People • Science • Regulation

PDA Letter

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September 9-11 | Bethesda, Maryland
www.pda.org/viruspikes

2013 PDA/FDA Joint Regulatory Course Series
September 19-20 | Washington, D.C.
www.pda.org/pdafdacourses2013

- Implementation of Quality Risk Management for Commercial Pharmaceutical and Biotechnology Manufacturing Operations (September 19)
- GMPs for Manufacturers of Sterile and/or Biotechnology Products (September 19)
- CMC Regulatory Requirements in Drug Applications – *New Course* (September 19)
- Implementing Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations: *Case Studies in the Manufacturing of Biotechnological Bulk Drug Substances* – *New Course* (September 20)
- Implementing Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations: *Case Studies in the Packaging and Labeling of Drug Products* – *New Course* (September 20)
- Implementing Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations: *Case Studies in the Manufacturing of Pharmaceutical Drug Products* – *New Course* (September 20)

2013 Lyophilization Week
September 30-October 3 | Bethesda, Maryland
www.pda.org/lyophilization

- Fundamentals of Lyophilization (September 30 – October 1)
- Validation of Lyophilization (October 2 – October 3)

OCTOBER 2013

Fundamentals of Cleaning and Disinfectant Programs for Aseptic Manufacturing Facilities – *New Course*
October 1-2 | Bethesda, Maryland
www.pda.org/disinfection

An Introduction to Visual Inspection – Session 2
October 9-10 | Bethesda, Maryland
www.pda.org/visualinspectionlab2

2013 Aseptic Processing Training Program
Bethesda, Maryland
www.pda.org/2013aseptic

Session 5: October 14-18 and November 4-8

Single Use Systems for Manufacturing of Parenteral Products
October 23-24 | Bethesda, Maryland
www.pda.org/singleusemanf2013

PDA 8th Annual Global Conference on Pharmaceutical Microbiology Course Series
October 24-25 | Bethesda, Maryland
www.pda.org/microcourses2013

Validation of Biotechnology-related Cleaning Processes
October 29-31 | Bethesda, Maryland
www.pda.org/biotechcleaning

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

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PDA Letter

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28 Management, We Have a Problem

Over the past decade, several large pharmaceutical companies have entered into consent decrees with the U.S. FDA and it seems that the Agency has increased its use of this enforcement tool. So far, very few companies have been successful in terminating a consent decree with the FDA. One of the few companies that successfully completed the items agreed upon with the FDA, and demonstrated continuous compliance with cGMPs, is Abbott Laboratories. This article discusses the main pitfalls in dealing with a consent decree and methods for handling one.

Cover Art Illustrated by Katja Yount

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The PDA Letter spoke with **Rick Friedman,** Associate Director, OMPQ, CDER, and **Mahesh Ramanadham,** PharmD, Acting Team Leader, OMPQ/OC, both from the U.S. FDA and members of the planning committee for the *2013 PDA/FDA Joint Regulatory Conference.* Friedman is also the co-chair for the subsequent *2013 PDA/FDA Improving Investigations Workshop.* Friedman and Ramanadham were excited to discuss topics of interest that will be discussed at the conference and workshop.

36 **cGMPs Continue to Evolve as U.S. FDA Expands Regulatory Authorities Under FDASIA**

The U.S. Food and Drug Administration Safety and Innovation Act (FDASIA), passed last year, includes provisions that give the U.S. FDA greater statutory authorities with regard to cGMPs. The PDA Letter spoke with **Cathy Burgess,** Partner, Alston & Bird, who will speak about the evolution of cGMPs as they relate to the FDASIA legislation during the third plenary session at the upcoming *2013 PDA/FDA Joint Regulatory Conference.*

38 **Common Elements of a Consent Decree with the U.S. FDA**

This issue's infographic looks at some of the common elements of consent decrees.

Over 30 Regulators Scheduled to Speak in Sept.

The *2013 PDA/FDA Joint Regulatory Conference* is one of our most popular events, no doubt because it offers the chance for you to interact directly with regulatory experts on the pressing topics of the day. This year's conference is no different. Over 30 regulatory speakers have been invited to speak. The following is a list of confirmed regulatory experts, all of whom work for the U.S. FDA:

- **Janet Woodcock,** MD, Director, CDER
- **Laurie Norwood,** Deputy Director, DMPQ, CBER
- **Pankaj Amin,** Assistant Country Director, CBER
- **David Cummings,** Associate Director for Quality, CDER
- **Dennis Guilfoyle,** PhD, Pharmaceutical Microbiologist, ORA
- **Richard Friedman,** Associate Director, OMPQ, CDER
- **Colleen Hoyt,** Supervisor, Team Biologics, ORA
- **Marta Wosinska**, PhD, Director, Economics Staff, CDER
- **Stanley Liu,** Consumer Safety Officer, CDRH
- **Patricia Love**, Deputy Director Office of Combination Products, OC
- **Isabel Tejero**, Consumer Safety Officer, CDRH
- **Mai Huynh,** Supervisory Team Leader, CVM
- **Mahesh Ramanadham,** Regulatory Compliance Officer, OMPQ, CDER
- **Lawrence Yu,** PhD, Deputy Director, Office of Pharmaceutical Science, CDER
- **Kristen Anderson,** PhD, Senior Microbiologist, Division of Manufacturing Technologies, CVM
- **Steven Silverman,** Director, Office of Compliance
- **Martine Hartogensis,** Deputy Director, CVM
- **Armando Zamora,** Acting Director, OE
- **Steve Solomon,** Deputy Associate Commissioner, ORA

All of these speakers will discuss topics pertinent to industry. To learn more about the exciting event, see story on p. 48.

PDA Selected as 2013 Best of Bethesda Winner

Amelia Townsend, PDA

Each year, the Bethesda Award Program identifies companies that have achieved exceptional marketing success in their local community and business category. These are local companies that enhance the positive image of small businesses through their service to Bethesda, Md.

Based on information gathered by the program's organizers and third parties, PDA received a Best of Bethesda award for 2013.

According the organizers of the Bethesda Awards Program, these companies help make Bethesda a "great place to live, work and play.

PDA also received a Best of Bethesda Award in 2012.

PDA IN THE NEWS

Below is a listing of various news articles/websites that have mentioned PDA within the past six months.

FDA Voice Blog

Feeling Proud When Excellence is Noted—Twice
Lawrence Bachorik, PhD, U.S. FDA
tinyurl.com/Feeling-Proud-When-Excellence

IPQ Monthly Update Jan/Feb 2013

CDER Officials Shed Light on Forces Impacting Generic Injectable GMP Compliance and Drug Shortages

EMA Guidelines on Process Validation Filings for Biotech Substances and Drug Products Advancing Along with GMP Annex 15 Revision

EMA GMP Chapter Draft Revisions Focus on Current Compliance Focal Points from Shared Facilities to Defect Investigations

QP Review of More Complex Supply Chains and Applications, EU Member State Differences, Among Issues Facing EMA in Annex 16 Revision

Revamped EudraGMP Database May Make GMP Noncompliance Statements Public

IPQ Monthly Update April 2013

Search Intensifies for Options to Resource-Draining Redundancies of Multiple Agency Inspections

IPQ Monthly Update May 2013

Better Human Factors Analysis is Driving New Combination Product Technologies Designed to Reduce User Errors

FDASIA Title VII Implementation Priorities and Action Plans Taking Shape

The Sterility Risks in Pharmacy Compounding Can Be Limited, Not Eliminated, Experts Stress at USP Forum

APEC Supply Chain Regulatory Harmonization Effort Gaining Traction

Pharma Manufacturing

March 3, 2013

Uncommon Sense in Execution of Process Simulations **James Agalloco** tinyurl.com/UncommonSenseProcessSimulation

Pharmaceutical Technology

May 30, 2013

Manufacturers Seek Strategies for Life-Cycle Approach to Process Validation **Jill Wechsler** tinyurl.com/Life-Cycle-Approach-to-Process

BioProcess International

April 2013

Drug Products for Biological Medicines

Anthony Mire-Sluis, Donna French, Jennifer Mercer, Gerd Kleemann, John Dougherty tinyurl.com/Drug-Products-for-Biological

April 2013

Broadening the Baseline S. **Anne Montgomery, Kevin Ott, Jeanette McCool** tinyurl.com/Broadening-the-Baseline

May 2013

Artifacts of Virus Filter Validation **Paul Genest,** et al., tinyurl.com/Artifacts-of-Virus-Filter-Val

PDA Volunteer Spotlight

Ghada Haddad

- Associate Director, Engineering, Biosterile Validation
- *Merck*
- Member Since | 2003
- Current City | Philadelphia, Pennsylvania
- Originally From | Beirut, Lebanon

In general, PDA technical reports are aimed at helping the industry understand regulatory requirements

Congratulations on your technical report being published in June! Why do you think technical reports are important for the PDA community to have access to?

Thank you. I am very proud of the work the task force put together. This TR is very beneficial to the PDA community because it provides examples of different applications of Quality Risk Management in packaging and labeling. Plus, it is a supplemental annex to *Technical Report No. 54: Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations.*

What advice would you give a PDA member that is interested in getting involved with a task force?

I would encourage those who are interested to definitely come forward and participate. It is a great opportunity to be part of the PDA community and to work on publications that serve as a "how to" guide in our industry.

You have been a PDA member for ten years, why is PDA membership important to you?

Being part of PDA means belonging to a family of talented, hardworking subject matter experts that I am constantly learning from.

What was your first volunteer experience with PDA?

A previous manager of mine, who chaired TR54, gave me the opportunity to participate and be one of the contributors to that technical report. She then gave me the opportunity to volunteer and lead the effort on building the case studies for QRM in packaging and labeling.

If you could live anywhere in the world, where would you live?

Tough question. I would say I love where I am right now, but sometimes after a long day, being in a tropical location on the beach sounds more appealing.

What is an issue or trend in QRM during the packaging and labeling process that you think more people should be talking about?

I would have to say the process of producing printed packaging material is error prone and has been identified as one of the major risks within the industry.

Meet Some Most Valuable PDA Volunteers (MVPs)

At the *2013 PDA Annual Meeting,* we began a new program that paired established volunteers (MVPs) with relatively new members (Rookies). The program proved to be such a success that we are continuing it for the upcoming *2013 PDA/FDA Joint Regulatory Conference.*

Here is some feedback from those who participated at the Annual Meeting:

I think the program was a great success and the new members I spoke to were greatly impressed and found it very useful.

—***Ian Elvins,*** ***MVP***

The experience was great. I am glad we are continuing this program.

—***Sue Schniepp,*** *Allergy Laboratories,* ***MVP***

It was good to get an overview of what to expect from the PDA.

—***Kiran Sekhon,*** *Genentech,* ***ROOKIE***

The goals of the program are to introduce new members to veteran PDA volunteers, offer expanded networking opportunities and provide additional information about the Association and volunteer opportunities. MVP mentors include *2013 PDA/FDA Joint Regulatory Conference* planning committee members, current or former PDA board members and chapter leaders.

If you're a new member interested in being a "Rookie" paired with a MVP mentor, please contact Volunteer Coordinator Megan Kuhman at kuhman@pda.org. You will need to make yourself available before and during the conference to meet with your MVP. Feel free to ask questions and enjoy your time with them!

chapter update

Southern California Chapter Cruises to a Successful Night

John Holmgren, Allergan, and William Nichols, W J Nichols Electric Co.

On May 9, PDA's Southern California chapter hosted its third annual industry summit cruise off the Newport coast of California. The event featured two technical seminars as well as industry exhibitors and networking opportunities with industry colleagues. The topics of the technical seminars were "Best Practices in Regulatory Inspections," presented by **E.J. Brandreth,** SVP, Quality and Regulatory Affairs, Althea Technologies and "Sterilizing Grade Filtration Update and Necessities," presented by **Maik Jornitz,** VP, Business Development, G-Con Manufacturing.

The chapter partnered with the local ISPE chapter to bring in more service providers to interact with members. As a result, the event had tremendous support with 59 exhibitors and over 200 attendees. This even has become the signature local PDA event in Southern California. During the evening, chapter officers could definitely sense renewed spirit and passion within the members who attended the event. The chapter looks forward to riding this momentum toward future events.

The success of this event can be attributed to the chapter officers, speakers and PDA staff members involved. If you are a Southern California chapter member and you missed the event, please contact the chapter to learn more about upcoming events, benefits and resources available to you. For more information on the chapter please visit http: //www.pda.org/Chapters/North-America-cont/Southern-California.aspx.

The Southern California Chapter sails off into the sunset.

PDA would like to give special thanks to the following members of the PDA Southern California Chapter:

President-Elect **John Holmgren;** Program Director **Randy George;** Treasurer **Bill Nichols**; Program Committee members **Stefany Goldman, Stephanie Powers-Kurtz, Ruchika Raval;** Program Planning volunteers **Larry Chan, Bonnie Ward, Brian Underhill, Tony Steinberg, Vicki Deason** and **Dilip Parikh.**

Additionally, the Chapter would like to thank outgoing President **Saeed Tafreshi** who made the evening possible. Saeed will be stepping down and his leadership will be truly missed. When he first became president in the mid-2000s, he established a number of exciting chapter initiatives, including webcasting as an alternative to multi-day meetings. Not long after setting these up, the webcasting evolved from two or three locations simultaneously to as many as six locations within our territory and reaching many people.

Three years ago, his idea of the industry summit cruise became a reality, resulting in a wonderful setting for industry col-

Members of the Keck Graduate Institute student chapter pose aboard the cruise boat.

This is the third year the chapter has hosted its annual cruise, which close to 200 attended.

leagues to interact and build relationships. He also encouraged and helped support the student program at Keck Graduate Institute (KGI) in the Los Angeles area, where they have established the Student Chapter of SCPDA last year.

To acknowledge the success of its inaugural year, the chapter extends a special appreciation to **Jennifer Lee,** Chapter President of the student chapter at the Keck Graduate Institute and incoming student chapter President **Joanna Naymark**, plus approximately 15 KGI students who attended the event and expressed strong energy in building relationships as future leaders in the industry. The chapter extends its gratitude to **Hassana Howe**, Director of Membership & Chapters at PDA, who took the time to travel to our event and interact with our board members, exhibitors and attendees on the yacht. She reminded us that we have the backing for any support that we need as a chapter.

P5: How to Best Assess, Validate and Monitor the Parenteral Fill/Finish Process to Ensure Integrity of the Container Closure System

(l-r) Mihaela Simianu, PhD, Eli Lilly; Kalavati Suvarna, PhD, U.S. FDA; Dana Guazzo, PhD, RxPax; Lei Li, PhD, Eli Lilly

P6: The New Age for Protection and Safety During Storage and Distribution

(l-r) Derek Duncan, PhD, Lighthouse Instruments; Diane Paskiet, West Pharmaceuticals; Frederick Stearns, Keller Heckman Law Firm

Refreshment breaks

Attendees and exhibitors congregate during one of the refreshment periods.

An attendee learns about a product from SiO_2 medical products.

Attendees discussing hot container closure topics during a coffee break.

Two attendees network during a break at the workshop.

2013 PDA/FDA Glass Packaging Conference

May 15–16 | Bethesda, Md.

P3: Raw Material to Tubular Vial

(l-r) Nicholas DeBello, Wheaton Industries; Boris Schmidt, Ompi; Mark Fitzgerald, Nipro Glass Americas; John McDermott, Gerresheimer Glass

Opening Plenary: Introduction — Overview

(l-r) Cesar Matto, U.S. FDA; Richard Johnson, PDA; Steven Wolfgang, PhD, U.S. FDA; Ronald Iacocca, PhD, Eli Lilly

P5: Analytical Techniques and Testing Protocols

(l-r) Daniel Haines, Schott Pharma Services; John Shabushnig, PhD, Insight Pharma Consulting; Henning Katte, ilis GmbH

P4: Material Science Considerations for Glass Containers

(l-r) Desmond Hunt, PhD, U.S. Pharmacopeia; Carol Rea Flynn, Gerresheimer Glass; Robert Swift, Amgen

P2: Glass Raw Materials

(l-r) Daniel Haines, Schott Pharma Services; Juan Cerdan-Diaz, PhD, Nipro Glass Americas; Steven Wolfgang, PhD, U.S. FDA; Mihaela Simianu, PhD, Eli Lilly; Mads Reedtz Espersen, Novo Nordisk A/S; Folker Steden, PhD, Schott AG

P6: Integrated Measures to Control Glass Quality during Manufacturing Processes

(l-r) Gregory Pitt, Eli Lilly; Mads Reedtz Espersen, Novo Nordisk A/S; Roger Asselta, Genesis Packaging Technologies; Patrick Begley, Becton Dickinson

Opening Plenary: Introduction—Regulatory Perspective

(l-r) Scott Bozzone, PhD, Pfizer; Jeffrey Baker, U.S. FDA; Vijay Chiruvolu, PhD, Amgen

P2: Process Design—Where to Begin

(l-r) Hal Baseman, Valsource; Patrick Swann, PhD, U.S. FDA; Michael Blackton, ImClone

Attendees packed the meeting space, eager to learn about the latest in process validation.

P3: Process Qualification Part II—Case Studies

(l-r) Vijay Chiruvolu, PhD, Amgen; Greg Sears, Lonza; Wayne Taylor, PhD, Taylor Enterprises

P4: Process Qualification Part II—Case Studies

(l-r) Scott Bozzone, PhD, Pfizer; David Paolella, PhD, GlaxoSmithKline; Timothy Watson, PhD, Pfizer; Chris Ames, Genzyme

P5: Continued Process Verification Part I–Confirmation and Vigilance

(l-r) Wendy Zwolenski Lambert, Novartis; Cliff Campbell, Cliff Campbell Consulting; Steven Hertz, U.S. FDA; John McShane, Roche

P6: Continued Process Verification Part II–Case Studies

(l-r) Rebecca Devine, PhD, Consultant; David Reifsnyder, PhD, Microbiological Environments; Raj Jani, Baxter; Stephen Galvin, Eli Lilly

Breakout Sessions

Jeff Baker, PhD, U.S. FDA, raises a point during a breakout group discussion.

Breakout sessions offered opportunities for debate and discussion.

Rebecca Devine, PhD, Consultant, looks on during a breakout session discussion.

Breakout groups took notes during sessions that were later discussed in the closing plenary session.

Opening Plenary: Lessons Learned in Supply Chain Management Outside of Pharmaceutical

(l-r) Steven Wolfgang, U.S. FDA; W. Payton Pruett, PhD, The Kroger Co.; Bill Bronrott, Federal Motor Carrier Safety Administration

Breakout Session: Securing the Future Supply Chain

Edwin Rivera-Martinez, Sanofi, leads one of the interactive breakout sessions.

Refreshment breaks allowed attendees to discuss topics raised during the conference.

Breakout Session: Supplier Key Performance Indicators (KPI's)

(l-r) Paula Katz, U.S. FDA, Matthew Anderson, Merz; Susan Schniepp, Allergy Laboratories

P2: Partnership for Supply Chain Management

(l-r) Brian Johnson, Pfizer, Kevin Siver, PhD, Amgen; W. Dale Carter, IPEC-Americas; Cindy Marin Velez, Eli Lilly

Edwin Rivera-Martinez (right) looks on during a refreshment break discussion.

P3: Pharmaceutical Supply Chain: Raw Material to Quality Standards

(l-r) Susan Schniepp, Allergy Laboratories; Neil Wilkinson, NSF; Jean Poulos, J&J; Mary Storch, Ben Venue

P4: Pharmaceutical Supply Chain Import Compliance

(l-r) Steven Wolfgang, PhD, U.S. FDA; Judith-Anne Webster, U.S. Customs and Border Protection; David Ulrich, Abbvie; Huascar, Batista, U.S. FDA

P7: Ask the Experts Panel Discussion

(l-r) Mark Paxton, U.S. FDA; Mary Storch, Ben Venue; Cesar Matto, U.S. FDA; Susan Schniepp, Allergy Laboratories; Edwin Rivera-Martinez, Sanofi; Gwyn Murdoch, Eli Lilly; Steven Wolfgang, PhD, U.S. FDA

P5: Breakout Working Group Readout Reports

(l-r) Matthew Anderson, Merz; Edwin Rivera-Martinez, Sanofi; Susan Schniepp, Allergy Laboratories; Gwyn Murdoch, Eli Lilly; Mary Storch, Ben Venue

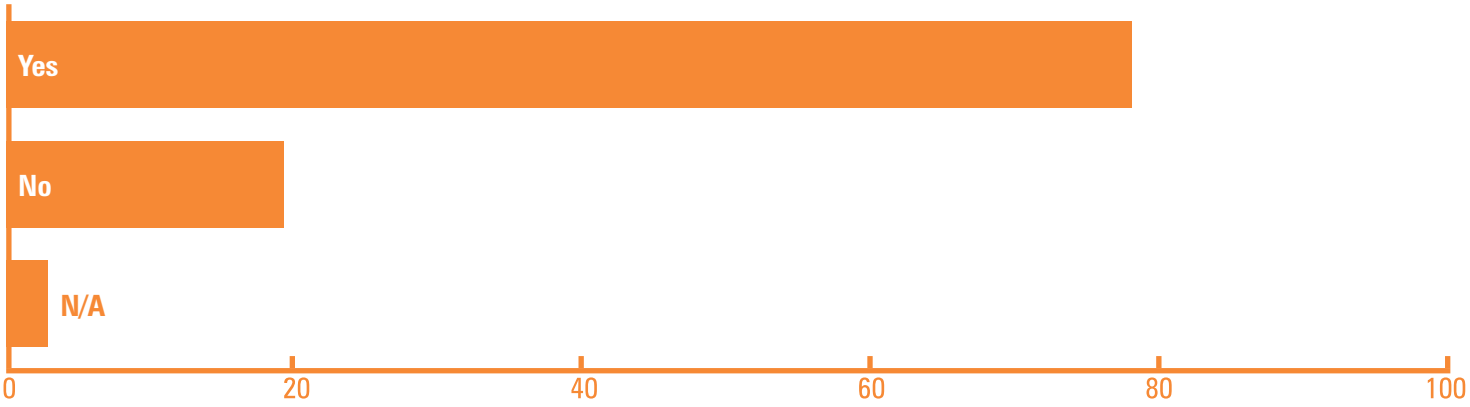
P6: Tracking and Tracing Prescription Drug Packages

(l-r) David Ulrich, Abbvie; Lucy Cabral, Genentech; Gregg Goneconto, Baymar Consulting

PDA Pulse

Association Membership Impacts Hiring Decisions

In early June, PDA ran a survey of members with hiring authority, asking if membership in an association impacts their hiring decisions. As you can see, over 78% said "yes." With this in mind, it's a good idea to ensure your membership remains active in PDA.



PDA Thanks Chapter Leaders for Attending Annual Meeting

PDA wants to thank those chapter leaders who attended the *2013 PDA Annual Meeting* in Orlando, Fla.

(top l-r) Trevor Swan, Roland Bizanek, Greg Jordan, John Holmgren, Junko Sasaki, Hassana Howe, Austin Caudle, Sabrina Ullah, Enrique Dilone, Allen Burgenson, Maggie Filipowicz, Ken Paddock, Rusty Morrison, Anne Greene, Jeff Hargroves

(seated l-r) Renee Morley, Michele Creech, Beth Kirschenheiter, Melissa Seymour, Shelley Preslar, Melissa Morandi, Lara Soltis, Stefany Goldman

TOOLS FOR SUCCESS

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

10 Ways to Get Ahead in a Bad Economy

Margaret Buj

In both my recruitment and coaching jobs, I hear from a lot of people who are currently looking for a new job, but they are starting from a defeated attitude. They figure there aren't many jobs and it's impossible to get a pay raise in the current economy.

There are also others who do have a job they don't enjoy, but they are worried they won't find anything better so they are staying in a job that is draining them.

I blame the media a lot. They turn a little bit of negativity into a mountain of pessimism. We become socially conditioned to expect the worst. Companies, however, are always looking for superstars. Just in the last couple of weeks, I've made offers to a few candidates—most of which had other offers on the table.

But if you tune out all the negativity and maintain a grip on rational thought, you'll find there are lots of opportunities for superstars, and many of them can choose from multiple offers—yes, even in this economy!

So how do you get ahead in a "bad" economy? Let me give you a few tips:

1 PUT YOUR TIME AND ENERGY INTO CREATING AND DELIVERING REAL VALUE

Find a way to give your employer/customers what they want and/or need.

2 BE THE BEST

Arrive early at work, take on extra assignments, get creative and connect with your manager to see if there's anything you can help with. Outstanding performers become known through the company grapevine.

3 ATTEND AND PARTICIPATE

Every event your company hosts is an opportunity to meet other managers. Be there.

4 DEVELOP YOUR MARKETING PITCH

That's the pitch that sells the product spelled Y-O-U. Have a concise statement about the impact you've made on your business unit and how your skills could translate to your next assignment.

5 TAKE A STEP BACK

It sounds counterintuitive, but reducing your compensation a bit in order to grow your experience can make sense when you're aiming for a new role. If you perform, responsibilities and compensation will match your performance.

6 CHASE YOUR DREAM JOB

Finding it requires speaking with a wide range of people at your company. Getting it requires developing the skills to present yourself as a serious candidate.

7 THINK BIG PICTURE

In order to advance, identify ways you can affect the whole organization rather than just focusing on your career. How do you get the big picture? By broadening your experience and your exposure to other managers at the company.

8 SHOW YOUR PASSION

The number one requirement for advancement is passion and enthusiasm. Managers are impressed by people who love the business. You'd be surprised how often I need to reject candidates because they did not sound like if they were really interested in the role and the company

9 BECOME THE GO-TO PERSON

Volunteer for projects and take on leadership of the task. This gives you an opportunity to showcase your abilities.

10 DON'T BRUSH OFF COMPLIMENTS

When someone tells you, "Well done!" don't brush it off saying, "It was nothing." (We women are particularly guilty of that!) Say that you've worked hard and appreciate the compliment.

About the Author

Margaret Buj is an interview coach who's helped hundreds of professionals across Europe and the United States to get the jobs and promotions they really wanted.

snapshot

Technical Report *Watch*

Technical Report No. 3 Revised

PDA has revised Technical Report No. 3, originally issued in 1981. *Technical Report No. 3 (Revised 2013): Validation of Dry Heat Processes Used for Depyrogenation And Sterilization* offers a modern, scientific approach to dry-heat depyrogenation and sterilization processes and includes recommendations for use by industry and regulators. References to appropriate and current scientific publications, international regulatory documents, journal articles, technical papers and books are used where more detail and supportive data can be found.

This technical report provides information to the manufacturers of pharmaceutical products for validating dry-heat depyrogenation and sterilization processes. The concepts and methods presented within this technical report are not intended to be a regulatory standard, but rather as points to be considered during the validation of dry-heat processes. Other technically equivalent methods may exist and may be used if they can be supported by sound scientific methods.

The technical report authoring team is composed of diverse professionals to ensure the methods, terminology and practices of dry-heat depyrogenation and sterilization processes reflect sound science and can be used globally. This technical report was disseminated in draft for public review and comment prior to publication to ensure its suitability as a recommendation of best practices to industry.

The PDA Training and Research Institute is offering a 3-day course based on TR-3, August 13-15. The course focuses on the microbiology and engineering qualification of dry heat depyrogenation processes. This course will provide a foundational understanding of depyrogenation science that will then be applied in the design and verification of equipment, depyrogenation process development, process performance qualification for new systems and ongoing maintenance of the validated process.

James Cooper, consultant, and **Brian Jordan,** ValSource, LLC, teach the course.

PDA Validation of Dry Heat Processes Used for Depyrogenation and Sterilization Technical Report Team

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Meeting *Preview*

Interest Group Meeting Schedule

The business of the Association will be conducted, as always, at the *2013 PDA/FDA Joint Regulatory Conference*. Below is a schedule of the Science and Biotech interest groups. **Note:** All interest group meetings are open to meeting registrants. (For Regulatory Affairs IG, see the Regulatory Snapshot, p. 41.)

Monday, Sept. 16	*Tuesday, Sept. 17*	
4:45 p.m. – 6:00 p.m.	**4:45 p.m. – 6:00 p.m.**	
Filtration Interest Group	Blow Fill Seal Interest Group	Pre-filled Syringe Interest Group
Process Validation Interest Group	Packaging Science Interest Group	Facilities and Engineering Interest Group
Visual Inspection of Parenterals Interest Group		

Interest Group *Report*

New Interest Group Tackles Combination Products

Mark A. Chipperfield, F. Hoffmann-La Roche and Lee H. Leichter, P/L Biomedical

Drug delivery combination products are forecasted to become an increasing part of the marketplace for new drugs and biologics as well as for lifecycle management, generics and biosimilars. More companies will find themselves having to incorporate and/or market a device in order to ensure the delivery and/or market success of their product. In addition, best practices and regulatory requirements in this area are rapidly evolving.

PDA has recognized the growing need for industry peers to share experiences, drive technical guidance and help influence regulatory expectations and requirements. The Interest Group for Combination Products has been reinitiated to address these areas and will shortly embark on its first phase of growing a membership base. Joining this interest group will enable PDA members to stay abreast of these changes as well as possibly having the ability to influence them.

The reinitiation of this interest group could not be timelier.

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Tech *Trends*

Parenterals Enter the Regenerative Medicines Era

James Akers, PhD, Akers Kennedy & Associates

Regenerative medicines represent a new approach to human medicine that promise to provide treatments for diseases that are presently considered incurable. These products rely on human cells and tissue to prepare treatments that are personalized for each patient. The source of cells or tissues used in cytotherapy and regenerative medicine is typically from the actual patient being treated. The use of autologous cells mitigates issues with immune rejection of foreign tissues. Replacement cells, or even tissue sheets, can be grown from cells harvested from a patient and then reintroduced to that patient within the clinical setting. There are presently more than 50 regenerative medicine systems/approaches approved for marketing globally, and another 150 or so in clinical study.

These technologies, which are evolving rapidly and becoming more technically sophisticated each year, represent a very different approach to therapy than traditional drug or biological preparations. Regenerative medicine products, unlike the parenterals that with which PDA members, standard setters and regulators are familiar, will present new and unique challenges. These products will not be made in large factories with timelines stretching into

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In *Print*

Setting Controls for Endotoxins

Karen Zink McCullough

The following is excerpted from the chapter "Endotoxins," which appears in the PDA/DHI book, Contamination Control in Healthcare Product Manufacturing: Volume 1, *edited by* ***Russell E. Madsen,*** *The Williamsburg Group, and* ***Jeanne Moldenhauer,*** *Excellent Pharma Consulting. The book is currently available and can be purchased through the PDA Bookstore (www.pda.org/bookstore).*

The author is also scheduled to speak at the upcoming PDA 8th Annual Global Conference on Pharmaceutical Microbiology.

Pharmaceutical manufacturing is a complex series of interdependent processes designed to create an effective therapeutic product that is free from contamination that can harm a patient. "Contamination" can take many forms and can come from many sources. Nonviable particles can be found in raw materials, excipients, the manufacturing environment and process, or in primary packaging. Chemical impurities may be found in raw materials, they may be the result of incomplete or improper processing, or they may be long-term degradation products. Microbial contamination can come from many sources as well

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Task Force *Corner*

Task Force Plans Revision to Technical Report No. 27

Rebecca Stauffer, PDA

Integrity resting remains a hot topic in the area of sterile packaging. Just ask those who attended the *2013 PDA/FDA Container Closure Components and Systems Workshop* in May. The subject arose during a session focusing on the planned revision of *Technical Report No. 27: Pharmaceutical Packaging Integrity.*

Heino Prinz, PhD, Head of Research and Development, Wilco, and member of the task force working on the TR27 revisions, agreed that integrity testing is a prime concern in this segment of the industry, stating that testing "Is a challenge out in the field."

In fact, the task force intends to use USP <1207>, a draft which deals with integrity evaluations of sterile packaging, as the foundation for the technical report.

"It [Technical Report No. 27] was planned in the beginning, to complement USP <1207>," said Prinz. "It's sort of complementary to the report. We want to bring all this information together in that report. And also the learned lessons from past."

According to Prinz, the original technical report detailed the

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Interest Group Report continued from page 21

The U.S. FDA has made a considerable effort to define the appropriate regulatory path for combination products in terms of regulatory jurisdiction, cGMP's and technical performance requirements. Since 2002, the Office of Combination Products (OCP) has expanded the regulation of such products due to escalating and significant quality and safety issues. The heightened awareness and changing expectations have significantly affected the development of combination products and have created numerous challenges for the companies involved. This impact has been felt by PDA members who develop and market drug delivery combination products, which are regulated as drugs and biologics.

In one area of focus, OCP finalized the new *cGMP Rule for Combination Products* (21 CFR 4) in January 2013, making it law in the United States. As the FDA maintains that *all* GMP laws apply to combination products, this rule does not create any new requirements, but suggests ways to streamline compliance for co-packaged or integrated combination products.

Although the term and definitions for "combination products" are used in the USA by the FDA, they are not universally adopted. In the European Union, combination products as such do not exist. These products are characterized as borderline products (for which there is guidance on which regulation to follow), medicinal products or medical devices. In this region, medicinal products and medical devices are regulated under separate directives; namely the Medicinal Product Directive and the Medical Device Directive; that primarily focus upon marketing approval. There is a recent proposal to recast the Medical Device Directives as regulations which may also impact the way these products are regulated.

To learn more about this interest group or to learn how you can join, contact PDA's Volunteer Coordinator, **Megan Kuhman** at kuhman@pda.org.

About the Authors

Lee Leichter has over 35 years of experience providing hands-on assistance to global pharmaceutical, biotech and device companies on business, technical, regulatory and quality issues for drug delivery and combination products. He also serves as an expert on international and U.S. technical committees, helping establish international standards for safety and performance of these products.

Mark A. Chipperfield has spent the last 19 years working within large pharma in the field of drug delivery devices and special purpose packaging. Through his career to date he has been heavily involved in development of medical devices for combination products in several forms.

Tech Trends continued from page 21

weeks or months. They will not rely on bulk products formulated in batches of hundreds, or even thousands, of liters and then processed, containerized and packaged on high-speed production/packaging lines.

Instead, these products will be made in small quantities for individuals; manufacturing will occur in cell or tissue factories located, in many cases, right in a clinic or laboratory. Regenerative medicine products will be risky products in terms of microbiological contamination and expensive to produce. There is no way that these products can follow the same rigid microbiological analysis approach used for traditional parenterals. Time will be of the essence, and there is no practical way that 14-day incubation periods for sterility testing or 5-day environmental monitoring cycles will be applicable or beneficial. On the other hand, well-defined and standardized methods for physical sterilization, decontamination and disinfection will be applicable and can be used based on existing standards and precedence.

Evidence is emerging that the best way to manufacture regenerative medicines will be in the implementation of modular isolator technology able accommodate cell harvesting, modification, growth and preparation for delivery to the patient. I've had the privilege over the last few years to work with a Japanese affiliate manufacturing advanced automated cell processing systems. These systems can be customized to meet specific regenerative medicine manufacturing requirements and are being delivered to regenerative medicine laboratories/producers at this time. Data indicate that these advanced aseptic systems aim to reduce the cost and increase the efficiency of regenerative medicine production by up to tenfold or more over traditional cleanroom approaches.

It is important for intelligent standards and regulations to be applied to worldwide regenerative medicine manufacturing. The recovery and growth-based microbiological assessment programs that have been applied with increasing intensity to large-scale parenteral manufacturing will not work for these new therapies. Asepsis and safety must be engineered into these systems, or there will be no reason or value in attempting to test or monitor these attributes into regenerative medicine products.

Applying validation concepts from the 1980s to 21st century medicine will not enable these products to reach those they can help at reasonable cost. Perhaps lessons can be learned from this effort that will help us take a more modern scientific approach to large scale parenteral production as well.

Those interesting in seeing what a regenerative medicine factory will look like in practice may enjoy a noncommercial video, which can be found at this link showcasing work done at Tokyo Women's Medical University: tinyurl.com/TokyoWMU.

About the Author

James Akers, PhD, is President of Akers Kennedy & Associates. He has over 32 years of experience in the pharmaceutical industry and has worked at various director level positions within the industry.

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technologies available at the time it was written, which was around 1997.

"During that time the technology was not very developed," he explained. "We had some testing methods such as vacuum pressure testing. And there was something about dye ingress testing. And all this is what we have today in the field. [These tests were] found during that time. And this was the first technical approach to tackle all the questions related to the technology."

He added, "Today we have very, very comprehensive technologies available—a lot of different techniques to look into for container integrity."

As far as updating the technology portion, Prinz said the task force wants the report to cover a variety of new packaging topics, including X-ray inspections, multidose devices, ultrasonic leak signature technology, cryogenic storage, medical device packaging and containers for biologics, among other trends.

The task force currently has about 14-15 members around the globe. If anyone has any background in areas related to USP Chapter <1207> or other aspects of container closure packaging, the group would certainly welcome additional input.

Ultimately, Prinz said, the task force hopes the report expands discourse on packaging technologies in the industry.

"We want to give a voice," he said. "And to make the industry aware about the challenges."

About the Expert

Heino Prinz, PhD, joined Wilco AG in August 2010 and is responsible for research and development. His expertise in physics and chemistry helps customers around the world to deeply and better understand pharmaceutical processes, thus improving quality and dramatically reducing QC costs such as rework.

Sterility Testing Proves Hot-Button Issue at Task Force Meeting

[Editor's Note: During the Q&A portion of the breakfast session covering Technical Report No. 27, some audience members expressed concerns about the necessity of sterility testing, particularly its relation to stability testing. **Mihaela Simianu,** PhD, Research Advisor, Eli Lilly, and member of the task force commented on these issues.**]**

Simianu: I think that's the first misconception associated with integrity testing—that we either associate it with sterility testing or we associate it with a particular product stability test. I would say that the best way to apply CCI testing is to provide evidence that the appropriate product protection is secured over product shelf life. Now, if the protection level relative to your particular product is sterility (because we all, in the parenteral world…we're all making sterile products) and you have no other concerns but sterility—then the focus will be on using integrity testing to support protection against ingress of microbes. If that product requires a different level of protection because it's oxygen sensitive, or because it's moisture sensitive, etc., you have to demonstrate CCI for different level of protection. And so there is no method that fits all products in all container closure systems. There is no one single CCI testing method that anyone can prescribe to your application.

And I will go back to your question about what's hot. With sterility, we have to demonstrate it since we make a sterile product (sterility is a critical quality attribute). So, the question is, what method do you use to demonstrate maintaining sterility in a CC system? And you all know that from 2008, the FDA guidance allows for replacing sterility tests on stability (sterility test is not a good stability indicating method). So, not only one has to demonstrate, and of course, have a sterile product to start with (at release) but also you have to demonstrate that you maintain sterility across your shelf life and until the products it's used by the patient. So, CCI associated with maintaining sterility…is a CCI assurance strategy [it is best to have a CCI control strategy]…is to ensure the desired product protection as you develop your product, as you validate your process, as you make the product day in and day out, as product is packaged into delivery systems, stored and distributed…until the end of the shelf life. Now, can you do that with one CCI testing technology? Or do you need a combination of testing methods to cover all the requirements? These are questions that industry is asking. So, to your question, what's hot for us is reading better the specific demands of different regulatory agencies and the degree of scientific evidence that one has appropriate CCI testing.

About the Expert

Mihaela Simianu, PhD, is Research Advisor in Global (Parenteral) Technical Services/Manufacturing Science with Eli Lilly and Company. She manages activities related to product and process monitoring for marketed products to achieve world class manufacturing goals.

snapshot

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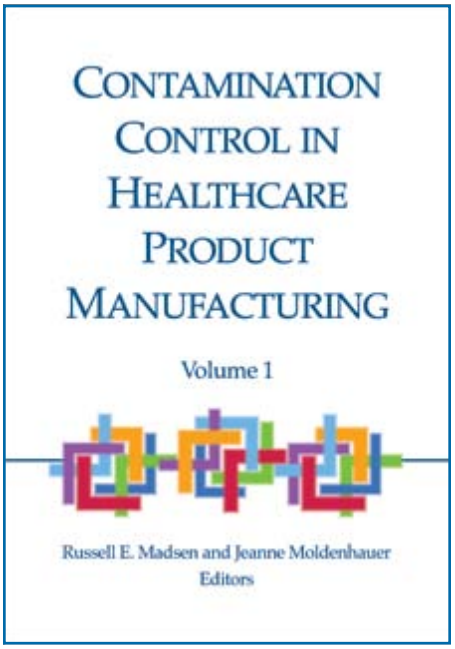
including water and other raw materials, Active Pharmaceutical *Ingredients (API), improper processing,* improper cleaning of product contact surfaces, lack of control over the environment in which the product is manufactured, incomplete sterilization of equipment or product, and perhapsmost importantly, the operators who manufacture the product.

There are two microbiological attributes that are required of every parenteral product. One is sterility and the other is non-pyrogenicity, or the absence of fever-causing agents. By far the most prevalent and important pyrogen in pharmaceutical manufacturing is endotoxin, a component of the outer cell membrane of Gramnegative bacteria. Gram-negative bacteria are ubiquitous in nature. They can be found in and on plants and animals, including people. Gram-negatives are also found in water and in soil. They are introduced into the pharmaceutical manufacturing facility by the source water, raw materials, improperly cleaned and stored equipment, and the people working in the area.

The toxic entity of endotoxin is chemically defined as lipopolysaccharide (LPS). Although endotoxin standards consist of purified LPS, the endotoxin found in nature and as a contaminant in parenteral products is really a collection of live cells, dead cells and cell wall fragments that contain LPS. Endotoxin is a resilient molecule, and it can survive as a toxic entity embedded in cell wall fragments after vegetative cells are killed. It is possible, therefore, that a sterile product may contain a significant level of active endotoxin.



To purchase a copy of the survey go to store. store.pda.org/ProductCatalog/Default.aspx

The Bacterial Endotoxins Test (BET) is the compendial method of choice for the detection and quantitation of endotoxin in pharmaceutical waters, raw materials, in process samples, and finished drug product, as well as for the determination of the efficacy of depyrogenation and cleaning procedures. This harmonized chapter can be found in the three major pharmacopeia (United States Pharmacopeia, Japanese Pharmacopoeia, European Pharmacopoeia) but can also be found in many national pharmacopeias. A well-controlled BET assay is essential for the accurate determination of endotoxin at all critical points in a process.

Identification of Endotoxin Control Measures

The types of endotoxin control measures that a company may choose are dependent on the formulation of the product being manufactured, the design of the manufacturing process, and the process equipment. Essential elements of control can be divided into two broad categories—preventivemeasures and reactivemeasures.

Preventive measures are designed to keep endotoxin out of the process, and are closely linked to control of biocontamination in manufacturing. If conditions in a manufacturing facility are not conducive to the growth ofmicroorganisms, Gram-negativeswill not grow and generate endotoxin. Given the resiliency of the endotoxin molecule, microbial control measures will help with limiting the generation of new endotoxin, but there may be residual endotoxin in or on a material that is an indicator of previous Gram-negative contamination. Commonly utilized preventive measures include:

- *Properly cleaned and dried equipment*
  Once cleaned to remove any residual endotoxin, equipment should be rinsed with Water for Injection (WFI), dried and stored in a dry state to discourage microbial proliferation.
- *Screening of raw materials and APIs for endotoxin content*
  To assure that APIs and other formulation components do not introduce significant amounts of endotoxin, these materials, particularly those that are derived from natural sources, should be screened using a BET assay for which suitability with the material under test has been demonstrated. If a raw material supplier provides an endotoxin value on a Certificate of Analysis (CoA), the supplier qualification audit should include an assessment of its BET procedures to assure that the reported value is accurate. Ongoing surveillance of values reported on the CoA should include periodic confirmation of the vendor's reported value.
- *A validated and well-controlled WFI system*
  Attention to preventive maintenance designed to
  – control microbial proliferation in carbon and deionization beds
  – to discourage biofilm development in piping and ambient storage or distribution

  is essential to preventing high levels endotoxin in WFI (Soli, 2012).
- A validated and well-controlled manufacturing process. When validating a manufacturing process, hold steps for water and non-sterile bulk should be considered as critical control points for the possible generation of endotoxin by Gram-negative organisms.

Reactivemeasures are designed to remove or destroy endotoxin that finds its way into the system. Common reactive measures include:

- *removal of endotoxin by rinsing with WFI,* as in the depyrogenation of plastics, elastomeric closures and process equipment

- *removal of endotoxin from product streams by adsorption or filtration,* as in the depyrogenation of product streams
- *destruction of endotoxin by dry heat,* as in the depyrogenation of glass and heat stable materials
- *destruction of endotoxin by chemical means* such as exposure to base during a cleaning procedure

Preventive measures must be validated and monitored to assure effectiveness and consistency.

Identification of Sources Of Endotoxin Contamination

Pharmaceutical manufacturers employ a combination of preventive and reactive measures to control endotoxin contamination in their finished drug products. Risk assessments to determine possible sources of endotoxin contamination along with the identification of associated endotoxin control measures begin well before the manufacture of the first batch of drug product, during pharmaceutical development. Periodic reassessment of these control points and control measures is an integral part of the product's lifecycle (ICH/FDA 2009a; PDA 2012a).

Understanding the formulation of a drug product is essential to identifying appropriate endotoxin control measures. Endotoxin limits for the finished products are based on the dose of the active ingredient, and assures that the sum of the endotoxin contributed by all formulation components and primary packaging including the active ingredients, excipients, vials and stoppers will not exceed the calculated limit for the drug product.

Since there are no compendial endotoxin limits for APIs and excipients, a firm is responsible for assigning limits to formulation components based on a number of inputs including but not limited to:

- the risk that the component will contribute endotoxin
- the amount of each component in the final formulation
- the history of endotoxin levels in the component (Cooper and Williams, 2007; Dawson, 2011)

APIs that are manufactured for use in parenteral products should be subject to endotoxin control as part of their processing to assure that they do not contribute significant levels of endotoxin to the drug product (ICH/FDA 2001a,b; FDA, 2004).

From a risk perspective, it's reasonable to expect that materials extracted from natural sources will be more likely to contribute endotoxin to a formulation than inorganic or synthesized materials. Looking at the formulation example, mannitol, a natural product, is a formulation component that is likely to contribute some endotoxin, and it is also the most prevalent of the formulation components, by weight, in the product. If the API is a biological molecule, particularly if it's the product of fermentation, it could also be considered as a potential significant contributor of endotoxin. However, the sodium chloride and paraben are lower risk components because they are not biological products and they do not, by themselves, support the growth of bacteria.

If we assume that the contribution of the WFI from a validated and well-controlled system is negligible, we are left to assign limits to the remaining four components. Assuming for the example thatthe API is not a biological molecule, there are a number of ways to look at the assignment of limits.

1. In some cases, excipients are also listed in the compendium as active ingredients. There are times when it may be appropriate to adopt those active ingredient limits and apply them to excipients, but "blind" adoption of these compendial limits is ill advised in the absence of assessment of the dose and route of administration, and without the context of understanding the potential endotoxin contributions the other formulation components.
2. The formulation contains 40mg of solids. In theory, we could divide the 40 mg by the four components and allow each of the components to contribute 25% of the total allowable endotoxin for the drug product.

   When corrected for EU/unit weight of each component, this distribution is unreasonable, as the component that is in the highest concentration in the formulation and is the most likely to contribute endotoxin (mannitol), has the lowest assigned endotoxin limit per unit weight. Likewise, the component that isin the lowest concentration in the formulation and is the least likely to contribute endotoxin, the paraben, has the highest assigned endotoxin limit.
3. The formulation has 40 mg of solids. We can take the endotoxin limit for the final product, divide it by 40mg and assign each mg of solid the same endotoxin limit of 0.125 EU/mg. While marginally better than method #1 in that we have increased the allowable contribution of the mannitol and decreased the allowable contribution by the paraben and sodium chloride, we still have a situation where the limit is not assigned based on the risk of contamination.
4. We can assign endotoxin limits based on the percentage contribution of the component to the final formulation.

   When endotoxin limits are assigned based on the percentage of the component in the final formulation, and then corrected to EU/unit weight of that component, the result is the same as method #2, and all components are allowed the same contribution/mg, regardless of origin or risk to the formulation.
5. In the fourth method, endotoxin contributions are assigned based on risk of contamination. Though there are no "rules" for this assessment other than justification of the logic used, allowable contribution is assigned based on a number of factors including amount of the material in the formulation, source of the raw material, its testing history, and the ability of the vendor to consistently provide material that meets certain endotoxin levels.

Low Endotoxin Recovery (LER) in Drug Products

Kevin L. Williams, Hospira

Low endotoxin recovery (LER) is a recently observed phenomenon referring to the inability to recover known amounts of endotoxin from specific stored biological drug products ***(1).*** Investigators from Genentech have identified two common drug excipients associated with this phenomenon: polysorbate and citrate. The Sigma-Aldrich catalog describes polysorbate 20 as greater than 40% lauric acid and polysorbate 80 as typically 70% oleic acid with both having a balance of fatty acid constituents. The U.S. FDA included a stability screen requirement in their 2012 pyrogen and endotoxin guidance, presumably to address questions raised by the Genentech study that centers on the "Stability of assayable endotoxin content." The issue has come to the forefront of industry in regard to the performance of the Bacterial Endotoxin Test (BET).

Joseph Chen, PhD, and **Anders Vinther,** PhD, from Genentech, described this phenomenon hypothetically as the formation of a product complex that blocks the ability of factor C (the LAL biosensor) to bind endotoxin. In looking at the various substances involved including unspecified products (presumably protein and/or monoclonal antibodies), polysorbate and citrate, a few different potential mechanisms of action arise as listed below (a-e). Users may consider various cross currents as they collectively monitor stability conditions and consider, via a process of elimination, the LER mechanism of action.

(a) Protein aggregation: Many proteins are known to form complexes with endotoxin and thus mask endotoxin in solution ***(2).*** Additionally, monoclonal antibodies (MAbs) are known to form aggregates in aqueous solution, particularly as added surfactants (such as polysorbate) degrade spontaneously ***(3).***

(b) Polysorbates: Polysorbate is used to prevent protein aggregation and loss of drug utility. Per **Edward Maggio:** "Aggregation, which is prevented by the addition of surfactants, and peroxide damage, which is caused by surfactant-generated peroxides cause an increase in unwanted protein immunogenicity" ***(4).***Protein degradation has been recognized as so severe that some ***(5)*** recommend the replacement of polysorbates as stabilizers in drug formulations. Fatty acids are another degradation product of polysorbates. A major coconstituent of polysorbate 20 (up to 25%) and polysorbate 80 (up to 5%) is myristic acid—the key marker in gauging endotoxin content via GC methods. Studies of hydroxymyristic acid as a marker for endotoxin detection date to the '70s ***(6,7).***

(c) Mild hydrolysis: Endotoxin, biochemically synthesized by bacteria (seven separate enzymatic steps including the use of acyltransferases to add fatty acid acyl groups to the core) ***(8),*** is a hardy molecule, removed by washing/rinsing/ binding or destroyed using dry heat (250˚C for 30 min, USP). Less severe conditions, however, have also been found to modify the molecule so it's much less active or inactive, particularly the use of acids or bases with heat. Tirsoaga, et al. ***(9)*** found even milder acidic conditions can prompt the reaction in the presence of surfactant (SDS): "Milder hydrolysis conditions such as pH 4.4-4.5 in sodium acetate buffer were shown to be efficient for lipid A liberation and were usually improved by the addition of sodium dodecylsulfate (SDS) when the hydrolysis kinetics were too slow or ineffective."

Thus, mild acid, a surfactant/ detergent (SDS versus polysorbate) and sodium salt (acetate versus citrate) brought about significant hydrolysis. Mild basic hydrolysis of LPS has also been shown using a 1: 3 dilute solution of NH_4OH at room temperature for 16 hours ***(10).*** Changes in endotoxin acyl chain distribution are known to bring about different biosensor responses to endotoxin across the animal kingdom.

(d) Sample hold conditions: Products containing polysorbates may require the absence of oxygen and light to prevent degradation. Singh, et al. suggest that recently introduced ultrarefined polysorbate 80 (>99% oleic acid) may prevent peroxide formation and thus increase the photostability of formulated solutions ***(11).*** The high variability of polysorbate fatty acid content for any given formulation is evidenced in USP/EP requirement ranges and as detailed by various vendor COAs.

(e) Immunogenicity and the Pyrogen test: Many may wonder: "What is wrong with a self-depyrogenating solution?" The fear is that endotoxin may be unmasked in the body as positive pyrogen data would suggest. The possibility remains, however, that solutions have been inactivated in terms of endotoxin and the fever in rabbits came from immunogenicity ***(12)*** via the therapeutic protein itself. It is not clear if non-spiked solutions were tested side by side with endotoxin spiked solutions to preclude this possibility. The LER issue could turn out to be overstated as the current basis of the differential reaction said to exist between LAL and the pyrogen assay may be based upon borderline pyrogen responses (all the data is not public). The pyrogen test sets called "pyrogenic" would have to be repeated on five more rabbits (only day 0 and day 7 data shown) and have at least four of eight total rabbits with >0.5˚ C temperature rise to be considered pyrogenic, as per USP <151>.

Explanations that fit the Quality by Design paradigm of increasing product and process knowledge should be explored by characterizing drug products, polysorbates, and degradation constituents in biologics exhibiting the phenomenon. At this point there are many more questions than answers—and answers cannot come without widespread dissemination of details. By understanding the conditions in which LER occurs, BET users can identify situations requiring greater scrutiny as to whether specific drugs are affected by LER.

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[Editor's Note: Low endotoxin recovery will be addressed during a session at PDA's upcoming *8th Annual Global Conference on Pharmaceutical Microbiology*. See also the Science Snapshot on p. 20 about the recently released Technical Report No. 3 which covers endotoxin recovery. **]**

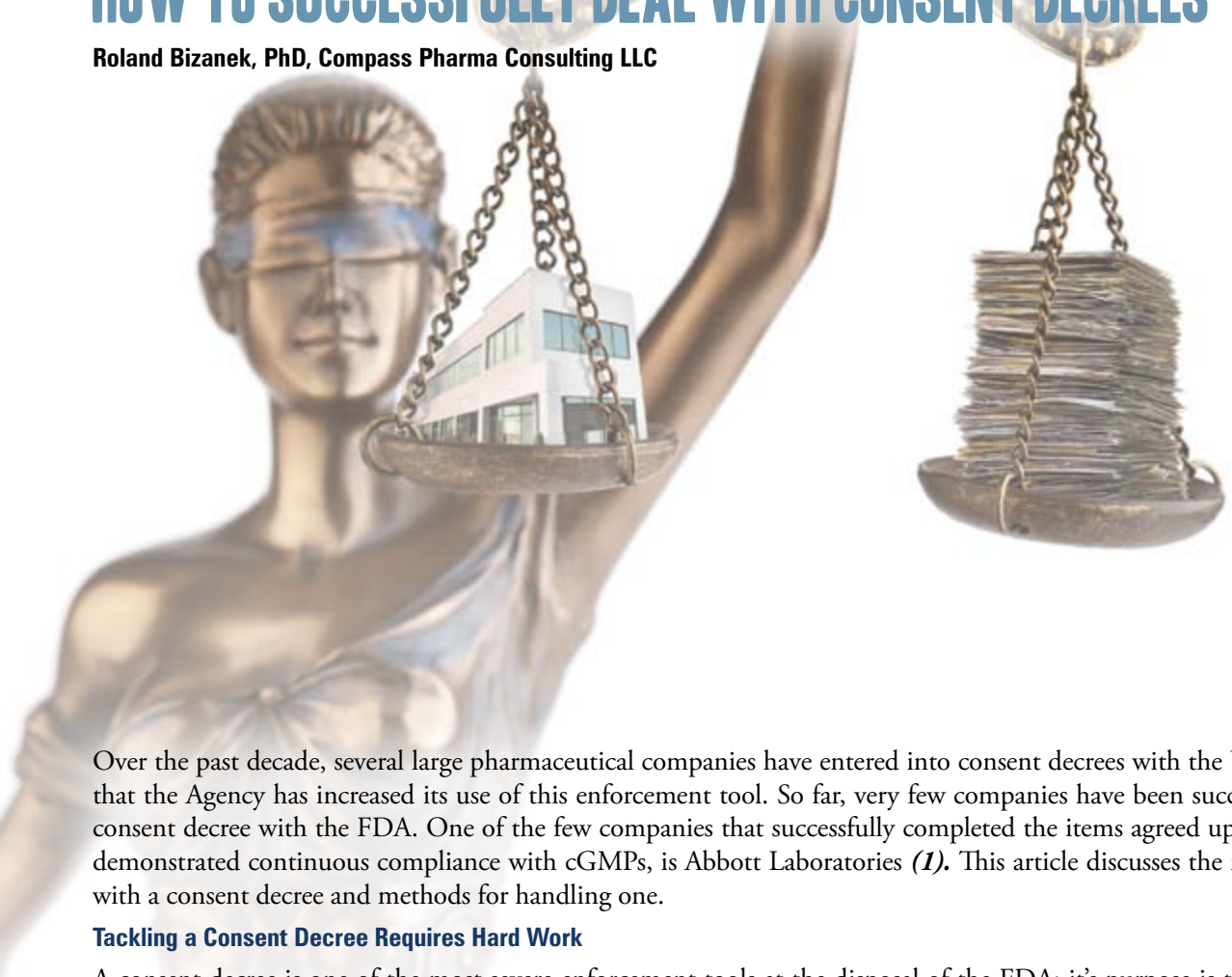
About the Author

Kevin L. Williams, currently at Hospira, has 30 years of experience in the pharmaceutical industry, specializing in endotoxin testing and control. He has written extensively on the subject of LAL technology.

MANAGEMENT, WE HAVE A PROBLEM

HOW TO SUCCESSFULLY DEAL WITH CONSENT DECREES

Roland Bizanek, PhD, Compass Pharma Consulting LLC



Over the past decade, several large pharmaceutical companies have entered into consent decrees with the U.S. FDA and it seems that the Agency has increased its use of this enforcement tool. So far, very few companies have been successful in terminating a consent decree with the FDA. One of the few companies that successfully completed the items agreed upon with the FDA, and demonstrated continuous compliance with cGMPs, is Abbott Laboratories ***(1).*** This article discusses the main pitfalls in dealing with a consent decree and methods for handling one.

Tackling a Consent Decree Requires Hard Work

A consent decree is one of the most severe enforcement tools at the disposal of the FDA; it's purpose is to force companies into compliance with applicable regulations ***(2).*** The consent decree is a voluntary agreement to an injunction between the company and the FDA, represented by the U.S. Department of Justice in U.S. District Court in return for withdrawal of further litigation by the DOJ and FDA. It usually names the CEO, Chief Operating Officer and the Head of Quality of the affected company as defendants. These defendants agree to remedial actions that deal with the documented nonconformances, including quality systems improvements. Additionally, a third party is required to certify that certain aspects of the quality system are in compliance with regulations.

The breakdown of the quality management system usually involves the following systems:

- Investigations
- Corrective action and preventive action (CAPA)
- Validation and qualification of processes, methods and equipment
- Change control
- Batch production record review and product release

The consent decree is reserved for severe situations where the FDA has documented repeated and continued violations of the regulations through Form 483s and warning letters. Even if a company has been in constant communication with the Agency about the violations, the Agency may view the company as offering insufficient clarity on how the company is progressing to fix identified repetitive failures of its quality management system. The consent decree will require a detailed work plan for the various remediation activities to the quality management system, which needs to be ap-

Article at a Glance

- Organizational culture is key to success for transformation
- Exiting a consent decree requires a dedicated effort across the company
- Senior leadership must set an example and encourage change

proved by the FDA. It will include certain milestones and key deliverables. Any delay in these may prompt severe monetary penalties. This system allows for the necessary remediation activities to be executed, while under certain circumstances allowing the company to continue manufacturing and distributing some of their medically necessary products.

Avoiding Common Consent Decree Pitfalls

A good description of the common pitfalls of consent decree management can be found in the slide presentation by **Bryan Kelly *(3).*** Most consent decrees require outside subject matter experts (SME) to assist in the remediation effort at the company, and to certify that certain aspects of the quality management system are in compliance with regulations and the specifics of the consent decree. Depending on the size of the particular manufacturing site(s) under consent decree, a large number of consultants will descend upon the company to implement various aspects of the work plan. It is common that the initial company supplying SMEs hires these consultants as subcontractors, and it is also not uncommon that different consulting companies are working on the remediation activities versus third party certification.

This situation can and will cascade out of control if the third party expert(s) are given complete reign over the company, especially if executive management of the company is not actively involved in the various activities. The employees of the company will grow more frustrated with the situation; often the most experienced leave for other opportunities elsewhere within the industry. This can inadvertently lead to an increased reliance on outside consultants rather than establishing an experienced workforce to sustain the quality management system after the consultants leave the "battlefield." Lastly, the third party experts may lose control over subcontracted consultants, delaying the work plan, which can trigger certain penalty payments for missing milestones and/or key deliverables.

Eight-Step Plan Can Help Prevent Failure

In order to successfully deal with a consent decree, management of the affected company has to realize that this particular situation cannot be fixed by bringing in an expert to fix the gaps of the quality management system. While procedures and methods need to be overhauled, there are two other aspects, which have to be adequately addressed to obtain a sustainable and compliant quality management system. First, there are questions of management oversight. How did the company get into so much trouble with the FDA? Did management ignore the indicators from the quality management system or employees? Were certain information and issues not elevated to the highest level of management? The other one, which rarely gets addressed adequately, is that of the organization's culture: what is the status of the quality culture in the organization?

This transformation of the organization is a long journey, taking years to complete

A 2004 article pointed out that the "FDA uses consent decrees to change the overall corporate culture of biopharmaceutical companies"***(4).*** Therefore, culture change is at the heart of successful efforts to lift the constraints of the consent decree. This cannot be accomplished by hiring an army of consultants to fix all the gaps in the quality management system, but rather by a concerted effort of transforming the organization and its culture. Most remediation activities fall short in this area because the process of leading change is not followed. In 1995, **John Kotter,** one of the gurus of change management, published an eight-step program to successfully implement change ***(5).***

1 Establishing a Sense of Urgency

You would think that agreeing to a consent decree would be sufficient to create a sense of urgency for everyone within an organization to realize that the organization has to change in order to survive. Some companies, however, establish a certain code of secrecy, where observations and warning letters from the FDA are not openly discussed with everyone.

Executive management—the defendants named in the consent decree—must "own" this problem and communicate a sense of urgency to every employee at the company. If business is conducted as usual, any efforts to transform the organization will be doomed from the start.

2 Creating the Guiding Coalition

Executive management must assemble a group of internal team members from the affected functional areas. One of the team members should be the head of the Program Management Office, who serves as the main contact for the third party SME and coordinates all the different aspects of the remediation and certification activities. The team members are now empowered to lead the change effort.

3 Developing a Change Vision

The guiding coalition or steering committee develops not only the vision of the transformed organization, but also the strategies to get to this future state. If the consent decree and work plan has already been signed off, the committee needs to carefully evaluate whether the vision and its strategies fit into the constraints of the work plan. If needed, discussion with the FDA must be initiated to adjust the work plan to actually reach the goal of a sustainable and compliant quality management system.

The work plan should always be a "living document" that is periodically reassessed and updated as appropriate. The consent ➤

2013 PDA UPCOMING EVENTS

JULY EVENTS

9-10
Current and Emerging EU Regulations and Inspection Trends
Dublin, Ireland
https://europe.pda.org/EU2013

11
GDP – The new EU Good Distribution Guideline Training Course
Dublin, Ireland
https://europe.pda.org/GDP2013

11
Managing Outsourced Operations Training Course
Dublin, Ireland
https://europe.pda.org/MOO2013

11-12
Risk Based Design and Qualification of Aseptic Processes Training Course
Dublin, Ireland
https://europe.pda.org/RiskBased2013

11-12
An Introduction to Visual Inspection Training Course
Dublin, Ireland
https://europe.pda.org/TCVisInsp2013

11-12
Process Validation and Verification: A Lifecycle Approach Training Course
Dublin, Ireland
https://europe.pda.org/Process2013

18
PDA West Coast Chapter: The Role and Duties of the Eu Qualified Person
San Francisco, California
www.pda.org/roleEUqp

29-2 August
2013 Filtration Week
Bethesda, Maryland
www.pda.org/filtrationweek2013

31
PDA Southeast Chapter 2013 Lab Conference
Raleigh, North Carolina
www.pda.org/SELabConf

AUGUST EVENTS

12-16
Pharmaceutical Products Supply Chain Integrity: A Five Day Training Series
Bethesda, Maryland
www.pda.org/pharmaintegrity

13-15
Validation of Dry Heat Processes Used for Depyrogenation and Sterilization Training Course
Bethesda, Maryland
www.pda.org/valdryheat

26-30
2013 Aseptic Processing Training Program – Session 4
(Week 2, September 23-27)
Bethesda, Maryland
www.pda.org/2013aseptic

www.pda.org

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

Save these dates!

SEPTEMBER EVENTS

9-10
Implementation of Quality Risk Management for Commercial Pharmaceutical and Biotechnology Manufacturing Operations Training Course
Basel, Switzerland
https://europe.pda.org/QualityRisk2013

9-10
Summary and Discussion of EMA Expert Workshop: Process Validation for the Manufacture of Biotechnology-Derived Active Substances
Basel, Switzerland
https://europe.pda.org/WSMonoclonal2013

9-11
Preparation of Virus Spikes Used for Virus Clearance Studies and Virus Filtration Training Course
Bethesda, MD
www.pda.org/viruspikes

11-12
6th Workshop on Monoclonal Antibodies
Basel, Switzerland
https://europe.pda.org/Monoclonal2013

16-18
2013 PDA/FDA Joint Regulatory Conference
Washington, DC
www.pda.org/pdafda2013

18-19
2013 PDA/FDA Improving Investigations Workshop
Washington, DC
www.pda.org/investigations2013

19
PDA UK Single Use Workshop
Billingham, UK
www.pda.org/UKSingle

19-20
2013 PDA/FDA Joint Regulatory Conference Course Series
Washington, DC
www.pda.org/pdafdacourses2013

23
Selection Considerations for Manufacturing Freeze Dryers Workshop
Düsseldorf, Germany
https://europe.pda.org/WSFreezeDrying2013

24-25
Pharmaceutical Freeze Drying Technology
Düsseldorf, Germany
https://europe.pda.org/FreezeDry2013

25-26
PDA Ireland Chapter: Capturing Opportunity through Innovation and Excellence
Dublin,Ireland
www.pda.org/Irelandopp

26
ICH Q9: Application of a Risk-based Approach to Freeze Drying Processes Training Course
Düsseldorf, Germany
https://europe.pda.org/ICHQ92013

26-27
Development of a Freeze Drying Process Training Course
Düsseldorf, Germany
https://europe.pda.org/TCFreezeDrying2013

30-3 October
2013 Lyophilization Week
Bethesda, MD
www.pda.org/lyophilizationweek

decree will not be lifted in a short time frame and the plan must be flexible for changing circumstances.

4 Communicating Buy In

Now, that the new vision and strategies have been developed, these need to be communicated to all internal and external stakeholders by leadership. Develop a communication plan and use all communication tools available to send out a consistent message. Once this has been communicated, leadership needs to talk and walk the new vision and strategy. Their actions—specifically, difficult and painful decisions—have to be consistent with the new vision in order to lend credibility to the new vision. Keep in mind, one wrong step or decision could undermine the whole transformation. The guiding coalition teaches others in the organization by setting examples and living the new vision.

5 Empowering Broad-Based Action

This step of the transformation process is critical to success, as the leader (executive management) needs to assess whether all team members are on board with the change. Any obstacles to change need to be removed, including any long-serving managers who only halfheartedly support the transformation. Additionally, this creates the perception that transformation is here to stay and is not just the flavor of the month.

The leadership team needs to also work actively in changing any part of the system which does not fit the new vision, even if that part of the quality management system was not mentioned in the consent decree or work plan.

At this point, others in the organization, "change agents," must be empowered to affect and implement change consistent with the new vision in their respective areas.

6 Planning for and Creating Short-Term Wins

This transformation of the organization is a long journey, taking years to complete; therefore, it is vital to the success of the transformation to early on create some success stories. These can be small projects which are implemented quickly that have visible and significant improvements. These success stories need to be communicated; the employees involved in these efforts also need to be adequately rewarded. Be mindful, however, of "mission accomplished syndrome." If victory is declared too early, the organization can revert back to old habits shortly after the victory party.

7 Never Letting Up

Due to the quick wins mentioned above, the credibility of the transformation effort increases and employees are reinvigorated to become agents of change. More complex projects are started at this point, the success of which generates more credibility for the transformation.

Early on, it is important to keep in mind that a lot of changes must happen and the change control system needs to be adapted so that it does not become an obstacle to change, but rather the means to managing the change.

This is also the stage for hiring, promoting, developing and rewarding employees who are implementing the new vision.

8 Incorporating Changes into the Culture

In the last step, it is important to show that the new behaviors have led to corporate success. At this point, the organization and its quality management system are again compliant with the regulations, showing that the organization has been transformed. The new vision and organization needs to prove itself by being sustainable. It needs to be vigilant about its new vision and quality culture.

Remember that changing an organization's culture requires great commitment from the leadership team and takes a long time. This cannot be accomplished by just hiring some consultants to fix the quality management system. Furthermore, the eight-step approach to transforming an organization should also be considered when addressing observations and warning letters on systemic issues, not just when the consent decree is handed down. Otherwise, the next move by FDA may entail negotiating a consent decree with your company.

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About the Author

Roland Bizanek, PhD, is the owner of Compass Pharma Consulting LLC, which specializes in quality and compliance. Previous to his consulting role, he held various positions in compliance, quality, process support and development at Biogen-Idec and Abbott Laboratories.

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PARTICLE MEASURING SYSTEMS

Regulators to Offer Perspectives on Investigations, Metrics at Joint Regulatory Conference

Rebecca Stauffer, PDA

The PDA Letter *spoke with* ***Rick Friedman,*** *Associate Director, OMPQ, CDER, and* ***Mahesh Ramanadham,*** *PharmD, Acting Team Leader, OMPQ/OC, both from the U.S. FDA and members of the planning committee for the* 2013 PDA/FDA Joint Regulatory Conference. *Friedman is also the co-chair for the subsequent* 2013 PDA/FDA Improving Investigations Workshop. *Friedman and Ramanadham were excited to discuss topics of interest that will be discussed at the conference and workshop.*

PDA Letter: Rick, can you elaborate on why the topic of "investigations" was chosen to for the workshop? How will the workshop complement the conference?

Friedman: "Investigations" was chosen as the workshop topic so that the FDA and industry could discuss the challenges, expectations and goals of investigations of adverse trends, deviations and batch failures. Inadequate investigations continue to be one of the leading 483 observations in drug manufacturing inspections every year. Investigations of proper depth and breadth are critical to ensuring the manufacturer remains in control, and that a firm can dependably deliver consistently high quality products to patients. So, this workshop is an opportunity for regulators and industry to share knowledge that can improve investigation capabilities. Topics will include: staffing the investigation team with the appropriate subject matter experts, handling manufacturing problems at a CMO, using quality risk management to maintain a state of control and implementing operational excellence programs that establish the habits of preventive action and process improvement as norms in the organization.

PDA Letter: In the initial plenary talk at the workshop, an FDA representative from your office will discuss the Agency's observations and expectations as they pertain to investigations, specifically the link between poor investigations cited in 483s/warning letters and quality systems. What are two of the observations that FDA will discuss in this talk?

Friedman and Ramanadham: FDA is being asked to open the workshop by presenting inspectional and compliance trends that illustrate where investigations are sometimes lacking. The speaker will discuss several examples in depth, and provide perspectives on how we have seen the most successful companies implement robust quality systems that provide for resources, expertise and work processes that assure, and indeed reward, early problem identification and implementation of sustainable solutions. The two common elements of deviations that will be emphasized are the lack of inquiry into root causes of quality failures and inadequate justifications of scope of some investigations.

PDA Letter: The development of quality metrics has been a major topic for both regulators and industry. What would you characterize as good quality metrics? How does a company balance the fine line between meeting metrics vs. having metrics be the "end all be all?"

Friedman and Ramanadham: Metrics are not new. We all have heard the terms such as KPIs, process performance and product quality monitoring system (ICH Q10) and performance measures. So, metrics play a major role in any quality assurance program. But their use is inconsistent and we have heard that some metrics are better than others. The industry and the Agency are working together to better define how quality metrics can be used to better measure quality, and we have found the feedback very useful. Product quality metrics should provide objective measures and be supported by valid data from reliable data systems. Effective metrics should provide a signal when a product or process is experiencing an adverse trend, or is not consistently meeting its established standards. We will continue to work with industry to design quality metrics that are robust, and provide both leading and lagging indicators of manufacturing and quality issues. We have heard that it is critical to pick the right metrics, as they can drive unanticipated and undesirable behaviors if not carefully chosen. We also understand that metrics are only valuable in a quality system if an appropriate response is undertaken, with emphasis on continually understanding the potential impact on the patient. Collecting data is only part of the job, and it is critical to monitor for adverse product quality signals or process drift to assure reliable processes and safe, effective and available drugs products.

PDA Letter: At the Joint Regulatory Conference prior to the workshop, Rick, you will moderate "Plenary Session 3: Understanding GMPs." The session description says the session will focus on:

> How safety and efficacy is assured by routine adherence to the quality assurance and a manufacturing control practices embodied in the GMPs. Presenters from FDA and industry will discuss how GMPs have evolved, and why responsive systems and good governance are so important to assure reliable pharmaceutical operations and safe products. Presenters will also discuss quality assurance lapses that led to major defects and manufacturing problems. The session will mix universal quality assurance principles with practical findings, and emphasize the essential role of robust quality systems in assuring the core business goals of reliable drug quality and availability.

Rick and Mahesh, why do feel this session is necessary, considering the high level of experience among those attending the joint conference? Would I learn something if I've been in

the industry for 20 years? Do you recommend companies send junior-level staff to the meeting so they can experience this and other sessions?

Friedman and Ramanadham: Our industry is constantly evolving—new products, improving technologies, as well as more emphasis on design and quality systems, statistical approaches, global supply chain challenges, outsourcing, and evolving regulatory paradigms. The session on "Understanding GMPs" includes these aspects and four great panelists with extensive experience in the area of drug quality. The session will start with a unique take on the evolution of GMPs, which is a fascinating part of FDA history and not that well understood. It will also address how quality begins and ends with a patient focus, and how good governance means assuring an ongoing state of control through sound decision making. This includes having strong systems that use quality risk management principles, and some practical insights and case studies will be shared by the speakers to illustrate the fundamental link between quality and safety. The panel will include legal, industry, regulatory and medical perspectives, and the Q&A session should be an interesting one. So, this unusual session aims to provide a unique opportunity for attendees to learn about the critical role of GMP from experienced leaders in four different disciplines that are all integral to daily quality assurance.

About the Experts

Rick Friedman, is the Associate Director, Office of Manufacturing and Product Quality, Center for Drug Evaluation and Research (CDER), Office of Compliance, FDA. In this position, he is responsible for oversight of CGMP and drug quality programs to assure scientific and risk-based decisions.

Mahesh Ramanadham, PharmD, is currently the Acting Team Leader in the Division of Good Manufacturing Practice Assessment/New Drug Manufacturing Assessment branch within the Office of Compliance/Office of Manufacturing and Product Quality (OC/OMPQ) and a licensed pharmacist.

cGMPs Continue to Evolve as U.S. FDA Expands Regulatory Authorities Under FDASIA

Rebecca Stauffer, PDA

The U.S. Food and Drug Administration Safety and Innovation Act (FDASIA), passed last year, includes provisions that give the U.S. FDA greater statutory authorities with regard to cGMPs. The PDA Letter *spoke with* ***Cathy Burgess,*** *Partner, Alston & Bird, who will speak about the evolution of cGMPs as they relate to the FDASIA legislation during the third plenary session at the upcoming* 2013 PDA/FDA Joint Regulatory Conference.

The entire interview with Burgess was recorded and is available at www.pda.org/pdaletter. Below are selected questions and answers from the interview.

PDA Letter: Your presentation at the *2013 PDA/FDA Joint Regulatory Conference* is titled "Evolution of GMP Provisions in the Act: Important Lessons Learned from History." Can you tell us one or two of these lessons that you will be sharing at the meeting?

Burgess: First of all, as all of the attendees will know, over the past ten to 15 years the pressure to reduce costs and increase productivity has driven manufacturers to lower cost suppliers in India and China and other parts of the world. Supply chains now extend all over the globe. Over 80% of APIs are from foreign sources, and approximately 40% of all finished drug products are being manufactured overseas. In order to address GMP challenges associated with globalization, FDA asked Congress for some additional statutory authority, which it received under FDASIA.

The enactment of FDASIA last year represents the first major expansion of FDA's authority related to cGMPS in 50 years. So, at the meeting, we're going to discuss these new authorities under FDASIA and their importance in the Agency's enforcement of cGMPs. A key lesson that I think we've learned is that the Agency and industry need to be alert to changes in the global supply chain, and if FDA determines that it does not have adequate statutory authority to protect the public from violative products, it should not hesitate to go back to Congress for additional authority. Future legislation has to be developed with input from industry and must give FDA appropriate tools to ensure that drug products introduced into interstate commerce are safe, effective and comply with cGMP requirements.

PDA Letter: And so you're talking about lessons that we've learned and you mentioned how there's the issue of 80% of API's are coming from foreign sources.

Burgess: Yes.

PDA Letter: So, what do you foresee as some of the future challenges that will be arising from this situation that we've fallen into with the global supply chain?

Burgess: Well, I think that what we've seen over the past few years is that FDA has not had adequate resources and has not had appropriate authorities to enforce cGMP requirements. There simply are not investigators in the international inspection cadre. There are all sorts of language barriers and cultural issues that can impede the progress of an inspection. Some of the new authorities under FDASIA are going to enable the Agency to overcome some of those challenges. For example, Section 710 under FDASIA provides for some information sharing between government agencies. And these are government agencies in countries that won't have the same challenges in terms of language and in terms of cultural differences—so that could lead to smoother inspections, both from FDA's side and from industry's side—and could enable the Agency to more readily obtain information that it needs to determine whether an establishment is in compliance.

PDA Letter: On the topic of metrics, which has started to gain traction within the industry I was just at the supply chain conference that PDA and FDA cosponsored this year, and that was a topic for discussion. So, if you're a company and you're working with a supplier overseas, how can metrics help in that situation, if at all?

Burgess: Well, I'm speaking as a lawyer not as a quality assurance professional, but in my view, metrics are essential for monitoring a company's performance and for evaluating compliance. Companies obviously need to strive for perfection, both in-house and in their supply chain, but it's important for them to acknowledge that nothing's ever going to be perfect in a manufacturing environment. And so for that reason the quality metrics that a company uses for its own purposes and to ensure that its suppliers are in compliance need to be used to understand and solve problems, and not mask them.

So, for example, the fact that a firm has not received any 483 observations in two or three years is useful information but it does not necessarily give you an indication that a company is in compliance because an FDA inspection is merely a snapshot in time. In my view, an example of a good quality metric would be a successful effectiveness check for a CAPA.

PDA Letter: Anyway, I want to go back to earlier when you mentioned raw materials, especially with 80% of them coming from foreign sources. I read an article that covered your talk at a Food and Drug Law Institute meeting last December, and you discussed the new FDASIA requirement. You mentioned that it's "Brand new in the area of drug regulation." Could you give me an idea

of how companies are working with their suppliers to meet this new requirement?

Burgess: Before I do that, let me just clarify the comments that I made at FDLI. What's brand new is the statutory authority. There has always been an expectation that companies would ensure that they're getting appropriate supplies or that their suppliers are in compliance—but that's never been part of the Act. So, what this does is it gives FDA a lot more legal authority to enforce these types of supply chain requirements.

With regard to how companies are working with their suppliers, I can only speak from my experience with our own clients, and what we're doing with clients is we're working with them to ensure that they're focused on negotiating appropriate quality agreements, and in structuring robust supplier quality programs. Those supplier quality programs must include on-site audits, particularly for critical components. Suppliers, regardless of whether they're in the United States, in Europe or in India or China, it doesn't matter—the location of the supplier should be irrelevant.

Earlier this month, FDA released a draft guidance related to quality agreements for contract manufacturing arrangements, and this new draft guidance makes clear that the parties to quality agreements need to understand which responsibilities can be outsourced and which cannot be outsourced. I think what has happened is that the Agency has gone in and seen where companies have tried to outsource their own regulatory obligations through contract. And as this draft guidance makes clear, to the Agency that's not acceptable.

So, in light of the new statutory language in Section 711 of FDASIA, clearly establishing roles and responsibilities in a manner that is consistent with the regulations is now more important than ever.

PDA Letter: I want to go back to your talk at the *2013 PDA/FDA Joint Regulatory Conference*. It's going to be part of the third plenary session, the theme of which is "Understanding Good Manufacturing Practices." The other two speakers will be discussing the role of quality in manufacturing. And I know you're coming more from the legal aspect but would you be able to tell us sort of what your personal view is of the role of quality in manufacturing?

Over 80% of APIs are from foreign sources, and approximately 40% of all finished drug products are being manufactured overseas

Burgess: Yes, quality is the lynchpin of drug manufacturing. It has to be designed and built into products. You can't test products into compliance. Or inspect them into compliance. The building in…the infusion of quality has to start in the early stages of the design of the product, and all throughout the manufacturing process. Every person within a regulated establishment has an obligation to promote quality. That's critical. And the ways in which staff members promote quality is by participating in ongoing training, following SOPs, following good documentation practices and reporting nonconformances and noncompliance.

But even if you have all of that, if senior management in the company is not properly engaged or promotes a different type of culture, that makes the work of individual employees who are focused on quality much more difficult. And it really does not bode well for the company. The tone and culture of a company begins at the top of the organization and companies that do not promote quality are really…they're looking for trouble. They're more likely than not to have significant compliance problems.

PDA Letter: For my last question, I want to get a sense for what are two key takeaways that you hope audience members will leave with from your presentation?

Burgess: I'll give you two key takeaways. First, cGMPs are not static. They will continue to change as technology changes. As business models change, cGMPs will change as well—they may not always keep exact pace with technological advances but they will continue to change. So, for this reason, companies can't be complacent about cGMP compliance. Just because you're in compliance today doesn't mean that you can sit back and relax and assume that you'll be in compliance a year from now. It's hard work. It is important work and companies need to be constantly focused on compliance and cGMPs.

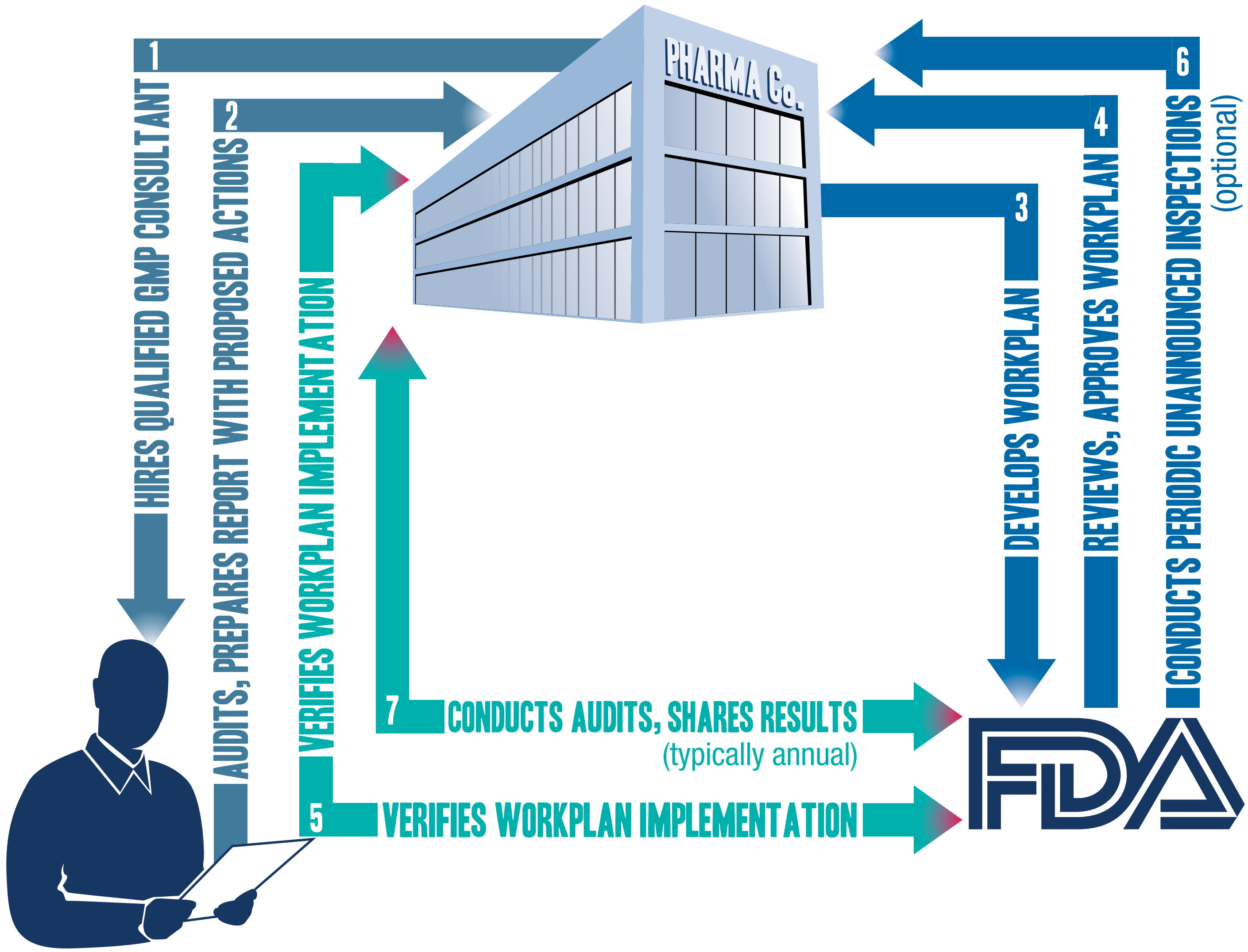
The second key takeaway is that companies have to have appropriate mechanisms for remaining current and in compliance with cGMPs. For example, cGMP compliance has to be a key component of a company's corporate compliance program. Far too often, this is viewed as the sole responsibility of the quality unit. And this can be a huge issue, particularly if management has different priorities, and is constantly at odds with quality assurance. In a strong corporate compliance program, senior managers will be held responsible and accountable for the success of the program and for cGMP compliance.

So, just to restate that, point one: cGMPs will continue to change and evolve and companies have to be alert, and have to constantly work on continuous improvement; and second, they have to have the appropriate structures and mechanisms in place to ensure that at an organizational level, they're capable of remaining in compliance.

About the Expert

Cathy Burgess is a partner in Alston and Bird's Health Care Group. Her specialty focuses on regulatory compliance, product risk management, enforcement and U.S. FDA policy matters and regulations.

Common Elements of a Consent Decree with the U.S. FDA



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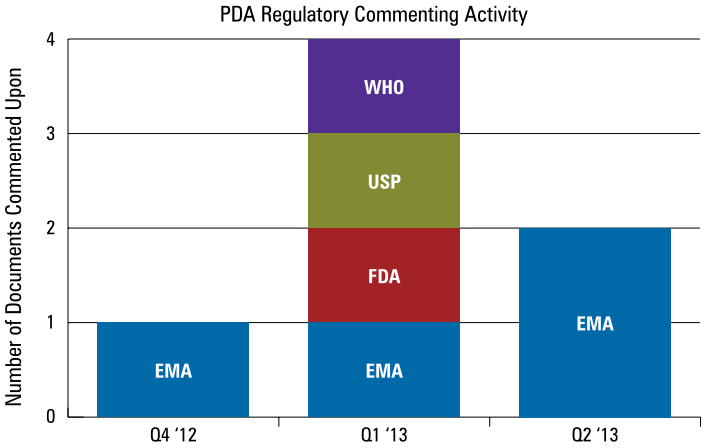
snapshot

July/August 2013 RAQAB Quarterly Report

RAQAB Leadership Changes

Sue Schniepp, Allergy Labs, became Chair of RAQAB on July 1. She is joined by **Jeff Broadfoot,** Cangene Corporation, as Vice Chair. Jeff has been a member of RAQAB since 2009; he recently served as the liaison to RAQAB-sponsored interest groups. **Stephan Rönninger,** Amgen, will be moving into the role of Immediate Past Chair and **Steve Mendivil,** Amgen, will be stepping down from RAQAB. Steve has membership in RAQAB dating back to 1999 and has served as Chair and Past Chair. We thank Steve for his many contributions and welcome Jeff to this leadership role. Members in RAQAB are eligible to serve two consecutive three-year terms starting in July.



New RAQAB Projects

In April, RAQAB commissioned a new task force to apply Quality Risk Management tools and approaches to the challenge of avoiding and mitigating drug shortages. **Emabelle Ramnarine,** Genentech, and **Mike Long,** ValSource, are the coleaders. They will explore the use of value stream mapping and risk management tools to identify weak links in the overall demand to supply process for drugs. Then, they will apply a decision making approach to determine action/rigor for managing drug shortages based on criticality. Outcomes will be discussed at the QRM Interest Group meeting at the *2013 PDA/FDA Joint Regulatory Conference* in September.

PDA Response to U.S. FDA Drug Shortage Task Force

In February 2013, the U.S. FDA's Drug Shortages Task Force requested public input on questions related to the development of the drug shortages strategic plan. This task force was created by the July 2012 Food and Drug Safety and Innovation Act (FDASIA), and seeks new ideas to encourage high quality manufacturing and evaluation of product manufacturing quality and quality metrics.

PDA provided seven pages of responses developed through active involvement of several members of RAQAB and the Board of Directors. In addition to the general comments excerpted below, PDA provided numerous examples of current metrics used in manufacturing and metrics of potential interest to purchasers and prescribers of medicinal products. PDA also suggested actions FDA could take to address impending shortages and ways to improve existing tools available to FDA. A copy of the complete response is available on the PDA website.

> *"The development of consistent and transparent quality metrics across the pharmaceutical industry is a concept that requires further exploration and discourse between the various stakeholders. Multiple factors should be taken into account when determining the risk of potential shortage and appropriate contingency preparations. For example, some biological products that require long product disposition cycle times, may necessitate more stringent contingency planning with additional agency scrutiny of inventory levels to prevent and mitigate potential shortages. Other products available from multiple suppliers may require the creation and tracking of an overall market inventory."*

Continue at bottom of page 56

"Guidance for Industry: Contract Manufacturing Arrangements for Drugs: Quality Agreements"

Draft, Issued May 2013

This new guidance applies to commercial manufacturing of APIs or drug substances, or their intermediates, finished drug products, combination products and biological drug products. The guidances's intent is to provide a framework for delineating responsibilities of all parties involved in contract manufacturing via sound quality agreements. The guidance expands upon principles set forth in ICH Q7, 9 and 10, regarding quality assessment and oversight of contracted facilities.

Specifically FDA states that a quality agreement should minimally contain the following elements:

- the purpose and scope of the contract manufacturing agreement
- the terms of the agreement, including its effective dates and termination clause
- process for dispute resolution
- responsibility of each respective party, including an overview of the subparts of the cGMP regulations and communication expectations and mechanisms
- change control and revision practices

FDA states that "From a cGMP perspective, the most critical elements of a Quality Agreement are the sections delineating the parties' respective responsibilities and the discussion of change control."

Quality agreements are not required per regulations, however, FDA recommends their implementation to help assure the overall quality, safety and effectiveness of products.

Interest Group *Corner*

Procedure Follow Through is a Major Concern, According to Inspection Trends Interest Group

Rebecca Stauffer, PDA

The Inspection Trends Interest Group meeting, held at the *2013 PDA Annual Meeting* in conjunction with the Sterile Processing Interest Group meeting, offered attendees an overview of the top ten U.S. FDA inspection citations between October 2010 and October 2012.

Former Group Leader, **Bob Dana,** Sr. Vice President, Education, PDA, began by stating that the "No. 1 cause of problems were procedures that were either not in writing or not fully followed…absence of written procedures, by the way, is second, so when you take a look at those two things, procedure-related issues, it turns out, look like a relatively significant area of findings during of inspections."

The other citations, he pointed out, included laboratory controls, investigations of discrepancies/failures, control of written procedures to validate performance, written procedures not established or followed, training in operations and GMPs, SOPs not followed, cleaning/sanitation/maintenance, and testing and release for distribution.

Still, the majority of inspection findings are procedure-related, Dana emphasized.

"Based on these data, the issue of adequate written procedures and making certain that those written procedures are followed is an area I think that we can make some improvements in," he said.

"There are several areas where we've seen FDA express an interest; these are things they are likely to follow up on during the inspection process," he continued. "Obviously, aseptic processing is probably at the top of the list but so are things like contract manufacturing operations and knowledge transfer between the contract giver and the contract acceptor and how that works."

The Agency is also concerned about drug shortages; Dana said that if you take a look at recent warning letters, the companies involved are being asked to notify FDA if any responses to regulatory citations could result in a shortage.

Other areas of interest for the Agency are environmental monitoring, quality metrics, failure investigations, particulates and visual inspections and sterilization and training.

Following some Q&A, Dana announced that **Zena Kaufman,** Sr. Vice President, Global Quality, Hospira, will be taking over as leader for the Inspection Trends Interest Group. Anyone interested in joining this interest group, is encouraged to contact PDA's Volunteer Coordinator **Megan Kuhman** at kuhman@pda.org.

Meeting *Preview*

Interest Group Meeting Schedule

The business of the Association will be conducted, as always, at the *2013 PDA/FDA Joint Regulatory Conference.* Below is a schedule of the interest groups falling under the Regulatory Affairs and Quality Advisory Board umbrella.

Note: All interest group meetings are open to meeting registrants. (For Science ancillary meetings, see the Science Snapshot, p. 20)

Monday, Sept. 16	*Tuesday, Sept. 17*
4:45 p.m. – 6:00 p.m.	**4:45 p.m. – 6:00 p.m.**
Supply Chain Management Interest Group	Clinical Trial Materials Interest Group
Pharmacopeial Interest Group	GMP Links to Pharmacovigilance Interest Group
Inspection Trends Interest Group	Quality Risk Management Interest Group
Quality Systems Interest Group	

About Continued and Continuous Process Verification

Stephan Rönninger, PhD, Amgen

[**Editor's Note:** The article below discusses the differences between *Continued* and *Continuous Process Verification,* two terms often treated as interchangeable, which is incorrect. Even the *PDA Letter* made this mistake; see the correction on p. 46 of the June *PDA Letter.*]

At recent PDA conferences, interest group discussions and courses, it became apparent that there is confusion when talking about Continued and Continuous Process Verification. In both cases, the abbreviation is "CPV." Usually, it's more often understood as *Continuous Process Verification,* a term that describes an enhanced approach for process validation.

This article summarizes a presentation given at the 2012 *PDA/EMA Joint Conference* that highlights the differences and proposes clarification on the use of these terms in the context of process validation. Definitions are provided **(Table 1).**

Table 1 Definitions

	Process Validation	Continued Process Verification	Continuous Process Verification
Source	ICH, U.S. FDA	FDA term	ICH term
Abbreviation	PV	CPV	CPV
Definition	*"The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes"* ***(1)****; and "The collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product"* ***(2)***	*"Assuring that during routine production the process remains in a state of control"* ***(2)***	*"An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated"* ***(3)***
Result	This term describes "What to do"	This term describes "What to do"	This term describes "How to do"

Concepts should describe "What to do" only. On the other hand, the next level of detail is describing "How to do" (e.g., by suggesting special tools or specific methods).The most important difference between the definitions given by the U.S. FDA and ICH Q8 (R2) is that Continued Process Verification describes "What to do" as a stage of the lifecycle for process validation, whereas Continuous Process Verification is a "How to do."

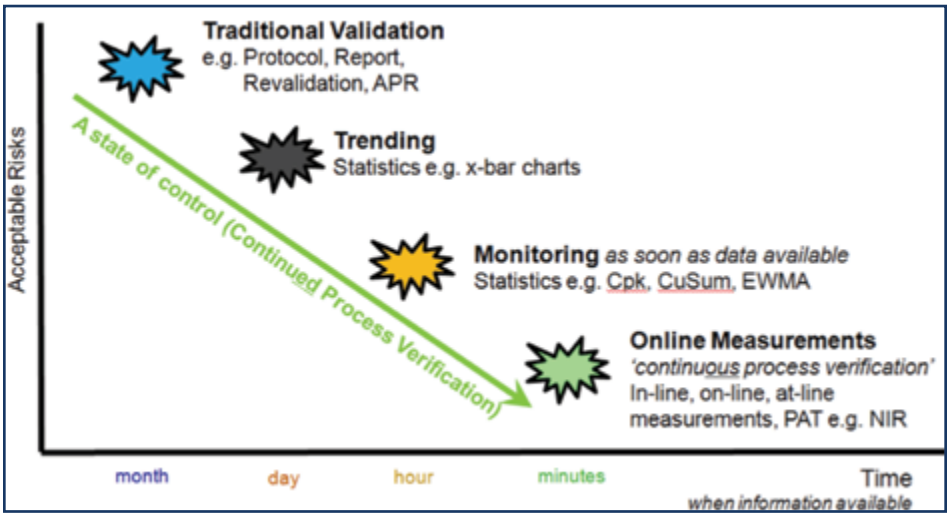
According to the principles described in ICH Q7, Q8, Q10 and Q11, a manufacturing process should be designed to yield an API and/or drug product meeting its predefined quality criteria. The concepts of Quality Risk Management, according to ICH Q9, highlight the need for managing risk by taking into account severity, probability and detectability. Consequently, in the context of process validation, different systems and statistical tools can be applied across the lifecycle (for example, in process and formulation development) when defining the control strategy and for commercial manufacturing.

Looking at the definition of risk from a high level, the risk factor of severity is managed by appropriate pharmaceutical development as described in ICH Q8 (R2)–Part II with the application to API (ICH Q11) and drug product (ICH Q8 [R2]–Part I) development. The probability that something might go wrong can be linked to the control measures, which are described in the Pharmaceutical Quality System as per ICH Q10. Process validation activities can be considered as controlling the risk factor of detectability to demonstrate the robustness of a manufacturing process and/or analytical method applied within the quality system.

The traditional validation approach represented the standard before the recent FDA guidance was issued. The concepts of ICH Q8-11 provided enhanced approach opportunities which can now be implemented. Successful process validation can be achieved by implementing these ICH concepts at different levels of risk, all of which are regarded as acceptable. These levels differ by the time passed followed manufacturing of a batch and the information available to be assessed **(Figure 1).** Although the traditional approach is acceptable, implementing continued monitoring or continuous process verification results in the lowest risk of failure.

The traditional approach to process validation shows that *repetition is possible*. This is achieved by usually three validation batches, accompanied by additional sampling. Under the enhanced development approach the outcome can be described as a *robust process which is functioning*. Continued Process Verification is Stage 3 of process validation in commercial manufacturing, as described in the recent FDA and drafted EMA guidance. Implementing Continued Process Verification can be achieved by ongoing moni-

Figure 1 Process Validation to Manage Detectability



toring and implementing CAPAs as risk control actions, if applicable. Controls, as described in the control strategy of the regulatory filing (e.g., using "Continuous Process Verification" is an alternative approach to validation). In addition, it is important to realize when talking about "CPV" on which of these approaches the discussion focuses. In some countries performing "process validation" is a legal requirement (e.g., Japan).

In discussions it is often stated, that continuous process verification (i.e., online monitoring with PAT tools like NIR, etc.) is not required to be implemented. Continued process verification, however, is in the process of becoming a requirement outside the United States (see draft EU documents and discussions in Japan). Please be also aware that in the European Union the scientific guideline on "process validation" is a document for regulatory submission purposes.The GMP elements of process validation are described in EUDRALEX Vol. 4 (EU-GMP)—Annex 15.

In addition, both continious and continued process verification use the term "verification." Here are two aspects to consider when talking about verification:

a) A verification of consistency in batch-to-batch quality, verifying the quality postmanufacturing, based on data and information. (e.g., Annual Quality Product Review) or

b) A verification of consistency during manufacturing of a batch, done in real time and without interruption.

Consequently, b) utilizes real time comparison and is an alternative approach to process validation.This typically is accomplished by introducing Process Analytical Technology.

The biggest challenge and impact on manufacturers is once guidance from other regulatory authority comes into effect. It is important that companies and regulators (both inspectors and reviewers) understand the options of running process validation, either as a three batch validation, implementing trending, performing monitoring and/or continuous process verification (for details on statistics see PDA Technical Report No. 59 and for process validation see PDA Technical Report No 60). Additionally, there is and should be the flexibility to use these different concepts of process validation in commercial manufacturing for different steps of API or drug/medicinal product manufacturing.

In conclusion, implementing different approaches for process validation adds to the scientific understanding of the process and the quality of its outcome. It provides business benefits for having assurance that a manufacturing process is appropriate and reliably controlled. *Continued* and *Continuous Process Verification* both describe ways to achieve process validation. *Countinued Process Verification* describes the concept of assuring a stage of process validation over time by monitoring batches, while *Continous Process Verification* refers to a "how to" alternative approach to process validation using PAT and real time monitoring.

References

1. GMP for API's (ICH Q7), *International Conference on Harmonisation (ICH)*, **2001**; and Qualification and Validation, *EUDRALEX Vol. 4 (EU-GMP)*, Annex 15, Glossary.
2. Process Validation: General Principles and Practices, *Guidance for Industry*, Revision 1, US-FDA, **2011**.
3. Pharmaceutical Development (ICH Q8(R2)), *International Conference on Harmonisation (ICH)*, **2009**, Glossary. See also ICH Quality Implementation Working Group Points to Consider (R2), *International Conference on Harmonisation (ICH)*, Section 7, **2011**, 14-16 and the related documents Pharmaceutical Quality System (ICH Q10), *International Conference on Harmonisation (ICH)*, **2008**, Development and manufacturing of Active Pharmaceutical Ingredients (ICH Q11), *International Conference on Harmonisation (ICH)*, **2012** and Quality Risk Management (ICH Q9), *International Conference on Harmonisation (ICH)*, **2005** as well as the ICH Q8,9,10 training material at www.ich.org

[The author thank **Scott Bozzone,** PhD, Pfizer; **Vijay Chiruvolu,** PhD, Amgen; **Mike James,** GSK; **Gerd Fischer,** PhD**,** Boehinger-Ingelheim; **Steve Mendivil,** Amgen and **Tets Takarada,** Mochida for the discussions**.]**

About the Author

Stephan Rönninger is the Head of External Affairs, Europe, International Quality of Amgen. He holds a PhD and engineering degree in organic chemistry. He is a member of PDAs Board of Directors and past chair of PDAs RAQAB.

Human Factors Remains Prime Topic for Industry, U.S. FDA

Rebecca Stauffer, PDA

By the close of the first decade of the 21st century, automaker Chrysler's brand became synonymous with poor quality. Recalls of Chrysler brand vehicles occurred regularly. Regulatory oversight intensified due to reports of fires in Jeep Wranglers. Then, in 2009, *Consumer Reports* failed to recommend any Chrysler vehicles in its list of 166 models for the magazine's annual car issue. That same year, the company declared bankruptcy.

Following bankruptcy, the Italian car company Fiat purchased Chrysler in 2011. Upon taking the reins, CEO **Sergio Marchionne** began an ambitious series of continuous improvement initiatives to change the corporate culture surrounding the quality of the company's products, focusing on human elements of the production process.

Parallels can be made between Chrysler's quality issues and those of many pharmaceutical manufacturers. Yet, one common factor stands out for both pharma and Chrysler: the human factor.

Since publication of the June 2011 U.S. FDA draft guidance, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design*, human factors has been a hot topic within the pharmaceutical industry (see the January 2012 *PDA Letter* cover story for an evaluation of the guidance). This guidance marked the first time that the FDA took a prescriptive stance toward human factors in the manufacturing of medical devices, including new requirements for human factors validation testing. These new requirements apply not only to traditional devices, but combination products as well. Since then, the Agency's focus on human factors has expanded beyond devices and drug products themselves to the actual manufacturing environments where these drugs are made.

But how are human factors defined?

"This is really a good definition that always stays with you: an accident 'is an error with sad consequences,'" **Najmedin Meshkati,** PhD, said during the opening plenary of the *2013 PDA Human Factors and Human Error Reduction Workshop*. Many erroneously believe human factors-related incidents occur due to error-prone individuals but Meshkati quoted his mentor, James Reason, PhD, who observed that of error-caused situations, "Most of them are rooted in error-provoking situations rather than in error prone people." Meshkati is Professor of Civil/Environmental Engineering at the University of Southern California.

Following Meshkati's presentation, **Bill Blunt,** Director, Operations Human Performance, Amgen, offered his perspective on human factors in drug manufacturing, based on his experiences in the nuclear industry.

"As Director of Human Performance that not only means error management or error reduction programs, but also means how can we actually psychologically set up our workstations and work experiences so that people will be successful," he said.

Rick Friedman, Associate Director, Office of Manufacturing and Product Quality, CDER, FDA, who also spoke at the workshop, drew a parallel with Chrysler's management situation when he said that managers play a key role in human factors within industry. He then expressed that the basic role of a manager is "to understand the hazards and failure modes and processes and to prevent product quality lapses."

He then pointed out that many of the product detects noted by FDA between 2007 and 2012 involved defects that went unnoticed by the company but were uncovered by Agency investigators during inspections. One of the events he cited involved cross contamination of product due to repackaging of penicillin products.

"There's a human factor there, which understanding of what the consequences are of packaging beta lactams on non-beta lactam equipment," Friedman said.

The Food and Drug Administration Safety and Innovation Act (FDASIA) now includes a requirement for management oversight to encompass risk management as part of cGMPs, he said, further stating, "That's not just quality assurance but operations too."

Common errors in risk management, he noted, involve inadequate attention to tradeoffs, disregarding uncertainty, failing to link current decisions with future decision making, failing to develop a range of alternatives, overlooking key consequences of the alternatives, failing to account for risk tolerance, working on the wrong problem, failing to clearly identify objectives and experts not calibrated.

Some of the biggest risks, Friedman emphasized, involve human operators working closely with products.

"There's a lot of human/machine interaction," he said. "The industry is not nearly as automated as some other industries."

Highly variable, examples of human/machine risks include: malfunctions while fixing equipment, equipment set-up, tray dryers, line clearance and other operational factors resulting in labeling problems, interventions on an aseptic processing line, product transfer, mix transport and manual issues.

So, how can companies tackle risk management?

"There's been a lot of talk at FDA recently about metrics," Friedman said. By "metrics," he refers to both a company's internal metrics as well as "as metrics we may want to start to look at more closely at FDA."

The hope is that well-defined quality metrics would drive change, creating an environment supportive of quality operations as well as methods to more readily detect emerging risks.

"The way I see it, the drug industry creates value through reliable supply of consistent, high quality drugs," he said.

While errors due to human factors cannot be totally eliminated, they can be minimized. In an interview with NPR, Marchionne attributed the company's turnaround on an analysis of human elements in manufacturing.

"We worry about ergonomics. We worry about the unnecessary expenditure of physical labor to make things," he explained. "One of the things that unfortunately happens in organizations that become dysfunctional, is that the very first thing to go is the amount of care and attention that you place on the workplace and the environment within which people work."

Indeed, reducing pharma manufacturing errors will involve moving beyond the equipment to analyzing the person behind the machine.

About the Experts

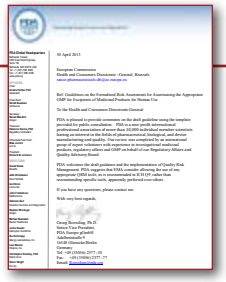
Bill Blunt, is currently applying his techniques in the biotechnology manufacturing arena, as the Director, Operations Human Performance for Amgen, Inc.

Rick Friedman, is the Associate Director, Office of Manufacturing and Product Quality, Center for Drug Evaluation and Research (CDER), Office of Compliance, FDA.

Najmedin Meshkati, PhD, CPE, is a (tenured, full) Professor of Civil/Environmental Engineering and a Professor of Industrial and Systems Engineering at the Viterbi School of Engineering, University of Southern California (USC). F

PDA Comments on Risk Assessments for Excipient GMPs

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



30 April 2013

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

Ref: Guidelines on the Formalised Risk Assessment for Ascertaining the Appropriate GMP for Excipients of Medicinal Products for Human Use

To the Health and Consumers Directorate-General:

PDA is pleased to provide comments on the draft guideline using the template provided for public consultation. 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 review was completed by an international group of expert volunteers with experience in investigational medicinal products, regulatory affairs and GMP on behalf of our Regulatory Affairs and Quality Advisory Board.

PDA welcomes the draft guidance and the implementation of Quality Risk Management. PDA suggests that EMA consider allowing the use of any appropriate QRM tools, as is recommended in ICH Q9, rather than recommending specific tools, apparently preferred over others.

If you have any questions, please contact me.

With very best regards,

Georg Roessling, Ph.D.
Senior Vice President,
PDA Europe gGmbH

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Explore the Evolving Regulatory Landscape

Program Committee Members Maria Guazzaroni Jacobs, PhD, Pfizer, and Steven Mendivil, Amgen

The *2013 PDA/FDA Joint Regulatory Conference* is an event not to miss! Join your industry colleagues and FDA representatives in Washington D.C. this September for an unforgettable learning experience.

Register before August 7 and save $200
Take advantage of the discount and register now!

This year's presenters include U.S. FDA CDER Director **Janet Woodcock,** MD, who will discuss how the agency is progressing in the areas of quality systems and Quality by Design. She will also speak about the agency's strategies addressing the drug shortage issue. More than 25 FDA speakers have been invited to talk and many have already confirmed.

Most sessions include an industry representative to provide an industry viewpoint along with the regulatory perspective. This allows regulators and industry an opportunity to discuss topics of common interest.

The subjects covered during the three-day conference include a wide range of topics that deal with quality, manufacturing, process development, regulatory submissions and distribution of products. Many of the recently published draft and final regulatory documents will be discussed, including: quality agreements and the newly published EU Good Distribution Practices guideline.

Following the workshop, from Sept. 19–20, PDA's Training and Research Institute (TRI) will host six standalone training courses that cover quality risk management, CMC regulatory requirements and GMPs for sterile and biotech products. To learn more about these courses, visit www.pda.org/pdafdacourses2013.

2013 PDA/FDA Joint Regulatory Conference • Washington, D.C. • September 16–20 • www.pda.org/pdafda2013

All attendees are welcome to attend the PDA Interest Group sessions to share experiences and lessons learned. There are 14 interest groups sessions to choose from, covering key topics like pharmacopoeias, inspection trends, process validation, packaging sciences, clinical trials, prefilled syringes and much more.

Previous attendees have described interacting with regulators in both formal and informal settings as well as during sessions, at breakfast or in breaks as the main highlight of the conference.

Follow the link in the box for the latest program, which provides more information on each session. See you in D.C.! Be there!

New Technologies Highlighted at Virus Detection Conference

Kathryn King, PhD, U.S. FDA and Program Committee Member

Recent virus contamination events in biologics highlight the limitations of current virus testing methods and the need for broad ranging, sensitive assays for the detection of unexpected viruses. Methodologies that are currently available for use include: massively parallel sequencing, virus microarrays and broad range PCR followed by mass spectrometry. These new technologies will be the focus of the upcoming PDA virus detection conference.

The conference will open with talks on the need for, and potential applications of, new technologies from both the regulatory and the industry perspective.

Bioinformatics and a comprehensive virus database are critical components of all of the new technologies, as it is necessary to have access to high quality reference sequences in order to be able either to appropriately design primers or probes for broad range PCR followed by mass spectrometry and virus microarrays, or to be able to accurately assess the output of massively parallel sequencing studies.

Prior to the *PDA/FDA Advanced Technologies for Virus Detection in the Evaluation of Biologicals Conference,* PDA's Training and Research Institute (PDA TRI) will be hosting two one-day courses on Nov. 12 to complement your learning at the conference. One course will cover virus contamination in biomanufacutring and the other will focus on advanced molecular methods for virus detection. To learn more about these courses, please visit www.pda.org/viralcourses2013.

PDA/FDA Advanced Technologies for Virus Detection in the Evaluation of Biologicals Conference • Bethesda, Md. • Nov. 12–14 • www.pda.org/virusdetection2013

These are just a few highlights of the exciting three-day program. We hope that you will join us for the conference!

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Learn the Latest in Analytical Methods this October

Earl Zablackis, PhD, Sanofi Pasteur and Program Committee Member

PDA is pleased to host the *2013 Analytical Methods Development & Validation Workshop*. The workshop will provide participants a wide overview of the laboratory and documentation standards expected during the entire lifecycle of analytical methods from development through qualification, validation, transfer or replacement. Sessions will include current recommendations appropriate for each step of the analytical method lifecycle in accordance to ICH, the U.S. Pharmacopoeia, PDA technical reports and other relevant regulatory documents. In addition, the application of Quality by Design to analytical method development and validation will be discussed via case studies.

The workshop will also feature some of the foremost scientists from leading pharmaceutical companies and task force contributors who will speak on the various aspects involved in the lifecycle of analytical methods.

Attendees at this workshop will gain practical information on regulatory expectations and current industry best practices for analytical method lifecycle documentation, control and management for biopharmaceutical products.

If your job encompasses any aspect of the management of an analytical method, including: development, qualification, validation, compendial verification, transfer or replacement, you need to come to this workshop to hear the most up-to-date discussions and case studies from a renowned panel of experts who are shaping the way in which analytical methods are viewed.

We look forward to seeing you at this exciting and informative workshop!

2013 PDA Analytical Methods Development & Validation Workshop • Baltimore, Md. • Oct. 7–8 • www.pda.org/amd2013

Micro Conference Offers an Overview of Hot Topics

Edward Balkovic, PhD, Genzyme

Industrial and regulatory pharmaceutical microbiologists from around the world will be gathering again this fall for PDA's *8th Annual Global Conference on Pharmaceutical Microbiology.* The theme for this year's conference is *Staying Ahead of the Curve: Proactive Pharmaceutical Microbiology.*

Each morning will open with a stimulating keynote address from a scientific, industrial or regulatory expert. The first day will begin with **Karen Nelson,** PhD, from the J. Craig Venter Institute, speaking on recent findings from the Human Microbiome Project on the role of our microbial flora in human health and disease. The second day will open will a talk by **Ian Critchley,** PhD, from Cerexaon the challenges facing companies in developing new antimicrobial agents. Finally, on the third day, **Monica Caphart** from the Office of Regulatory Affairs at the U.S. FDA will provide an update on global inspection issues and current policies relevant to cGMP manufacturing.

PDA 8th Annual Global Conference on Pharmaceutical Microbiology • Bethesda, Md. • October 21–25 • www.pda.org/microbiology2013

Concurrent sessions will provide the latest information on areas such as, lean lab concepts, risk assessment/management, industrial perspectives of environmental monitoring, endotoxin testing issues, advanced rapid micro methods, challenges of globalization, workforce development, improved contamination responsiveness and USP updates.

The conference will also provide an excellent opportunity to view the latest lab equipment and technologies offered by a broad range of vendors and specially designed for the pharmaceutical microbiology laboratory.

Three courses will be offered after the conference by PDA's Training and Research Institute. The first course, "Investigating Microbial Data Deviations," will be held on Oct. 24 and will provide practical insights into both the regulatory and scientific considerations which must be taken into consideration when investigating microbiological data deviations.

The second course, "Validation of Microbiological Test Methods," also offered on Oct. 24, has been designed to assist those in quality assurance, regulatory compliance, quality control and validation.

The third course, "Evaluation, Validation and Implementation of Alternative and Rapid Microbiological Testing Methods" will be held Oct. 24–25. This new course provides attendees with an overview of the revised *PDA Technical Report No. 33: Evaluation, Validation and Implementation of Alternative and Rapid Microbiological Testing Methods.*

Prevent Inadequate Investigations by Attending Workshop

Program Planning Committee Co-chairs Anders Vinther, PhD, Genentech, and Rick Friedman, U.S. FDA

Building on the success of the *Responsibilities of Executive Management ICHQ10 Workshop* held last fall, PDA and the U.S. FDA continue to hold workshops designed to help industry implement robust quality systems that ensure a sustainable state of control. Each year, when the Agency reviews the top ten GMP observations, inadequate investigations is always listed and usually appears toward the top of the list! This workshop will not only share current regulatory expectations and offer tried and true solutions, but will also deliver a hands-on series of educational sessions. These sessions should provide tools you can take to your workplace to improve investigations.

2013 PDA/FDA Improving Investigations Workshop • Washington, D.C. • Sept. 18–19 • www.pda.org/investigations2013

There are numerous benefits to a well-executed and documented investigation. When a firm gets to a true root cause and confirms the effectiveness of the implemented corrective and preventive actions, there is a positive impact to the financial bottom line. Each investigation *not* performed allows resources to be deployed in other continuous improvement and growth activities.

Throughout the two-day workshop, the following key industry opinion leaders will share their approaches and lessons learned:

- **Martin VanTrieste,** SVP, Quality, Amgen, on management review and the responsibility for investigations
- **Juan Torres,** SVP, Quality, Biogen Idec, on the benefits and elements of establishing an investigation process
- **Swroop K. Sahota,** PhD, VP, Quality Operations, Catalent Pharma Solutions, on forming an investigation team
- **Thomas J. Arista,** National Expert Investigator, ORA, FDA, on the essential components of a thorough investigation

But be forewarned—this is not your average sit and listen workshop! Participants will have the opportunity to participate in one of three breakout session tracks in which they will be presented with a situation easily faced in our operations. Throughout these sessions, participants analyze the situation before reaching decisions as to corrective actions.

While we all hope there will come a time when there are no issues to investigate, until that time arrives, attending this workshop is a first step toward assuring good investigations.

Hone Your Skills at the Visual Inspection Forum

Program Co-chairs John Shabushnig, PhD, Insight Pharma Consulting, LLC and Markus Lankers, PhD, rap.ID GmbH

Our industry has moved from being centered on small molecules to a research and development environment driven by biotech. These changes touch API production, formulation, analytics and packaging technology to name just a few. Particulate matter control would seem little affected by these changes, but has proven to present some new challenges. A closer look shows that inspection departments, inspection machine builders and regulators are all faced with new problems like inherent particles, protein aggregation, shear induced degradation and turbidity.

Visual inspection continues to be an important element of the manufacturing process and the quality assurance of injectable products of all kinds. Product inspection provides necessary information for lot release, and contributes to a strategy of continuous process improvement. Since 2000, PDA has organized the *Visual Inspection Forum* to discuss new technical and regulatory developments in this field. This annual meeting alternates between the United States and Europe; this year's meeting will be held in Bethesda, Md. The meeting will provide a forum to present and discuss new developments in the field of visual inspection, including a basic understanding of the sampling and inspection process, special aspects of biotech products, practical aspects of manual and automated methods and the regulatory and compendial requirements that govern them. Special attention will be given to packaging component quality requirements and qualification/validation case studies for the visual inspection process.

We look forward to seeing you at this exciting and informative meeting.

2013 PDA Visual Inspection Forum • Bethesda, Md. • October 7–10, 2013 • www.pda.org/visualinspection2013

We are also pleased to add again an optional two-day training course offered through PDA's Training and Research Institute. This course covers the basics of the inspection process and its application to injectable products. It will be a combination of lecture/discussion and hands-on laboratory exercises used to develop and practice practical inspection skills. The skills developed through this course may be applied to both manual human inspection and automated machine inspection. This course will be held immediately following the *2013 PDA Visual Inspection Forum* Oct. 9-10 at TRI, a short two-block walk from the conference hotel.

Meet European Prefilled Syringe Suppliers This Fall

Rebecca Stauffer, PDA

The *PDA Letter* spoke with **Adalberto Ramirez,** VP, Quality, Amgen, and **Yu Hu,** PhD, Director, Molecular Biology, Fermentation and Cell Culture, Eli Lilly, who cochaired last year's *Universe of Prefilled Syringes and Injection Devices* conference in Las Vegas, for their take on this year's conference, which will be held in Basel, Switzerland this November.

What are the benefits of attending this conference?

Ramirez: This conference provides the latest information and advances in syringe manufacturing technologies.

Hu: The biggest benefit is probably to see what other people are doing. This conference has been very successful in bringing in different companies. And you get to meet a lot of people. Last year, we had 700 people attending, representing approximately 100 companies.

What topics do you expect will be up for discussion at this year's conference?

Ramirez: The use of medical or drug delivery devices continues to grow in the industry. Novel approaches have been shared in the past and this is an opportunity to learn about the latest techniques.

Hu: I would think there would be some new advances in syringes—both from the syringe design and the pharmaceutical manufacturing process as well as the device and how you integrate those. And also how you maintain and ensure the compliance. Those will be key things this year.

I'm based in the United States, why should I attend the European conference?

Ramirez: This is a great opportunity to interact with the rest of the industry from around the world and discuss the challenges and the approaches being followed as well as develop a common understanding of the issues. Several suppliers from all around the world will share the latest advances and techniques to improve quality and productivity.

Hu: Typically, a lot of suppliers in Europe don't normally come to the United States for the conference. So you get a chance to meet a lot of European companies. And local companies tend to send more people to the Europe-based conferences, so you get more chances to talk with people and to network.

The Universe of Pre-filled Syringes and Injection Devices • Basel, Switzerland • November 5–6 • https://europe.pda.org/UPS2013

Three New QRM Courses Follow Joint Reg Conference

Stephanie Ko, PDA

One of TRI's most popular lecture courses is based on *PDA Technical Report No. 54: Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations.* This course will be offered on Sept. 19, 2013 in conjunction with the *2013 PDA/FDA Joint Regulatory Conference* in Washington, D.C. This year, however, TRI will be offering three new courses based on the following supplemental annexes to Technical Report No. 54:

- *Case Studies in the Packaging and Labeling of Drug Products*
- *Case Studies in the Manufacturing of Biotechnological Bulk Drug Substances*
- *Case Studies in the Manufacturing of Pharmaceutical Drug Products*

These courses are taking place on Sept. 20, 2013, the day following the course on Technical Report No. 54. This means you will have the opportunity to take up to two courses on Quality Risk Management after attending the *2013 PDA/FDA Joint Regulatory Conference.* Ultimately, TRI hopes the new courses can further your knowledge on topics specific to QRM.

The first course, "Case Studies in the Packaging and Labeling of Drug Products," provides specific case studies based on subject matter experts' real life experiences on QRM in pharmaceutical manufacturing, specifically in packaging and labeling operations. The course will go over the challenges with implementing a QRM program and how to integrate the concept into routine manufacturing operations.

Like most TRI courses based on technical reports, this course is taught by one of the authors, **Ghada Haddad,** Associate Director, Biosterile Validation, Merck. She is the leader of the Paradigm Change in Manufacturing (PCMO[SM]) Initiative in QRM in Packing and Labeling Task Force and has spent over 15 years developing and implementing QRM programs, training on the concepts and tools, and integrating QRM into the quality systems.

The second course is based on *Case Studies in the Manufacturing of Biotechnological Bulk Drug Substances.* It will cover the different aspects of biologic manufacturing, including not only the standard topics of upstream and downstream processing, but also cell banking, raw material selection and control, facility considerations and leachables and extractables. These are covered in the context of risk identifica-

tion and risk control.

This course is different from others out because the content was generated by a committee of experts from the largest to the smallest biotech companies. U.S. FDA and ICH experts also provided input. The participation in the committee was international, including experts from Europe and Asia, and from every major biotech center in the United States. This course will be based on, and represent best practices from, an excellent cross section of the industry, not just the opinions of a particular speaker.

Coauthor of the annex, **Scott Rudge,** PhD, COO, RMC Pharmaceutical Solutions, will teach the course. He has 24 years of experience in the development of pharmaceutical products, ranging from recombinant biologic molecules from cell culture and bacterial fermentation to peptides to delivery of drugs in controlled release and targeted release settings.

The third course addresses the annex, *Case Studies in the Manufacturing of Pharmaceutical Drug Products.* Contributing author **William Harclerode,** Associate Director, Forest Laboratories, has over 20 years of experience in the pharmaceutical industry; he will guide you through QRM for various manufacturing applications (sterile and nonsterile), as well as to how to effectively communicate quality risk within your organization.

You will benefit from this course by learning to utilize different QRM tools, assign levels for risk, use QRM as a tool to proactively manage risk and incorporate QRM into your quality systems.

So, what makes this course different than others which may be out there? Well, this course will provide an overview of QRM and then look into some specific case studies in drug product manufacturing.

Harclerode is also coauthor to TR54, *Technical Report No. 44: Quality Risk Management for Aseptic Processes,* and a chapter in the book, *Risk Management Applications in Pharmaceutical and Biopharmaceutical Manufacturing.*

Take these courses and you will have opportunities to interact with our expert instructors, discuss topics of interest with your peers and ask questions about your current QRM programs and how to improve them. Go to www.pda.org/pdafdacourses2013 to learn more about each of the courses mentioned here. You can also go to www.pda.org/courses for a list of other training courses offered throughout the year.

Sue Schniepp, Allergy Laboratories

PDA and U.S. FDA Working Together to Prevent Drug Shortages By Developing Sound Quality Metrics

The PDA Board of Directors has met a number of times over the first half of 2013. As a result of these meetings the Board has identified a number of areas where they feel PDA can help establish best practices or offer solutions to important issues facing our industry.

One key area of focus for PDA involves the development of quality metrics to alleviate drug shortages. In the Feb. 12 *Federal Register,* the U.S. FDA announced that the Agency sought input on "Drafting a strategic plan on drug shortages as required by the Food and Drug Administration Safety and Innovation Act," or FDASIA. Additionally, the notice stated that "The Agency is seeking public comment from interested persons on certain questions related to drug and biological product shortages." The notice went on to mention that "To assist in the evaluation of product manufacturing quality, FDA is exploring the broader use of manufacturing quality metrics."

In recognition of the seriousness of the issue, the Board realized PDA could offer expertise on the drug shortage issue and sanctioned a task force to draft comments for submission to the agency. The Board also liaised with the *2013 PDA/FDA Joint Regulatory Conference* planning committee to see if there were opportunities to discuss the drug shortage and quality metrics issue at the conference. As a result, this year's conference, scheduled for Sept. 16–20 in Washington D.C., will feature FDA's **Janet Woodcock,** MD, Director CDER, speaking at the opening plenary session. Her talk is titled "Regulatory Perspective: Quality Systems, Quality by Design and Drug Shortages – Where are we?" The conference also offers some smaller sessions where drug shortages will be discussed in greater depth.

The Board also worked with PDA members with experience developing quality metrics and their use in determining product quality to develop a specialized conference on the topic. The *2013 PDA/FDA Pharmaceutical Quality Metrics Conference* will be held in Bethesda, Md. Dec 9–10. More details on this exciting new conference will be coming soon in the *PDA Letter.*

Additionally, a RAQAB task force has been commissioned to analyze the application of Quality Risk Management tools in determining methods for minimizing shortages (see page 40 for more information about this project).

The Board of Directors will continue to work with our membership to identify important and emerging topics, offering various venues where these issues can be discussed in an open and collaborative manner.

[Editor's Note: In August, the PDA Letter will publish an online-only article based on an interview with the **Marty Murawski,** VP of Quality Management and Continuous Improvement, Hospira, which will feature his perspective on quality metrics.**]**

July/August 2013 RAQAB Quarterly Report continued from page 40

Update on RAQAB Projects

RAQAB met face to face at the *2013 PDA Annual Meeting* in Orlando, Fla. One of the main topics discussed involved RAQAB involvement with management and communication with PDA interest groups. The RAQAB coordinates activities with a number of interest groups including Management of Outsourced Operations, Quality Systems and Regulatory Affairs. Working together, RAQAB and the interest group leaders discuss and comment on key regulatory proposals in a timely manner. RAQAB is working to achieve a similar interaction with PDA chapter leaders. In addition to working with interest group and chapter leaders to remain current on developing issues, RAQAB has members who monitor the activities of regulatory authorities worldwide, including—but not limited to—China, Brazil, South Korea, Australia and India. The goal is to identify activities impacting PDA membership and report back to them regarding RAQAB recommendations and/or comments communicated to the regulatory bodies. RAQAB has commented on a number of documents in the past (such USP changes to reference standard requirements and EU Good Distribution Practices), and is currently working on comments for EU GMP Revisions to Chapters 6 and 8 as well as the U.S. FDA's draft guidance *Contract Manufacturing Arrangements for Drugs: Quality Agreements.*

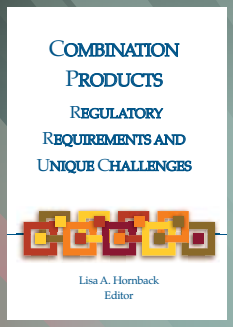
Related Publications for the

2013 PDA/FDA Joint Regulatory Conference

September 16-18, 2013

Renaissance Washington DC Hotel | Washington, D.C.

www.pda.org/pdafda2013



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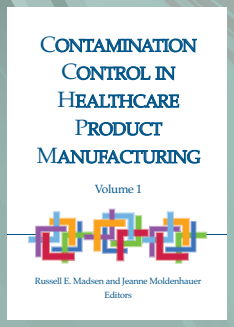

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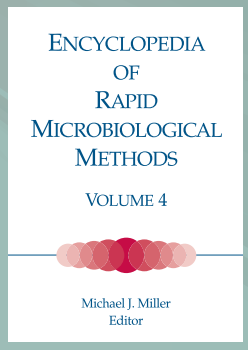

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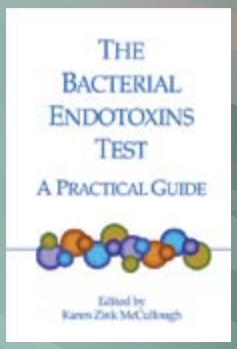

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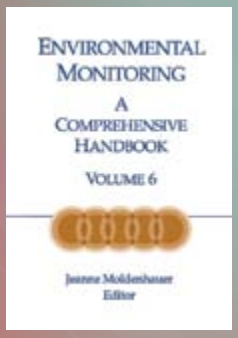

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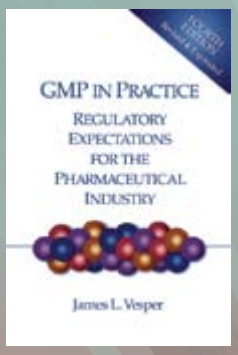

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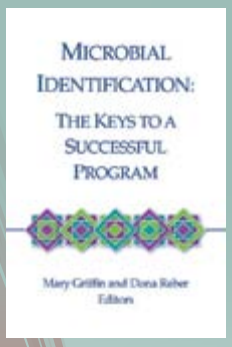

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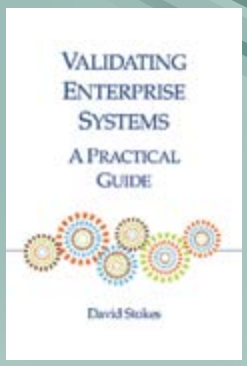

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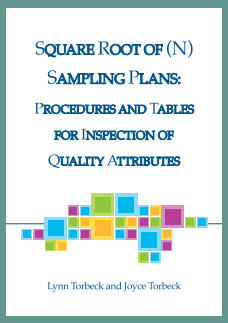
Upcoming New Release at the PDA Bookstore



Item No. 17314

Save 15% on these publications at the *2013 PDA/FDA Joint Regulatory Conference*

Showcasing PDA/FDA at a Time of Regulatory Transition

It seems just like yesterday when all the buzz was about center-level review of U.S. FDA warning letters which slowed down to a degree the amount of enforcement actions coming out of the Agency. But the reality is, those days are long gone. Enforcement has ramped up in recent years, and the consent decree is once again taking headlines away from the good work that the pharmaceutical industry does. As such, the *PDA Letter* Editorial Committee wanted us to take a look at the consent decree.

We received an article on how to successfully manage a consent decree: "Management, We Have a Problem" (cover). **Roland Bizanek,** an experienced consultant on these matters, provides an 8-point plan, that hopefully none of you will have to use. However, as he points out, his strategy is most useful for any company in trying to resolve compliance matter prior to the point of injunction. The issue's infographic (page 38), put together by the editorial team, dissects common elements of consent decrees.

Additionally, we include a pullout from **Anders Vinther** and **Jennifer Magnani** at Genentech, which offers checklists that help define the various roles of quality professionals. We hope our members find this pullout a valuable resource in preventing quality issues.

This brings us to the *2013 PDA/FDA Joint Regulatory Conference*. This is a unique meeting that truly connects regulators and the industry so that they can discuss all matters related to compliance. **Rebecca Stauffer** interviewed two FDA officials who are on the committee that planned a the PDA/FDA workshop on improving investigations (p. 34). **Rick Friedman** and **Mahesh Ramandham** discuss with Rebecca the importance of internal investigations to stave off regulatory actions and the role of quality metrics. Friedman, who also sits on the Joint Conference planning committee, will moderate an important session on "Understanding GMPs" and he explains to Rebecca why the session is important to industry vets and rookies alike.

Rebecca also spoke with industry consultant **Cathy Burgess** about her talk in the GMP session on the evolution of GMPs. Portions of the interview are included on page 36, and the entire interview is online for the PDA Letter's July Podcast.

We introduce two new columns in this month's issue: "PDA Pulse" and "PDA in the News." The former is in the People Department (see p. 18) and is the result of an email survey conducted by the PDA Membership team on the impact of PDA membership on hiring decisions. Look for more PDA Pulses in future issues. PDA in the News (see News and Notes, p. 7) is a periodic listing of articles that mention PDA members, speakers, events, courses and/or publications—or anything else "PDA." Sources include trade publications, magazines, journals, and new media like blogs.

This issue is full of other important articles. We know it is summertime, and members are looking to relax, but as the only issue published during this time of vacation and holiday, we hope this issues proves a valuable and entertaining addition to your summer reading.

The *PDA Letter* podcast is available at www.pda.org/pdaletter.

PDA Letter

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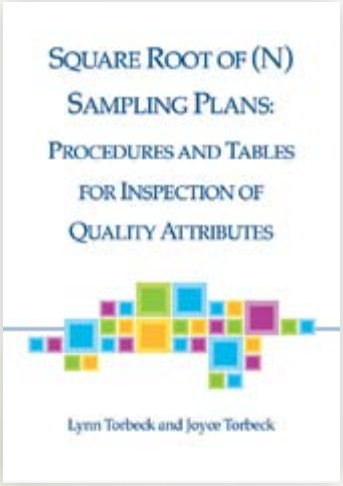
New Releases at the PDA Bookstore



Item No. 17314

Square Root of (N) Sampling Plans: Procedures and Tables for Inspection of Quality Attributes

By Lynn Torbeck and Joyce Torbeck

The goal of Lynn and Joyce Torbeck's book, Square Root of (N) Sampling Plans: Procedures and Tables for Inspection of Quality Attributes, is to show that the sqrt (N) plans are statistically correct and can be used in applications that minimize risk to the patient.

This book presents technical and practical information for the correct use of the three sqrt (N) attribute sampling plans.

While the book is oriented to the domestic and international pharmaceutical industry, the material is general enough to be adapted to other industries and applications.

www.pda.org/squareroot

Item No. 13010

Pharmaceutical Legislation of the European Union, Japan and the United States of America – An Overview

Second Reprint

By Barbara Jentges, Nobuo Tateishi, Kate Denton, Michel Mikhail

This book gives an overview of the pharmaceutical legislation of the three ICH regions through chapters on Regulatory Bodies and Health Authorities: Functions and Responsibilities, Pharmaceutical Legislation, Marketing Authorization Application Procedures and Drug Master File Systems. The authors of this book hope that it provides a mutual (regulatory) understanding and provide at least a sign on the promising road to harmonization.

www.pda.org/EUJUSA

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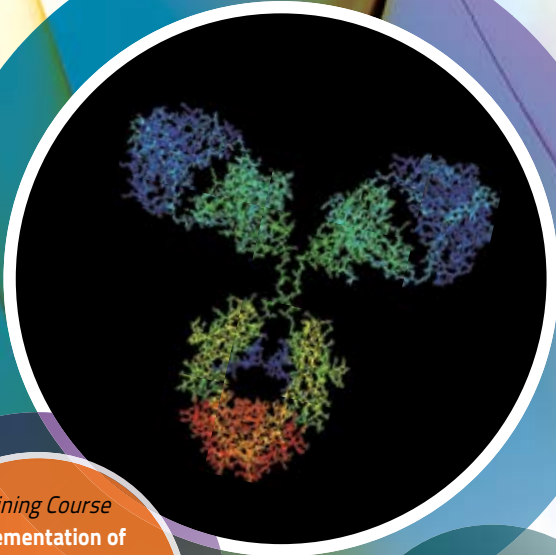
Session 4: Implications of Immunogenicity on the Development of Biosimilars



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11-12 September 2013

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