People • Science • Regulation

PDA Letter

Volume L • Issue 7 www.pda.org/pdaletter July/August 2014

Industry, FDA Still Wary of Supply Chain Security 32

PDA/FDA Show Issue

Follow the logo to find articles on the *2014 PDA/FDA Joint Regulatory Conference*

Volunteer Opportunities at PDA

Leadership

- PDA Executive Officers
- Director
- Scientific Advisory Board
- Biotechnology Advisory Board
- Regulatory Affairs and Quality Advisory Board
- PDA Committee Chair/Co-Chair
- Task Force Co-Chair

- Author/Contributor to the *PDA Letter*
- Author/Contributor to the *PDA Journal*
- Poster Presenter
- Attend Chapter Committee/Planning Meetings
- Technical Report Peer Reviewer

- Speaker
- Chapter Leader
- Task Force Member
- TRI Instructor
- Interest Group Leader

PDA Committees:

- Program Planning Committee
- Membership Committee
- PDA Letter Committee
- Education Committee
- Audit Committee

- PDA Membership
- Attend Global PDA Meetings
- Attend Chapter Events
- Survey Reviewer
- Interest Group Member
- Attend TRI Courses

Getting Involved

1,000 Over 1,000 volunteers worldwide actively carry out PDA's Mission

volunteer@pda.org

Aseptic Processing is the heart of PDA's core competencies. Our most popular course, the two-week Aseptic Processing Training Program, provides an in-depth, comprehensive learning experience into what is involved with the manufacture of aseptically produced products associated with manufacture of aseptically produced products, and our other courses in this area complement that program.

ASEPTIC PROCESSING TRAINING PROGRAM

October 13-17 and November 3-7 | Bethesda, Maryland
www.pda.org/2014aseptic5

PDA TRI's two-week comprehensive training program, taught by numerous industry leading experts in their fields with over 300 years of combined experience, will give you and your personnel the training and information needed to properly evaluate and improve your aseptic processes to ensure sterile products. This course provides 50 hours of hands-on laboratory training, equipping you with tools and actual experience you can bring home and apply immediately on the job.

RECOMMENDED PRACTICES FOR MANUAL ASEPTIC PROCESSES

November 12-13 | Bethesda, Maryland
www.pda.org/MAP1

This course will provide valuable and practical insights into the technological challenges associated with designing, operating and evaluating manual aseptic processes. Participants will come away with an understanding of how manual aseptic processes differ from automated ones, and what should be addressed as they work with manual aseptic processes in their own plants. They will also learn how process simulation testing should be designed and carried out to evaluate the manual aseptic processing operation.

QUALITY SYSTEMS FOR ASEPTIC PROCESSING

November 17-21 | Bethesda, Maryland
www.pda.org/quality

Optimize your Quality Systems associated with Aseptic Processing. You will receive a blend of theoretical knowledge in the lecture setting and hands-on application in PDA's clean room and microbiology laboratories, which provide the complete learning experience.

PDA Letter

Volume L • Issue 7 www.pda.org/pdaletter

Cover

Cover photo courtesy of Jim Greipp of Pau Hana Productions for Custom Processing Services (www.customprocessingservices.com). This photo depicts the GMP blending suite with two all-stainless double-ribbon blenders at Custom Processing Services' dedicated GMP facility in Reading, PA. As a CMO, CPS follows ICH Q7A and their API processing conforms to part 210/211 of CFR 21 from the U.S. FDA.

Departments

News & Notes

People

Science

Regulation

Voices of PDA

Contents

Features

Over 30 Regulators Scheduled to Speak in September

This September, over 30 experts from various U.S. FDA product centers and the field operations will speak about the topics important to you at the *2014 PDA/FDA Joint Regulatory Conference.* This is one of PDA's more popular conferences—no doubt because it offers you the chance to interact directly with regulatory experts. These speakers include CDER Director **Janet Woodcock,** MD.

The following is a list of confirmed FDA speakers:

- **Jeffrey Baker,** CDER
- **Kimberly Benton,** PhD, CBER
- **Ilisa Bernstein,** CDER
- **Monica Caphart**, ORA
- **David Cummings,** CDER
- **Gerald Dal Pan,** CDER
- **Bernadette Dunham,** DVM, PhD, CVM
- **Carl Fischer,** CDRH
- **Richard Friedman** CDER
- **Martine Hartogensis,** CVM
- **Mai Huynh,** CVM
- **Robert Iser,** CDER
- **Valerie Jensen,** RPh, CDER
- **Mansoor Khan,** PhD, CDER
- **Nancy Kirschbaum,** CBER
- **Steven Kozlowski,** MD, CDER
- **Mark Lee,** PhD, CBER
- **Rapti Madurawe,** PhD, CDER
- **Mary Malarkey,** CBER
- **Karen Midthun,** PhD, CBER
- **Ann Marie Montemurro,** ORA
- **Alicia Mozzachio,** CDER
- **Laurie Norwood,** CBER
- **Thomas, O'Connor,** PhD, CDER
- **Mahesh Ramanadham,** CDER
- **Carol Rehkopf,** CBER
- **Steven Silverman,** CDRH
- **Steven Solomon,** ORA
- **Douglas Stearn,** ORA
- **Janet Woodcock,** MD, CDER

Joining these FDA speakers is **Jeffrey Skene,** PhD, Senior Biologist/Evaluator, for Monoclonal Antibodies Division with Health Canada .

All of these speakers will discuss topics pertinent to industry. To learn more about this exciting event, see story on p. 50.

FDA Acting Chief Scientist Ostroff to Speak at PDA/FDA JRC

The U.S. FDA's **Stephen Ostroff,** MD, Acting Chief Scientist in the Office of the Commissioner will speak in a session on "FDA's Views on Manufacturing of the Future" at the *2014 PDA/FDA Joint Regulatory Conference.*

Ostroff joins 30 other confirmed FDA officials speaking at the conference, including Center for Drug Evaluation and Research Director **Janet Woodcock,** MD.

"Participation of the Agency's Chief Scientist in a session on the future of manufacturing shows that the *PDA/FDA Joint Regulatory Conference* offers a wider range of information beyond just regulatory information," said PDA President Richard Johnson. "The agenda includes many talks that are science and technology oriented, with a slant towards the Agency's role and activities in these areas."

Ostroff is responsible for leading and coordinating FDA's cross-cutting scientific and public health efforts. The Office of the Chief Scientist works closely with FDA's product centers, providing strategic leadership and support for FDA's regulatory science and innovation initiatives.

These initiatives include the Advancing Regulatory Science Initiative, the Critical Path Initiative, scientific professional development, scientific integrity, and the Medical Countermeasure initiative (MCMi).

Ostroff joined FDA in 2013 as Chief Medical Officer in the Center for Food Safety and Applied Nutrition and Senior Public Health Advisor to FDA's Office of Foods and Veterinary Medicine. Prior to that he served as Deputy Director of National Center for Infectious Diseases at the Centers for Disease Control and Prevention (CDC), where he was also Acting Director of CDC's Select Agent Program. He retired from the Commissioned Corps of the U.S. Public Health Service at the rank of Rear Admiral (Assistant Surgeon General).

PDA Volunteer Spotlight

Edward Smith, PhD

- Principal Consultant
- *Packaging Science Resources*
- Member Since | 1978
- Current City | King of Prussia, Pennsylvania
- Originally From | West Conshohocken, Pennsylvania

I believe that pharma and device packaging will continue to evolve

Edward's parents let him experiment with mixing household products before giving him a Gilbert Chemistry Set for Christmas

What is your favorite part about participating on a PDA Task Force?

Contributing to an effort that leads to something of value for those in the pharma industry. Seeing a publication or a PDA technical report that summarizes the many task force conference calls, meetings, and emails is very satisfying. Working with other task force members who have very different points of views and experiences is a learning experience.

Why did you choose to join PDA?

After several years of teaching and academic research, I joined the West Co. (now West Pharmaceutical Services) which was not a pharma company but provided packaging components and services to the pharmaceutical industry. PDA was my "window" into the world of pharmaceuticals. Although the industry is highly documented, there was much to learn from personal interactions at PDA meetings and other events.

How can PDA benefit someone who is established in the pharmaceutical industry?

Pharmaceutical science is an ever-evolving subject; keeping current is necessary whether you have one or 31 years in the industry. PDA provides lots of opportunities to keep learning…both from formal courses to one-on-one discussions with fellow members.

What is the most challenging part of your job?

Having retired from Wyeth Pharmaceuticals (now Pfizer) six years ago, I now provide consulting services in parenteral packaging. For the past three years, my work has been focused on the subject of Extractables & Leachables from packaging materials for injectables. The most challenging part of the job is keeping current on the evolving regulatory expectations so that I can provide my clients with the best guidance regarding their projects.

Tell us something surprising about yourself.

While not artistic, I do enjoy photography. I especially like to read about how photographers have captured a particular image.

Take a Sneak Peak at the Schedule at a Glance!

PDA 9th Annual Global Conference on Pharmaceutical Microbiology

Pharmaceutial Microbiology – Lessons from Today and Advice for Tomorrow

October 20-22, 2014 | BETHESDA NORTH MARRIOTT HOTEL & CONFERENCE CENTER | BETHESDA, MD

SCHEDULE AT A GLANCE

Monday, October 20, 2014

7:00 a.m. – 5:15 p.m.
Registration Open

8:00 a.m. – 9:15 a.m.
Welcome and Opening Keynote Address: Investigation of Norovirus Outbreaks

10:00 a.m. – 12:00 p.m.
Breakout Sessions
A1: Biofilms and Bioburden Control
B1: Parametric Release

12:00 p.m. – 1:15 p.m.
Exhibitor Roundtable Luncheon

1:15 p.m. – 3:15 p.m.
Breakout Sessions
A2: Developing Sterilization Technologies
B2: Objectionable Microorganisms in non-Sterile Pharmaceutical Drugs

4:00 p.m. – 5:30 p.m.
Session P2 – Urban Myths

5:30 p.m. – 6:45 p.m.
Networking Reception and Poster Presentations in Exhibit Hall

Tuesday, October 21, 2014

7:00 a.m. – 5:15 p.m.
Registration Open

8:15 a.m. – 9:15 a.m.
Session P3 – Day 2 Keynote Address: The Original Description of the LAL Test – Past to Present

10:00 a.m. – 12:00 p.m.
Breakout Sessions
A3: Endotoxin Testing
B3: Micro Data Deviations Sterile and Non-Sterile

12:00 p.m. – 1:15 p.m.
Networking Luncheon

1:15 p.m. – 3:15 p.m.
Breakout Sessions
A4: Innovative Technologies: Microbiology Testing Technologies
B4: Risk Assessments

3:45 p.m. – 5:15 p.m.
Session P4 – Emerging Leader

Wednesday, October 22, 2014

7:00 a.m. – 12:30 p.m.
Registration Open

7:00 a.m. – 8:00 a.m.
Interest Group Session: Sterile Processing IG

8:15 a.m. – 9:30 a.m.
Session P5 – USP Updates

9:45 a.m. – 10:30 a.m.
Session P6 – Day 3 Keynote Address: Regulatory Updated

11:00 a.m. – 12:30 p.m.
Session P7 – Ask the Regulators Panel Discussion and Closing Remarks

LEARNING OBJECTIVES

At the completion of this conference, participants will be able to:

- Discuss many areas of microbiology on topics such as managing microbial risk, microbial contamination and risk management in aseptic processing/manufacturing
- Explain the elements of microbiology data deviations
- Identify current trends in microbiology (new technologies in both testing and sterilization)
- Summarize new advances in rapid microbiological methods, microbial identification technologies, endotoxin testing.
- Identify local regulatory and pharmacopeial expectations
- Implement appropriate strategies for maintaining a non-sterile manufacturing environment (the importance of microbial identification, testing for and understanding the impact of objectionable organisms and resolving microbial challenges associated with non-sterile operations)

WHO SHOULD ATTEND

Departments: Microbiology, Compliance, Engineering, Manufacturing, QA/QC, Development, Regulatory Affairs, Research and Development, Validation

Level of Expertise: Executives, Management, Scientists/ Technicians

Job Function: Scientist/ Technician, Research, Analyst, Bench personnel

Visit **www.pda.org/microbiology2014** for more information.

EXHIBITION: OCTOBER 20-21 | COURSES: OCTOBER 23-24

tails from the trail

PDA President Travels Full Circle to Support Activities

Richard Johnson, PDA President

This spring has been another busy travel period for me, meeting members and spreading the word about PDA. I would like to share with you some of the highlights of these trips.

2014 PDA Annual Meeting, San Antonio, Texas

The 68th *PDA Annual Meeting* was a great success, and one of the highlights for me was the annual awards banquet, where we recognized the many members who have made great contributions to PDA **[Editor's Note:** see story on p. 6 of the June *PDA Letter* for an overview of these award winners**].**

Metro Chapter, Somerset, N.J

The Metro Chapter was kind enough to invite me to speak on PDA's perspectives on regulatory compliance. I shared many of our ongoing activities designed to help advance science-based understanding of improvements in quality and regulatory compliance.

(l-r) Richard Johnson, PDA; Anthony Grilli, Focus Scientific, Chapter Secretary; Pramod Sharma, Chapter Vendor Committee member; Mary Huynh, Sanofi, Chapter Treasurer

Korea Chapter, Seoul Korea

I met with Chapter President **Dr. Paik** and other PDA Korea Chapter board members, and we discussed ways in which PDA can serve members in Korea. I pointed out that Korea is an important pharmaceutical manufacturing base, and this chapter is in the vanguard of meeting the needs of these industry professionals.

Singapore Chapter, Inaugural Event

Trevor Swan and I traveled to Singapore, along with PDA board member **Junko Sasaki,** to support the first event of the newest PDA chapter. The event was well attended by members from industry and the Health Sciences Authority (Singapore regulatory authority). With active chapter leaders like **Maureen Hertog, Sateesh Yelisetti, C.P. Kok,** and **Wayne Lee,** I am sure that this chapter will continue to grow.

Texas Chapter, Fort Worth, Texas

Finally, I was able to attend our latest chapter event in Texas, this time in Fort Worth. PDA Chair **Hal Baseman** and I met with members in Alcon/Novartis, and then had a great chapter meeting at Rahr's Brewery. The setting was pure Texas casual, but the discussions and networking were classic PDA.

PDA Who's Who

Woo-Hyun Paik, PhD, Korea Pharm. Tech. Education Center (KPTEC)

Trevor Swan, Manager, Membership and Chapters, PDA

Maureen Hertog, Site Quality Head, Novartis Singapore Pharmaceutical Manufacturing

Sateesh Yelisetti, Baxter

Chia Phei Kok, Senior CSV Consultant, Visentic Solutions

Wayne Lee, PhD, Director, Asia – Global Technical Support, Pall Life Sciences

Hal Baseman, Chief Operations Officer, ValSource

Build Your Network: Attend the 2014 PDA/FDA JRC

Building your network is critical to advancing your career, and no PDA event offers networking opportunities like the *PDA/FDA Joint Regulatory Conference*. Year after year, this event offers a number of exciting networking events and access to the most important FDA officials to the drug and device industries.

Attend one or all of the following networking opportunities to mingle, share lessons learned from conference sessions and make career-long (and in some cases, lifelong) connections!

Orientation Breakfast (Monday, Sept. 8, 7–8 a.m.)

New PDA members can learn more about the Association from our Membership team as well as volunteers. Members will also learn how they can volunteer for PDA. (*By invitation only*)

Networking Reception (Monday, Sept. 8, 6:15–7:30 p.m.)

All conference attendees are invited to attend a networking reception in the Exhibit Area and encouraged to chat with our exhibitors. Refreshments will be provided.

Gala Event: Emerald City (Tuesday, Sept. 9, 6:30–9 p.m.)

All conference attendees are invited to follow the yellow brick road to interesting twists and turns that will lead you to an amazing event that is sure to satisfy your appetite and curiosity. As you enter Emerald City, be prepared to expect the unexpected.

There will be additional opportunities for networking during refreshment breaks throughout the conference. To learn more, see story on p. 50.

PDA Visitors | PDA Headquarters

Single-Use Systems Cross-Organizational Meeting

A cross-organizational meeting was held at PDA headquarters on May 14 for organizations with scientific and technical agendas related to single-use systems. The primary goal of the meeting was to create a shared understanding of what each group is planning regarding SUS implementation. The following organizations were represented: ASTM, ASME-BPE, PDA, BPOG, BPSA, ELSIE, U.S. FDA (CBER, CDER), PQRI and USP.

Medical Perspective on Visible Particulates Task Force

(l-r) Alan Baseman, MD, J&J; Stan Bukofzer, MD, Hospira; Janie Miller, Senior Project Manager, PDA; John Shabushnig, PhD, Insight Pharma; Minerva Devera, Emergent; John Ayres, MD, Eli Lilly; Richard Watson, Merck; Morgan Holland, Coordinator, PDA

2014 PDA Pharmaceutical Quality Metrics Conference Planning Committee

(l-r) Steven Mendivil, Amgen; Neil Stiber, PhD, CDER, U.S. FDA; Denyse Baker, PDA; Joyce Bloomfield, Merck; Wanda Neal, PDA; Russell Wesdyk, CDER, FDA; Anil Sawant, PhD, J&J; Rich Levy, PDA

Representatives from Chinese Associations and Regulatory Bodies Visit PDA

On May 19, PDA welcomed a Chinese delegation consisting of Li Huifen, Chinese Pharmacopoeia committee; Yu Hui, Zhejiang Institute for Food and Drug Control; Zhang Weimin, China National Pharmaceutical Packaging Association; Robin Song, Baxter (China) Investment Co.

Robert Dana, Sr. Vice President, TRI, PDA, (left) and PDA President Richard Johnson pose behind the delegation.

2014 PDA Knowledge Management Workshop

May 19–20 | Bethesda, MD

P3: Experiences from Other Industries

(l-r) Robert Woolfenden II, Amgen; Cindy Hubert, American Productivity and Quality Center; Edward Hoffman, PhD, NASA

P1: Role and Value of Knowledge Management in the Development of Process Understanding

(l-r) Lara Collier, Genentech; Justin Neway, PhD, Accelrys; David Reifsnyder, PhD, Genentech

P2: Process Validation/Stage 3 – Role Knowledge Management

(l-r) Igor Gorsky, ConcordiaValSource; Eda Ross-Montgomery, PhD, Shire; Paige Kane, Pfizer; Joseph Brennan, PhD, Pfizer

Volunteer Recognition

PDA President Richard Johnson recognized volunteer Tor Gråberg for his contributions to PDA's international activities with the Michael S. Korczynski Award.

(l-r) Christopher Smalley, PhD, Merck; Tor Gråberg, Medical Products Agency Sweden; Richard Johnson, PDA; Stephan Roenninger, PhD, Amgen

P1: Pharmaceutical Packaging Systems: An FDA Perspective on Quality and Risk Management

(l-r) Donald Klein, PhD, CDER, U.S. FDA, Destry Sillivan, CBER, FDA; Diane Paskiet, West

P2: Challenges Facing the Pharmaceutical Industry

(l-r) Ronald Iacocca, PhD, Eli Lilly, Steven Badelt, PhD, Suttons Creek; Theodore Randolph, PhD, University of Colorado

P3: Drug Firm and Supplier Relationships

(l-r) Roger Asselta, Genesis Packaging; Nicholas DeBello, DeBello & Associates; David Cady, Amgen

P5: Understanding Container Closure Systems and Potential Risks to Pharmaceutical Quality

(l-r) Daniel Norwood, PhD, Boehringer; Diane Paskiet, West; Derek Duncan, PhD, Lighthouse Instruments

P6: Potential Problems for Primary Packaging Variations

(l-r) Olen Stephens, CDER, U.S. FDA; Michael Regn, Hospira; Daniel Haines, PhD, Schott Pharma

P7: Track & Trace

(l-r) Greg Cathcart, Excellis; Richard Johnson, PDA; Bryan Orton, Eli Lilly

P2: The Impact of Globalization of the Biopharmaceutical Supply Chain

(l-r) Atul Tandon, BMS; Kevin Nepveux, Pfizer; Allan Coukell, Pew; Ilisa Bernstein, PharmD, CDER, U.S. FDA; Leon Hayward, U.S. Customs and Border Operations; Martin VanTrieste, Amgen

P8: Best Practices in Supply Chain Temperature Management, Purchasing Controls and Security

(l-r) Rafik Bishara, PhD; Gwyn Murdoch, Eli Lilly; David Ulrich, AbbVie

P4: Q&A With the U.S. FDA

(l-r) Steven Wolfgang, PhD, CDER; Connie Jung, PhD, CDER; Mark Paxton, CDER; Brian Johnson, Pfizer, T.J. Christl, ODSIR, CDER,

P6: Tools to Deal with Multi-tier Supplier Challenges

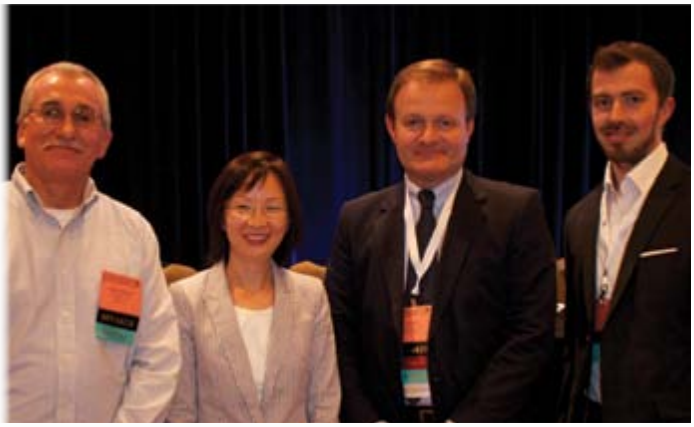
(l-r) Lucy Cabral, Genentech; Patricia Turney, Amgen; Bindiya Vakil, Resilinc

P7: FDA's Supply Chain Security Pilot Program

(l-r) Wes Schmidt, AbbVie; Elizabeth Tritt, U.S. Customs and Border Protection, T.J. Christl, ODSIR, CDER, U.S. FDA, Jennifer O'Brien, AbbVie

P9: Overview of Worldwide Legislation, Regulation and Guidance

(l-r) Mark Paxton, CDER, U.S. FDA, Susan Schniepp, Allergy Laboratories, Martin VanTrieste, Amgen



P7: Virus Clearance 2: Virus Removal/Inactivation

(l-r) Christopher Gallo, Pfizer; Qi Chen, PhD, Genentech; Thomas Kreil, PhD, Baxter; Christian Bell, PhD, Roche

P2: Emerging Viruses and Testing

(l-r) Dayue Chen, PhD, Eli Lilly; Marc Eloit, PathoQuest; Arifa Khan, PhD, CBER, U.S. FDA; Ivar Kljavin, PhD, Genentech

P9: Update on TSE Risk

(l-r) Johannes Bluemel, PhD, Paul-Ehrlich-Institut; Luisa Gregori, PhD, CBER, U.S. FDA; Olivier Andreoletti, National Institute of Agronomic Research (France)

P8: Viral Clearance/Strategic Considerations

(l-r) Johannes Bluemel, PhD, Paul-Ehrlich-Institut; Bryan Dransart, Amgen; Hannelore Willkommen, PhD, RBS Consulting; Thomas Kreil, PhD, Baxter; Kurt Brorson, CDER, U.S. FDA; Christopher Gallo, Pfizer; Christian Bell, PhD, Roche

P10: Evolving Detection Methods for CJD and vCJD

(l-r) Albrecht Groener, PhD, CSL Behring; Johannes Bluemel, PhD, Paul-Ehrlich-Institut; Dorothy Scott, CBER, U.S. FDA; Olivier Andreoletti, National Institute of Agronomic Research (France); Luisa Gregori, PhD, CBER, FDA; Hermann Schaetzl, MD, University of Calgary

P5: Viral Safety Risks with Reagents Used During Expression Cell Cloning

(l-r) Dayue Chen, PhD, Eli Lilly; Christian Sauder, CBER, U.S. FDA; Kurt Brorson, PhD, CDER, U.S. FDA; Maria Tami, CDER, U.S. FDA

TOOLS FOR SUCCESS

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

DIY Resume Writing Advice

Perry Newman

THE FOLLOWING are some *insider insights* on how to create a solid DIY resume. That is, if you're brave enough to undertake the task on your own knowing full well the consequences if in the end, your resume turns out to be a faux 2 carat cubic zirconia instead of the brilliant 2 carat diamond you hoped it would be.

Style and Format: It is mind boggling how many different styles and formats exist for resumes today. Of course not every style works for each person and personality. Keep this thought in mind: in *Indiana Jones and the Last Crusade,* the villain looking for the Holy Grail chose the glittery cup and died. The Templar Knight said "he chose poorly." When Indy chose the most modest cup and lived, the Templar then told him, "you chose wisely." The moral is "you need to know what will work for you and not for someone else."

What you can do is what I do once a month to get new ideas. Google relevant resume samples in your field and related ones for style and format purposes. View at least 200 (I view >500 at a time) to see how many ways the same type of person can be presented to the same audience. Look for the ones that look generic, which are over used, which stand out in your mind, and which would most appeal to you if you were a decision maker and print out the 50–75 you like the most. Then choose the three styles and/or formats you think are best for you and create different resume versions around them.

Content: I'm fond of saying a resume is less about you and all about what the employer wants to buy. So, again, I would suggest you go online and print out 75 jobs that you want to apply for (location does not matter) and read them over, taking notes about what the common denominator is in each job posting. This will then be the basis of your core resume.

Wording: Once you know what you need to say, look over all the resumes and jobs you printed out to see how others phrased what you want to say. If a bullet or sentence fits your speech pattern and personality and reflects what you need to say, use it but not verbatim. Rewrite it and make it your own.

The Final Step: Never ever submit a resume without having it doubly proofed and critiqued. Wait at least one day before you proofread it yourself and then have someone with top grammar/spelling skills look it over for you. After seeing it so many times and knowing what should be there, you are prone to errors if you only proof it yourself. Also, have it critiqued by someone who knows what employers are looking for before you submit it. You may think it is great but they may have a different opinion from a more realistic perspective.

Whenever I come up with a new style or format, I test it out first by seeking feedback among a group of two dozen people I know and trust as subject matter experts who will give me critical feedback. They're brutally honest and tell me what they see and why it works or does not work in their expert opinion, and they make suggestions about what I might want to change. Then, I will take it all into consideration and make the necessary adjustment. If they all say it looks great but it won't sell, I'll abandon it for good.

The Consequences: In addition to a poor resume not generating interest in you from employers for jobs you've applied for, your poor resume will go into the company/recruiter applicant tracking systems (ATS) or database. So, if you upload or submit a better version at a later date, the original poor version can remain in the system for 30 days, or even up to a year, depending on how often the database is purged and a new resume can replace it. So, make sure the resume you send is the absolute best before you send it along.

About the Author

Perry Newman CPC/CSMS is a nationally recognized career services professional; an executive resume writer and career transition coach, certified social media strategist, and AIPC certified recruiter. For a complimentary critique, email your resume to perry@perrynewman.com.

New Electronic PDA/DHI Booklets in PDF Format

API Residues and Cleaning
Author: William E. Hall
Chapter excerpted from the book:
Cleaning and Cleaning Validation, Volume 2
Item No. 17954

Auditing the CMO
Authors: Thomas L. Thorpe and Jessica K. Walker
Chapter excerpted from the book:
Pharmaceutical Outsourcing: Quality Management and Project Delivery
Item No. 17955

Best Practices in Implementing Quality Agreements
Author: Ken Drost
Chapter excerpted from the book:
Pharmaceutical Outsourcing: Quality Management and Project Delivery
Item No. 17956

Cleaning Agents and Cleaning Chemistry
Authors: George Verghese and Nancy Kaiser
Chapter excerpted from the book:
Cleaning and Cleaning Validation, Volume 1
Item No. 17957

CMOs for Early Phase Biologicals Production: Contract Manufacturing and Control
Authors: John Conner, Rabi Prusti and Bill Minshall
Chapter excerpted from the book:
Pharmaceutical Outsourcing: Quality Management and Project Delivery
Item No. 17958

Endotoxins
Author: Karen Zink McCullough
Chapter excerpted from the book:
Contamination Control in Healthcare Product Manufacturing, Volume 1
Item No. 17959

Practical Approaches to Sterility Testing
Author: Tim Sandle
Chapter excerpted from the book:
Sterility Testing of Pharmaceutical Products
Item No. 17960

QbD and Process Validation – Complementary Lifecycle Approaches
Author: Paul L. Pluta
Chapter excerpted from the book:
Quality by Design — Putting Theory into Practice
Item No. 17961

Risk Management for Combination Products
Author: Edwin Bills
Chapter excerpted from the book:
Combination Products: Implementation of cGMP Requirements
Item No. 17962

Single-Use Systems for Contamination Control
Author: Maik W. Jornitz
Chapter excerpted from the book:
Contamination Control in Healthcare Product Manufacturing, Volume 1
Item No. 17963

Small Molecule Sterile Liquid Product Residues and Cleaning
Author: Valerie Welter
Chapter excerpted from the book:
Cleaning and Cleaning Validation, Volume 2
Item No. 17964

Meeting *Preview*

Interest Group Meeting Schedule

As always, relevant interest groups will meet for the first two days of the *2014 PDA/FDA Joint Regulatory Conference*. Below is a schedule of Science and Biotech interest groups. **Note:** All interest group meetings are open to meeting registrants (For RAQAB interest group meetings, see p. 50).

Monday, Sept. 8	Tuesday, Sept. 9
5 p.m. – 6:15 p.m.	**5 p.m. – 6:15 p.m.**
Process Validation Interest Group	Facilities and Engineering Interest Group
Visual Inspection Interest Group	Combination Products Interest Group
	Sterile Processing Interest Group

Journal *Preview*

July–August Issue Looks at Quality

What is the state of quality in the pharmaceutical industry today? Two articles try to answer this question in the July/August issue. **Robert Kieffer** explores how the role of Quality Assurance has changed in the industry while **Anthony Newcombe** looks at how Quality by Design has evolved for biologics development.

Guest Editorial

Geoffrey S. F. Lingand Eugene J. Choi. "Battlefield Medicine: Paradigm Shift for Pharmaceuticals Manufacturing"

Commentary

Robert G. Kieffer, "The Changing Role of Quality Assurance in the Pharmaceutical Industry"

Technology/Application

John K. Towns, "Human Factors Studies for Injectable Combination Products: From Planning to Reporting"

"Gary" Guiyang Lie, et al., "Classification of Glass Particles in Parenteral Product Vials by Visual, Microscopic, and Spectroscopic Methods"

Review

Anthony M. Cundell, "Justification for the Use of Aseptic Filling for Sterile Injectable Products"

Case Studies

Sue Walker and Ernie Jenness, "Advantages of Single-Use Technology for Vaccine Fill-Finish Operations"

Anthony R. Newcombe, "The Evolution of Quality by Design (QbD) for Biologics"

Volker Rupertus, et al., "A Quick Test To Monitor the Delamination Propensity of Glass Containers"

Research

Tejal A. Mehta and Kunal N. Patel, "Formulation Design and Characterization of an Elementary Osmotic Pump Tablet of Flurbiprofen"

Tech *Trends*

NASA Maps Out Knowledge Management Mission

Rebecca Stauffer, PDA

Are you retaining institutional knowledge within your organization to ensure its future success?

For NASA's Chief Knowledge Officer **Edward Hoffman,** PhD, ensuring the success of the Agency's space missions involves extensive collaboration, effective talent management and cultivating a culture of knowledge.

"It took me awhile to figure out how to fit knowledge into that equation but it's one of the essentials," he explained during his talk, "Knowledge at NASA," at the *2014 PDA Knowledge Management Workshop,* adding, "And so if we have failures, and those failures look a lot like failures that happened before, that's a serious problem for us."

In late 2013, NASA adopted a new knowledge management policy across the organization, following a decade of analysis from key stakeholders including the General Accounting Office, Aerospace Safety Advisory Panel and Office of Inspector General. These stakeholders cited weaknesses and inconsistencies in the sharing of knowledge and lessons learned across the Agency. NASA's new approach to knowledge management includes an official knowledge policy (this features a federated governance approach, formalized roles and responsibilities and development of common vocabulary across the organization), expanded knowledge networks with other government agencies and industry partners, and a knowledge map.

NASA's Knowledge Map is an online resource that can be found at km.nasa.gov/knowledge-map. The Knowledge Map includes hyperlinked information sorted by organizations, points of contact, and knowledge categories. These categories include case studies and relevant publications, face-to-face knowledge services, online tools, knowledge networks, lessons learned and taxonomy tools.

The online knowledge map is still a work in progress, Hoffman emphasized. While an online resource might be great for NASA, the knowledge management tool that your organization implements should reflect your organization's unique needs. According to Hoffman, whatever knowledge tool you implement should answer the questions of "what helps the system" and "what helps the team?"

About the Expert

Edward Hoffman, PhD, is the director of the NASA Academy of Program/Project and Engineering Leadership (APPEL) and NASA's Chief Knowledge Officer. He works within NASA to develop the agency's capabilities in program and project management and engineering.

Task Force *Corner*

How Clean is Your Manufacturing/Testing Space?

Jahanvi (Janie) Miller, PDA and Rebecca Stauffer, PDA

Can you identify the systematic elements essential to assuring an appropriate and compliant cleaning and disinfection program? Are you involved in the manufacturing of sterile products in an aseptic environment? Do you seek suggested best practices for designing a comprehensive disinfection program?

If you answered "yes" to any of these questions, the technical report team behind the upcoming PDA technical report on *cleaning* and *disinfection* hopes you will consider reviewing this guidance document. The report will cover cleaning and disinfection within both controlled and noncontrolled environments, offering suggested practices for nonproduct contact surface cleaning and disinfection.

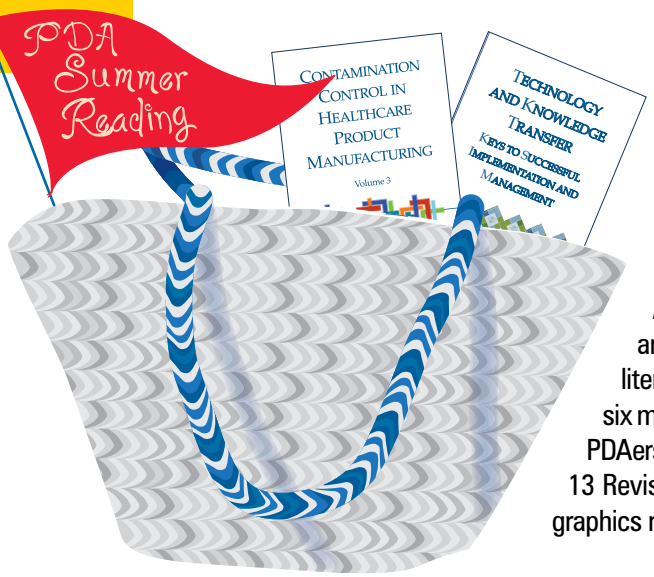
The technical report team, led by **Arthur Vellutato,** Jr. of Veltek Associates, consists of members from small and large companies as well as academia. In addition, the technical report was reviewed by regulators from the UK's Medicines and Healthcare Products Regulatory Agency to ensure a global perspective. New requirements in the EU's revised Annex 2 plus requirements under consideration for the Annex 1 update also needed to be taken into account in the document.

Another UK-based organization, the Pharmaceutical and Healthcare Sciences Society, is currently finalizing a white paper on contamination control strategy. This document will align with the cleaning and disinfection technical report as the Society supported the peer review of the PDA technical report in the first quarter of 2014.

This technical report will offer an overview of the critical elements of a comprehensive cleaning and disinfection program, including sound facility design and maintenance, established documentation systems, validated sanitation/disinfection procedures, reliable process controls, good housekeeping practices, effective area traffic and access controls, effective training, certification and evaluation programs, quality assurance of materials and equipment, and risk management strategies.

A consistent cleaning and disinfection program not only controls for microbial contamination but also serves as a corrective action for loss of control for viable excursions contamination. Implementing disinfection processes as a singular focus while not making adequate efforts to prevent contaminants from entering the environment lacks merit. By controlling the contaminants entering the manufacturing area with cleaning and disinfection, this enables acceptable and viable control of the environment.

This technical report should be available sometime in the third quarter of 2014.



Ah, summer! The perfect time to crack open a book. In honor of this age-old tradition, the Editorial Team with the *PDA Letter* chose to include an expanded "In Print" of PDA literature published over the past six months and found out what some PDAers are reading for fun (not that TR-13 Revised isn't fun!). References and graphics removed from excerpts.

excerpted from

"The Microbiologists Contamination Control Kit"

by **Hilary Chan, Lynn Johnson, and Jill Larivee, Pfizer**

from *Contamination Control in Healthcare Product Manufacturing: Volume 2*

edited by **Russell E. Madsen and Jeanne Moldenhauer**

The typical microbiologist contamination response may be viewed as being limited to testing and reporting of data. However, a microbiologist is a critical CRT member and can significantly improve the outcome of a contamination and expedite investigation closure by the application of tools and knowledge unique to their role. He or she has the ability to "think like a bug", understands the etiology of microbes, aids the team in identifying likely sources of the contamination, and develops studies in support of understanding and remediating the situation.

The role and impact of the microbiologist is well stated by Singer:

> "The mission of a microbiologist is to develop in the pharmaceutical organization a foundation for understanding of microbial origin, and parameters for proliferation and survival; to continuously improve/embed the concepts for protection, exclusion, reduction, removal or destruction of contaminating microbiological entities."

A successful contamination investigation relies heavily on a microbiologist's expertise, exemplifying the importance of establishing a sound scientific knowledge base and skill set.

Trending of microorganisms

It is important to establish a robust microbial identification program where reliable and consistent microbial identifications are generated. Understanding and trending the typical microorganism profile for a manufacturing facility, including microorganisms recovered from the process stream and surrounding environment (e.g., water, environmental surfaces, air, etc.) is a principal function of themicrobiologist. It is recommended that environmental reports are established on a predetermined frequency to track and trend the microbial flora recovered from the manufacturing facility . Trending also allows the microbiologist to observe any changes in microbial flora. Suggested types of trends that should be carefully assessed include:

- Comparing the type(s) of microorganism recovered (e.g., genus/species, Gram-positive cocci, Gram-negative bacilli)
  - within a specific product
  - between products manufactured in the same facility (e.g., multi-product facilities)
  - the environment (e.g., WFI, air viable) and in-process steps
- Environmental and bioburden levels for a particular process step or atypical growth
- Strain information, if available

Trending reports are beneficial in the course of an investigation, as the data will ➤

PDA's Personal Reading List

One Man's Wilderness: An Alaskan Odyssey, Sam Keith and Richard Proenneke
— PDA President **Richard Johnson,** and *PDA Letter* Editorial Committee Member, **Youwen Pan,** Genentech/Roche

The Emperor of All Maladies: A Biography of Cancer, Siddhartha Mukherjee
— PDA Board Member **Ursula Busse,** Novartis

American Catch: The Fight for our Local Seafood, Paul Greenberg; ***and Decide: Work Smarter, Reduce Your Stress, and Lead by Example,*** Steven McClatchy
— PDA Sr. VP, Scientific and Regulatory Affairs, **Rich Levy**

Written in My Own Heart's Blood, Diana Gabaldon
— *PDA Letter* Editorial Committee Member, **Barbara Sneade,** Grifols

An Officer and a Spy, Robert Harris
— Senior Advisor, Scientific and Regulatory Affairs **Denyse Baker,** PDA

The Ocean at the End of the Lane, Neil Gaiman
— Writer/Editor **Rebecca Stauffer,** PDA

Sink, Float or Swim, Scott Peltin and Jogi Rippel
— Sr. VP, Programs and Registration Services, **Wanda Neal,** PDA

Colorless Tsukuru Tazaki and His Years of Pilgrimage, Haruki Murakami
— PDA Board Member **Jette Christensen,** Novo Nordisk

Ulysses, James Joyce
— *PDA Letter* Editor and Director of Publishing, **Walter Morris,** PDA (his fourth attempt to read the "greatest English-language novel of the twentieth century")

Chasing the Monsoon: A Modern Pilgrimage Through India, Alexander Frater
— *PDA Letter* Editorial Committee Member, **Maik Jornitz,** G-Con

The World is Flat, Thomas L. Friedman
— *PDA Letter* Editorial Committee Member, **Robert Dream,** HDR

Command Authority, Tom Clancy
— PDA Sr. VP, TRI, **Robert Dana**

The Ghost Map, Steven Johnson
— *PDA Letter Editorial* Committee Member, **Peter Noverini,** Azbil BioVigilant

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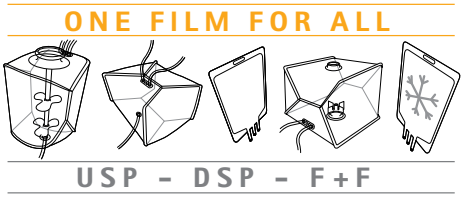

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demonstrate if the manufacturing environment was in a state of control during the time frame in scope of the contamination investigation. The environmental data may link to a potential entry point for a microorganism or may rule out the environment as a probable source for the contamination. For example, isolates identified from a purified water system with direct contact to the process stream may be of particular interest, as this may reveal the contamination source.

Raw materials, facility, and process streams should have established bioburden control limits. When results are consistently trending below a control limit, or if results exceed the acceptable limits, the microorganisms recovered should be profiled for Gram reaction, size (diameter), habitat, growth and metabolic requirements. Trending aids the microbiologist's ability to respond proactively and effectively to prevent potential future microbial excursions and to ensure process controls are effective regardless of bioburden level. **Table 6.1** outlines examples of common contaminating microorganisms and the manufacturing environment in which they are typically recovered from within a low-bioburden process.

Within a low-bioburden manufacturing process, it is more common for Gram-positive spore-forming and Gram-negative bacilli to be the source of contamination.Microorganisms that fall into these two categories are ubiquitous in nature (e.g., soil and water) and are more likely to persist in areas that are inaccessible to cleaning processes. Furthermore, these particular microorganisms are capable of responding to and surviving in an unpredictable environment. Gram-positive spore-forming bacilli produce endospores when nutrients are depleted or exposed to high or low temperatures. Gram-negative bacilli have the ability to change their protein and enzymatic profiles, which are essential for survival, when encountering environments that are nutrient deficient. Microorganisms in a stressed state are also more prone to surface adherence, allowing biofilm formation.

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excerpted from

"Use of Ozonated Water as an Aid to Contamination and Biofilm Control"

by

Bruce Hinkle, Purequest and Brian Hubka, BGH International

from

Contamination Control in Healthcare Product Manufacturing: Volume 3

edited by

Russell E. Madsen and Jeanne Moldenhauer

Biofilm is a complex structure of microorganisms that is embedded in a matrix of extra cellular polymeric substances (EPS) it has produced. Attached to either an inert or living surface and formed by one or more microbial species, it can cause a wide array of microbial contamination issues. Biofilm may only be only 10 nm thick (thinner than a human hair), but is abundant with bacteria, virus and fungi. Looking at biofilm through a microscope you would see a complex world of a matrix-like lattice of roots gradually filling in and getting thick, while venues are ready to disengage and spread to the next place to grow. Biofilm in a much simplified term is a thin, usually resistant, layer of microorganisms that form on and can coat various surfaces. Extracellular polymeric substances play an important

role in the attachment and colonization of microorganisms to contact surfaces. The problem of biofilm in the pharmaceutical industry is of growing concern with the emergence of resistant microbes to normal sanitizing practices. Ozone has the ability to oxidize and cut away at the bacterial complexes that bond and build biofilms. Chemical methods of biofilm intervention have included oxidizing biofilm with chlorine, chloramine, chlorine dioxide, and peroxides along with others, which bring the dangers of use, storage, residues and employee exposure. High pressure steam methods have been utilized with safety a factor of concern along with rising high energy cost. Ozonated water is a safe, easy to use chemical free process to sterilize using cold water. Chemical disinfectants have become ineffective against biofilm and emerging pathogens which have become resistant to those most commonly used today (e.g., chlorine, peracetic acid, peroxide, etc.). Because of the oxidizing process of the ozone molecule there is no possible resistance to this method of sterilization.

Preventing the formation of biofilm is a goal for everyone involved in the cleaning and validation process of a pharmaceutical water system and piping. However, there is no known silver bullet that is able to successfully prevent and control the formation of unwanted biofilm. Biofilm creates an environment on surfaces that promotes corrosion and sanitation and is difficult to achieve without causing the adverse effects from the chemical used. Biofilm species may vary with the microbial species present and the conditions of the environment. Ozone systems have the ability to sterilize an area on consistent basis of use, leaving no chemical residues, thus providing a positive attribute to the validation process of the plant's cleaning practices. An area where this type of technology may be useful is in the cleaning of bioreactors. This technology allows for the cleaning of the bioreactor and can also sterilize the bioreactor in the same step, without leaving behind chemical residues that could adversely affect the bioreactor's future contents.

excerpted from

4.1 Cleaning and Sanitization or Disinfection

from

PDA Technical Report 13 (Revised 2014): Fundamentals of an Environmental Monitoring Program

Implementation of cleaning and sanitization procedures is a critical component of overall contamination control within a facility. A common use of facility environmental monitoring data over time is determining the present and continued effectiveness of the cleaning and sanitization agents and procedures.

It is common knowledge that the ideal

cleaning agent does not exist. Generally, the three categories of sanitizing agents are sanitizers, disinfectants, and sporicides, which are commonly referred to as either sanitizers or disinfectants. However, sanitizers, disinfectants, and sporicides, although similar, vary in their level of destruction of microorganisms. The ability of the agent to destroy specific levels of microorganisms is based on the strength of the agent and the contact time for which the surfaces remain wetted (dry time). However, normal wetted times on hard, nonporous surfaces in cleanroom operations typically range from two to ten minutes.

Sanitizers (low-level disinfectants) reduce some level of microbial contamination and are the least effective agents . Common sanitizers include isopropyl alcohol (e.g., 70% IPA), ethyl alcohol or ethanol (e.g., 62% EtOH), and low active levels of hydrogen peroxide (e.g., below 3% H_2O_2). Sanitizers are effective against some level of vegetative cells but are ineffective against bacterial spores.

Per USP <1072>, the order of resistance to disinfectants and sporicides from least to greatest is:

Vegetative cells → Fungal spores → Bacterial spores

Disinfectants reduce higher levels of vegetative microorganisms than sanitizers depending on the strength and contact time. Common disinfectants include phenols, quaternary ammonium compounds, and hydrogen peroxide (above 3% is used for disinfection; however, above 30% is also used as a sterilant). Disinfectants that are not also classified as sporicides have a very limited ability, if any, to destroy bacterial spores.

Sporicides are effective against all microorganisms provided the required wetted or vapor contact time is achieved. This includes vegetative microorganisms and spores. Common sporicides include sodium hypochlorite, peracetic acid, and hydrogen peroxide (6% or greater). Sporicides may be corrosive to equipment (e.g., acidified bleach or peracetic acid and hydrogen peroxide on stainless steel) and should be used sparingly at a reduced frequency than sanitizers and disinfectants unless it is part of a validated process, for example, chamber surface decontamination with VHP. The negative effects of sporicides can be mitigated by subsequent rinse with a sterile solution such as isopropyl alcohol or water. Selection of sporicidal agents should incorporate an evaluation process that validates the required contact time, type of microorganisms that are to be eliminated, efficacy, type of surface to be treated, toxicity levels, residue, and means of application.

Qualification of established cleaning and disinfection procedures should demonstrate microbial reduction and maintenance of a microbiological state of control and provide confidence in the procedures' effectiveness. This typically includes laboratory carrier studies for contact time and reduction and is possibly supplemented by in-situ studies. An in-situ study validates the efficacy of the agent used, the appropriateness of the cleaning and sanitization SOP, and the effectiveness of training of personnel in actual use conditions.

In-situ studies encompass monitoring of an unclean and unsanitized area (dirty) and subsequent monitoring again after cleaning and sanitization of the area for a defined period. The dirtied area does not imply that microorganisms are specifically introduced into the controlled or classified environment. Typically the dirty environment is achieved as a result of use of the room, either before cleaning or after major construction or facility maintenance. The goal is to demonstrate that routine cleaning and sanitization procedures performed by trained cleaning personnel consistently result in microbial control and prove that the cleaning procedure is suitable for the intended use of the area.

It is recommended to periodically review challenge testing of the selected sanitizers, disinfectants, and sporicides if representative new isolates are routinely recovered in the environmental monitoring program. This supports the effectiveness of the sanitizer, disinfectant, or sporicide on new contaminants discovered in operations. The periodic alternation of disinfectant and sporicidal agent application is a common industry practice. For example, a rotation of two disinfectants in the same classification (such as a high pH phenol to a low pH phenol) is not considered to be as effective as alternating a disinfectant with a sporicidal agent. However, the environmental monitoring data provide continuous verification of effectiveness of the cleaning and sanitizing agents pertaining to the specific environment.

USP <1072> recommends the criteria for the efficacy studies for general-purpose disinfectants must demonstrate at least a three-log reduction for all vegetative cells and a two-log reduction for sporeformers. ➤

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For a comprehensive report on cleaning and sanitization, please refer to *PDA Technical Report No. 29: Points to Consider for Cleaning Validation.*

excerpted from

"Technology Transfer Organisation Strategy and Planning"

by **Steve Burns, AstraZeneca, and Mark Gibson, AM PHARMASERVICES**

from *Technology and Knowledge Transfer: Keys to Successful Implementation and Management*

edited by **Mark Gibson and Siegfried Schmitt**

There are likely to be separate technology transfer strategies relating to the transfer of drug substance, formulated drug product, packaging and analytical methodologies, respectively. Linked to these may be other supply, sourcing and training strategies. However, each of these strategies must be coordinated so that an integrated overarching technology transfer strategy is established and documented, outlining key information, timings and milestones. It may be obvious to point out, but vitally important, that the integrated technology transfer strategy must consider the timings and priorities for all aspects of the project. For example, there will be a logical priority order to transfer the analytical methods and cleaning methodology to the production site QC prior to transferring the drug substance or drug product. However, there may be other considerations that have to be built in to the strategy, such as investments in new facilities or equipment, and the sourcing of new materials. The timings will need to allow for purchasing, installing and validating any new facility or equipment prior to the start of drug substance or drug product technology transfer. If contract manufacturing or packaging organisations are to be employed, then these will have to be approved and commercial quality agreements established.

The strategy document should also identify key responsibilities and accountabilities of each of the functions involved in the technology transfer process and should also detail how these responsibilities change as the transfer progresses. It is appropriate that any unusual features of the proposed transfer process are identified, along with a brief description of how these will be addressed during the transfer.

The integrated technology transfer strategy document should also outline the sourcing strategy for both drug substance and drug product. The sourcing strategy should identify the proposed commercial manufacturing site and detail how the proposed manufacturing site will meet the expected capacity requirements.

The identification of the commercial manufacturing site should consider, among other things, the requirement for capital investment, tax and subsidy incentives, familiarity with the requisite technology, communication issues, and the availability of appropriately trained staff.

It is also appropriate that the strategy document indicates how sourcing of startingmaterials will be achieved and protected. Second sources of starting materials will probably not have been identified at this point, however, a preliminary assessment of business interruption risk should have been completed so that work can commence on securing second sources of critical or vulnerable materials.

Clear criteria for completion of the technology transfer project should be agreed to avoid ambiguity. Typically, these criteria might include completion of process validation, completion of preapproval inspection and launch in the first major market.

Is QbD Possible for Monoclonal Antibodies and Biologics?

Ursula Busse, PhD, Novartis, and Steffen Gross, PhD, Paul-Ehrlich-Institute

Five years after publication of the *Product Development and Realisation Case Study A-Mab* ("A-Mab Case Study"), QbD implementation for monoclonal antibodies is still a hotly debated topic. Although some benefits have been achieved through the application of QbD and risk management principles, there are still challenges that need to be mastered. Currently, only a limited number of QbD applications for monoclonal antibodies have been filed, and dossiers containing enhanced development information are far from standard, although certain QbD elements are being implemented by a number of companies.

Furthermore, acceptance of these submissions by regulators still seems low, and expected benefits of regulatory relief have not been realized. Looking into the depth of data is complicated and sometimes surprising, and there are issues which need to be clearly explained further within the dossier. There remains a need to clarify a number of topics between industry and regulators, including content of submissions and regulatory commitments. And although QbD for biologics is not an entirely new approach, industry and regulators need to come to a general consensus on the details of submissions claiming QbD.

PDA Europe has therefore decided to devote the content of its 7th monoclonal antibodies workshop entirely to QbD. The workshop will be held Sept. 24–25 in Basel, Switzerland. Contributing authors of the A-Mab Case Study will then describe how their company's development and regulatory strategies have been influenced by the case study. Emphasis will be placed on control strategy and regulatory lifecycle management. This will include discussions on the heavily debated real-time release testing.

For more information, please visit europe.pda.org/monoclonal2014.

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2014 PDA UPCOMING EVENTS

JULY EVENTS

29-31
Validation of Moist Heat Sterilization Processes
Bethesda, Maryland
www.pda.org/moistheat

AUGUST EVENTS

4-8
Fundamentals of Aseptic Processing – Session 2
Bethesda, Maryland
www.pda.org/apfundamentals2

12-14
Validation of Dry Heat Processes Used for Depryogenation and Sterilization SOLD OUT
Bethesda, Maryland
www.pda.org/DryHeat

18-22 and
September 22-26
2014 Aseptic Processing Training Program – Session 4
Bethesda, Maryland
www.pda.org/2014aseptic4

27-28
An Introduction to Visual Inspection – Session 2
Bethesda, Maryland
www.pda.org/visual2

8-10
2014 PDA/FDA Joint Regulatory Conference
Washington, DC
www.pda.org/pdafda2014

10-11
2014 PDA Drug Shortage Workshop
Washington, DC
www.pda.org/drugshortage2014

11-12
2014 PDA Joint Regulatory Conference Course Series
Washington, DC
www.pda.org/pdacourses2014

15
Pre-Conference Workshop: Spray Drying – An Alternative to Freeze Drying?
Brussels, Belgium
https://europe.pda.org/WSFreeze2014

16-17
Pharmaceutical Freeze Drying Technology
Brussels, Belgium
https://europe.pda.org/FreezeDrying2014

16-17
Fundamentals of an Environmental Monitoring Program
Bethesda, Maryland
www.pda.org/EMfundamentals

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

Save these dates!

SEPTEMBER EVENTS

18
PDA Southern California Chapter 4th Annual Industry Summit Expo
Santa Ana, California
www.pda.org/SoCalSummit

18
ICH Q9: Application of a Risk-Based Approach to Freeze Drying Process
Brussels, Belgium
https://europe.pda.org/API2014

18-19
PDA PICs Training Course on GMP for APIs
Brussels, Belgium
https://europe.pda.org/ICHQ92014

18-19
Development of a Freeze Drying Process
Brussels, Belgium
https://europe.pda.org/TCFreezeDrying2014

22-23
Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations
Basel, Switzerland
https://europe.pda.org/TCMonoclonals2014

23
Pre-Conference Workshop: Innovations in Downscale Processing Technologies
Basel, Switzerland
https://europe.pda.org/preWkshpMonoclonals2014

24-25
7th Workshop on Monoclonal Antibodies
Basel, Switzerland
https://europe.pda.org/Monoclonal2014

29-30
Mycoplasma
Berlin, Germany
https://europe.pda.org/Myco2014

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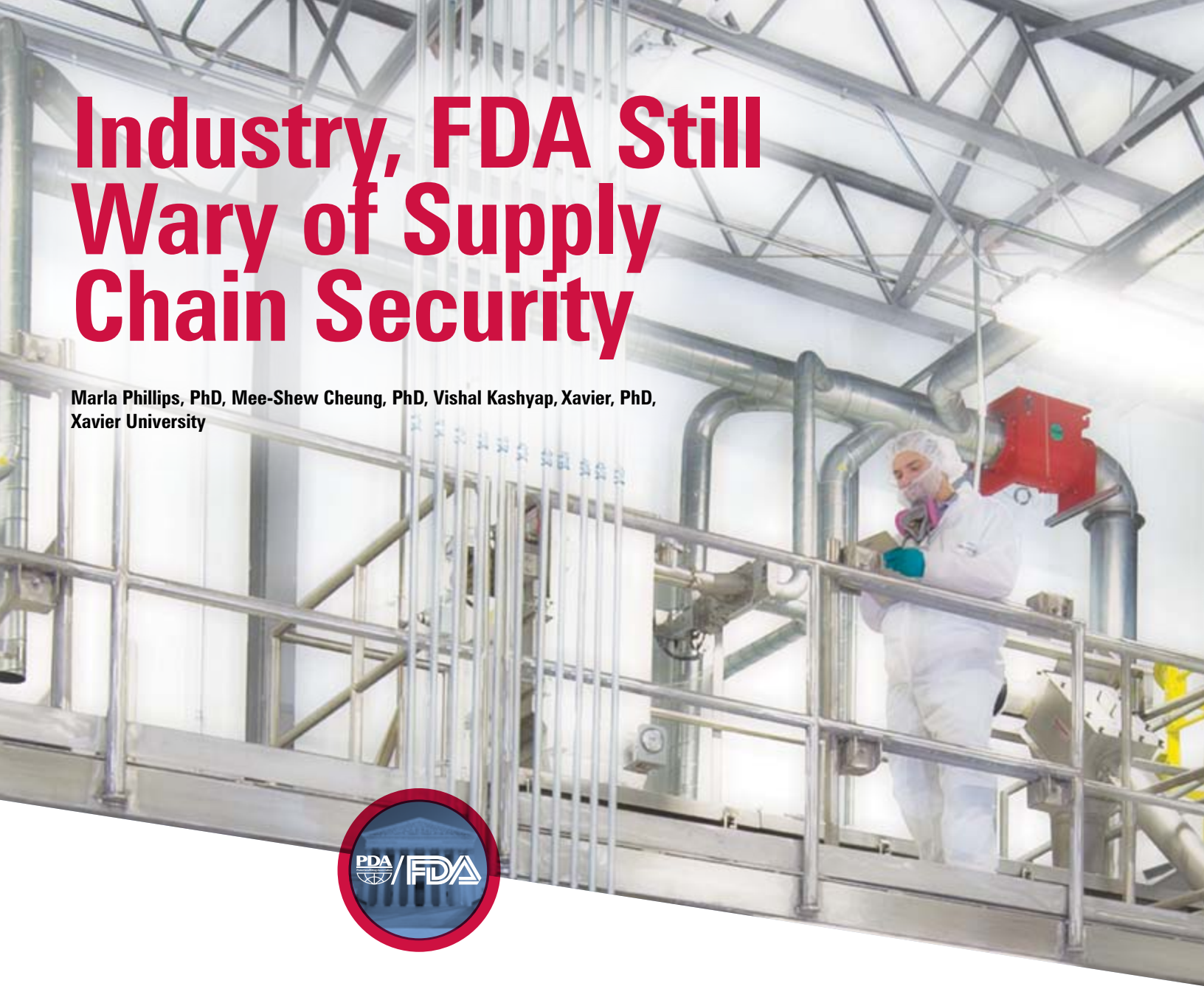
Industry, FDA Still Wary of Supply Chain Security

Marla Phillips, PhD, Mee-Shew Cheung, PhD, Vishal Kashyap, Xavier, PhD, Xavier University



Public confidence in pharmaceutical products has waned in recent years based on patient harm caused by adulteration ***(1),*** drug shortages ***(2)*** and poor quality resulting in recalls ***(3).*** Along with concern for patient safety, pharmaceutical professionals at all levels within their organizations have become keenly aware of the potential for damage to the company brand by such incidents.

In response to the risks that threaten the pharmaceutical supply chain, industry mitigation efforts have focused on improving supplier operations with the belief that supplier controls have been deficient. Recognizing that many of the criminal cases have resulted from rogue foreign suppliers who were economically motivated to contaminate the supply base, it is not difficult to appreciate why industry reacted this way. Further supporting industry's preconception that increased supplier controls are needed, the U.S. FDA publicly expressed its expectation that industry audit every supplier in each of their product supply chains as a means to reduce supply chain risk ***(4).*** In order to address FDA expectations and protect the patients they serve, industry ramped up auditor resources, increased metrics used to measure supplier performance, instituted risk-based audit plans, identified "strategic" suppliers, and initiated supplier training.

Despite mitigation efforts employed to date, throughout 2010 and 2011 Xavier University heard consistent concerns from professionals at all levels in both the pharmaceutical and medical device industries regarding the reliability of their supply ***(5).***

Article at a Glance

- Both industry and regulatory remain concerned about reliability of suppliers
- Xavier University conducted interviews of both industry and nonindustry representatives
- Pharma now realizing supplier quality issues often due to manufacturers

These unified concerns led to the launch of the Xavier University Integrity of Supply Initiative in August 2012, which is the basis of the presentation that will be given at the *2014 PDA/FDA Joint Regulatory Conference.*

The mission of the Xavier University Integrity of Supply Initiative is to determine the sources of dysfunction affecting the reliability of supply, and to implement sustainable solutions tied to return on investment—such as increased safety, improved quality and enhanced reliability—commensurate with need. Xavier University made a conscious decision to focus on factors affecting the reliability of incoming supply first. Those involved in the Initiative will identify and prove solutions for incoming supply, then these solutions will be assessed for application to the downstream supply chain.

There are 24 organizations engaged in the Initiative, which includes representatives from the FDA, pharmaceutical companies, medical device companies, and suppliers as follows: Abbott, Albemarle Specialty Pharmaceuticals, Amerikam, Baxter, Boston Scientific, Cook, Core Risks, CPKelco, Eli Lilly, FDA Office of the Commissioner, Huber, Johnson & Johnson, Lonza, Merck, Meridian Bioscience, P&G, Patheon, Perrigo, Puritan Products, Roche, Shire, Teleflex, Tornier, and WLS Enterprises.

In an effort to ensure the concern of reliable supply was felt widely across the industry, Xavier University conducted cross-functional interviews of each of the participating organizations involved in the initiative, two organizations from the food industry (Kroger and General Mills), and industry associations (GPhA, IPEC, MDMA, and PhRMA). The result echoed what was heard at the 2010 and 2011 FDA/Xavier conferences, thus verifying concerns expressed regarding supply chain reliability.

The interviews took the pharmaceutical and medical device manufacturers represented in the initiative through a Cause and Effect exercise followed by Pareto analysis, which led to the identification of three main sources of dysfunction related to reliability of supply: (1) incomplete product and process knowledge and development, (2) insufficient supply chain development and management, and (3) inadequate behavior and communication.

Xavier University heard consistent concerns from professionals at all levels in both the pharmaceutical and medical device industries regarding the reliability of their supply

Suppliers, through surveys and focus group sessions, corroborated the sources of dysfunction identified by the pharmaceutical and medical device companies. Additionally, *100%* of the input from audiences at the *FDA/Xavier University PharmaLink Conferences* in 2013 and 2014, the *FDA/Xavier University MedCon Conference* in 2013, the *Association of Food and Drug Officials Conference* in 2013, and the *ExcipientFest Americas Conference* in 2014 fell into these same three categories. Xavier University gathered information about these sources of dysfunction through an anonymous survey of suppliers, focus group sessions with suppliers and root cause exercises with manufacturers.

Product and Process Knowledge and Development

Due to common pressures that occur during product and process development (e.g., cuts in time, personnel and funding) manufacturers are often not able to fully understand what is needed from their suppliers to support the finished product. As a result, specifications on incoming materials default to industry standards (such as the U.S. Pharmacopeia) and historical use of the same material in other products, which may not be appropriate for the product in question. The survey found that only 18% of manufacturers ask for supplier technical input on specification setting.

As manufacturers are learning the critical process parameters of their process and critical quality attributes of their product, they do not take into consideration the process variability coming in from their suppliers. When asked, 54% of the suppliers surveyed indicated they would be willing to share process capability with their customers, but the information is requested only 29% of the time. Only 45% of the manufacturers share intended use, despite the fact that 64% of the suppliers expressed that it is critical for them to understand intended use to be able to provide what is truly needed by the manufacturers. A final example is that manufacturers do not gain internal alignment of cross-functional requirements before engaging suppliers. As a result, suppliers are told by their customers that the top priority is high quality, but then are told the cheapest cost is most important, and not to mention they want it faster than is possible. 68% of the suppliers indicated that they receive conflicting information from different members of their customers.

Supply Chain Development and Management

Suppliers were intentionally surveyed that serve industries outside the FDA regulated industries, manufacture many products of various volume and types, and have a large portion of their supply tied to specialty products to ensure the robustness of response. Interestingly, the survey revealed that 91% of pharmaceutical manufacturers employ poor forecasting methodologies, which is vastly different from other industries their suppliers support.

When manufacturers show disregard for the operations of their suppliers, then impossible demands lead to an increase in the potential for error. The survey found that the manufacturers generally have a methodical due diligence process, supplier selection process, and supplier qualification process. Partly due to cuts in time, however, resources and budget for these processes are often disregarded—as reported by the manufacturers themselves. Even suppliers indicated that

only 9% of their customers involve cross-functional representatives in the due diligence process, despite manufacturers indicating that their process requires it.

A final example related to this topic comes from a focus group's discussion revealing that contractual terms often conflict with other agreements in place (not to mention that only 14% of the suppliers expressed they have a Quality Agreement in place with their pharmaceutical customers). One story shared concerned a contract that stated than if a laboratory error occurred, the contract laboratory would not get paid for services. In response, the contract laboratory concluded in every investigation that no laboratory error occurred, so all failing data was considered valid. Obviously, an example of unintended consequences, but interesting that it was driven by the manufacturer.

Paradigm Shift Leads to Solutions

Perhaps the greatest discovery revealed through the initiative to date is the paradigm shift **(Figure 1)** that every area of dysfunction related to the reliability of incoming supply is caused by and/or can be controlled by the manufacturers themselves, not their suppliers. Instead of increasing controls over supplier operations, this paradigm shift will require manufacturers to assess how their own actions prevent their suppliers from consistently supplying reliable material.

Through this initiative, Good Supply Practices (GSPs) are being developed to improve the practices of the pharmaceutical manufacturers themselves. Each GSP will have components related to product and process knowledge, supply chain development and ideal behaviors in order to address the examples of dysfunction discussed above (and others not included in this article). The GSPs will be pragmatic, will include decision making tools when applicable, and will harmonize practices wherever it makes sense and is possible. Where appropriate, the requirement of critical functions will be stated, but otherwise will provide options for the manufacturers to consider—depending on need. Additional input will be gathered throughout the development stages of the GSPs, and pilot studies will be employed to demonstrate effectiveness.

Through research and interaction with other industries, many of the practices proposed to date have demonstrated real return on investment in those other industries, which is required in order to fulfill the mission of the Integrity of Supply Initiative.

Figure 1 Major Paradigm Shift Revealed Through the Integrity of Supply Initiative

Driving Ideal Behaviors

There is strong recognition that human factors play a large role in how the supply chain operates (as with everything else).

The survey indicated that most manufacturers feel transparency is not possible due to current paradigms of competitive advantage, despite the recognition that transparency increases trust and reliability.

The data also revealed that current metrics used by manufacturers do not trigger action, instead causing distractions that lead to dysfunction on multiple levels. Metrics should include key triggers and associated escalation tied to performance improvement on both sides of the contract. Otherwise, a general lack of understanding of the cultural alignment between the manufacturer and the supplier leads to frustration, performance not meeting expectations, and loss of trust.

[Editor's Note: Marla Phillips, one of the authors, will present "Increasing Supply Chain Reliability – Shifting Paradigms" in Session A3, "CMO" at the *2014 PDA/FDA Joint Regulatory Conference,* Sept. 9 at 11:15 a.m.**]**

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Outsourcing Management: Key Component of a QMS

Miguel Montalvo, Expert Validation Consulting

Regulatory agencies hold firms responsible for delivering high quality products that meet all established requirements and specifications. Suppliers and vendors (most recently referred to as "outsourced materials and services") play a key role in meeting GMP mandates, and it is a firm's responsibility to make sure vendors/suppliers are meeting specifications for the supplied materials, components, equipment and/or services. For many years, this was considered to be an "internal GMP compliance" responsibility, managed by internal controls in most cases.

Photo courtesy of by Jim Greipp of Pau Hana Productions for Custom Processing Services. This photo depicts a cleanroom/ flexible processing station showing a slant cone blender in CMO Custom Processing Services' dedicated GMP facility in Reading, Pa.

Even when the regulators demanded that users treat suppliers as an "extension" of their company, most companies did not have a "systematic" approach to evaluate, approve, monitor and control outsourced materials and services. For over 30 years, the industry has focused on internal GMP compliance but during recent years, the U.S. FDA has been working aggressively in the area of outsourcing management following specific events such as the Heparin case from 2008. Another factor is the globalization of our industry—more than 80% of our APIs come from outside the United States and most of our materials as well. There is a need for an effective plan, with clear and agreed-upon requirements for evaluation of suppliers/service providers including risk assessments which should include adequate resources to deal with outsourcing monitoring and controls. This area should also be addressed utilizing a continuous "lifecycle" concept—plan, do/implement, verify/monitor and act. Another reason to assign adequate resources to this system is the fact that, based on my own industry experience and discussions with colleagues and customers, the majority of the "quality problems" in a process/facility can be attributed to outsourcing issues—materials, components and services; either the quality standards are not the same, or supplier control and variation is causing issues in our own quality that we might not have projected. In 2013, the FDA published the draft guideline, *Contract Manufacturing Arrangements for Drugs: Quality Agreements,* focusing on the documented and agreed upon responsibilities of the "Owner" and the "Contracted Facility." A key component is the level of quality oversight from the owner of the drug product before, during contract negotiation and after the signed agreement is in place. This new draft guideline by the FDA is the first step in providing more specific requirements.

Understanding that contract manufacturing/packaging/sterilization and testing services are critical and are clearly required to follow the drug GMPs, the question is—are these outsourced activities the only ones that require a formal Quality Agreement? There are other outsourcing activities that should have the same level of formality, communication and documentation requirements such as excipients, primary packaging components and aseptic manufacturing process material suppliers, e.g., the single-use container manufacturers. The other aspect is—the Quality Agreement is important but it is only one step in the lifecycle approach to outsourcing management. Many companies have implemented procedures for selection, approval and qualification of suppliers and vendors but, in many cases, these were not being implemented effectively or formally documented. Making these programs part of a risk-based quality systems approach that the FDA and other regulatory agencies have come to expect from industry is critical. ICH Q10 and other Quality Management guidance documents also discuss the controls required over outsourced activities in general but not providing clear expectations on what the system needs to include and/or address. ICH Q10 states in Section 2.7 on Management of Outsourced Activities and Purchased Materials: "The pharmaceutical quality system, including the management responsibilities described in this section, extends to the control and review of any outsourced activities and quality of purchased materials. The pharmaceutical company is ultimately responsible to ensure processes are in place to assure the control of outsourced activities and quality of purchased materials. These processes should incorporate quality risk management."

The reasons to focus our efforts in the area of outsourcing management are varied.

- As mentioned before, the rapid globalization of outsourcing providers leads to supply chains becoming potentially very complicated and spread out due to cost pressures, use of brokers and intermediaries and the purchase of ➤

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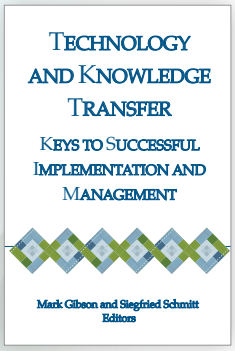

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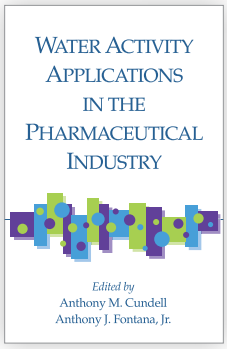

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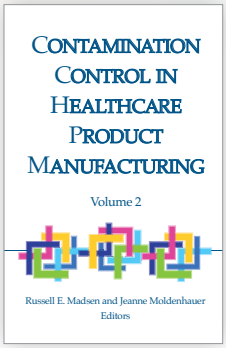

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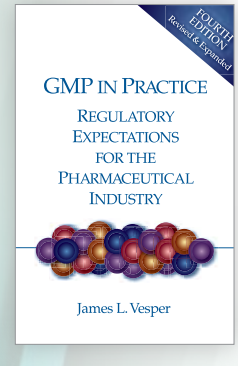

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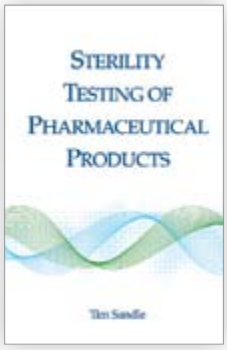

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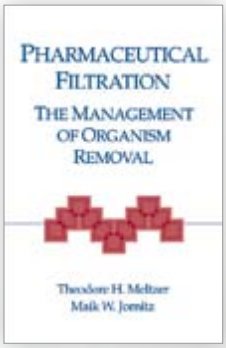

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ingredients from emerging markets which are not truly experienced with GMPs or very recently exposed to it. In addition, the "economically motivated adulteration" of our raw materials by the suppliers (criminal acts) is more common, as discussed in 2010 by **Edwin Rivera-Martinez *(1)*.**

- EU/U.S. regulatory oversight and continued demand for users (contract givers?) to step up their QMS controls—this implies that the user must demand a formal QMS approach by their suppliers/outsourcing.
- Business risks—company's revenue, impact market share, increased production cost and possible recalls which could have a detrimental effect on the brand image and reputation. As mentioned earlier, the effects of the supplied material quality has been considered in our industry as a major source of our own internal quality issues.
- Cost of supplier quality is seen as having limited ROI, thus the need to measure and track cost of poor supplier quality and implications.

The question is then—what are the elements of an "outsourcing management" subsystem within the company's Quality Management Systems? The elements will include the following (based on Deming's principles of Plan-Do-Check-Act):

- Planning—define requirements to be agreed upon (Quality Agreement) with the selected supplier/outsourcing provider
  - Categorization of providers—based on risk to product quality
    - Suppliers—type of material/service and factors such as certifications, inspections, experience
    - Materials/Service—Impact to product quality
- Do—Select/evaluate/audit/approve outsourcing provider using risk assessments as a basis. Document requirements and agreements in a contract or Quality Agreement.
  - Risk-based decision to rely on supplier testing/data—testing in-house every batch or monitoring
    - Test data comparison—criteria
    - Method/equipment comparison
    - Training
  - Foreign providers as a risk factor— location, local regulatory oversight, traceability, increased risk of illicit activities, personnel turnover, etc.
- Verify—collect samples, monitor results, establish feedback loop. Establish frequency for re-assessments of each provider.
- Act—deviations, nonconformances, trending of collected data, etc.

During my meetings with personnel from numerous companies, I always ask "do your providers have to meet GMPs?" Surprisingly, most of them believe that most (if not all) of our providers have to meet our drug GMPs. In reality, only suppliers of APIs (through the global application of the ICH Q7 guideline for API GMPs) and those considered to be contract manufacturers/packagers/testing services must meet our drug GMPs. The majority of them (materials except API, packaging components, calibration services, and many others) do not have to meet GMPs but they usually have their own Quality Management System. The key will be to evaluate their systems and even help them improve these systems because, in the end, it will result in our own benefit.

Some best practices that I have seen in our industry include:

- Use of automated data collection and analysis—some companies are establishing network communications with their providers to be able to communicate data instantly and evaluate the impact as quick as possible
- Measure Cost of Poor Supplier Quality (CPSQ)
- Cost recovery included in contracts —provider will be made responsible for effect of their own quality on our processes/product quality
- Effective use of audits—not only as a checklist item
- Use of metrics and scorecards—establish and agree on metrics and frequency of analysis as a team
- Include monetary incentives for good quality
- Visits that go both ways. These allow the provider to understand your needs and for you to understand how to better support them to improve their systems.

A recent survey conducted by Porsche Consulting GmbH in 2013, "Operational Excellence in the Pharmaceutical Industry," showed that 67% of respondents will enforce supplier management and integration into their operation. We need to remember that our goal is not to become the provider's quality function but to treat each other as a valued partner working toward a common goal.

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About the Author

Miguel Montalvo, has over 30 years of valuable experience in the areas of cGMP compliance, quality systems and validation functions/responsibilities.

Hear more about this topic from Miguel at the PDA TRI course, "Application of a Quality Systems Approach to Pharmaceutical CGMPs," following the 2014 PDA/FDA Joint Regulatory Conference, Sept. 11–12. To learn more, visit www.pda.org/pdacourses2014.

CMO Vet of 40+ FDA Inspections Discusses Reg Landscape

Robert Darius, GlaxoSmithKline Biologicals

Robert Darius, *VP, Regional Quality Unit, GSK Biologicals, interviewed* ***Joachim del Boca*** *for his thoughts on the U.S. FDA's aseptic processing guidance, harmonization, regulatory inspections and the role of Quality Agreements. del Boca, VP of Regulatory Affairs and Quality Compliance at Vetter, a contract development and manufacturing organization, has 31 years in the industry and is a veteran of over 40 U.S. FDA regulatory inspections.*

The entire interview was posted online as PDA Letter *Podcast, available at www.pda.org/pdaletter.*

Darius: A little over a decade ago, FDA issued a revised GMP guidance for aseptic processing. In the years since then, have you noticed a difference in inspections from the FDA? In other words, has the guidance created more certainty for companies like yours and the Agency inspectors? Do you think the guidance is showing its age as aseptic processes and technologies continue to evolve?

del Boca: Okay, first, I would like to say that for 25 years we had 40 different FDA inspections, GMP inspections, and also preapproval inspections. That means we have a lot of experience with the FDA, what happened in the past—ten years or 15 years ago—and what is now the approach of the FDA. And to be honest, I see no difference in the performance of the FDA inspection since the new guidance for aseptic processing was implemented. I see no big difference from the Agency, but I think it gives more information to us—to the company—so we can look to the guidance and discuss with the inspector. But with the performance of the inspection we see no difference.

Darius: Have you seen any difference in inspections performed by other regulatory authorities concerning aseptic?

del Boca: Not concerning aseptic…I see no difference. There are other issues—there are differences from other authorities, for example, from the Brazilian authority that is not focused on aseptic processing; it's more focused on what products you are handling with what API you are handling with.

Darius: So, there are efforts to harmonize the U.S. and EU aseptic processing regulations, yet differences still exist. What challenges to these differences are present in a company like yours, a CMO—a contract manufacturing organization? Why do you think harmonization is so difficult, and what about other global regulations? How do those compare in your view?

del Boca: I think the differences from the U.S. regulation to the European regulations are not [such] a big challenge for us, as a contract manufacturing organization…when there are differences we implement both systems, but the differences are not, I would say, between Annex 1, for example, and [the U.S.] guidance for aseptic processing. They are not so extremely different, so that causes no big problems for us.

Why there are the differences and why is it so difficult to eliminate the differences? I don't know, to be honest. I have no answer to this. And for other authority organizations, there are also differences, especially, again, for the Brazilian authority, ANVISA. There's a big issue in handling of hormones. Their GMPs require the handling of hormones in a segregated area. It is not easy to have this implemented. But then for all the other organizations, I think the differences are not too big.

Darius: Could you tell us about a challenging inspection you've experienced and your experience with that? What agency it was? And how did you resolve any differences during that inspection or even afterward?

del Boca: From time to time, we have challenges in inspections. And I remember one inspection recently performed by the FDA, and the challenge was the manner in which the inspection was performed. There was no open discussion…it was not a friendly manner but at the end of the day we managed all of this inspection…we got some 483s which we responded [to] and got the approval letter.

Darius: Why do you think that manner, as you said, wasn't "friendly?"

del Boca: It was the way it was performed. It was not friendly; it was very aggressive from time to time. And really, it was not a good experience for us.

Darius: What do you see as the future of aseptic processing? What does it look like to you?

del Boca: The future of aseptic processing, I think, will be much more automated than we have now. That means robotic systems will be more implemented in the processing…maybe the isolator will have a bigger role than now. That, I think, is my opinion about the future of aseptic processing. ➤

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

Darius: In your many years in the pharmaceutical business, what have you really learned as you look back over time?

del Boca: I have learned that the systems which are implemented—quality systems, production systems—are [all] the time changing. Systems, which today are very good and working and acceptable, maybe two years later they are not anymore acceptable. It's always changing. Also, the requirements from the authorities are always changing and the costs are all the time increasing to produce aseptic products.

Darius: Did you have any preconceptions about the industry prior to joining it that later proved to be not true?

del Boca: No, but when I look back 31 years ago to when I started my career, again, the quality systems were very rare. When I started, you cannot imagine today, [there were] no media runs, for example.

Darius: So, the next question is about leadership. What advice would you give to someone who's considered becoming a Qualified Person today?

del Boca: The Qualified Person has to have experience in the production department and also in the Quality Control department. I think it's necessary to have some years' experience—maybe five years—in each department, so that he can perform the responsibility of a Qualified Person. In German law, it's necessary for a Qualified Person to have an education at a university to be a pharmacist. And if it's not possible that they are a pharmacist, they have to have more lessons at the university [on] pharmaceutical technology, pharmacology, and so on. But I think most important is experience for a Qualified Person in production and Quality Control and testing of products.

Darius: What advice would you give to someone starting a career in industry like you've done, who wants to stay in that industry for a long time?

del Boca: I would give the advice always to learn, to be open, for things which are going on in the production and also in the quality control laboratory. To be open to new ideas. To try to have your own ideas. To learn every time. I think that is most important.

Darius: What leadership challenges do you see in creating quality in organizations? Not just at your company, but in industry in general?

del Boca: I think most important is to have a good relationship between costs and [the] quality system. And that is also important to defend the quality system, maybe, to the management, so that the costs of the system are accepted from the management.

Darius: What is a typical cycle time to get a quality agreement signed between a company and another?

del Boca: Could be very long because the lawyers are implemented in these discussions. So, sometimes it needs some years.

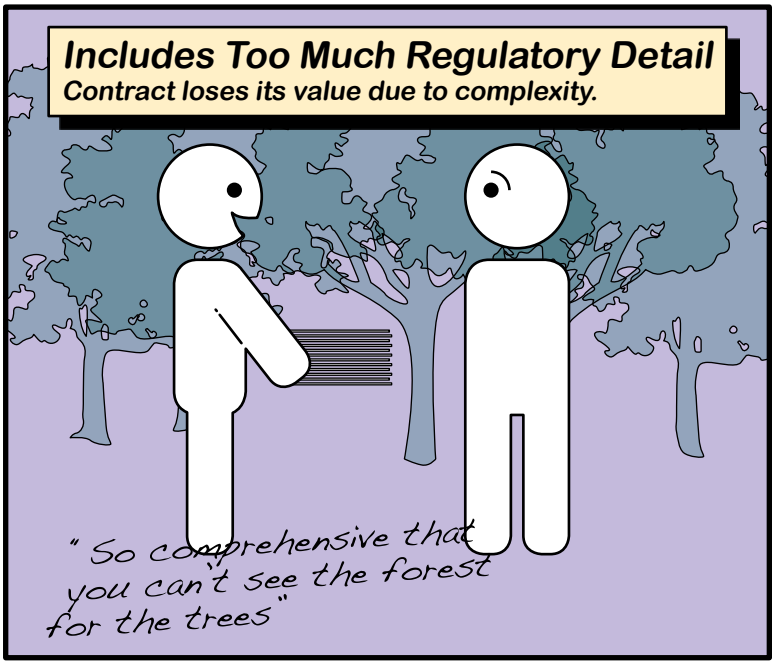
Darius: What are some of the challenges you see with clients?

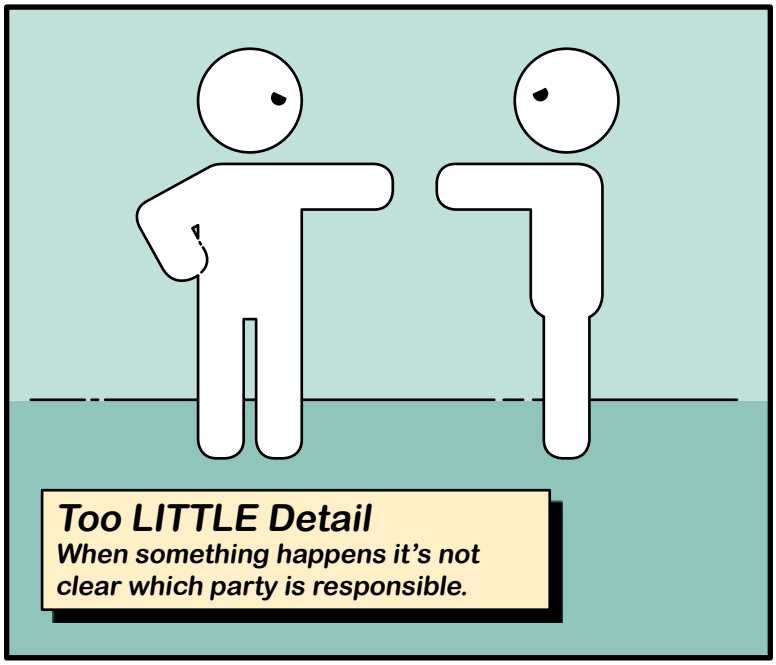
del Boca: We see that our clients—and we have a lot of different clients—each client tries to implement their own systems in our system and that's not possible for us as a contract manufacturing organization to implement a lot of different systems. We have to have our systems and we have to defend these systems against the requirements of our customers. This is a thing which happens very often and we are used to defending our systems.

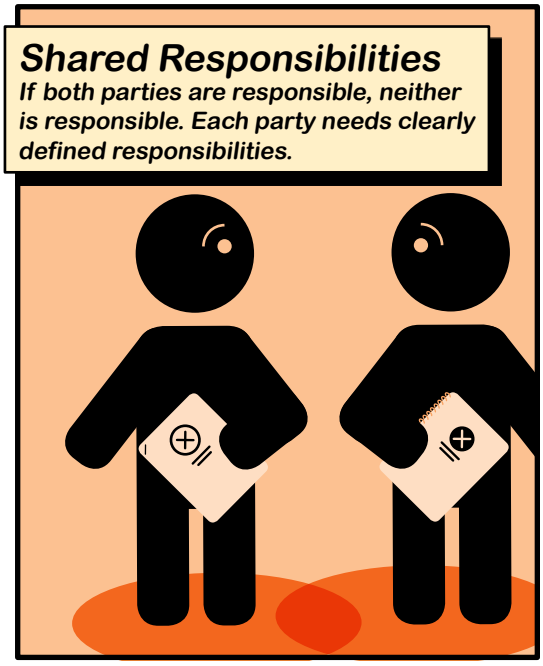
Darius: So, could you share with us some approaches you've taken or experiences you've had about how a company can build an effective, efficient relationship with a CMO? How can the client work better with the CMO?

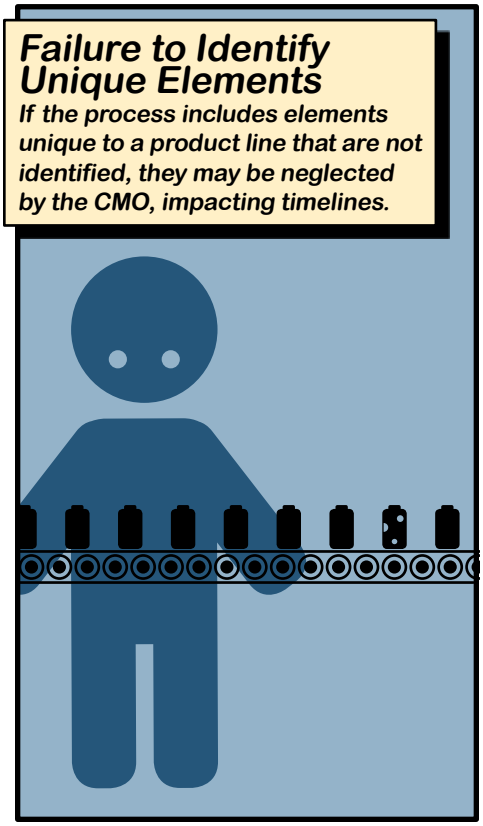
del Boca: I would very much recommend that there are regular quality management reviews…quality management meetings. In these meetings, all the quality key performance indicators have to be discussed, deviations or complaints, and any projects. And we do it nearly for all of our customers on a regular basis—sometimes 2–3 times a month. Quality management review for one day, sometimes two days. And I think it's a very, very important for the relationship to our customers.

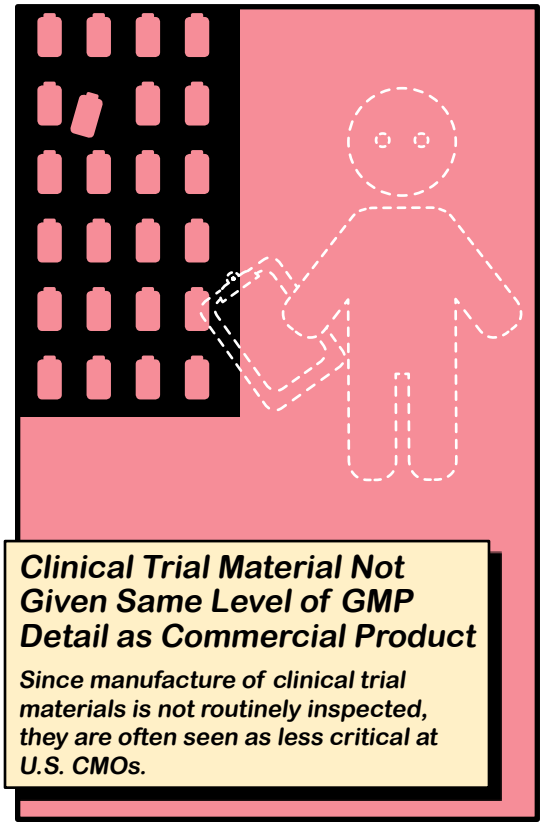
FIVE TYPICAL MISTAKES FOUND IN QUALITY AGREEMENTS





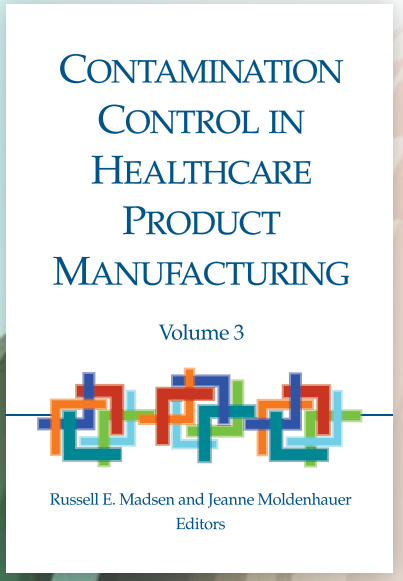






Special thanks to **Karen Ginsbury** of PCI for her assistance with this infographic. She recommends reviewing last year's U.S. FDA draft guidance, *Contract Manufacturing Arrangements for Drugs: Quality Agreements* (tinyurl.com/pqxzczt).

New Release at the PDA Bookstore



Item No. 17321

Contamination Control in Healthcare Product Manufacturing, Volume 3

Edited by Russell E. Madsen and Jeanne Moldenhauer

Volume 3 discusses extensive subjects related to water considerations and also includes invaluable advice regarding:

Volume 3 discusses extensive subjects related to water considerations and also includes invaluable advice regarding ventilation systems, the microbiology laboratory, mold, microaerophillics, Burholderia cepacia, a life cycle approach to cleaning validation, extensive coverage of risk management with details about IREM, cleanroom classifications and disinfectant qualification testing.

All chapters were written by subject matter experts, each of them bringing their extensive knowledge and experience to all personnel involved in aseptic contamination control.

The first volume of Contamination Control contained chapters that are predominantly centered on microbial issues, and Volume 2 addresses some microbial issues, but also focuses on other types of contamination.

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snapshot

RAQAB *Update*

RAQAB Quarterly Report Q2 2014—Health Authority Publications on Slower Pace in 2014

Denyse Baker, PDA

Fewer Commenting Opportunities So Far in 2014

Driven primarily by a slowdown in the draft guidelines coming out of the European Union, PDA has so far commented on fewer regulatory documents than in 2013. There were none in Q1 and just a handful in Q2. PDA did develop comments to a Health Canada publication on new drug and abbreviated new drug submissions. There had not been any Health Canada comments submitted for several years prior. There has been one set of comments submitted to the U.S. FDA on the draft guidance *Analytical Procedures and Methods Validation for Drugs and Biologics* **[Editor's Note:** see page 48 for a comparison of this guidance with PDA Technical Report No. 57**],** and one set of comments to *EudraLex Volume 4 EU Guidelines for GMP Annex 15: Qualification and Validation,* detailed below. RAQAB and Regional Liaisons continue to identify potential documents for comment. Anyone who would like to suggest a document for commenting or would like to participate on a commenting task force can contact **Denyse Baker** at baker@pda.org.

RAQAB Reaching Out to PDA Chapters

In an effort to raise awareness of the PDA Regulatory Affairs and Quality Advisory Board's role and opportunities to participate, the group set a goal of attending one PDA chapter meeting per quarter in 2014. **Alan Burns** was commissioned to develop a set of slides giving an overview of the members, the structure and the activities of the RAQAB. So far presentations have been made to the Southeast and Missouri Valley Chapters and plans are underway for presentations to the Delaware and Midwest Chapters. Any chapter leaders interested in having an RAQAB member attend one of their future meetings should contact **Trevor Swan** at swan@pda.org.

PDA Comments to EU Annex 15

Annex 15 was originally published in Sept. 2001. Since then there have been significant changes in the GMP regulatory environment, including publication of ICH Q9 and Q10, the increased use of advanced manufacturing technologies—such as Process Analytical Technology (PAT), continuous manufacturing concepts and the broader application of risk assessment. There have also been many changes to other chapters and Annexes in the GMP guide having potential impact on the existing Annex 15.

In summary, PDA welcomed this extensive revision to align with Chapter 1, Annex 11, and ICH Q8–11. PDA found the new annex to be a positive adaptation to the current knowledge and technology. There is more flexibility in designing the qualification, validation and technology transfer plans and acceptance criteria, based on prior knowledge, experience, and risk assessments. PDA appreciated that this draft provides for both traditional approaches and newer QbD approaches.

More specifically, PDA recommended the addition of these definitions for Qualification and Validation based on those from ICH Q7 with the addition of the lifecycle considerations.

Qualification: *Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.*

Validation: *A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria* ***throughout the lifecycle.***

Finally, PDA also recommended deleting the specific reference to three validation batches in clause 4.18. PDA took the position that if the Annex continues to refer to a specific number of batches, some firms will continue to use that as a default and not apply QRM principles nor perform the needed analysis to determine a more appropriate approach.

RAQAB thanks the following task force members for their diligent work to complete these comments.

Vijay Chiruvolu (lead), **Norbert Hentschel** (colead), **Raphy Bar, Hal Baseman, Jeff Broadfoot, Soren Damkjaer, Veronique Davoust, Becky Devine, Jeff Hartman, Steven Ostrove, Siegfried Schmitt,** and **Wendy Zwolenski-Lambert.**

PDA Who's Who

Denyse Baker, Senior Advisor, Scientific and Regulatory Affairs, PDA

Alan Burns, Fresenius Kabi

Trevor Swan, Manager, Membership and Chapters, PDA

Vijay Chiruvolu, PhD, Amgen

Norbert Hentschel, Boehringer Ingelheim

Raphael Bar, BR Consulting

Hal Baseman, ValSource

Jeffrey Broadfoot, Emergent BioSolutions

Soren Damkjaer, Novo Nordisk

Veronique Davoust, Pfizer

Rebecca Devine, PhD, Regulatory Consultant

Jeffrey Hartman, Merck

Steven Ostrove, PhD, Ostrove Associates

Siegfried Schmitt, PhD, PAREXEL

Wendy Zwolenski-Lambert, Novartis

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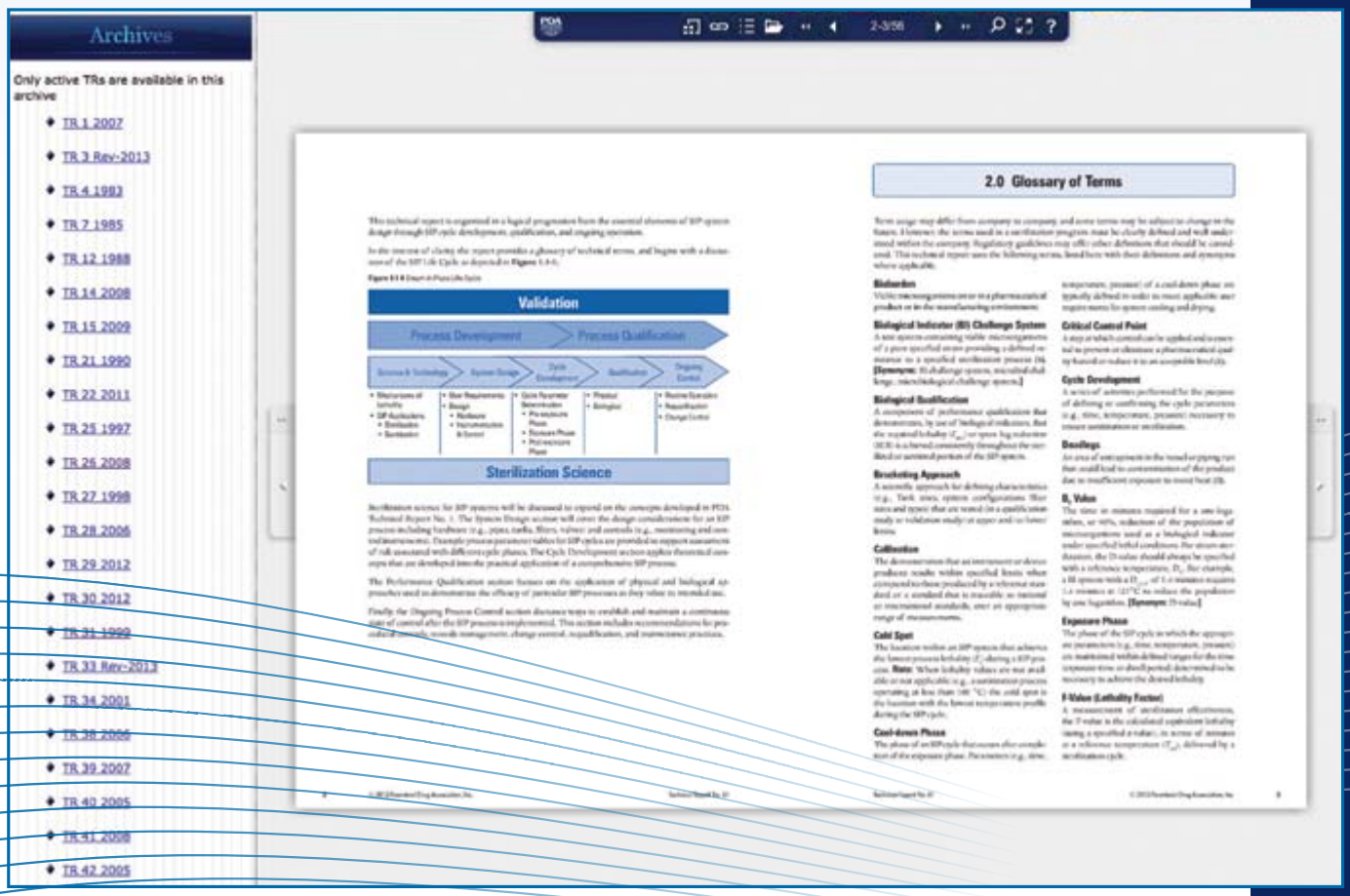

PDA
Parenteral Drug Association

trarchive.pda.org/t/26426 | Licensing options available; contact Janny Chua at chua@pda.org

snapshot

The Value of PDA Technical Reports

Stephan O. Krause, PhD, MedImmune/AstraZeneca

In February 2014, the U.S. FDA published the draft guidance, *Analytical Procedures and Methods Validation for Drugs and Biologics*. Once finalized, this 2014 draft guidance will replace the 2000 FDA draft guidance, *Analytical Procedures and Methods Validation.* I want to highlight the development of *PDA Technical Report 57: Analytical Method Validation and Transfer for Biotechnology Products*, and its influence on the content of the new FDA draft guidance.

After PDA's Science Advisory Board (SAB) accepted the need for TR-57 following my presentation in 2006, I assembled a team of both PDA member and nonmember volunteers. Drafting of the document kicked off in 2007. We wanted to provide more practical guidance to readers, so we focused on topics where ICH, FDA, and/or industry guidance was missing. Later, TR-57 was well received by reviewers from U.S. and EU regulatory agencies (FDA/CDER and the Paul-Ehrlich-Institute in Germany) along with industry representatives. Ultimately, TR-57 influenced the content of the FDA draft guidance.

Reviewers from the FDA and Paul-Ehrlich-Institute provided positive feedback on the guidance in 2011. **Siegfried Giess,** PhD, Head, Section of Immunochemistry with the Paul-Ehrlich-Institute, said: "…From my point of view the advantage of this report is that it covers not only the classical validation process but also method transfer, comparability and maintenance. Another advantage is that the report gives a lot of guidance regarding the details of the different validation steps. I think you have developed a very helpful document not only for lab people but also for assessors. I hope that many companies will use this document in the future."

Rashmi Rawat, PhD, Acting Team Leader, Regulatory Science and Policy, CDER, U.S. FDA, also expressed support for TR-57: "I wanted to thank you for coming to us and giving an excellent presentation. It was very useful for us to know the industry perspective. Your talk provided a better understanding for the method validation and comparability issues. It was the first talk in many years that focused on these topics, so everybody here appreciated the talk. Lately, this topic has gained more importance as the companies are increasingly replacing old method technologies with new ones and transferring methods globally. Lots of people are now waiting for this PDA technical report to be published."

A summary of those TR-57 topics, covered in the new FDA draft guidance, and aligned with the published technical report, is given in the table below.

PDA technical reports have served our industry well and TR-57 is no exception. We, as PDA volunteers and authors, take

pride in making valuable documents available to industry and regulators, and with that, improving industry standards. The results speak for themselves here and the experience and recognition gained for us authors is more than worth the effort and time it takes. I wrote this short article to reflect on the value of PDA technical reports and my positive experience writing TR-57. Maybe it will convince some of you to do the same?

About the Author

Stephan O. Krause is a Principal Scientist at MedImmune/AstraZeneca. He has over fifteen years of management experience in QA/QC. He is the PCMO L01 Task Force Leader and a member of PDA's Biotech Advisory Board.

Alignment of TR-57 and FDA Draft Guidance

PDA TR-57 topics presented (in blue) to FDA CMC Product Quality Reviewer Teams, or, otherwise covered in PDA TR-57	**FDA Product Quality Reviewers' questions/comments during June 2012 presentation**	**Alignment of PDA TR-57 with current FDA draft guidance content**
Risk-Based Validation Studies (Categories) and AMV studies completed prior to PV Stage 2	When are the method validation studies completed?	Similar risk-based method validation strategies and completion timing (clinical phase 3)
Compendial Method Verification Studies for each Method Type	Are compendial methods always (formally) verified?	Both clarify the performance characteristics to focus on
Analytical Method Transfer (AMT) comparison of variability and bias. AMT case study shown	How exactly does a comparison/equivalence study fail in AMT?	Both clarify the performance characteristics to focus on. Both are based on USP <1224>
Analytical Method Comparability (AMC) • Use of ICH E9 models • Representative sample types and sizes for AMC studies • Justification of above	Why is ICH E9 used for AMC models? Can AMC models be switched once data becomes available? Are justifications used for E9 model, acceptance criteria, and sample sizes?	Same use of noninferiority, superiority, and equivalence models for AMC and how comparison studies are to be set up and justified
Use of confidence interval (CI) limits for the E9 models and the treatment of bias	How were CI limits justified? What to do if 90% CI overlaps or 90% CI out of limit(s)?	Same use of CIs, acceptance criteria setting and justification, and treatment of bias.
Analytical Method Maintenance (AMM): Periodic method performance and validation status reviews	How often should AMV status be reviewed and validity of AMQ/AMV studies reassessed when specifications change?	Both encourage the use of the concept of AMM (continuous validation)
AMV failures and protocol deviations • Investigation process similar to OOS	No questions/comments.	Not covered in FDA draft guidance
Method characteristics to be evaluated	N/A	Same performance characteristics to be evaluated
Method robustness studies—timing, use of data, DOE concept	N/A	Both suggest DOE for robustness
Use of method development data in method validation (report)	N/A	Both provide this option
Use of ASTM E29-02 for significant digits	N/A	Both suggest E-29-02
Validation of stability-indicating methods	N/A	Similar validation considerations
FDA approved methods can be verified (instead of validation)	N/A	Both allow for this option
Use of recommended statistics for method validation studies	N/A	Both suggest the same statistics
Use of retains for method comparability studies	N/A	Similar use of retains for method comparability studies
Revalidation triggers and characteristics to be studied	N/A	Similar risk-based revalidation requirements to be confirmed

Have a Reg Change Headache? Take Two Aspirins and Attend the PDA/FDA JRC

Carol Rehkopf, U.S. FDA

The pharmaceutical industry has a tough job. It must provide lifesaving, life-enhancing, preventative and meaningful medical treatments for patients while at the same time keep pace with technical and scientific advances and satisfy regulatory expectations. How do companies find the right balance?

First, they need to understand the ever-changing regulatory expectations. Sound familiar? The U.S. FDA user fee legislation changes every five years. Even though industry takes a large role in the user fee negotiations, there is always stipulations that have impact. This is also true of regulatory expectations for products not subject to user fees. Take the Drug Quality and Security Act (DQSA) legislation that became law in 2013 for example. This Act requires that drug manufacturers, wholesale drug distributors, repackagers, and many dispensers to work closely with FDA on developing a new system to identify and trace certain prescription drugs as they are distributed in the United States. This, again, will require change for a wide range of products. And how about changes using new technologies and personalized medicine? Industry and regulators are still trying to figure out the regulatory balance for these important advances. Keeping up with all this change is enough to give anyone a pounding headache!

This doesn't have to be the case. Attending the *2014 PDA/FDA Joint Regulatory Conference* can help. The conference will be held in Washington, D.C., Sept. 8–12. As in the previous 20 years, the FDA is supporting the conference by offering expert presenters on the pressing regulatory topics of the day. These pressing topics include the future of manufacturing, FDA Safety and Innovation Act implementation, risk and control strategies, clinically related risk assessments, regulatory submission quality, supply chain concerns, quality systems, etc.

PDA's regulatory-focused interest groups falling under its Regulatory Affairs and Quality Advisory Board (RAQAB) will also convene during the conference. On Monday, Sept. 8 at 5 p.m., the Pharmacopeial, Regulatory Affairs, Quality Risk Management and Inspection Trends interest groups will meet. On the following day, the Quality Systems, GMP Links to Pharmacovigilance, and Supply Chain Management interest groups will meet at 5 p.m. as well. All conference attendees are welcome to attend an interest group meeting. For the schedule of science and biotechnology-focused interest groups, see page 20.

To learn more about the conference, please visit www.pda.org/pdafda2014. For information about PDA Training and Research Institute courses following the meeting, please visit www.pda.org/pdacourses2014.

ICH Q10 Expectations Climb: Are You Prepared?

Anders Vinther, PhD, Sanofi Pasteur

How well has your company been able to move its focus and efforts from reactive to proactive using the pharmaceutical quality system (PQS) enablers Quality Risk Management (QRM) and Knowledge Management (KM)? Have QRM and KM crossed the line from theory to a process that's actively and dynamically used in your daily business activities?

ICH Q10 Pharmaceutical Quality System 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 in order to ensure high quality products are produced and that 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 findings and drug shortages. PDA is developing a technical report on use of QRM to help avoid drug shortages, yet it has applications that go beyond mitigating drug supply issues.

When it comes to knowledge management, many companies are still challenged with institutionalizing KM. Even though KM allows companies to continuously learn about their products and our processes, many companies struggle with how knowledge is effectively gathered and shared across the enterprise, from site to site, and even between departments.

FDA and PDA have jointly developed a very comprehensive program for the *2014 PDA/FDA ICH Q10 Implementation Workshop* that 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

Come join us Nov. 3–5 in Baltimore, Md. For more information about this workshop, visit www.pda.org/ichq10.

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The closing plenary of the 2013 PDA Pharmaceutical Quality Metrics Conference

Amgen's Martin VanTrieste discusses the U.S. FDA's proposal for offering quality metrics

Mark Sebree of BD Rx talks about his company's new line of generic sterile injectables

Lawyer Cathy Burgess speaks about greater U.S. FDA regulatory oversight of cGMPs

Katja Kotter of Vetter addresses the new combination products rule

Yuexia Li, Jeffrey Baker and Cesar Matto offer perspectives on transitioning to U.S. FDA careers after many years in industry

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2014 PDA Joint Regulatory Conference Course Series

September 11-12 | Washington, DC
www.pda.org/pdacourses2014

Immediately following the *2014 PDA/FDA Joint Regulatory Conference*, the PDA Training and Research Institute will host six courses to complement what you learned at the conference.

For more information, please turn to page 12.

Fundamentals of an Environmental Monitoring Program

September 16-17 | Bethesda, Maryland
www.pda.org/EMFundamentals

The course will discuss, in detail, controlled environmental test methods, with a focus on microbiological control.

OCTOBER 2014

Fundamentals of Cleaning and Disinfectant Programs for Aseptic Manufacturing Facilities

October 1-2 | Bethesda, Maryland
www.pda.org/disinfection

Covers the critical steps to developing and validating a complete contamination control program within controlled and non-controlled environments using chemical agents that reduce or destroy micro-organisms.

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

October 9-10 | Huntington, CA
www.pda.org/PFScourses2014

Immediately following the 2014 PDA Universe of Prefilled Syringes and Injection Devices, PDA Training and Research Institute will be hosting four courses to complement your learning.

- 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 10)
- 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
www.pda.org/2014aseptic5

With almost 50 hours of hands-on laboratory training and group project work, in addition to extensive coverage of topics during the lecture sessions, this is the most complete aseptic processing training program offered.

Single-Use Systems for Manufacturing of Parenteral Products

October 21-23 | Bethesda, Maryland
www.pda.org/sus

Provides you with critical concepts to consider when implementing a single use system (SUS) strategy in a pharmaceutical manufacturing process.

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)
- Exclusion of Objectionable Microorganisms from Pharmaceutical and OTC Drug Products, Consumer Health Products, Medical Devices and Cosmetics – *New Course* (October 24)
- Microbiological Risk Assessment of a Pharmaceutical Manufacturing Process – *New Course* (October 24)

Validation of Biotechnology-related Cleaning Processes

October 28-30 | Bethesda, Maryland
www.pda.org/biotechcleaning

Provides you with a complete, hands-on cleaning validation education program covering both automated (CIP) and manual cleaning for biotech manufacture.

For more information on these and other upcoming PDA TRI courses, please visit www.pda.org/courses

 Laboratory Courses

The PDA Training and Research Institute is accredited by the Accreditation Councilfor Pharmacy Education (ACPE) as a provider of continuing pharmacy education.

Drug Shortage Issues Continue to Plague Industry

Ursula Busse, PhD, Novartis

Shortages in the supply of critical medicines ("drug shortages") are an important global issue that impacts patients worldwide. The urgency to address this issue and develop sustainable solutions is the driving force behind ongoing collaboration efforts between regulators, legislators, healthcare providers and industry. These efforts are coordinated and supported by industry and membership-based associations such as PDA, ISPE, the European Federation of Pharmaceutical Industries and Association (EFPIA), and the European Generic Medicines Association (EGA).

The causes underlying drug shortages are varied; however, almost half of the shortages are due to issues related to manufacturing quality and supply continuity. These issues are often exacerbated by lack of investment in current technologies and facility upgrades, insufficient proactive end-to-end supply chain risk management, and regulatory hurdles to postapproval changes that limit innovation. Increasingly, it appears that investing in state-of-the-art technologies and facilities, building resilience into the supply chain and improving interactions between industry and regulators are key elements to ensuring reliable supply of safe and efficacious medicines to patients.

To promote further dialogue between stakeholders, PDA is holding a workshop on drug shortages, Sept. 10–11 in Washington, D.C. Focusing on root causes and solutions related to manufacturing quality and supply continuity, the workshop will convey the global regulatory perspective by the U.S. FDA and EMA, along with lessons learned by senior industry leaders from manufacturing, supply chain, quality assurance, and regulatory affairs. Risk management approaches to ensuring continuity of supply will be discussed, along with incentives for new technologies to mitigate risks in aging facilities.

To learn more about the program, visit www.pda.org/drugshortage2014. There will also be a session (B5) on drug shortages at the *2014 PDA/FDA Joint Regulatory Conference* Tuesday, Sept. 9 at 3:15 p.m.

PDA at the Forefront of Meeting Temp Sensitive Challenges

Erik J. van Asselt, PhD, Merck, and Rafik H. Bishara, PhD

Can your company identify all the nodes of the supply chain for its temperature-controlled products? Can it describe its risk mitigation strategies to prevent damage to the product, theft, counterfeiting and a whole host of supply chain risks? Does it have a stability budget in place to assure the quality of product from the beginning of the distribution process to when it arrives in patients' hands?

Product integrity and supply chain visibility are of vital importance for manufacturers and suppliers of medicinal products to provide the right product with the right quality and quantity at the right time and place. During manufacturing, handling, storage and distribution these medicinal products are exposed to risk of damage, theft, temperature extremes, counterfeiting, tampering, and other conditions which might impact the product availability, efficacy, and quality to the end user: the patient. Application of risk mitigation actions should protect the patient, the product and the supply chain. Other solutions include implementation of good distribution practices (GDPs) related to regulation, contract management, temperature control and transport integrity and serialization of products.

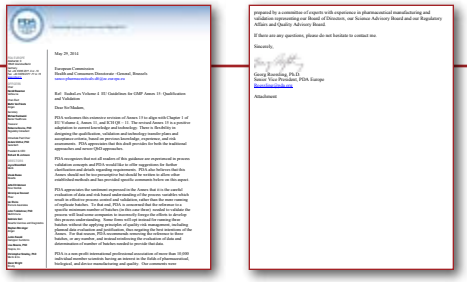
PDA's Pharmaceutical Cold Chain Interest Group (PCCIG) has been at the forefront of many of these changes. Additional answers to your pressing question for distribution of temperature-controlled products can be found in many of the interest group's efforts, including *Technical Report No. 39 (Revised 2007): Guidance for Temperature-Controlled Medicinal Products, Technical Report No. 46: Last Mile, Technical Report No. 52: Guidance for Good Distribution Practices (GDPs) for the Pharmaceutical Supply Chain, Technical Report No. 53: Guidance for Industry: Stability Testing to Support Distribution of New Products, Technical Report No. 58: Risk Management for Temperature-Controlled Distribution,* and *Technical Report No. 64: Active Temperature-Controlled Systems.*

In addition, to encourage additional dialogue on the topic, PDA Europe will hold a conference dedicated to supply chain and temperature-controlled product logistics in Berlin, Germany, Oct. 14–17. Representatives from numerous supply chain- and pharma-oriented organizations, along with international regulators and PCCIG members, will discuss current issues and help find solutions for common supply chain concerns.

For more information about this event, please visit the PDA Europe website at europe.pda.org/supplychain2014.

PDA Comments on EU Annex 15 Revision

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



May 29, 2014

European Commission
Health and Consumers Directorate –General, Brussels
sanco-pharmaceuticals-d6@ec.europa.eu

Ref: EudraLex Volume 4 EU Guidelines for GMP Annex 15: Qualification and Validation

Dear Sir/Madam,

PDA welcomes this extensive revision of Annex 15 to align with Chapter 1 of EU Volume 4, Annex 11, and ICH Q8 – 11. The revised Annex 15 is a positive adaptation to current knowledge and technology. There is flexibility in designing the qualification, validation and technology transfer plans and acceptance criteria, based on previous knowledge, experience, and risk assessments. PDA appreciates that this draft provides for both the traditional approaches and newer QbD approaches.

PDA recognizes that not all readers of this guidance are experienced in process validation concepts and PDA would like to offer suggestions for further clarification and details regarding requirements. PDA also believes that this Annex should not be too prescriptive but should be written to allow other established methods and has provided specific comments below on this aspect.

PDA appreciates the sentiment expressed in the Annex that it is the careful evaluation of data and risk based understanding of the process variables which result in effective process control and validation, rather than the mere running of replicate batches. To that end, PDA is concerned that the reference to a specific minimum number of batches (in this case three) needed to validate the process will lead some companies to incorrectly forego the efforts to develop this process understanding. Some firms will opt instead for running three batches without the applying principles of quality risk management, including planned data evaluation and justification, thus negating the best intentions of the Annex. For that reason, PDA recommends removing the reference to three batches, or any number, and instead reinforcing the evaluation of data and determination of number of batches needed to provide that data.

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

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

Sincerely,
Georg Roessling, Ph.D.
Senior Vice President, PDA Europe
Roessling@pda.org

[Editor's Note: please see page 46 for a list of the commenting task force members.**]**.

Stephan Rönninger, PhD, Amgen

PDA Facilitates Understanding Of CMO Management and Quality Agreements

It's always a pleasure to see the variety of activities our volunteers engage in that are facilitated by PDA staff to connect people, science and regulation®. Today, I want to draw your attention to the challenge of managing development of a *Quality Agreement* in an intercompany setup with a *contract manufacturing organization* (CMO). The significant effort to resolve this challenge is a great example that demonstrates how volunteers can be involved in PDA and benefit from interacting with each other (e.g., commenting on draft guidelines, working in conference committees, taking part in interest groups or writing articles and books). Participating in one of these activities will enhance your knowledge and establish new contacts with peers, companies and regulators.

Contract manufacturing should be a partnership between two parties. Remember that the responsibility for quality still lies with the company giving the contract. The outsourced operation should be seen as an extension of their own operations and network. The management philosophy of the CMO should be "we consider your product to be our product." The CMO (contract acceptor) has to have a flexible and robust quality system in place with processes reflecting best practices and their own company's culture. They are challenged to fulfill the expectation of all their customers. Consequently, it can be a challenge when there is a request to work according to the contract giver's quality system. How can the CMO and contract giver come to a better understanding of best practices for working with a CMO?

To help you and your company resolve these questions, PDA has an interest group and a task force under the oversight of the Paradigm Change in Manufacturing Operations (PCMO℠) project to develop best practices for establishing quality processes that are robust and flexible. PDA also offers our "GMP of APIs" training on harmonized GMPs and ICH Q7. PDA Europe manages this training jointly with PIC/S. During this training, topics are explained in detail with examples of good and bad practice by inspectors, allowing significant time for participants' interactive discussions.

Quality Agreements as part of GMP requirements have become a very important tool to facilitate communication. These legal documents ensure companies have aligned expectations on responsibilities and deliverables. Quality Agreements can vary in length from two to about 50 pages. The people behind an agreement are typically more important than the document itself. This raises the question of whether long and detailed SOPs and/or agreements are really needed. If everything needs to be described in detail, then there might be something wrong with the relationship and quality may also lag. This is why there are companies who believe that a more intense personal relationship based on trust and technical oversight is key in the relationship with their CMOs.

Whatever approach a company decides on, the quality of the product must be ensured. The level of effort and formality should align with the level of risk (see ICH Q9). Quality performance measures, usually called "Key Performance Indicators" (KPIs), or quality metrics could be included. To strengthen the regulatory framework, PDA volunteers compiled comments on the U.S. FDA draft guidance *Contract Manufacturing Arrangements for Drugs: Quality Agreements*, released last year by the Agency.

If you are now interested in additional information, I recommend attending the conference on Contract Manufacturing/Outsourcing organized by PDA Europe in Berlin, Germany for Dec. 2–3. In September, there will be a session on CMOs at the *2014 PDA/FDA Joint Regulatory Conference* (Tuesday, Sept. 8, 10:45 a.m.) in Washington, D.C. Take these opportunities to talk with peers and regulators about expectations and their experiences. You might also discover additional details in a recently published PDA book, *Pharmaceutical Outsourcing: Quality Management and Project Delivery*, which provides in-depth discussion on this subject.

The pharmaceutical industry faces many challenges with the supply and quality of materials. PDA offers the unique opportunity to informally connect suppliers and contractors and share science and best practices as well as learn from regulators.

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Summertime Reading, Storms Underway!

It is a challenge to be a writer, editor and publisher of periodicals in the summertime, because during this time of year, not only are we competing with all the great books and magazines people typically read during increased times of leisure, we are competing with increased consumption of the web, television, movies, and outdoor activities. So we put together this issue with that in mind, shortening the features and publishing content that we hope will be a little more fun than usual.

For one, we launched the first *PDA Letter* "Summer Reading," an expanded "In Print" with excerpts of PDA books published over the last half year. In addition, we surveyed our editorial committee, board members and staff to see what they are reading for fun, and decided to include that list as well. If you think it strange that I chose *Ulysses* by James Joyce as my summer fun reading, it is a curious choice for sure. This is my fourth attempt to read the novel, and I'm committed to get through it this time. But also, I have the pleasure of reading a host of great literature for young adults as I have two children who still enjoy hearing me read to them. So that blooming novel is competing with books like *The Eyeball Collector*, *Artemis Fowl the Atlantis Complex,* and *Amulet: The Stonekeeper's Curse.* Staff really enjoyed sharing their reading plans with us, except for Rich Levy, who became stressed that his management read might make him seem nerdy. Fortunately, he is reading another book, so we included that one too, though I'm not sure it is any less nerdy, but it does sound good. Richard Johnson and PLEC member Youwen Pan are coincidently reading the same book, which only proves that great minds think alike.

We also bring to you an interview of Vetter VP **Joachim del Boca,** conducted by PLEC member **Robert Darius.** We always are looking for members to contribute articles, and interviews are a great way to provide us with content. We thank Bob for taking the time to do it for us and Joachim for putting up with Bob's probing questions! It is such an informative piece, we featured it as the April *PDA Letter* Podcast.

Bob is one of those PDA members who can be frequently found traversing the halls of the PDA headquarters. But there are others who are here more, and each week, one can find a PDA member at the headquarters, either teaching a course at the Training and Research Facility or meeting with a task force, or just saying "hi." So for the first time, we've included in the PDA Photostream photos of members who have visited over the past several months. We will continue this new tradition moving forward.

As I write this and as we close out the July/August issue, I'm sure PDA members in the United States are preparing for Independence Day festivities, which might or might not include weathering Hurricane Arthur. I'm still awaiting the day when Hurricane Walter hits the Atlantic coast, but that would be quite a few storms, wouldn't it? Maybe they ought to consider starting at Z every other year?

To all our members enjoying summertime (and that's only us denizens of the northern hemisphere, I know), don't forget about PDA while you're off having fun!

PDA Letter

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

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