recovery (LER), also referred to as Low Lipopolysaccharide Recovery (LLR).

She said, "the LLR phenomenon is observed when purified lipopolysaccharide (LPS) is added to undiluted biologics that contain chelating citrate or phosphate buffers with polysorbates. Purified LPS could not be recovered from these buffered products with the standard LAL assay because the lipid A molecule fails to activate the clotting cascade due to a masking effect."

Not surprisingly, this has generated controversy within the industry. Platco's own observations suggest that the original LER study, which utilized purified LPS as an artificial endotoxin surrogate, brought to light the effect of chelating buffers and polysorbates on the LPS molecule in selected product matrices.

"What we're trying to measure with the compendial LAL test methods is the activity of any naturally occurring contaminant endotoxin," she said. "The endotoxin test is an assay meant to detect clinically relevant endotoxin. Natural endotoxins which are the true contaminants in products are easily recovered. There are also certain matrices that may actually destroy or inactivate both LPS and natural endotoxin. Efforts to reactivate LPS molecules to active states are simply academic exercises if they cannot be demonstrated to be clinically relevant."

Platco is concerned that this confusion may be the result of a new generation of microbiologists who may not be fully aware of the complex nature of the compendial LAL test. Also, when dealing with biological molecules such as monoclonal antibodies and therapeutic proteins, it is important to discern between pyrogenicity from endotoxin versus pyrogenicity as side effect of the active ingredient protein molecule itself.

"I do think some of the confusion is due to a lack of understanding of the assay," she said. "Some do not understand how the rabbit pyrogen test and endotoxin standards were developed and what the LPS standard represents."

Although considerable background information on the LAL test is available from general USP chapters, older U.S. FDA guidances, as well as PDA books such as *The Bacterial Endotoxins Test: A Practical Guide,* Platco wonders if "there is a real need for us to pass down this information that's in all these books about how the reference standard was originally defined, how the test was qualified against the rabbit pyrogen test...so that there's a better understanding that this was very variable."

One way, she suggested, might be for USP to develop a general chapter that not just instructs on how to run the test but also explains its variability and offers a comprehensive view of the exact nature of the LAL assay.

Continued on page 37

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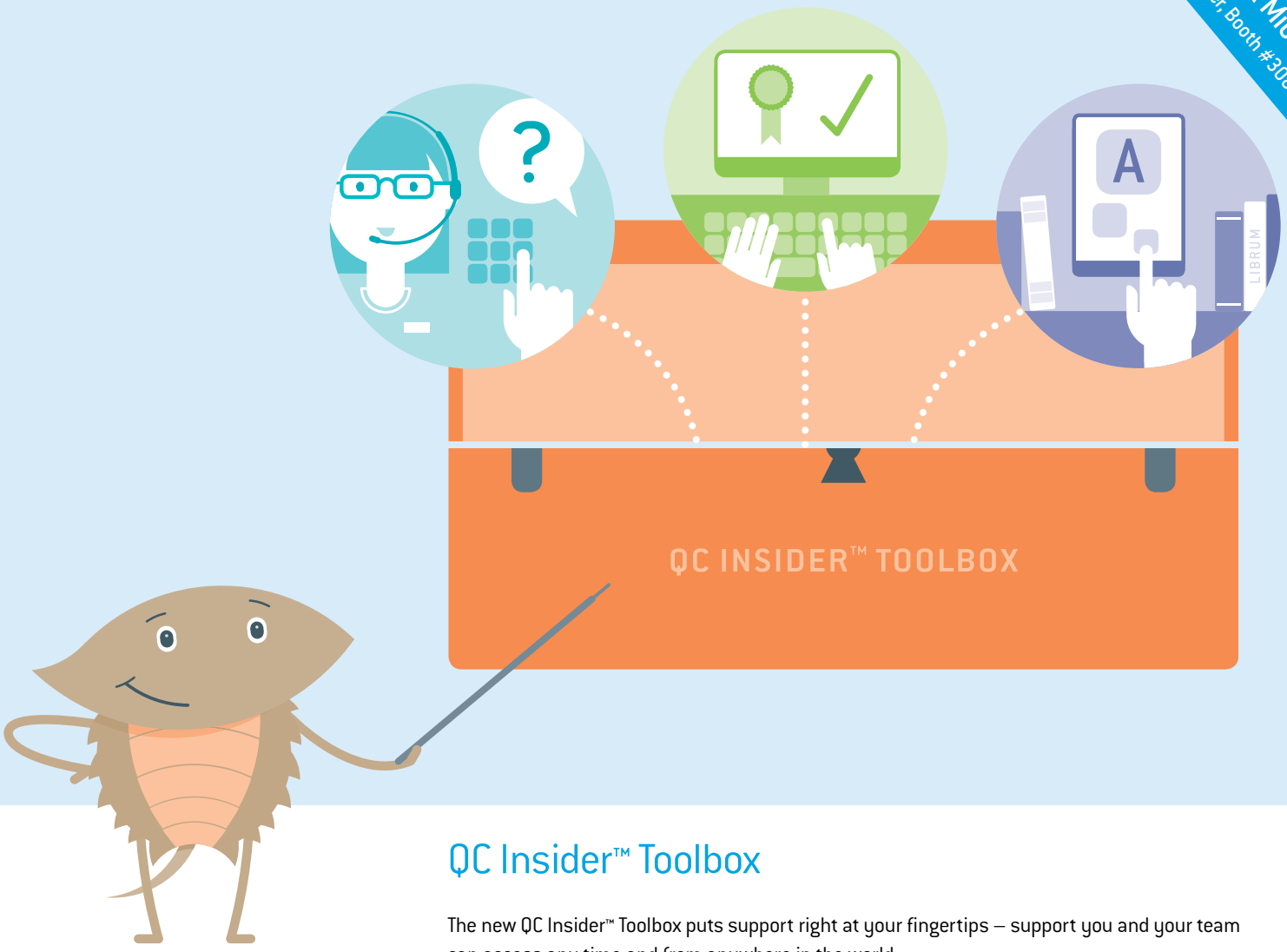

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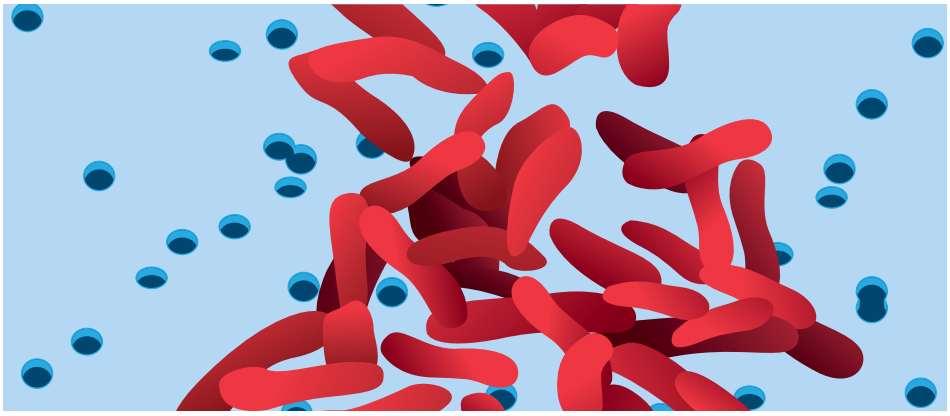
The Story Behind the 0.45 µm Membrane Pore Size Rating

Claire Fritz Briglia, EMD Millipore

Production personnel generally conduct filtration using membranes with pore size ratings of 0.22 µm or lower, focusing on retention of microbes and particulates, while those in the microbiology laboratory choose membranes with 0.45 µm pore size ratings. This begs the question, do your QC analysts understand why they use a different membrane pore size rating than that used in production?



In order to answer this query, it makes sense to review the use of membrane filtration in the QC laboratory. This technique for recovering microbes has a long history that began in the 1950s. Membrane filtration was first recognized as a suitable method over most probable number for recovering enterococci from water when enterococci were being studied as an indicator of fecal contamination ***(1).*** Pharma took another ten years to study membrane filtration for microbial limit tests used for antibiotic products. In the early 1960s, some users in the pharmaceutical industry discovered that membrane filtration with rinses of peptone solution had significant better recoveries than direct inoculation ***(2).*** As a result, membrane filtration became an appropriate method for detecting microorganisms in pharmaceutical products that contained antibiotics. Then, later on in the 1980s, additional studies showed that membrane filtration along with peptone rinsing and β lactamase addition was suitable for sterility testing because it demonstrated complete removal of cephalosporins ***(3).***

The ability to rinse away inhibition is one of the primary advantages of using membrane filtration in the QC lab. When pharmaceutical product contains antibiotics or preservatives, there is a risk of a false negative result if these chemicals are not diluted or neutralized. Developing a suitable method with rinse fluids helps ensure that contamination can be detected. USP <71> *Sterility Tests* describes the recipes for the various rinsing or diluting fluids. Fluids A, D, and K all contain peptone while both Fluid D and K also have some polysorbate 80, a common surfactant. Fluid K is appropriate for those "difficult to filter" products, and is easily identified as the "smelly" fluid with beef extract as one of its ingredients. All of these fluids are commonly used to assist in removing growth inhibition in pharmaceutical products.

Another benefit of using membrane filtration for QC microbiology is its capability to test large sample volumes. Traditional spread plate and pour plate methods have a lower sensitivity because only a small volume of product can be tested. USP <71> states that "the technique of membrane filtration is used whenever the nature of the product permits." Oily products and ointments as well as cell-based products can be challenging to filter. Certain solvents, detergents, and filtration additives, however, have been used successfully to assist in filterability. For example, isopropyl myristate is a solvent that is often used to dissolve sterile ointments in a sterility testing application.

Recovery of each type of microorganism can be influenced by chemistry of the membrane, pore size rating, type of growth media as well as incubation temperature. While there is some guidance and published information available on optimum growth media and incubation temperatures for specific organisms, there is little published data on pore size rating. Unlike a sterile filtration application in production, the microorganisms need the nutrients from the media in order to replicate and develop into a colony forming unit. If the flow of those nutrients is not consequential, the total recovery will be less. The majority of the industry utilizes a 0.45 µm pore size filter for microbiological testing. Still, few know why or can easily reference a study.

Study Looked at Range of Pore Sizes

In 2000, another study, itself also drawing on a 1996 study, evaluated recovery rates from different membrane pore size ratings versus colony sizes for various microorganisms ***(4-5).*** Mixed esters of cellulose served as the membrane type used in testing. The range of pore size ratings included: 0.22, 0.45, 0.70, 0.80 and 1.20 µm. Typical growth media for USP testing were selected based upon the microorganism tested. Acceptable recovery for membrane filtration was set as ≥90% relative to recovery from the spread plate method as a control. Each membrane was also challenged with ➤

Traditional spread plate and pour plate methods have a lower sensitivity because only a small volume of product can be tested

Brevundimonas diminuta to show retention capabilities; the filtrate was saved for enumeration.

Br. diminuta, *Enterbacter aerogenes*, and *Bacillus subtilis* all showed similar colony sizes for both 0.22 and 0.45 µm membrane pore size ratings but somewhat smaller than that of the spread plate method. The 1.20 and 0.80 µm filters had larger colonies than the spread plate while 0.70 µm was about the same size, or only slightly larger, than that grown on the spread plates. The other five organisms (*Pantoea agglomerans, Micrococcus luteus, Candida albicans, Clostridium sporogenes,* and *Escherichia coli*) tested did not demonstrate any difference in colony size when grown on spread plates.

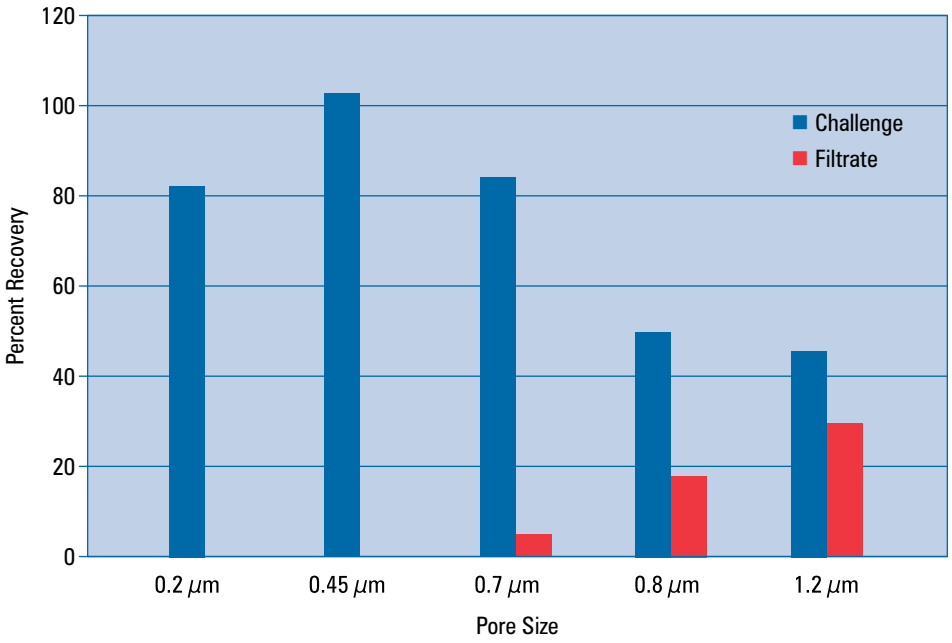
The average microbial recovery on each pore size rating was calculated using all eight test organisms. Membrane pore size ratings 0.45 and 0.70 µm both had recoveries ≥90% compared to the spread plate method for all eight organisms while pore size rating 0.80 µm demonstrated acceptable recoveries for all organisms. These recoveries, however, were lower than 0.45 and 0.70 µm.

Recovery Data Supports 0.45 Pore Size

This study also determined that some organisms like *Micrococcus luteus* and *Candida albicans* did not reveal any difference in recovery or colony size with any of the pore size ratings tested. *Pantoea agglomerans* also showed no difference in colony size for any pore size rating tested but still had low recoveries on both 0.22 and 1.20 µm like the other organisms tested.

In conclusion, the larger pore size ratings of 0.80 and 1.20 µm permitted significant passage of *Br. diminuta* at low levels but 0.22 and 0.45 µm demonstrated no passage **(Figure 1).** The 0.45 µm pore size rating had the best recovery for all tested organisms and had a similar colony size as 0.22 µm. Thus, this study confirmed why 0.45 µm is the best pore size rating for total count microbiology testing. Some specific organism testing, like total yeast and mold count, may benefit from using a larger pore size rating especially in regards to flow or colony size. If a pore size rating other than .45 µm is selected, however, relevant microorganisms should be tested for retention. This data clearly showed that even though 0.22 µm has excellent retention capability, its flow rate of nutrients may not suffice in recovering certain organisms.

Figure 1 Recovery of Challenge Versus Pore Size *(4)*



Because traditional microbiology methods in the pharmaceutical industry remain imprecise, it is very important to develop and validate robust and repeatable methods. If the product is filterable, large volumes can be tested to increase sensitivity. Inhibition can then usually be rinsed away to reduce the risk of false negatives. QC laboratory personnel realize the importance of media type and incubation conditions for optimum recovery with membrane filtration but few consider pore size rating, which is also a critical variable. Retention of the 0.45 µm pore size rating is similar to that of 0.22 µm, but does show better overall recovery of different organisms. This is why it is the chosen pore size rating in the QC laboratory.

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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.

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Profiling Leachables in Single-Use Biocontainers

Jian Liu, PhD, Hans Lee, PhD, Kiyoshi Fujimori, Michael Ronk, Matthew R. Hammond, PhD, and Yasser Nashed-Samuel, PhD, Amgen

In the face of unprecedented competition within the industry, biopharma companies must now undergo significant transformation in order to meet the challenge of reducing costs while also providing safe and effective therapies. The adoption of single-use systems (SUS) is one key strategy for those companies actively involved in this transition ***(1).*** Compared to traditional manufacturing technology, SUS deliver many advantages, such as reduced requirements for process validation, higher manufacturing flexibility, etc., which ultimately translate into higher operating efficiency and reduced manufacturing costs ***(2).***

In spite of these merits, the possibility exists that the plastic materials used for SUS may leach organic compounds, or inorganic substances, into the processing fluid or the final drug product; this remains a major concern. Such an undesired event could eventually compromise bioprocessing and/or significantly impact the safety, quality and purity of the drug product ***(3).*** Unfortunately, direct analysis of such leachates is difficult due to their low concentrations and their existence in complex matrices. Rather, indirect methods are normally used by extracting the component of interests under exaggerated conditions to produce an extractables profile—generally predictive of leachables ***(4).*** The capability to predict leachables from an extractable profile, however, depends to a large extent on the experimental conditions used. The most relevant information can be expected from an extractable profile generated with conditions close to those used in the processing or storage of the drug product.

Recently, researchers developed an effective extraction method in a study of extractable profiles of single-use biocontainers (SUBs), in which SUBs were extracted at 50°C for two days using an organoaqueous solvent containing 20% acetonitrile, 20% ethanol, and 60% water ***(5).*** The extraction conditions, along with a nontargeted analytical strategy, allowed for the generation and identification of an array of extractables compounds from the SUBs, including one later found harmful to mammalian cell growth ***(6).***

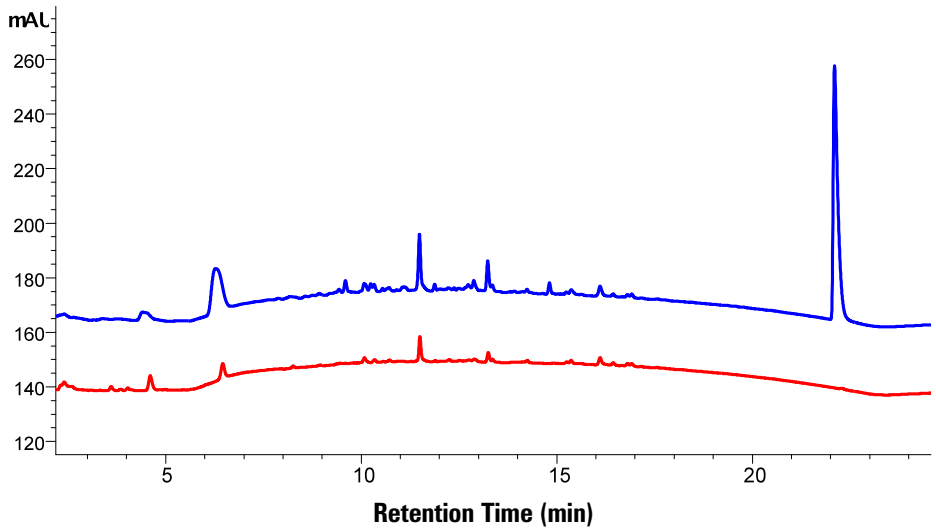
Conditions Showcase Leaching Danger

The researchers selected an extraction solvent with 60% water due to the fact that SUBs are largely intended for use with aqueous-based systems such as cell cultures or process buffers. As a polar solvent, water permits discovery of potential leachables, but has limited extraction strength toward poorly water-soluble extractables (e.g., hydrophobic compounds, fatty acids, etc.). These may leach out in some application systems containing organic components, such as proteins, surfactants and/or excipients, etc. The addition of 20% ethanol and 20% acetonitrile to water increased its extractive effectiveness, both in terms of the number of chemical species and the levels at which they are present in the extracts, as ethanol and acetonitrile are capable of solubilizing a wide range of organic compounds. An even larger number of organic compounds could be expected with a solvent of high organic content. More is not necessarily better, however; extractables generated from such solvents may not represent leachables generated from SUBs in aqueous-based applications, and would be of diminished value in predicting possible leachables.

Elevated temperatures and/or prolonged extraction are commonly used in extractables studies. A maximum temperature of 60°C is typically recommended by most SUB suppliers in order to avoid thermal degradation or loss of mechanical integrity. After preliminary testing with different temperatures, researchers considered 50°C as the most suitable extraction temperature that provided a large number of extractables without affecting the integrity of the system. With a temperature of 50°C, an incubation duration of two days was selected to approximate a condition of four days of cell culture at 37°C. This followed the Arrhenius-like time/temperature equivalence typically used in accelerated aging studies of polymers ***(7).***

The RP-HPLC/UV (reversed-phase high performance liquid chromatography/ultraviolet) analysis of the extraction from a commercially available SUB shown in **Figure 1** clearly demonstrated the advantages of using 40% organoaqueous solvents. Compared to water extraction, extraction with 40% organoaqueous solvent reproduced all the extractables, with most of the compounds extracted in much higher abundances. The higher levels of extractables produced provided significant ➤

Figure 1 RP-HPLC/UV chromatograms of extracts from a single-use biocontainer



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advantages in their identification and quantification, especially when only instruments of low sensitivity were available. As expected, unique extractables were also observed with the 40% organoaqueous solvent. In fact, observation of the excessive amount of the compound corresponding to the most abundant peak in **Figure 1** served as a critical clue to the discovery that excessive leaching of this compound, identified as (2,4-di-tert-butylphenyl) phosphate, into the cell culture significantly interfered with the growth of mammalian cells ***(6).*** Analysis of only the water extract from this SUB would give an incorrect impression that this compound would not present a problem for the SUB.

Nontargeted Approach Creates Results

In the study, a total of four commercially available SUB types, presterilized with gamma radiation, were extracted using the conditions described above. In total, 53 organic compounds (**Table 1**) were detected and identified using a nontargeted approach with an array of analytical methods, including GC (Gas chromatography)/MS (Mass spectrometry), RP-HPLC/MS and RP-HPLC/UV. The combination of these orthogonal analytical methods detected a wide range of volatiles, semivolatiles, and nonvolatile compounds of various physicochemical properties.

Table 1 Chemical compounds identified from extracts of the four SUBs studied; the compounds are tentatively grouped according to their proposed source

Proposed Source	Extractables from SUBs
tris(2,4-di-*tert*-butyl phenyl)phosphite	2,4-Di-tert-butylphenol [a,c]; 1,3-Di-tert-butylbenzene [a,c]; 2,4-Di-tert-butylphenylphosphate [b,c]; bis(2,4-di-tert-butylphenyl) phosphate [b,c]
Hindered phenolic antioxidants	7,9-Di-tert-butyl-1-oxaspiro (4,5)deca-6,9-diene-2,8-dione [a,b,c]; 3,5-Di-tert-butyl-4-hydroxyphenylpropionic acid [c]; 3,5-Di-tert-butyl-4-hydroxybenzoic acid [c]; 2,6-Di-tert-butyl-4-hydroxy-4-methyl-2,5-cyclohexadiene [a,b,c]; 3,5-Di-tert-Butyl-4-hydroxyacetophenone [b,c]; 3,5-Di-tert-butyl-4-hydroxybenzaldehyde [a,c]; 3-Tert-butylphenol [c]; 2,6 -dimethylbutylphenol [c]; 3,5-dimethylphenol [c]; 2,4,6-trimethylphenol [c]
Phthalates	Diethylphthalate [a,b,c]; Dibutylphthalate [b,c]; m-Dimethylisophthalate [b,c]; p-Dimethylterephthalate [b,c]
Polycarbonate	Bisphenol A [b,c]; Poly(Bisphenol A carbonate) containing substance [b,c]
Degradation of polyethylene	Octane [a]; Octene isomers [a]
Slip agents	Nonanoamide [b,c]; Decanamide [b,c]; Undecaneamide [b,c]; Tetradecaneamide [b,c]; Hexadecaneamide [b,c]; Oleamide [b,c]
Degradation of ethylene-vinyl acetate copolymer (EVA)	Acetic Acid [a]
Other	Decanedioic Acid [a,b]; Dodecenylsuccinic acid [a,b]; Benzoic Acid [b,c]; Benzyl alcohol [b,c]; 2-Phenoxyethanol [a]; Glycerol [a,b]; 2-Ethyl-1-hexanol [a]; Hexaethyleneglycol Dimethylether [a,b]; Tetraethyleneglycol [a,b]; Tetraethyleneglycol monomethylether [a,b]; Dipropylene glycol [a,b]; Tripropylene glycol [a,b]; Polypropylene glycol [a,b]; Isolongifolan-7-ol [a]; Dimethyl-1,4-cyclohexanedicarboxylate [a]; Butyl cyclohexanecarboxylate [a]; Hexanal [a]; Toluene [a]; 2-(2-butoxyethoxy)-ethanol [a,b]; Polyethylene glycol [b]; Polydimethylsiloxane [a,b]; Ethyl-4-ethoxybenzoate [a,b,c]; Ethyldiphenylphosphine oxide [b,c]; Caprolactam [b,c]

[a] Identified by GC/MS, [b] Identified by RP-HPLC/MS, [c] Identified by RP-HPLC/UV

Of the 53 compounds, 28 were identified by GC/MS, 31 by RP-HPLC/UV and 34 by RP-HPLC/MS using a combination of commercial and in-house databases and structure elucidation. The majority of the 53 extracted compounds were confirmed against reference standards. For extractables generated with 40% organoaqueous solvent, RP-HPLC/MS appeared to be a very powerful analytical technique, since a large portion of the extracted compounds were polar, hydrophilic-like, thus falling into the category of compounds best suited for RP-HPLC/MS analysis.

Overall, the majority of the identified extractables were degradation products of polymers and their additives (**Table 1**). For example, the most abundant compounds detected in the four SUBs were degradants of (2,4-di-tert-butylphenyl) phosphite, an antioxidant commonly added to polyolefins and other plastics. Also evident were degradants from other antioxidants such as butylated hydroxyl toluene, octadecyl (3-(3,5-di-tert.butyl-4-hydroxyphenyl)-propionate) or pentaerythritol tetrakis (3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate). Intact additives were also observed such as plasticizers (e.g., fatty acids, fatty acid esters and phthalates) and slip agents (e.g., fatty acid amides).

Inorganic elements, especially some heavy metals, can influence the stability, safety, and efficacy of drug products and cell culture. Using ICP (Inductively Coupled Plasma)/MS, the following elements were detected in the SUB water extract: boron, sodium, silicon, calcium and potassium. The estimated levels of these inorganic elements were in the range of ng/cm^2 levels and consistent across all four tested SUBs.

Conclusion

Selection of appropriate extraction conditions and analytical approaches is critical

for an extractables profile to be predictive of leachables produced in a specific application. The extraction condition described herein has proven to be effective for the profiling of organic extractables from SUBs. The profusion of extractable information obtained from this extraction protocol, along with the nontargeted analytical approach, indicates its great usefulness in the study of extractables from SUBs and other SUS materials used primarily for aqueous-based bioprocesses.

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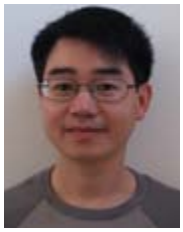
About the Authors



Jian Liu is currently a scientist at Amgen working on extractables/leachables assessment and nonconformance investigations related to clinical and commercial products.

Hans Lee has been with Amgen since 2003 and is responsible for extractables/leachables activities related to assessing product contact of manufacturing/infusion/device equipment and bulk/primary containers.

Kiyoshi Fujimori has been working for Amgen for 11 years in studies regarding extractables and leachables.

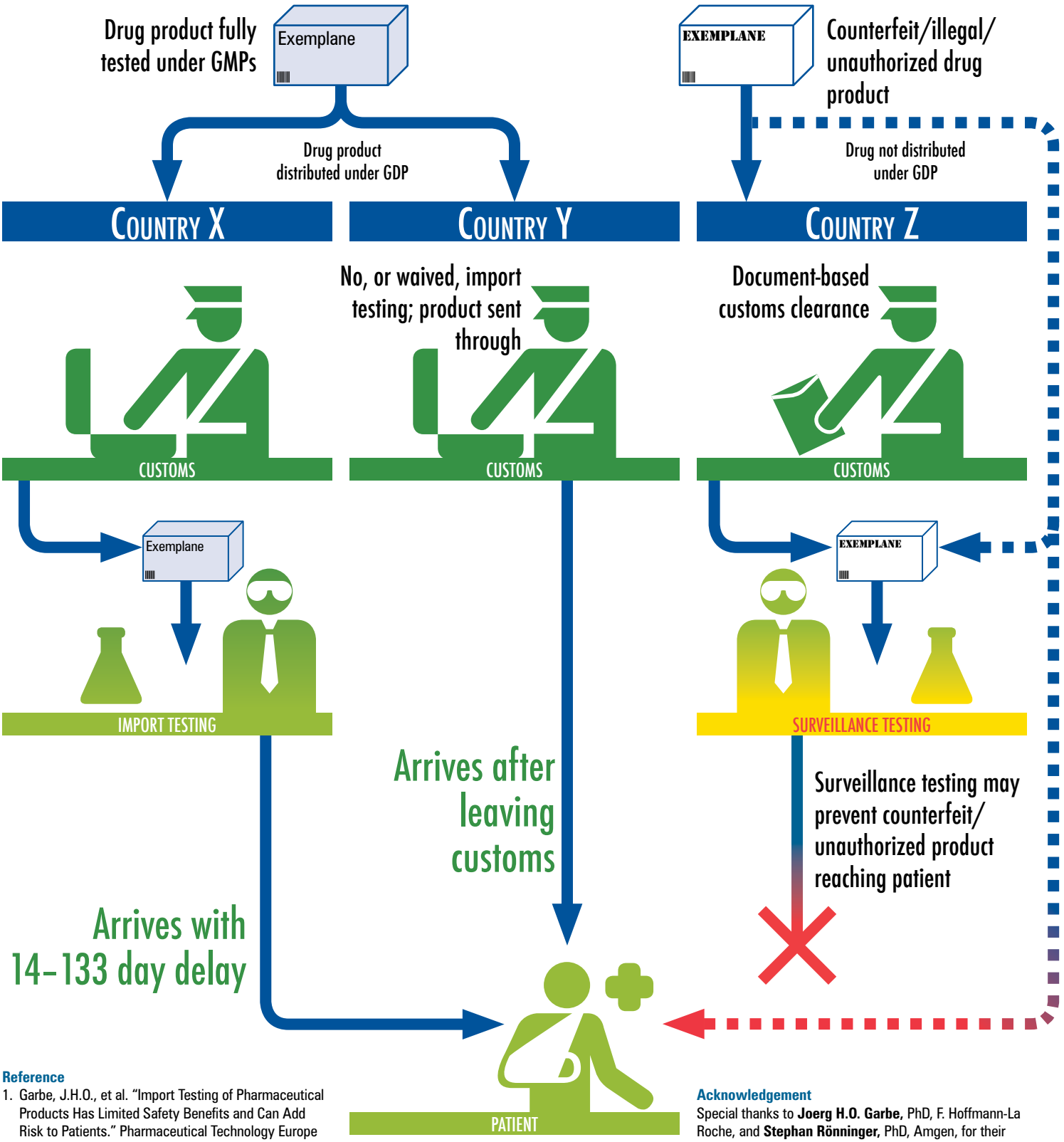
Mike Ronk is an analytical chemist with 30 years of experience in the structural characterization of proteins, peptides and small molecule pharmaceuticals.

Matthew R. Hammond's work in the Materials and Systems Analytics group at Amgen focuses on correlating raw material properties to process outcomes or product quality attributes, specializing primarily in plastic or polymeric materials.

Yasser Nashed-Samuel, PhD, is currently a principal scientist at Amgen in the Attribute Science, Process Development, Operation group.

The Value of Import Testing versus Surveillance Testing

Many countries and regions require import testing of pharmaceuticals entering the country/region. A batch may be analyzed up to 24 times ***(1).*** Postmarketing surveillance testing, however, offers the possibility to execute risk-based quality testing without delay to supply (i.e., significant reduction of remaining shelf life, RSL and risk of potential drug shortage) and is better suited for detecting counterfeit/illegal medicines or unauthorized imports.



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Acknowledgement

Special thanks to **Joerg H.O. Garbe,** PhD, F. Hoffmann-La Roche, and **Stephan Rönninger,** PhD, Amgen, for their assistance with this infographic.

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2015 New Releases

PDA Technical Books are scientific and regulatory books specifically developed for the resource needs of pharmaceutical and biopharmaceutical professionals. Check out the newest releases for 2015, many of which have quickly become best sellers. Responding to the needs of valued customers like you, all of our 2015 releases are also available in digital format.

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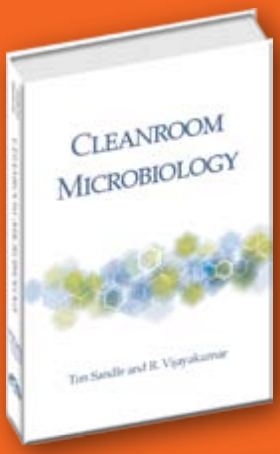

Cleanroom Microbiology
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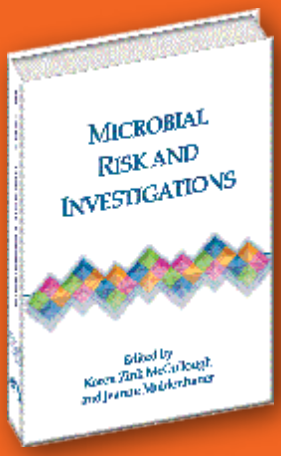

Microbial Risk and Investigations
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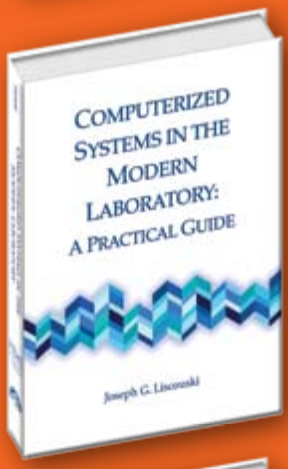

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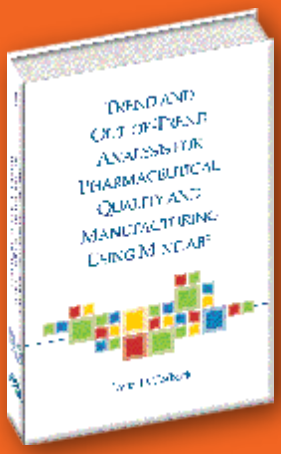

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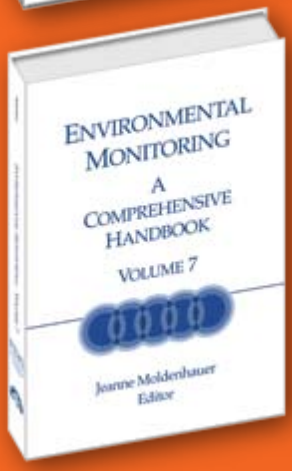

Environmental Monitoring: A Comprehensive Handbook, Volume 7
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snapshot

ICH Meeting Nails Hot Topics, Hammers Out Org Changes

Stephan Rönninger, PhD, Amgen

Twelve ICH working groups met in Fukuoka, Japan, June 5–11, to review a number of global guidelines, including four of special interest to PDA's membership that will significantly impact the industry. This same meeting also saw ICH outline plans to become an indepentent entity in 2016.

One ICH deliverable involves the Q&A document on the ICH Q7 guideline on GMPs for APIs, which is now available on the ICH website (tinyurl.com/qbtefp6). Not only will it be implemented in ICH regions but PIC/S and WHO expect to implement it as well. The U.S. FDA will publish the Q7 Q&A document in the *Federal Register* sometime in the coming months.

Another document, the draft Addendum to the ICH M7 Guideline on Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, will be submitted for public consultation in the United States, European Union and Japan. To further update existing guidance, an addendum to the guideline for residual solvents (ICH Q3C(R6)) includes two solvents.

The ICH Q12 Expert Working Group on Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management also met in Fukuoka for the second time and finalized a first draft of ICH Q12 for internal review.

The ICH Q11 Implementation Working Group continues to develop Q&A covering selection and justification of starting materials for manufacturing drug substances, and announced plans to meet in September for further discussion.

ICH to Leave IFPMA Umbrella in January

ICH also officially hammered out structural changes within the organization. Currently, it falls under the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA); however, ICH will become an independent entity with its own budget Jan. 1, 2016, retaining the ICH name.

In addition, both SwissMedic and Health Canada joined ICH as official parties. These two regulatory bodies join the U.S. FDA, PhRMA, the European Commission/EMA, the European Federation of Pharmaceutical Industries and Associations, Japan's PMDA, and the Japan Pharmaceutical Manufacturers Association. More regulatory agencies are also joining the technical discussions in selected EWGs and IWGs, such as agencies from Brazil, China, Singapore and South Korea.

PDA continues to support many ICH activities. ICH developments are frequently discussed at PDA conferences. For example, ICH Q12, which covers postapproval changes, served as a topic of discussion at the recent PDA–PIC/S regulatory conference in Brussels. Additionally, a PDA task force is developing a technical report on postapproval changes.

PDA also encourages understanding of ICH guidelines through international conferences, such as the Quality Systems meetings and the PDA–PIC/S trainings on GMP of APIs. PDA also seeks to work closer with regulators and members of industry on ICH topics in Brazil, South Korea and South Africa. PDA task forces also elaborated Quality Risk Management concepts in Technical Reports No. 44 and 54, and by providing practical examples in the four annexes to Technical Report No. 54.

We will continue to monitor ICH developments in the *PDA Letter* as they occur. If you're interested in volunteering on our ICH initiatives, please contact **Denyse Baker** at baker@pda.org.

About the Author

Stephan Rönninger, PhD, is the Head of External Affairs Europe, International Quality at Amgen (Europe) GmbH.

Science Driving New State-of-the-Art Practices for Microbial Control continued from page 22

Platco concedes that hers is just one opinion regarding the LER controversy. But the concern about newer microbiologists having a complete understanding of standard testing methods and protocols is valid.

While there are considerable developments under way to innovate microbial control, microbiologists still must have a complete understanding of existing methods. After all, building on the past is the epitome of good science. Without this holistic understanding, the future of microbial testing could become murky, especially as new control methods become available. Reviewing the latest research and existing literature will be the key to successful control programs. Still, these programs will need to use sound science and logic, or as Tidswell put it: "We've got to aspire to be more like Spock!"

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About the Experts

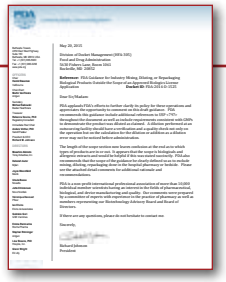
Edward C. Tidswell, PhD, is Quality Director for Baxter Healthcare. This global role covers the entire breadth of microbiological control, sterilization and sterility assurance across a diversified healthcare company.

Mark Pasmore, PhD, currently works for Baxter Healthcare Corporation as a Sr. Principal Engineer in the Technology Resources Sterility Assurance department.

Cheryl Platco currently oversees the Research Microbiology laboratory, performing microbiological testing for both pharmaceutical and vaccine development products.

PDA: FDA Guidance Should Add More USP <797> References

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



May 20, 2015

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

Rockville, MD 20852

Reference: FDA Guidance for Industry Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application Docket ID: FDA-2014-D-1525

Dear Sir/Madam:

PDA applauds FDA's efforts to further clarify its policy for these operations and appreciates the opportunity to comment on this draft guidance. PDA recommends this guidance include additional references to USP <797> throughout the document as well as include requirements consistent with GMPs to demonstrate the product was diluted as claimed. A dilution performed at an outsourcing facility should have a verification and a quality check not only on the operation but on the calculation for the dilution or addition as a dilution error may not be noticed before administration.

The length of the scope section now leaves confusion at the end as to which types of products are in or out. It appears that the scope is biologicals and allergenic extracts and would be helpful if this was stated succinctly. PDA also recommends that the scope of the guidance be clearly defined so as to exclude mixing, diluting, repackaging done in the hospital pharmacy or bedside. Please see the attached detail comments for additional rationale and recommendations.

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 the practice of pharmacy as well as members representing our Biotechnology Advisory Board and Board of Directors.

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

Sincerely,
Richard Johnson
President

PDA Commenting Task Force

Christopher Smalley, PhD, Merck (Lead) **Olivia Henderson ,** PhD, Biogen Idec **Matthias Henz,** Hospira Adelaide

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North America

FDA Releases Quality Metrics Guidance

In late July, the U.S. FDA released the draft guidance, *Request for Quality Metrics.* This document outlines a set of measurements the Agency will use to evaluate the quality of facilities and manufacturing processes. These measurements are: lot acceptance rate, product quality complaint rate, invalidated out-of-specification (OOS) rate and annual product review (APR) or product quality review (PQR) on time rate. Manufacturers will need to submit data to FDA covering the number of attempted lots, lots pending disposition for more than 30 days, lots released, OOS results, etc.

[Editor's Note: See p. 43 for more information about PDA's metrics conference in December.**]**

Comments are due Sept. 25.

Central America

Panama to Require Excipient Warnings

In early June, Panama's Ministry of Health announced new labeling rules for excipients with potential side effects, including a list of excipients that, if used in the manufacturing of a drug product, will need specific warnings on the resulting drug product. These rules become effective in 2016.

Europe

Israel, Brazil Added to EC API List

The European Commission in early July added Israel and Brazil to its list of countries with API manufacturing standards equivalent to those of the European Union. This means that API manufacturers in Israel and Brazil will not need written confirmation from European regulators that their GMPs are equal to European GMPs.

Currently, the United States, Switzerland, Japan and Australia are already on the list. Other countries seeking to be added to the list include New Zealand, South Korea, Taiwan, India and China.

EMA Releases Guideline on Finished Dosage Forms

In mid-July, EMA released its guideline covering manufacturing of finished dosage forms. This guideline details information that must be included in CTD Module 3 of the marketing authorization application. In addition, the guideline looks at current practices as they relate to global supply chains and manufacturing and takes the ICH Q8 guideline on pharmaceutical development into account.

Comments are due Jan. 9, 2016.

Key Regulatory Dates

Comments Due

September 25 — FDA Releases Quality Metrics Guidance

January 9 — EMA Releases Guideline on Finished Dosage Forms

January 31 — ICH Guideline Looks at Mutagenic Impurities

ICH

ICH Guideline Looks at Mutagenic Impurities

Following completion of Step 2b of the ICH process, the Addendum for ICH M7 Guideline Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk is now available for comment. This addendum complements the current harmonized M7 guideline and summarizes known mutagenic impurities regularly found during synthesis.

The deadline for comments is January 31, 2016.

Q&A for ICH Q7 Now Published

In July, ICH published the Q&A on GMP of APIs for ICH Q7 following over a decade of uncertainty over interpretations of sections covering GMP of APIs. ICH worked with PIC/S on the Q&A, which both entities hope harmonizes regulatory expectations in this key area.

Cargo Firms Vital to Drug Supply Chain

Schiphol Airport

Cargo and transport firms play a major role in the pharmaceutical supply chain—no small task considering the precautions and preparations required for the storage and transport of temperature-sensitive drug product. Those involved in the industry as well as regulators may have questions regarding these companies' abilities to handle such precarious cargo.

These questions come up frequently at various industry events and in trade publications. "How long will my cold chain product sit on the tarmac in Dubai?" "What systems are in place to prevent diversion?" "How will my product be monitored in transit?"

Well, this year's PDA *Pharmaceutical Cold & Supply Chain Logistics* conference offers an opportunity for attendees to receive answers to these questions directly from some cargo firms. The 2015 conference is being staged with the close involvement of Schiphol Cargo. As a result, the program is preceded by a half-day tour of Schiphol's pharma-related cargo facilities on Oct. 5 at Amsterdam's Schiphol Airport. There will be two alternative tour options available: visits to Menzies World Cargo and Yusen Logistics, or to Aviapartner Cargo and IJS Global. Both tours will culminate in a visit to Schiphol Group headquarters, where attendees will view a joint presentation by Air France KLM Cargo and C-Safe, followed by a networking reception.

"Schiphol cargo is delighted to welcome this important global event and its delegates to Amsterdam for the first time, and to have the opportunity of contributing to the program," said Schiphol Cargo pharma expert **Bart Pouwels.** "Pharma is one of Schiphol Cargo's key business targets, and we believe that demonstrating the correct handling of pharmaceuticals at Schiphol is vital for our future growth in this sector. We look forward to this opportunity of showcasing the Schiphol community's capabilities, to a distinguished gathering of pharmaceutical industry executives."

For more information, visit https://europe.pda.org/coldchain2015.

Quality Metrics: The Discussion Continues

Anil Sawant, PhD, Merck

The U.S. FDA published its long-awaited quality metrics draft guidance on July 27. We are now one step closer to making metrics a key, universally accepted driver of risk-based decision-making and continuous improvement. Regardless of the final formula used by FDA to calculate metrics from the submitted data, it remains prudent for companies to create and use metrics within their organizations that not only make a difference but are also uniquely valuable to their products and cultures (for more on quality culture, see the the report of PDA's quality culture survey in the September/October issue of the *PDA Journal of Pharmaceutical Science and Technology*). In fact, the draft guidance encourages companies to submit optional culture and process capability metrics and adopt a broader range of operational metrics.

With this in mind, how can we as manufacturers build quality metrics within our quality systems effectively? And where can we find the latest information on best practices from both regulators and industry leaders?

This year's *PDA Pharmaceutical Quality Metrics Conference* looks at current thinking and best practices for operationalizing quality metrics that drive continuous improvement within a firm. For the third year, the conference is co-chaired by an FDA representative (**Russell Wesdyk**) and an industry representative (**Steven Mendivil**). Presenters will discuss successful strategies to implement quality metrics into a pharmaceutical quality systems program, how to build an efficient and effective quality metrics program with limited resources and how a metrics program can drive not only product quality improvements but also foster a strong quality culture to prevent unintended consequences, such as too much emphasis on metrics that fosters bad behavior. Attendees will also hear from FDA and industry informatics experts on how to enable a metrics program and assure data accuracy and integrity during the transfer and submission process.

FDA will also provide an update on their quality metrics program, and industry leaders will provide their vision on the value of FDA's program.

Please mark your calendars and make plans to attend this year's *PDA Pharmaceutical Quality Metrics Conference* and engage in the dialogue for the next frontier for quality metrics. For information about the date and location, visit www.pda.org/metrics2015. To learn more about the PDA Education course following the meeting, please visit www.pda.org/metricscourse.

Anders Vinther, PhD, Sanofi Pasteur

PDA Advances Technological Innovation with gCPs

Do you want to advance new technologies for your manufacturing processes and analytical methods both quickly and globally?

Of course you do! Well, we might have a solution to this challenge here at PDA. Global change protocols, which are currently under development, are intended to facilitate innovation worldwide with an approach at the core of everything we do at PDA—applying sound science and the fantastic technological competences of our members to solve common problems.

What is this all about? It's been seven years since the ICH Q10 document on the Pharmaceutical Quality System (PQS) came out. That document outlines an expectation for manufacturers to continually improve and innovate. That expectation is also written in various regulatory documents, and, of course, the industry as a whole seeks to innovate and improve processes and methods, reduce variability, enhance the safety profile for drug products and make operations more cost effective. Once a company reaches the point of submitting an application for the introduction of a new technology of an already approved product, however, this is where "it" usually "hits the wall." Different countries have different postapproval change (PAC) processes in terms of classification and documentation requirements; getting a new technology approved globally from first to last country can take up to five years. These differences lead to chaos which encourages the status quo—certainly not innovation. But that is not what any of us—regulators, companies or patients—really want. So, let's think hard. ICH has decided to develop a harmonized and structured approach to the product lifecycle, which is also intended to facilitate innovation and ease the PAC chaos.

At PDA, we have decided to work from the angle of sound science to facilitate global harmonization, support the ICH Q12 work and to simply insist on technological advancement of our biopharmaceutical and pharmaceutical operations. Our work will be published as a series of standardized global Change Protocols (gCPs). Imagine implementing isolator technologies and transitioning from the use of traditional fill lines. Validating such isolators and comparing them with traditional lines should be based on sound science and not vary much from country to country. This is key to the gCPs. One protocol for one new technology applied and submitted globally, and only adapted to a company's specific conditions. And this is one protocol written by our expert members representing all segments of the globe from industry, academia and regulatory agencies. We plan to write gCPs for a number of new technologies.

Do you want to help us and learn more about this exciting initiative? There's still time to attend the *2015 PDA Manufacturing Science Workshop* at the end of this month. You can also contact PDA's Volunteer Coordinator at volunteer@pda.org to let us know if you are interested in helping us out.

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2015 Theme: *Operationalizing Quality Metrics: Putting Theory into Practice*

The long awaited FDA draft guidance on quality metrics has been published. At more than 20 pages long, there are many details and important consequences to understand.

The *2015 PDA Pharmaceutical Quality Metrics Conference* will advance the discussion regarding the FDA's s short- and long-term vision for metrics as the program evolves over time. Case studies that have been most valuable for improving quality and measuring and assessing a site's quality culture will be shared. Learn from industry leaders from companies that have successfully moved the needle on quality culture to improve product quality.

Hear from noted experts such as:

- **Barbara Allen, PhD,** Senior Director, Global Quality Systems, *Eli Lilly & Company*
- **Tara Gooen Bizjak,** Senior Science Policy Advisor for Pharmaceutical Quality, CDER, *FDA*
- **Gerald Heddell,** Director, Inspection Enforcement & Standards Division, *MHRA*
- **Karthik Iyer,** Consumer Safety Officer, CDER, *FDA*
- **Steven Lynn,** Global Head, Group Quality Compliance and Audit, *Novartis Services, Inc.*
- **Martin VanTrieste,** Senior Vice President Quality, *Amgen, Inc.*
- **Russell Wesdyk,** OPS Scientific Coordinator, CDER, *FDA*

To learn more and register, visit pda.org/metrics2015.

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

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

Keeping Our Industry Grounded in Sound Science

PDA published *Technical Report No. 69: Bioburden and Biofilm Management in Pharmaceutical Operations* in June. While reading it, I was surprised to learn that control strategies have not kept up with changing scientific knowledge: "In the latter part of the 20th Century, there was a fundamental shift in the understanding of microbial growth in various environments. The commonly held historical perception of bioburden was that it consisted of individual planktonic (free-floating) organisms….However, evidence accumulated over the past three decades suggests that biofilms are actually the preferred mode of microbial growth, with sessile cells sometime outnumbering planktonic organisms by several orders of magnitude." Yet, the technical report notes that "nearly all of the commercially available bioburden detection systems are based on planktonic cell detection."

Fascinating.

This is not the only area of pharmaceutical manufacturing that lags behind the science, but it is an important one. Other discrepancies exist, particularly in the area of microbiology. Look no further than the reliance on sterility testing over rapid methods. As such, it is important for companies to keep up with the latest trends in microbiology and microbial control.

PDA's *Annual Global Conference on Pharmaceutical Microbiology,* now in its tenth year, is an important forum for doing just that, and that's why we chose to make it the focus of this issue and this issue's cover. Each year, those involved in microbiology gather in a single location to discuss state-of-the-art technologies, advances in scientific understanding, and changes to regulatory and compendial policy. The articles included in this issue provide just a small window in the full breadth of topics covered at the conference.

Another area that isn't particularly grounded in sound science is the practice of import testing. PDA member **Stephan Roenninger** has been looking into import testing with a team of collaborators, and shared their findings with the *PDA Letter* for this issue's InfoGraphic. The results of their analysis are surprising.

We closed out the second *PDA Letter* Readership Survey. Response rates were excellent, and we've already suggested improvements to the *PDA Letter* Editorial Committee and the PDA Portfolio Steering Committee. Next year, thanks to your input, you will find more Science articles, which kind of loops us back to where this column started. We want to thank all the readers who provided their input. And also, we want to announce that **Chen Chen** of Lilly Suzhou Pharmaceutical Co. won a $100 gift card from MasterCard.

Finally, the new *PDA Letter* online launches with this issue. The new website brings a fresh design and opens up the possibility of more multimedia presentations and real-time publishing. Please check out the new site; all content is now available in mobile-responsive HTML.

PDA Letter

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