People • Science • Regulation

PDA Letter

Volume XLVIII • Issue #4 www.pda.org/pdaletter April 2012

Rx Distribution Licenses: A Matter of State

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The Parenteral Drug Association presents the...

2012 PDA/FDA Joint Regulatory Conference

Compliance through Quality Systems: Implementing & Advancing a Sustainable Global Quality Culture

Register before June 29, 2012 – the first registration savings deadline!

September 10-12, 2012

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Although we, the medical products industry, are more than a decade into the new millennium and nearly a decade into the FDA's Good Manufacturing Practices for the 21st Century (Product Quality) initiative, we must continue to strive to improve the quality, compliance, and security of our products around the globe.

Attendees of the *2012 PDA/FDA Joint Regulatory Conference* will be in the center of this conversation on the new paradigm and will have the opportunity to interact with FDA, PDA, industry representatives, and other experts as we continue our exploration of topics including:

- Risk management and quality risk management systems
- Quality systems
- Regulatory Considerations during Development
- Cell Therapy Innovations
- GMP Foreign Inspection Findings
- Innovation and collaboration with the goal of advancing the industry and impacting public health on a global scale

Be the first to know – Sign up to receive an email when more information is available about this event! Visit www.pda.org/pdafda2012.

"The 2011 PDA/FDA Joint Conference was excellent. I was impressed by the large number of participants which expanded my networking opportunities."
Lynn Collins, *BD*

Visit **www.pda.org/pdafda2012** for more information.

Exhibition: September 10-11
Post-Conference Workshop: September 12-13
Courses: September 13-14

The last chance to save on registration ends May 4!

"Time well spent. Probably the most efficient way to get a sense on where the industry is on the topics of 'glass quality' and 'lamellae'."

Martin Browne,
GE Healthcare

The Parenteral Drug Association presents the...

PDA/FDA Glass Quality Conference

June 4-5, 2012

Renaissance Downtown Hotel | Washington, D.C.

Participate in PDA's Benchmarking Survey on Glass Quality.
Results to be shared at this conference.

If you are involved in the selection and quality assurance of glass packaging; manufacturing of products packaged in glass; are a glass supplier; or regulator then this is the meeting to attend to find out what the pharmaceutical and glass industry are doing to make glass quality better.

Pharmaceutical manufacturers, regulators, and glass suppliers all share a common goal of assuring the highest quality products, including packaging for patients. The *PDA/FDA Glass Quality Conference* will discuss these issues; best practice to preventing and/or detecting at risk glass packaging; and review current expectations to ensure that recalls are avoided and container closure integrity is assured.

Plenary sessions at this year's meeting include:

- Development Considerations/Glass
- Pharmaceutical Packaging in Glass
- Glass Handling Equipment Manufacturers Perspective
- Quality Control Issues
- Distribution/Packaging/Transportation
- Monitoring Customer Feedback & Other Factors to Consider in Glass Defect Prevention
- What Are We Going To Do To Make It Better?

Immediately following the conference, PDA's Training and Research Institute (PDA TRI) will be hosting two stand-alone training courses on-site on June 6-7.

www.pda.org/glass2012

Exhibition: June 4-5 | Courses: June 6-7

PDA Letter

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Cover

Cover Art Illustrated by Katja Yount

Departments

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PDA's Mission

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

PDA's Vision

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

PDA® Parenteral Drug Association

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Three New PDA Technical Reports Now Available

Technical Report No. 55 is now available for free member download. Technical Report 30 (Revised 2012) will be available soon. And TR-54 is available for purchase.

Ripped from the Headlines: TR-55

PDA Technical Report No. 55: Detection and Mitigation of 2,4,6-Tribromoanisole and 2,4,6-Trichloroanisole Taints and Odors in the Pharmaceutical and Consumer Healthcare Industries offers timely guidance on a challenging issue. The TBA/TCA Task Force worked very rapidly in response to the pressing need within industry for guidance on this topic. Formed at the end of 2010, the group drafted one of the most comprehensive technical reports in PDA's library in record time.

The group is now working on a training that would cover mitigation steps with lumber products. Led by Task Force Leader **Anil Sawant,** PhD, Vice President, Regulatory Compliance, Quality & Compliance, Johnson & Johnson, the busy task force will also request companies to participate in a multicompany, multigeography survey later this year.

PDA would like to thank the volunteers who contributed to this report:

Anil Sawant, PhD, Task Force Leader, Johnson & Johnson Consumer Companies

Jeffrey Burris

William Callahan, PhD, Depomed

John Clark, MD, Risk Benefits

Anthony M. Cundell, PhD, Merck

Jonine Greyling, PhD, Johnson & Johnson Consumer Products Company

Robert Johnson

Douglas Knawby, PhD, Johnson & Johnson Consumer Products Company

Janet Lim, MD, Johnson & Johnson Consumer Companies

Wendy Luo, PhD, Bristol-Myers Squibb Company

William J. Powers, Jr., PhD, Johnson & Johnson Consumer Companies

Megan Sewell, Merck

Edward J. Smith, PhD, Packaging Science Resources

Katherine A. Stetson, GlaxoSmithKline

Dirk E. Stevens, PhD, Covidien Pharmaceuticals

James Strickland, Pfizer

Eric Thostesen, Janssen Pharmaceutical Company

Annalisa Torrente (Project Manager)

David A. Ulrich, Abbott Laboratories

Christine Vietri, AstraZeneca Pharmaceuticals

Gary E. Wilson, West Pharmaceuticals Services

William Beierschmitt, PhD, Pfizer

Michael Fairbanks, Perrigo

Rachael Humphreys, Mylan

Nirdosh Jagota, PhD, Genentech, a Member of the Roche Group

Richard V. Levy, PhD, Parenteral Drug Association

Gustavo S. Rodriguez, Rexam Healthcare

Doug Ross, MD, Pfizer

Sarah Sellers, PharmD ➤

Interested in volunteering on a task force and contributing to a technical report? If so, contact **Iris Rice** at rice@pda.org.

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A Classic TR Revised

The Parametric Release Task Force, led by **Mike Sadowski,** Director, Sterile Manufacture Support, Baxter Healthcare, has published an update on the 1999 PDA *Technical Report No. 30(Revised 2012): Parametric Release of Pharmaceuticals Terminally Sterilized by Moist Heat*. This update provides current demonstrated best practices of this sterile product release method with an emphasis on use of science-based approaches during the development of a parametric release program for pharmaceutical and medical device products terminally sterilized by moist heat.

PDA would like to thank the volunteers who contributed to this report:

Mike Sadowski, Task Force Leader, Baxter Healthcare
Marion Andersen, Fresenius Medical Care
Tom Berger, PhD, Hospira (Retired)
Steve Douglas, Hospira
Julian Kay, GlaxoSmithKline
Genevieve Lovitt-Wood, G.I. Lovitt & Associates
Terry Munson, Parexel Consulting
Ronald J. Nekula, Sr., Bayer HealthCare
Radhakrishna Tirumalai, PhD, USP
Bob Tomaselli, Johnson & Johnson
James P. Agalloco, Agalloco & Associates
Rick Friedman, U.S. FDA
Thomas Genova, PhD, Johnson & Johnson
Andrew Hopkins, MHRA
David Jaworski, U.S. FDA
Russell Madsen, The Williamsburg Group
John Metcalfe, PhD, U.S. Food and Drug Administration
Steffen Prowe, PhD, Beuth University for Applied Sciences
Christopher Smalley, PhD, Merck & Co.
Marla Stevens-Riley, PhD, U.S. FDA
Kevin Trupp, Hospira (Retired)
Brenda Uratani, PhD, U.S. FDA

For Sale: The First PCMO℠ TR

PCMO℠ PDA Technical Report No. 54: Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations provides detailed guidance for the application and implementation of quality risk management (QRM) principles throughout the product lifecycle. Led by Task Force Leader **Emabelle Ramnarine,** Senior Technical Manager, Corporate Quality Risk, Genentech, this technical report is intended to align with ICH Q9 and present information that can be helpful to the reader on how to implement QRM, the report emphasizes QRM application during commercial manufacturing and integrating QRM into the pharmaceutical quality system.

PDA would like to thank the volunteers who contributed to this report:

Emabelle Ramnarine, Task Force Leader, Genentech
Jeffrey L. Hartman, Co-Leader, Merck
Thomas Genova, PhD, Johnson & Johnson
Laura Huffman, U.S. FDA
Kathy Lee, U.S. FDA
Michael A. Long, PhD, ConcordiaValSource
Kevin O'Donnell, PhD, Irish Medicines Board
Jayesh Patel, F. Hoffmann-La Roche
Siegfried Schmitt, PhD, PAREXEL Consulting
Rebecca Spohn, Amgen
Edward C. Tidswell, PhD, Baxter Healthcare
Robert P. Tomaselli, Johnson & Johnson SPT
Anthony C. Warchut, PAREXEL Consulting
James Agalloco, Agalloco & Associates
James E. Akers, Akers, Kennedy and Associates
Kristen Anderson, U.S. FDA
Véronique D. Davoust, PhD, Pfizer
Lance D. Goodreau, New England BioLabs
Ghada Haddad, Genentech
William Harclerode, Forest Labs
Kristin Murray, Pfizer
Stephen Reich, Pfizer

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Volunteer

Rafik H. Bishara, PhD, Technical Advisor, RHB Technical Advising

PDA Join Date: 2005

Interesting fact about yourself: I enjoy learning, teaching and helping others.

Why did you join PDA? It is one of the best trade Associations that focuses on science and technology. I am honored to work on resolving domestic and international issues/challenges in the area of cold chain management practices and temperature–controlled medicines and vaccines.

Of your PDA volunteer experiences, which have you enjoyed the most? Leading the very active and dedicated Pharmaceutical Cold Chain Interest Group with the result of publishing four PDA Technical Reports:

- PDA *Technical Report No. 39, Revised 2007, Guidance for Temperature-Controlled Medicinal Products: Maintaining the Quality of Temperature-Sensitive Medicinal Products Through the Transportation Environment*
- PDA *Technical Report No. 46, Last Mile: Guidance for Good Distribution Practices for Pharmaceutical Products to the End User*
- PDA *Technical Report No. 52, Guidance for Good Distribution Practices (GDPs) For the Pharmaceutical Supply Chain*
- PDA *Technical Report No. 53, Guidance for Industry: Stability Testing to Support Distribution of New Drug Products*

I continue to be excited about my work with PDA's European colleagues which has resulted in the publication of a new technical report on the guidance of risk management for temperature controlled distribution. Additionally, two of the PDA Cold Chain Interest Group task teams are finalizing the work on a couple of technical reports that cover the implementation of active packaging and thermal blankets for the handling, storage and distribution of temperature controlled pharmaceuticals.

Another exciting area is the planning and executing of PDA's Annual Cold Chain Conferences and Trainings in Bethesda, Md., and in Berlin, Germany. At the 2011 Berlin conference, there was participation from regulators from Egypt, Israel, Spain, the Netherlands and representatives from the European Medicines Agency, World Health Organization, India, Jordan and Saudi Arabia. The PDA two day Cold Chain training has been well received as we continue to update it. It has been sold out many times.

How has volunteering in PDA benefited you professionally? I continue to learn and work to solve some of the challenges of the supply chain and logistics for temperature–controlled medicines. Recently, we have started to focus on ambient temperature products, cryogenic containers, security, track and trace, labeling and real time data.

Which PDA conference/training course is your favorite? PDA's Annual Cold Chain Conferences.

What would you say to somebody considering volunteering with PDA? It will be a wonderful experience. You will be introduced to some 10,000 members dedicated to the advancement of science, technology, training and pragmatic solutions to common issues bothering our industry. You will benefit from the PDA's publications, conferences and training. You will have outstanding opportunities to network with colleagues in your own discipline as well as other areas of expertise. Just do it!

New President for Missouri Valley Chapter

Thomas Pamukcoglu, Director, Quality, SAFC, has stepped down as President of PDA's Missouri Valley Chapter due to his relocation to the Maryland area. The former President-elect **Eldon Henson,** Director, Operations Technical Services, Pharmaceutical Operations, Covidien, has taken Pamukcoglu's vacated spot. **Jeff Hargroves,** President, ProPharma, has been elected to the vacated President-elect position.

The chapter currently has an opening on its Board for the position of Secretary.

Contact Eldon with any questions at Eldon.Henson@Covidien.com.

Missouri Valley Chapter President Eldon Henson

Register for this Workshop and the *PDA/FDA Virus & TSE Safety Conference* and Save!

PDA Parenteral Drug Association

FDA

The Parenteral Drug Association presents the...

Applying QbD Principles in Vaccine Development: PDA/FDA CMC Workshop

Implementing Quality by Design Principles in Vaccine Development: A-Vax Case Study

May 14, 2012

Hyatt Regency Bethesda | Bethesda, Maryland

Five vaccine manufacturers (GlaxoSmithKline, MedImmune, Merck, Pfizer and Sanofi Pasteur) have joined forces to form the CMC-VWG, to create a case study describing the development of the fictitious vaccine A-Vax. The goal of the workshop is to initiate discussion of the case study and to provide a review of the QbD approaches employed for the development of A-Vax.

The workshop will stimulate discussions within industry as well as between industry and regulatory agencies to better understand the challenges associated with attempting to apply QbD to vaccine development; including Critical Quality Attributes (CQA) and a control strategy for the vaccine.

Confirmed industry experts to participate at this year's workshop include:

- **Amit Banerjee**, PhD, *Pfizer, Inc.*
- **Jeffrey Blue**, *Merck & Co., Inc.*
- **Pierre Chouvenc**, PhD, *Sanofi Pasteur*
- **John D. Finkbohner**, PhD, *MedImmune, LLC*
- **Christian Klock**, *Sanofi Pasteur*
- **Michael Kosinski**, PhD, *Merck & Co., Inc.*
- **Cecile Ponsar**, PhD, *GlaxoSmithKline Biologicals*
- **Robert Repetto**, *Pfizer, Inc.*
- **Joseph Schaller**, *Merck & Co., Inc.*
- **Mark Schenerman**, PhD, *MedImmune, LLC*
- **Michael P. Schwartz**, PhD, *GlaxoSmithKline Biologicals*
- **Annick Vandercammen**, PhD, *GlaxoSmithKline Biologicals*
- **Michael Washabaugh**, PhD, *MedImmune, LLC*
- **FDA Representatives Invited**

Attend this year's workshop as it marks a significant opportunity to expand critical discussions on the implementation of QbD concepts in vaccine development.

Visit **www.pda.org/cmc2012** for more information.

Exhibition: May 14

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How to Be a Memorable Leader

Jean Kelley

If you look back over your career, chances are you can identify one or two people who stand out as memorable leaders. Even if these people didn't hold an official leadership role, their actions and words rallied people together to achieve a common goal. And whether that goal was large or small, far reaching or contained, you remember these leaders for a long time.

While there are many great leaders in the world, not all of them are truly memorable—that is, they don't leave an impression that lasts beyond their current accomplishment or focus. But being memorable is essential if you want long-term success. So what makes one leader memorable and puts another in the "out of sight, out of mind" category? It comes down to three key elements. Develop these characteristics in yourself and you, too, can be a memorable leader.

Know Who You Are

Socrates said, "The unexamined life is not worth living." While that's a little harsh, it does make the point that everyone must examine their life. For what? To pinpoint your "moral compass"—your true values. Memorable leaders know their values, why those values are important and how those values play out in life.

Realize that you can't have one set of values in your work life and a different set in your personal life. You take your set of values with you everywhere, and a mess up in one area of life can easily affect another. For example, it was a seemingly personal value that distracted and somewhat derailed Bill Clinton's career, not a business value, which shows that values are not compartmentalized. So if you don't examine your life and know what you stand for, you can easily get sidetracked.

Getting to know yourself starts with honesty—with others and yourself. While most people have "cash register" honesty, meaning they'd never steal money from their employer, they aren't always honest in other ways. Perhaps they tell the world they value one thing, yet display something else. For example, some people will tout the value of hard work and claim they work harder than anyone else. Yet, when you really look at their work behaviors, you find that they're spending much of the day on long conversations that have little to do with work or are surfing the Internet—things that don't advance the company. That's not personal honesty or personal awareness.

If you're having trouble knowing who you are and what you stand for, ask a trusted colleague or family member to give you feedback. You can also opt to do a formal 360-degree feedback assessment, which enables others to give objective insight on how they view you.

Know Your Vision, Communicate It and Live It

A Harvard Business School professor once said, "The only thing a CEO needs to do is communicate their vision, communicate their vision and then communicate their vision." Why is communicating the vision so important? Because if you don't know where you're going and tell others where you're going, then you and everyone around you are going to lose the way. With all the things employees have going on in their lives, they're distracted during some of the week, so it's easy for them to get off track. Memorable leaders keep communicating the vision so everyone is always on the same page.

Living your vision and your company's core values means everyone—those you report to and those who report to you—knows the vision as well. If you don't understand your company's vision or core values, have a conversation with your boss about them. Without vision and values, both companies and people lose their way—people are floundering, no one knows what they should be doing, and people hide their potential talent. Not a good situation for sure! For example, in a manufacturing company, getting the product out on time isn't a core value and has nothing to do with the company's vision. In order to have a healthy and synergistic team, people need to connect to something bigger than a goal of moving product. Vision and values make the difference.

Also realize that communicating a vision does not mean the leader needs to be talkative. Many memorable leaders are quiet and reserved, such as presidents Truman and Eisenhower. People follow memorable leaders because they exemplify their vision, not just tout it.

Be Teachable

Being open to learning new things and admitting your limitations and your

struggles give you power; it's not a weakness. Realize that people don't want to think they're following a robot. They want to know that whoever they're following is real.

Memorable leaders teach other leaders and are interested in the development of people beneath them. That's why you need to be in touch with your direct reports and learn their dreams, goals and career aspirations. As the old quote says, "People don't care how much you know until they know how much you care." So the "teachable" part goes in two directions: you have to be willing to learn for yourself and you have to be willing to teach others.

Finally, Peter Drucker, the father of modern management, once said, "Leaders are readers." That means it's important you know what's going on in all industries, not just your own. Staying too focused on one viewpoint of issues makes you one-dimensional. Creativity comes from combining what you know with what other leaders know and then adapting it to your own industry in order to improve or innovate. That's why "overview" publications like *Harvard Business Review, Forbes* and *Inc.* are favorites of memorable leaders.

A Leader for the Ages

While few people are natural born leaders, you can learn to be a memorable leader and have people lining up, asking to work for you. All it takes is a commitment to lead others in a way that reflects your deepest held values, embraces your vision and encourages lifelong learning. The more you commit to practicing and living these three keys, the more memorable you'll be.

About the Author

Jean Kelley, author and entrepreneur, is the managing director of Jean Kelley Leadership Alliance whose faculty and Trainers have helped more than 750,000 leaders and high potentials up their game at work in the US and in Canada. For information on keynotes, in-house programs, or customized training, email jkelley@jeankelley.com or go to www.jeankelley.com.

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Preservative Formulation Discussed at Metro Chapter Event

Julie Barlasov, Perritt Laboratories

The PDA Metro Chapter held a dinner meeting on the preservative formulation and effectiveness in oral solutions and suspensions on February 15.

Promptly after the dinner, **Hang Guo** started his presentation, entitled, "Preservative Formulation and Effectiveness in Oral Solution and Suspensions." The first part of his presentation covered formulation with preservatives in oral solutions. Hang explained what the main considerations for preservatives are and that common preservatives for oral formulations are Benzoic acid, salts, Sorbic acid and parabens. He mentioned that it is very important that the pH levels stay the same throughout the shelf life of the product when acidic preservatives are involved. Preservatives such as Benzoic acid and Sorbic acid are not effective above their pKa, which is directly correlated to the pH level. Additional important things to consider are partition coefficient, impact of sweeteners, paraben interactions and toxicity of preservatives. He discussed what happened to Propylparaben after Maltitol was added to the product during re-formulation. He also mentioned the impact on a preservative system of the product when Propylparaben was substituted with Ethylparaben.

We would like to thank Accugenix who sponsored the event and **Simon Laufer** from IPS who took photos.

Chris Knutsen, PhD, (l) and Hang Guo (r) answer questions at the PDA Metro Chapter dinner. Photo by Simon Laufer.

He concluded his presentation telling the audience that it was important to contemplate the range of preservative and pH levels when considering the Antimicrobial Effectiveness Test (AET) so the product will pass its shelf life.

Chris Knutsen gave a presentation on AET and what has to be considered when

continued at bottom of page 15

Please Welcome the Following Industry

Erez Alfassi, Teva

Jens Altrichter, Leukocare

Yehudit Amor, Procognia

Shabbir Anik, Onyx Pharmaceuticals

Avital Arbel, Medingo

Gloria Arevalo, Biotest Pharmaceuticals

Michal Arnon, Perrigo

Esther Askew, Covidien

Zvi Avishar, Taro Pharmaceutical Industries

Gregoire Bagnoud, Forteq Nidau

Brenda Baxter, Celgene

Keith Beechler, Gilead Sciences

Tehila Beiser, Chiasma

Siminder Bhatia, Sanofi Pasteur

Gale Bibolet Graham, Merck

Chris Bland, Aptuit Glasgow Limited

Carmen Blanes Perez, Reig Jofré

Ofer Bonen, Enzymotec

Rita Boucher, Genzyme

Inge Briand de Crevecoeur, DHL

Bénédicte Broggi, Baccinex

Mary Anne Buckley, Interstate Corporation

Stephen Burr

Nicole Burton, OPK Biotech

Paul Butterly, Merck

Michael Callahan, Nipro Glass Americas

Doug Camposano, Merck

Travis Cannefax, Fresenius Medical Care

Christopher Carpenter, Microtest Laboratories

Cathleen Carson, Dendreon Corporation

Mark Caylor, Ben Venue Laboratories

Chianne Chen, Genentech

Mary Chilton, Qualicaps

Kimberly Christianson, Jubilant HollisterStier

Deborah Cohen, GE Healthcare

Jason Costigan, Alnylam Pharmaceuticals

Pascal Crottet, Swissmedic

Thomas D`Ambrisi, Bristol-Myers Squibb

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Fabio De Martino, Novartis

Silviano Del Monte, Haupt Pharma

Kumar Dhanasekharan, Genzyme

Anthony Driver, Hospira

Paul Duncan, Merck

Paul Dunne, Aptuit

Brigitte Duthu, Merck Serono

Hanna Filipek, Polpharma

Robert Fisher, Nipro Glass Americas

Thomas Flachmeyer, Prolong Pharmaceuticals

Kira Ford, Eli Lilly

Alan Forthman, Human Genome Sciences

Sari Gabber, Perrigo

Joerg Gampfer, Baxter

Kenn Garrett, Pacira Pharmaceuticals

Filippo Germano, Gipharma

Amit Gilad, Omrix

Parmajit Gill, Ben Venue Laboratories

Anijani Gossain, Bristol-Myers Squibb

Liat Gottlib, Kamada

Douglas Gravatt, CAI

Angela Green, Bayer Healthcare

George Greene, Merck

Mary Griffiths, EMD Millipore

Nathan Groathouse, Mangan Biopharm

Marco Guastalla, Parker Hannifin Ital

Edward Gugliotta, Ben Venue Laboratories

Dimpy Gupta, Ethicon

Liat Guttman, Teva

Nazila Habibizad, Onyx Pharmaceuticals

Adam Haring, Oncomed Manufacturing

Jason Harrod, CSL Behring

Christine Hartline, Teva

Netahnel Hayat, MedinolLtd

Ronan Hayes, Janssen

Heather Puffer, Parexel International

Henri Hebting, Eli Lilly

Sarit Heifetz, Abic Biological Industries

Michael Hendershot, Eli Lilly

Matthew Hermon, Genentech

Jessica Hinkle, General Electric Healthcare

Sugiyama Hirokazu, F. Hoffmann- La Roche

Christian Huber, Merck Serono

Ronald Iacocca, Eli Lilly

James Jackson, Novartis Vaccines & Diagnostics

Monika Jarocka-Wierzba, Main Pharmaceutical Inspectorate

Amy Jasek, Bausch and Lomb

Maithri Jayasekera, Bayer

William Jones, Medicago

Makuta Kamara, Pfizer

Todd Kapp, Renolit

Donna Keith, Molecular Insight Pharmaceuticals

Vadims Kisis, JSC Olainfarm

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David Martin, Genzyme

Sreenivasulu Megati, Ironwood Pharmaceuticals

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Amberina Naseeruddin, Genzyme

Ram Nechooshtan, Institute of Biological Research

Orly Niderman, Protalix

Veronica O`Connor, Ben Venue Laboratories

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Derek Owen, FHI 360

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JungMin Park, Celltrion

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Peter Pataro, Nipro Glass Americas

Manshi Patel, MedImmune

David Peers, Genentech

Andre Peters, Onctec Pharma Produktion

Tamar Pettel, Kamada

Juliane Pfuetzenreuter, Sartorius Stedim Biotech

Brigitte Philipp, F. Hoffmann - La Roche

Tony Pidgeon, Patheon

Leonid Polsky, Taro Pharmaceutical Industries

Carsten Poulsen, Novo Nordisk

Daniel Pratt, Pharmalucence

David Pritchett, MedImmune

William Pruett, Human Genome Sciences

John Punzi, Consumer Healthcare Products Association

Ariel Rachum, Teva

Srigiri Raja Sekhar Reddy, Dr Reddys

Teodoro Ranieri, Anteis

Susan Rebo, Genentech

Matthew Reeser, Morphotek

Matthias Reher, Sartorius Stedim Biotech

Martin Rhiel, ESBATech

Linda Rich, Abbott Laboratories

Molly Riege, Microbiologics

John Rigg, Eli Lilly

Stephenie Robertson, Novartis Vaccines & Diagnostics

Stephen Rolen, Fresenius Kabi

Marianne Romeo, Biogen Idec

Yuliya Rozenberg, Teva

Daniel Rudolph, Emergent BioSolutions

William Ryan, Werjr Associates

Michihiro Saito

Neema Saless

Adi Sasson, Taro Pharmaceutical Industries

Daniele Schaerrer, Geneva University Hospitals

Christoph Scheruebl, Boehringer Ingelheim

Amanda Scruggs, Boehringer Ingelheim

Robert Seltzer

Bradley Sepp, Emergent BioSolutions

Dipesh Shah, Baxter Healthcare

Scott Shearer, Teikoku Pharma

Shani Sherr, Teva

Mitsuo Shimada, TOA EIYO

Alon Shtainiz, Protalix

Mike Silvola, Regulatory Compliance Associates

Shay Slobodiansky, Taro Pharmaceutical Industries

Prerepa Sreenivasa Rao, Orchid Chemicals & Pharmaceuticals

Amy Stitt, M.S., Bristol-Myers Squibb

Thomas Storz, Ironwood Pharmaceuticals

Kazunari Tanaka, Dainippon Sumitomo Pharma

Shannon Thomas, Genentech

Roger Toll, Marchesini Packaging Machinery

Simon Toth, Dow Corning C

Karl Tradewell, Sharpstream

Genadi Tsatskin, Taro Pharmaceutical Industries

Keren Tzabar, Teva

Jon Underwood, Baxter Pharmaceutical Solutions

Marijke Van Craen, Roche

Olivier Van Houtte, Steris

Külliki Varvas, AS Kevelt

Deena Venezia, Venezia

Matthew Walczak, AMRI

Nicole Waldie, Nipro Glass Americas

Rodney Wallace, Ben Venue Laboratories

Jeffrey Wampole, Penn Tech

David Watkins, Alnylam Pharmaceuticals

Edna Weiss, Teva Animal Health

Alicia Whitney, Kadmon Pharmaceuticals

Dennis Wildes, St Jude Medical

Ralph Willette, TSI

Connie Wong, Onyx Pharmaceuticals

Xiaofeng Wu, Chengdu Kanghong Biotechlogy

Yi Xie, Eli Lilly

Christina Yazgulian, Pacira Pharmaceuticals

Ofer Yifrach, Ludan Engineering

Kevin Zen, Allergan

Preservative Formulation Discussed at Metro Chapter Event continued from page 13

running the test. It should be noted that this test is not fully harmonized and there are differences between different pharmacopoeias. He told the audience that all AETs should be performed in product development and validation of each AET is very important. Chris mentioned that in addition to the AET, the microbial limit test also has to be performed.

He said that additional organisms to those specified in the pharmacopoeia for the AET test might be used for example, *Serratia marscens* or *Streptococcus*. It is important to know that all products for AET are divided into categories and each category has its limits. He concluded his presentation by explaining that despite the short chapter on AET, the test itself requires a lot of planning and consideration. It is important that when outsourcing this test, to ensure that the testing laboratory has all the information about the product being tested, what category it belongs to and that they have enough experience to perform this test.

A few questions were asked at the end of the presentation.

Letica Quinones concluded this dinner/presentation by presenting a small token of appreciation to the speakers.

PDA Who's Who

Hang Guo, Research Scientist, Drug Product Science & Technology, Bristol-Myers Squibb

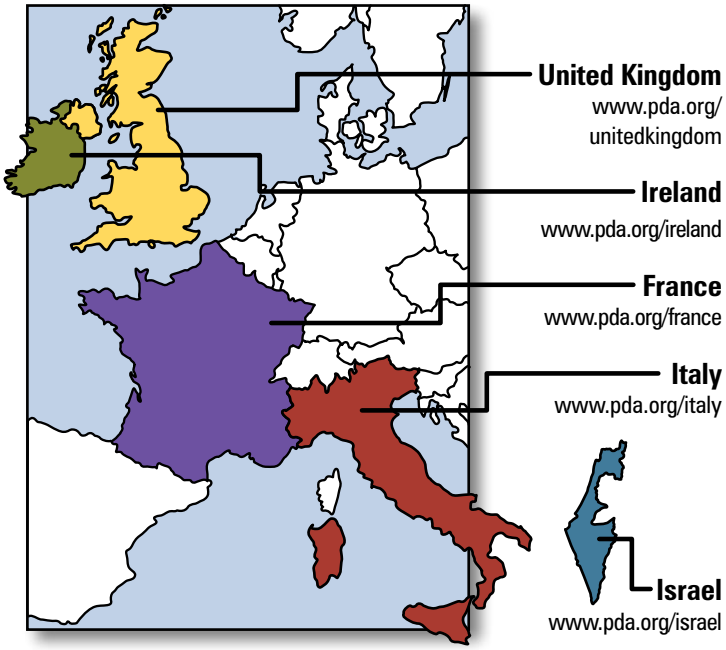
Chris Knutsen, PhD, Associate Director, Microbiology, Analytical & Bioanalytical Development, Bristol-Myers Squibb

Letica Quinones, Associate Director, Analytical & Bioanalytical Development, Bristol-Myers Squibb, and Vendor Liaison Chair for PDA Metro Chapter

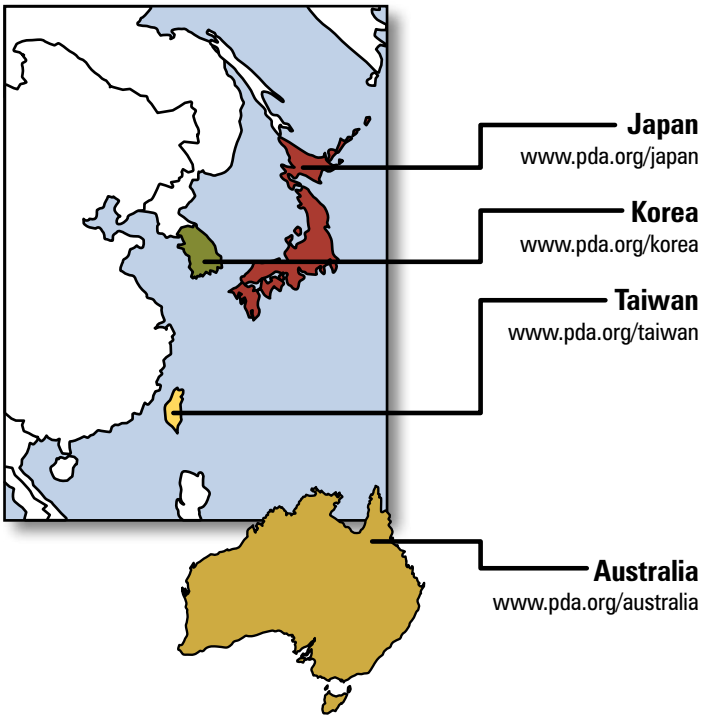
PDA Chapters

The following are PDA's Chapters, organized by the regions of the world in which they are located. For more information on the Chapters, including their leaders and upcoming events, go to their websites which are listed below.

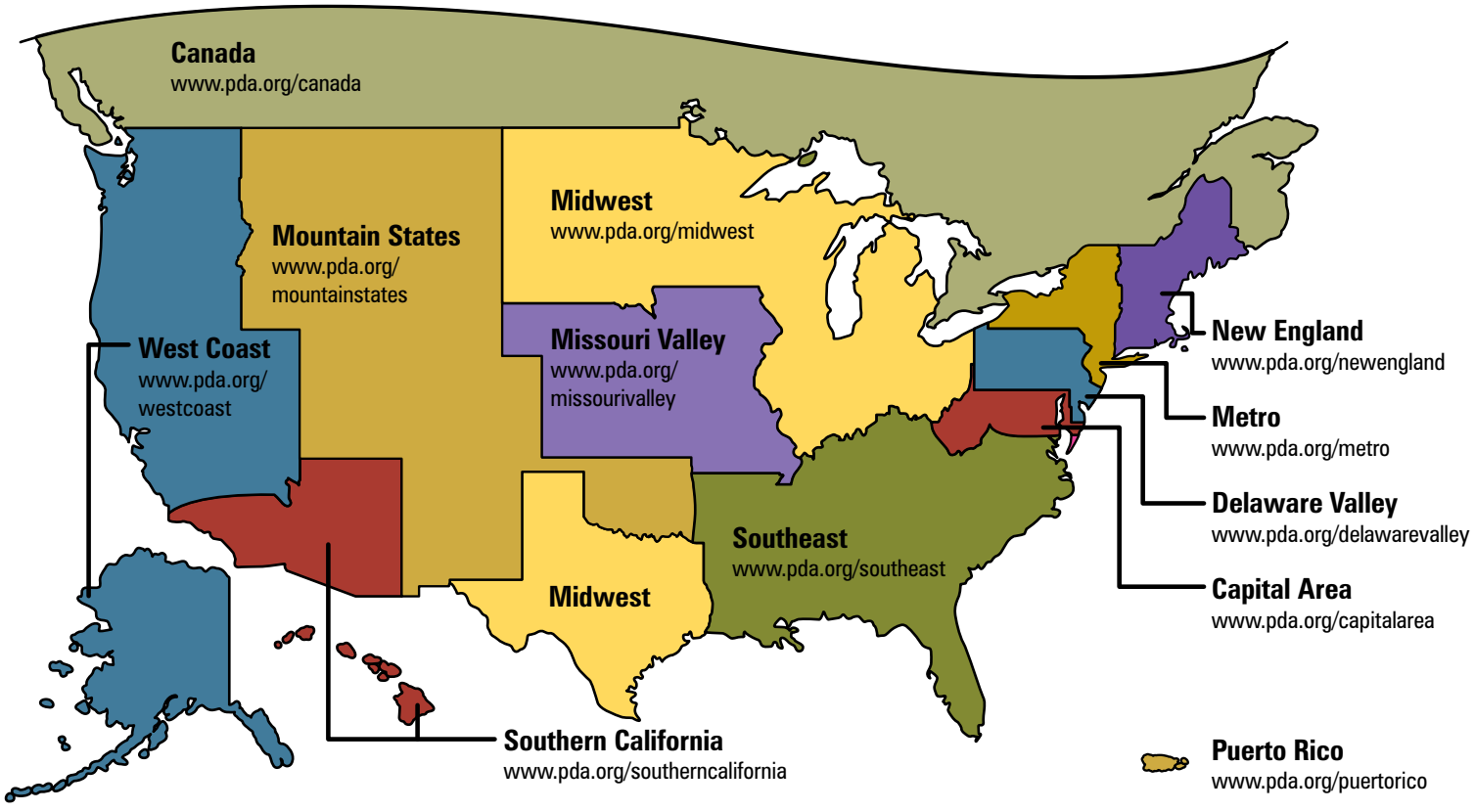
EUROPE



ASIA-PACIFIC



NORTH AMERICA



2012 PDA
Visual Inspection Forum
25-26 September 2012 | Berlin | Germany

Call for Papers and Posters

On behalf of PDA Europe and the Co-Chairs John Shabushnig and Markus Lankers we would like to invite you to submit a paper or poster abstract for presentation at the **2012 PDA Visual Inspection Forum** to be held in Berlin/Germany on **25-26 September 2012.**

Paper abstracts and posters must be essentially non-commercial in nature, describing new developments or work that significantly contributes to the knowledge relating to visual inspection processes as applied to injectables. **Case Studies by end users are particularly desired.**

Topic areas of interest include but are not limited to the following:

- **Qualification of manual inspections and validation of automated inspection systems**
- **Case studies in root cause investigation or process improvements by elimination of particle sources**
- **Case studies in the implementation of a two-step inspection process**
- **Preparation and use of standards and defect test sets**
- **Classification of defects and preparation of defect libraries**
- **Automated container integrity/leak testing**
- **Recent compendial and regulatory activity**
- **Recent component quality and supplier qualification**
- **Special considerations for the inspection of biopharmaceuticals**
- **Challenges of inspecting products in pre-filled syringes (e.g. silicon oil droplets)**
- **Detection and characterization of protein aggregation**
- **New inspection technologies**

All submitted abstracts will be reviewed by the Program Planning Committee for acceptance.
Upon review by the Program Planning Committee, PDA Europe will advise each submitter of the status of the paper for presentation in writing by **15 May 2012.** PDA Europe will provide one complimentary registration per podium presentation. Additional presenters and poster presenters are required to pay appropriate conference registration fees.

Submissions received must include the following information:

- Title
- Presenter
- Presenter's biography (approx. 100 words)
- Additional authors
- Full mailing address
- Phone number
- Fax number
- E-mail address of the presenter
- Key objectives of your topic
- 2-3 paragraph abstract, summarizing your topic

Please send your abstract and the required information to Bernd Krippner (PDA Europe) at krippner@pda.org. If you have any questions, please do not hesitate to contact us.

Attention Exhibitors
PDA is seeking vendors who provide excellent products or services in support of the conference. Space is limited and is allocated on a first-come, first-serve basis. To reserve your space, please contact Creixell Espilla-Gilart at espilla@pda.org or via telephone +49 (0) 33056 23 77 14.

Deadlines **Abstracts of papers for presentation: 13 April 2012**
Poster abstracts: 20 August 2012

CONFERENCE 25-26 Sep | **EXHIBITION** 25-26 Sep | **TRAINING COURSE** 27-28 Sep

PDA Interest Groups & Leaders

PDA Interest Groups are divided into five sections by subject matter. Any PDA member can join one or more Interest Group by updating their member profile (www.pda.org/volunteer). Please go to www.pda.org/interestgroups for more information.

BioAB

Biotechnology
U.S. Vince Anicetti, *PDA*
Anicetti@pda.org

Combination Products
Vacant

Lyophilization
U.S. Edward Trappler, *Lyophilization Technology*
etrappler@lyo-t.com

Pharmaceutical Cold Chain
U.S. Rafik Bishara, PhD
rafikbishara2@yahoo.com

EU Erik van Asselt, *Merck, Sharp & Dohme*
erik_van_asselt@merck.com

Vaccines
U.S. Frank Kohn, PhD, *FSK Associates, Inc.*
fsk@iowatelecom.net

RAQAB

Clinical Trial Materials
U.S. Vince Mathews
Independent QA Consultant
vinnykay@comcast.net

GMP Links to Pharmacovigilance
U.S. John Ayres, MD
Eli Lilly and Company
ayresjo@lilly.com

Inspection Trends
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Management on Outsourced Operations
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susan.schniepp@osobio.com

U.S. Karen Ginsbury, *PCI Pharmaceutical Consulting Israel*
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Quality Risk Management Interest Group
U.S. Michael Long, PhD, *Concordia ValSource*
mlong@valsource.com

U.S. Jeffrey Hartman, *Merck*
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Quality Systems
U.S. Anders Vinther, PhD, *Genentech*
vinther.anders@gene.com

EU Lothar Hartmann, PhD, *Crucell*
lothar.hartmann@jentges.com

Regulatory Affairs
U.S. Amy Giertych, *Baxter Healthcare Corporation*
amy_giertych@baxter.com

Supply Chain Management
U.S. Lucy Cabral, *Genentech*
Cabral.lucy@gene.com

SAB

Blow/Fill/Seal
U.S. Chuck Reed, *Weiler Engineering, Inc.*
creed@weilerengineering.com

Facilities & Engineering
U.S. Christopher Smalley, PhD, *Merck & Co., Inc.*
christopher.smalley@merck.com

Filtration
U.S. Russ Madsen, *The Williamsburg Group, LLC*
madsen@thewilliamsburggroup.com

Microbiology/Environmental Monitoring
U.S. Jeanne Moldenhauer, PhD, *Excellent Pharma Consulting*
jeannemoldenhauer@gmail.com

Packaging Science
U.S. Edward Smith, PhD, *Packaging Science Resources*
esmithpkg@msn.com

Pharmaceutical Water Systems
U.S. Phil DeSantis, *DeSantis Consulting Associates*
Phil.desantis@optonline.net

Pre-filled Syringe
U.S. Thomas Schoenknecht, PhD, *Schott AG*
Thomas.schoenknecht@schott.com

Process Validation
U.S. Scott Bozzone, PhD, *Pfizer, Inc.*
Scott.Bozzone@pfizer.com

Sterile Processing/Parenteral Drug Manufacturing
U.S. Ken Muhvich, PhD, *Micro-Reliance, LLC*
kmuhvich@comporium.net

U.S. Edward Tidswell, PhD, *Baxter Healthcare*
edward_tidswell@baxter.com

Technology Transfer
EU Mirko Gabriele, *Patheon*
mirko.gabriele@patheon.com

Visual Inspection
U.S. John Shabushnig, PhD, *Pfizer Inc.*
john.g.shabushnig@pfizer.com

2012 PDA Europe Conference on
Pharmaceutical Cold Chain Management & Good Distribution Practice

9-12 October 2012 | Berlin | Germany

Call for Papers and Posters

We would like to invite you to submit a paper or poster abstract for a presentation at the **2012 PDA Europe Conference on Pharmaceutical Cold Chain Management & Good Distribution Practice – Preserving Product Quality and Supply Chain Integrity** in Berlin/Germany on 9-10 October 2012.
Paper abstracts and posters must be non-commercial in nature, describing new developments or work that significantly contributes to the body of knowledge relating to Cold Chain Management of Pharmaceuticals.

Topic areas of interest include but are not limited to the following:

1. Thermal Protection
- Shipments with product storage statement of < -15°C, 2-8°C, and/or 15-25°C
- Use of phase change materials
- Guidance on qualification of active/ passive systems
- New technologies for protective packaging
- Temperature-controlled containers and warehouses
- Thermal blankets
- "Green" solutions
- Product protection for room temperature pharmaceuticals
- Aspects of temperature-controlled qualification and validation

2. Supply Chain Integrity
- Challenges in BRIC and Middle East countries
- Security measures in transport and its impact on temperature sensitive products
- Handling practices at airport warehouses and of ground handlers
- Stability budget and TOR
- Clinical trial cold chain shipments
- Qualification of shipping lanes
- Shock and vibrations during transport
- Technology developments in RFID/WIFI for temperature monitoring
- Last mile temperature indicators/data loggers
- Risk mitigation and continuous improvement/lean six sigma projects
- Wholesaler and pharmacist cold chain practices
- Distribution networks
- Benefit-risk analysis
- Distribution and traceability within companies
- Risk-based distribution
- Supply chain best practices
- Quality Agreements and Service Level Agreements

3. Global Compliance
- New global GDP regulation
- Shipment documentation (track & trace, record keeping, temperature data etc.)
- Trade compliance
- Temperature profiles for pharmaceutical products
- Generating stability data for transportation
- Specification and limit setting
- Experience with new regulation in relation to filing and implementation
- Regulatory perspective
- Temperature alarm management
- CAPA management
- Audit inspection observations
- Change control

All submitted abstracts will be reviewed by the Program Planning Committee for acceptance.
Upon review by the Program Planning Committee, PDA Europe will advise each submitter of the status of the paper for presentation in writing.

Submissions received must include the following information:

- Title
- Presenter
- Presenter's biography (approx. 100 words)
- Additional authors
- Full mailing address
- Phone number
- Fax number
- E-mail address of the presenter
- Key objectives of your topic
- 2-3 paragraph abstract, summarizing your topic

Please send your abstract and the required information to Bernd Krippner (PDA Europe) at krippner@pda.org. If you have any questions, please do not hesitate to contact us.

Deadlines **Abstracts of papers for presentation: 13 April 2012**
Poster abstracts: 28 September 2012

snapshot

Task Force *Corner*

"Best Practices" Technical Report Nearing Publication

The Application of Phase-Appropriate cGMP and Quality Systems to the Development of Protein Bulk Drug Substances Task Force is ready to publish its "best practices" technical report. The Task Force has been working for two years with regulators and reviewers to ensure that the document meets the needs and concerns of industry.

Task Force Leader **Amnon Eylath**, Director, Quality, Ariad Pharmaceuticals, spoke to the *PDA Letter* about his group's timely, but complex project.

PDA Letter: What does the technical report cover?

Eylath: The technical report identifies the recommended minimum requirements and best practices for appropriate quality systems and application of GMP especially in the early phases (Microdosing Study, Phase 1, Phase 2a) of API development, from process development (where Good Research Practice are relevant) through Toxicity Testing (where GLP applies) to clinical manufacturing (where GMP applies).

PDA Letter: What are some of the main challenges of the technical report?

Eylath: There is no alignment as of yet across biopharma companies and academic institutions as to what specific controls, monitoring and approvals must be in place for the production of early phase protein API, so the default approach in industry is to apply the same practices as in the later phases of development (Phase 2b, Phase 3). This may include practices that are impractical for the kind of simple or smaller-scale equipment used in the early phase manufacturing of API, leading to unnecessary deviations or implementation of complex control systems. In a similar fashion, process changes are inherent to the process development still going on during early phase clinical trials. Not understanding this can also lead to efforts that add no value and unnecessary deviations.

PDA Letter: How does the new technical report help the industry and regulators?

Eylath: The more the manufacturer can apply their resources and efforts to the critical-to-quality attributes and controls of the early phase process, the more likely they will be able to, in fact, ensure the quality and safety of the API going into the drug product. For the academic-setting manufacturer and the new start-up company, our goal was to ensure that they had the correct information in order to understand what must be in place for each stage of development. Especially for those who may "not know what they don't know." This specific aspect of the report was requested to be expanded on by the regulatory agency representatives on the task force, based on their experiences in the field.

PDA Letter: What is the most interesting part of the project for you?

Eylath: Initially, what struck me was the fact that across small and large biopharma and the consultants that were members of the task force, there already was close alignment on what the best practices should be. Aligning the technical report to meet the needs and concerns of the European biopharma and regulatory agencies was also very interesting, and we benefited from very valuable high-level input from our European counterparts. There was special value in getting the European perspective on TSE-risk mitigation and on viral safety expectations.

PDA Letter: What is the value of getting regulator input?

Eylath: The U.S. FDA representatives (overall, four for the duration of the task force) were of tremendous value to the team. Their direct input on GMPs for early phase manufacturing and the relation between CMC and GMP and their expectations for cell culture development, controls and safety were invaluable and ensured the drafting of a quality document. We especially appreciate **Rick Friedman**'s (Associate Director, Risk Science Intelligence and Prioritization, CDER, FDA) continuous support by making FDA subject-matter experts available to us since the beginning of the project.

PDA Letter: What stage is the technical report at?

Eylath: The technical report has been approved by the Biotechnology Advisory Board and by the Regulatory Affairs and Quality Assurance Advisory Board, and we have responded to and incorporated their comments. Now we are waiting to hear back for final approval by PDA Board of Directors regarding publication of the technical report.

PDA Letter: Has anyone stood out in their contributions to the task force?

Eylath: All task force members made substantial contributions to the report. However, I would like to thank PDA's **James Lyda** (Sr. Scientific Advisor, Scientific & Regulatory Affairs) and **Rich Levy** (Sr. VP, Scientific & Regulatory Affairs) for their great support. Especially during the last two years, PDA's involvement has helped get us input from European regulators, as well as facilitate the document approval process. Special appreciation must also go to **Iris Rice** (Manager, Scientific & Regulatory Affairs) for her continuous logistical

continued at top of page 22

Journal *Preview*

Dialogue Over Article on B. Cepacia

The March/April issue of the *PDA Journal of Science and Technology* includes dialogue between microbiologist and PDA member **Scott Sutton,** PhD, and a team of authors from FDA. In a letter to the editor, Sutton takes issue with three assertions in "Burkholderia cepacia: This Decision Is Overdue" (65/5/535) by the FDA authors. The authors were able to put together a reply to Sutton's letter, which also appears. In addition, **Govind Rao** writes an editorial about the biosimilars draft guides that the U.S. FDA released in February.

Editorial

Govind Rao, "Changes Are Coming and PDA Will Be There To Help"

Letter

Scott Sutton, "Letter to the Editor"

Richard Friedman, et al., "Response to the Letter to the Editor"

Research

Dheeraj T. Baviskar, et al., "Design and Evaluation of Patches for Transdermal Delivery of Losartan Potassium"

Vikram Chopra, et al., "A Case Study: Application of Statistical Process Control Tool for Determining Process Capability and Sigma Level"

Surendra G. Gattani, et al., "Formulation and Evaluation of Bilayer Tablets of Metoclopramide Hydrochloride and Diclofenac Sodium"

Emanuel Guadagnino, Daniele Zuccato, "Delamination Propensity of Pharmaceutical Glass Containers by Accelerated Testing with Different Extraction Media"

Yuh-Fun Maa, et al., "Syringe Siliconization Process Investigation and Optimization Chain Distribution"

Technology/ Application

Martha Folmsbee, Michael Moussourakis, "Sterilizing Filtration of Liposome and Related Lipid-Containing Solutions: Enhancing Successful Filter Qualification"

Commentary

Dennis Jenke, "A General Strategy for the Chemical Aspects of the Safety Assessment of Extractables and Leachables in Pharmaceutical Drug Products: The Chemical Assessment Triad"

Review

A. Yekta Özer, Mine Silindir, "The Effect of Radiation on a Variety of Pharmaceuticals and Materials Containing Polymers"

Journal *POV*

Changes Are Coming and PDA Will Be There To Help

Govind Rao, UMBC and Journal Editor

[Editor's Note: The following is from the March/April issue of the *PDA Journal of Science and Technology*.**]**

The U.S. FDA has released three draft guidances on biosimilars.

The following is excerpted from a February 9 FDA news release that can be found at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm291232.htm.

- *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product:* The draft guidance is intended to assist companies in demonstrating that a proposed therapeutic protein product is biosimilar to a reference product for the purpose of submitting an application, called a "351(k)" application, to the FDA. This draft guidance describes a risk-based "totality-of-the-evidence" approach that the FDA intends to use to evaluate the data and information submitted in support of a determination of biosimilarity of the proposed product to the reference product. As outlined in the draft guidance, FDA recommends a stepwise approach in the development of biosimilar products.

continued at bottom of page 22

Technology *Trend*

First Commercially Licensed Single Use Facility Built

Emily Hugh, PDA

In late February, Shire announced that it had completed the first commercially licensed single-use facility in Lexington, Mass.

This facility will utilize single-use bioreactor and disposable technology throughout cell culture processing. Cell culture processing is done the same as in traditional manufacturing facilities, but different machines lead to less contamination risk, etc.

The LEED-certified facility took three years to construct. Costing over $200 million in manufacturing infrastructure and technology, according to Shire's press release on February 22, this single-use plant uses approximately 80% less water and 50% less energy than its conventional manufacturing plant counterpart. Shire's total bioreactor capacity has also increased from 1000 to 8000L.

"Shire has invested strategically in new manufacturing facilities and state-of-the-art technology because we recognize the critical importance of ensuring the continuity of treatment for patients with rare and life-threatening diseases," said **Bill Ciambrone**, Senior Vice President, Technical Operations,

continued on page 23

Task Force Corner continued from page 20

and administrative support since day one of the project.

About the Expert

Amnon Eylath, Director of Quality, Ariad, is responsible for global oversight of API, pharmaceutical alliances, and GxP compliance. Amnon has over 20 years of experience in medical research, process & assay development, facility/process design validation, QA audits, development and deployment of quality systems, as well as disposition of clinical materials for US and global use. Amnon also originated Amgen's Isolator Technology Group, and Filling and Packaging Engineering Projects team.

Members of the Task Force

Vince L. Mathews, Pharmaceutical Consultant (Co-Chair)

Kurt A. Brorson, PhD, United States Food and Drug Administration

Robert Darius, GlaxoSmithKline Biologicals

Volker Eck, PhD, Eck Pharmaceutical Consulting

Teresa M. Feeser, PhD, Bristol Myers Squibb

Andrew W. Gunn, III, Becton Dickinson

Patricia F. Hughes, PhD, United States Food and Drug Administration

Renita Johnson-Leva, Advanced BioScience Laboratories

Matt Karpen, Amgen

Bryan Silvey, Baxter Healthcare Corporation

Kirsten L. Vadheim, PhD, BioCompliance Consulting

Journal POV continued from page 21

- *Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product:* The draft guidance provides an overview of analytical factors to consider when assessing biosimilarity between a proposed therapeutic protein product and a reference product for the purpose of submitting a 351(k) application. This includes the importance of extensive analytical, physico-chemical and biological characterization in demonstrating that the proposed biosimilar product is highly similar to the reference product notwithstanding minor differences in clinically inactive components.
- *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009:* The draft guidance provides answers to common questions from people interested in developing biosimilar products. The question and answer format addresses questions that may arise in the early stages of product development, such as how to request meetings with the FDA, addressing differences in formulation from the reference product, how to request exclusivity, and other topics.
- FDA will seek public comment on the guidance documents and instructions on how to submit comments will be announced in an upcoming Federal Register notice. In finalizing the guidance documents, the agency will consider the information received from the public.

These long-awaited documents will undoubtedly clarify many issues for our community. But, as in any science-driven enterprise, many questions will be raised. This is a time for those interested to use this opportunity for public comment.

[Editor's Note: PDA is planning to comment on the draft guides, for more information contact **Iris Rice** at rice@pda.org**.]**

As always, our Journal will strive to be at the forefront of these issues and use our unique regulatory-sciences platform to advance the state-of-the-art for the benefit of the community at large. In this regard, we are pleased to announce a new category of publication—the Technology Brief. These brief reports are intended to provide publishing opportunities for our many poster presenters who do not have the time to write full papers for publication, but who nevertheless have novel and interesting results to report. More details will be forthcoming in a call for papers together with a revised list of categories in the manuscript submission instructions—we hope that this new publication category will result in more submissions.

As always, your feedback is welcome!

Tech Trends continued from page 21

Shire's first commercially licensed single-use facility in Lexington, Mass.

Shire HGT in the press release.

According to **Courtney Fraser**, Corporate Communications Manager, HGT, contamination control and containment were primary considerations for employing single-use technology since the individual sterile bags that are used reduce the potential for batch-to-batch contamination.

The European Medicines Agency has already approved the facility for production of a drug substance that treats type 1 Gaucher disease. Ciambrone said, "The EMA approval of [the drug substance] in this manufacturing plant, only three years after breaking ground, is a testament to the hard work and dedication of Shire employees and represents crucial additional capacity for manufacturing our enzyme replacement therapies for Gaucher and Fabry patients." The U.S. FDA is expected to make a decision on the facility during the first half of this year.

Since single-use technology can lead to significantly shortened construction time, product will get to the marketplace faster, according to Fraser.

The PDA Taskforce for Single-Use Systems is completing a technical report on the implementation of single-use systems. Sterilization, supplier qualification, and extractables and leachables of single-use systems are a crucial concern in implementation, and the task force has devoted an entire section of the report to quality and regulatory topics.

PDA Web Seminars – Interactive Online Learning

PDA Web Seminars allow you to affordably hear from today's top presenters in the bio/pharmaceutical industry with no traveling!

Recordings from PDA's 2011 conferences are now available for purchase. The events include:

PDA 2011 Analytical Methods Development and Validation Workshop
www.pda.org/analyticalmethodsaudio
Individual sessions are available for purchase for $75/each. Sessions include:

- Qualifications and Compendial Methods Verifications
- Method Development – Applying Principles of QbD for Analytical Methods
- The Methods Life Cycle – The Overview
- Complete Life Cycle Case Study and Ask the Experts Panel Discussion
- Post-Qualification and Post-Validation Activities
- Method Validation: Validation Strategies and Acceptance Criteria
- Reference Standards and Method Transfers

PDA 2011 Combination Products Workshop
www.pda.org/comboproductsrecordings
Individual sessions are available for purchase for $75/each. Sessions include:

- Introduction to Combination Product cGMPs
- Design Input
- Design Verification and Validation
- Clinical Trial Considerations for Combination Products
- Human Factors for Combination Products
- Post Market Consideration
- Panel Discussion

Pharmaceutical Quality System (ICH Q10) Conference
www.pda.org/Q10audio
Recordings from the entire conference are available for purchase for $395 for members and $495 for nonmembers. Purchase includes:

- Recordings from all eleven sessions from the conference
- PDF handouts of every presentation
- Unlimited access to all session recordings for 60 days

For more information on PDA Web Seminars please visit
www.pda.org/webseminars

Rx Distribution Licenses: A Matter of State

Manufacturers must contend with a patchwork of wholesale distribution licenses in the United States

Joanne S. Hawana, JD, Arent Fox

Far from the laboratories and manufacturing facilities where fill volume, particulate matter and the stability of excipients are common topics of discussion, legal and regulatory departments of pharmaceutical companies contend with a much more arcane issue—what state licenses does the company need to distribute its products at wholesale? While the unindoctrinated would expect there to be a simple answer to this question, determining a drug manufacturer's state licensing obligations is not always straightforward, because states do not have uniform requirements. Thus, the question leads to further inquiries about an individual state's definition of terms such as manufacturer and wholesale distribution, whether the state recognizes any sort of licensing exemption for manufacturers and whether the state uses a "special" license for manufacturers or requires them to obtain a standard wholesale distributor license.

Article at a Glance

- The 50 U.S. states have enacted stronger licensing requirements in an attempt to weed out illegitimate "bad" actors in the distribution chain
- Manufacturers must ascertain whether a state requires manufacturers to be licensed, and if so, which kind of license
- Most states simply license manufacturers as wholesale distributors, but they may exempt such a manufacturer from certain regulatory obligations

Background

First, it is worth discussing the history of wholesale distributor licensing. In 1988, Congress enacted the Prescription Drug Marking Act or the PDMA. The PDMA was intended to increase safeguards in the drug distribution system and prevent the introduction and retail sale of counterfeit, adulterated, misbranded, subpotent or expired drugs. The legislation included a ban on the reimportation of prescription drugs manufactured in the United States, a prohibition on the distribution of drug samples by anyone other than the manufacturer or its authorized distributor and a requirement for distributors to give a purchasing distributor a statement that identifies each prior sale of the drugs (what is today referred to as a "drug pedigree"). Importantly for this discussion, the PDMA also provided that no person may engage in wholesale distribution of prescription drugs in interstate commerce without being licensed by a state, in accordance with guidelines established by the U.S. FDA.

FDA's guidelines on wholesale distributor licensing were codified in the *Code of Federal Regulations* at 21 C.F.R. Part 205. The Federal guidelines represent

the *floor* upon which states have implemented their licensing schemes over the past two decades—that is, many states have gone far beyond the minimum requirements set out by FDA. Those minimum requirements address topics such as the required information for licensure, distributor qualifications, personnel qualifications, storage and handling of prescription drugs and the maintenance of records. Some states have added more onerous requirements for distributors, with the most significant being the need to secure a large surety bond (*e.g.*, $100,000) and to have a so-called designated representative on-site during normal business hours to oversee the operations. The designated representative must have certain qualifications, training and in some cases a current license from the state regulatory authority to serve in that capacity.

But what is wholesale distribution in the first place? The PDMA and FDA's guidelines define "wholesale distribution" as the distribution of prescription drugs to a person other than the consumer or patient, but excludes intracompany sales and lists very narrow exemptions. Those exemptions include such things as the sale, purchase or trade of a prescription drug by a charitable organization to a nonprofit affiliate or the sale, purchase or trade for emergency medical reasons (which also are narrowly defined). The lawful distribution of drug samples by a manufacturer is not deemed to be wholesale distribution and neither is dispensing a prescription drug pursuant to a valid prescription, for example, in a pharmacy or hospital setting. Further, the Federal definition of "wholesale distributor" covers anyone engaged in the wholesale distribution of prescription drugs, including (among others) manufacturers, repackagers, private-label distributors, warehouses, including manufacturers' and distributors' warehouses and retail pharmacies that conduct wholesale distribution. Accordingly, a manufacturer that is selling or delivering prescription drugs—in other words, distributing those drugs—to wholesale distributors, pharmacies, hospitals or health care practitioners is by definition a wholesale distributor as well.

The potential complexity of the supply chain has directly increased the complexity of the determination of what state licenses may require

States have responded to the PDMA's licensing mandate by designating, in most cases, the Board of Pharmacy to oversee wholesale distribution into and within their borders ***(1)***. Over the past several years, in response to a perceived crisis in counterfeit drug products getting to consumers, states have enacted stronger licensing requirements in an attempt to weed out illegitimate "bad" actors. In addition to the surety bonds and designated representative requirements mentioned before, the stronger protections may include far-reaching background checks on executives or certain employees (which may require fingerprinting) and enhanced criminal penalties for knowingly introducing counterfeit product. An industry-backed voluntary accreditation program called Verified-Accredited Wholesale Distributors or VAWD also has become mandatory as a condition of licensure in at least three states ***(2).***

Application to Manufacturers

At the Federal level, a manufacturer is anyone who manufactures, prepares, propagates, compounds, processes, packages, repackages or labels a prescription drug. At the state level, however, what constitutes a "manufacturer" for purposes of a particular state's wholesale distributor licensing laws may be much broader than that. For example, Florida and Oregon consider a company that is the holder of an FDA-approved drug marketing application (NDA, ANDA, BLA or NADA) to be a manufacturer for licensing purposes. In some cases, it may be unclear whether the state licensing law applies to a particular entity, such as a contract manufacturer that never legally owns the drugs but ships them on behalf of the NDA-holder. When the laws were written in the "old days" of the 1990's and 2000's, the supply chain was relatively simple and manufacturers and distributors had more clearly delineated roles. Today, a supply chain for a single drug could involve many different parties:

- An NDA-holder who owns the drugs but doesn't manufacture or ship them
- A contract manufacturer and/or a contract labeler that holds the drugs but doesn't own them
- A co-licensee of the manufacturer that has its name on the label but doesn't directly engage in the manufacturing or shipping process (often just the marketing side of the business)
- A third-party logistics provider that serves as a warehouse and shipper for the owner of the drugs

The potential complexity of the supply chain has directly increased the complexity of the determination of what state licenses may require. Because the laws do not directly speak to these complex manufacturing and distribution arrangements, ensuring compliance has become an even more important task for legal and regulatory professionals in the pharmaceutical industry.

States have taken different approaches to licensing manufacturers that are engaged in wholesale distribution. In a few cases, only in-state facilities must be licensed, but those are by far the exception. The majority of states impose a license (or registration) requirement on manufacturers that either ship prescription drugs directly into the state or sell their drugs in the state. Consequently, in some cases the relevant facts involve who has physical possession of the drugs when they enter the state or are delivered to a customer within the state, while in other cases the relevant facts are who has legal title to the drugs at that point.

Once it has been determined that a particular state requires the manufacturer to be licensed, the next step is to figure out which type of license to get. Most states

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simply license manufacturers as wholesale distributors, but they may exempt such a manufacturer from certain regulatory obligations—the most significant exemptions are when the state does not require a manufacturer distributing its own products at wholesale to secure a surety bond or have a designated representative. Other states have their own "manufacturer-specific" license. For example, Florida's Non-Resident Prescription Drug Manufacturer Permit allows a manufacturer to distribute its own drugs at wholesale, but if the manufacturer plans to distribute third-party products, it would also need to obtain a wholesale distributor permit.

There often are other wrinkles to wrestle with as well. One interesting example is that certain states will not issue wholesale licenses to foreign companies, such as an FDA-registered prescription drug manufacturing facility that wants to ship finished products to its customers in the United States. Making those shipments without a valid license from the local regulatory authority (if required) could subject the foreign company to enforcement action for non-compliance. If the state follows the Federal definition of "wholesale distribution" and excludes intracompany sales or transfers from the activity, the company may have the option to ship to a United States affiliate or subsidiary, because that type of non-wholesale shipment would not subject the company to licensure. But, such a workaround may not be a possibility for everyone, and it seems likely that foreign companies are shipping to the United States without necessarily being in compliance with state law—although of course, other states do issue wholesale licenses to foreign companies so affected companies may be focusing their exportation to those states.

While space constraints do not allow for many examples, suffice it to say that states actually have enforced their licensing laws against manufacturers in recent years. Generally, they discover non-licensed entities from reviewing invoices and shipping documents during on-site inspections of resident wholesale distributor operations (the states do not inspect non-resident facilities, leaving those to their own jurisdictions). As a consequence, the question of what state licenses are needed to distribute your drug products at a wholesale level is not an academic one and failure to build compliance into your operations could cause a disruption to your supply chain, your business relationships and the goodwill of customers who rely on those medications.

[Editor's Note: More information on state laws and regulations can be found at the websites of the individual U.S. states.

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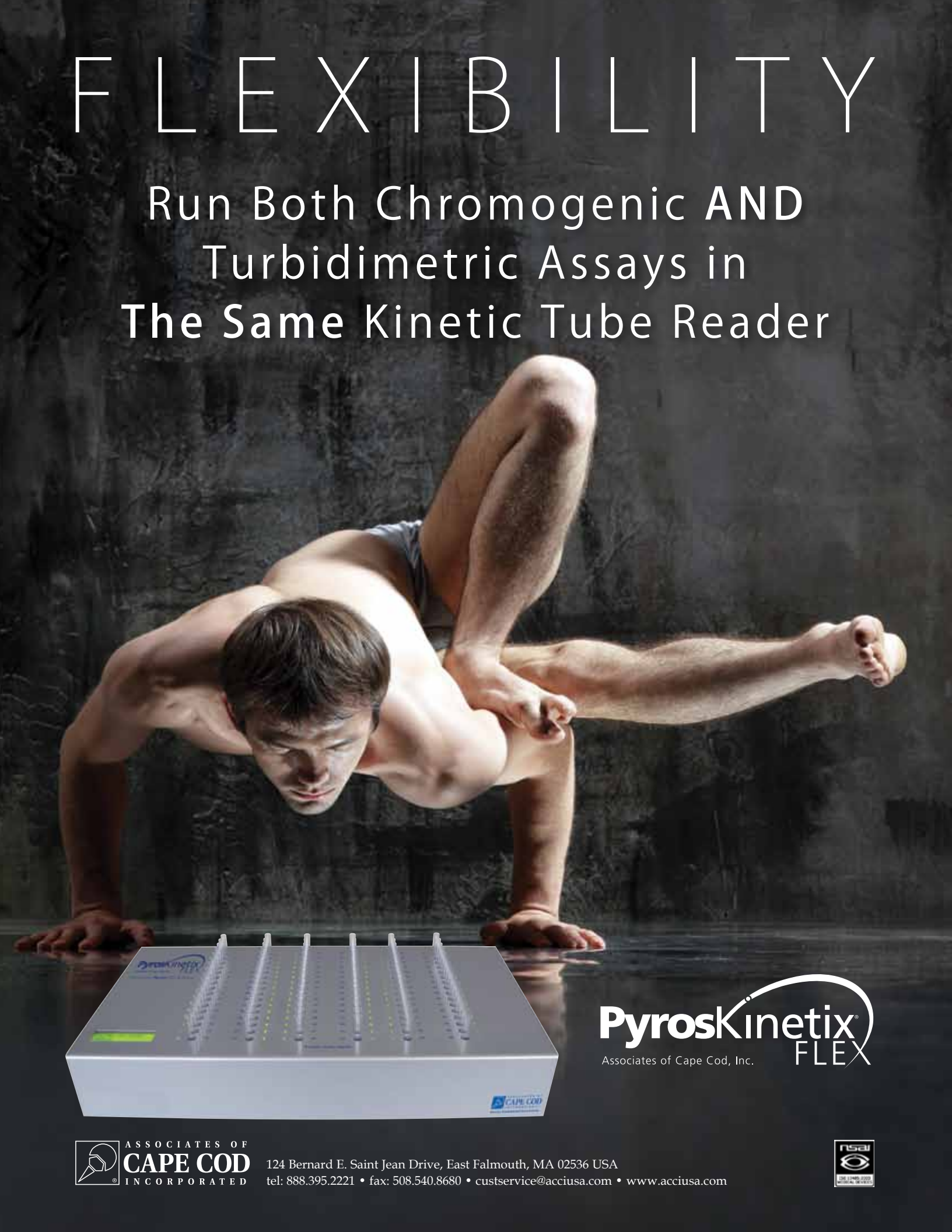

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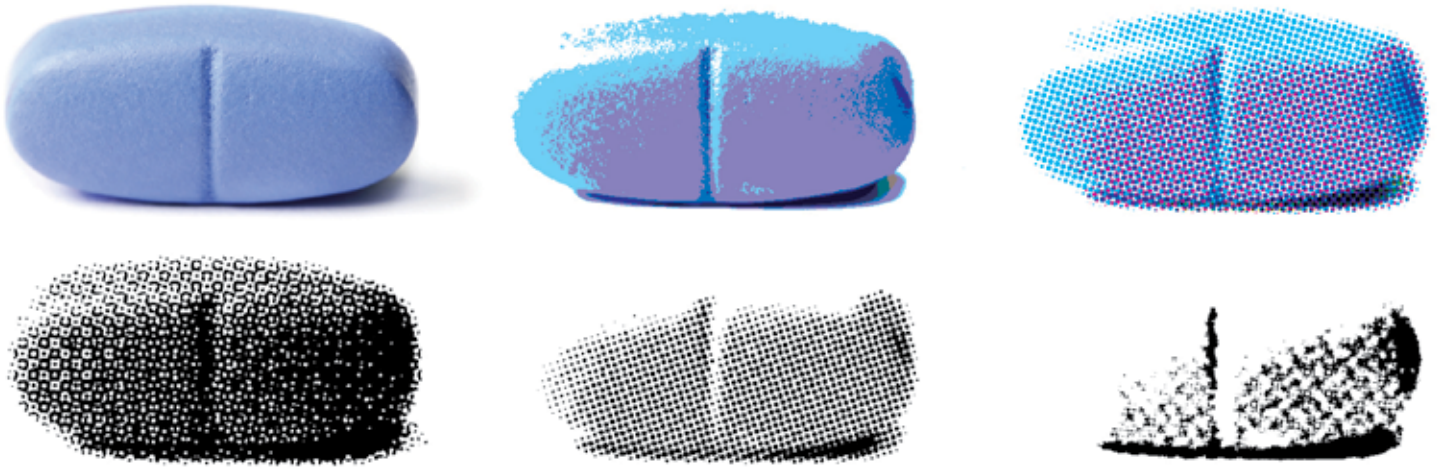
EU Directive to Thwart Noncompliant APIs

Barbara Jentges, PhACT and Karen Ginsbury, PCI Pharmaceutical Consulting



Medicinal products which are falsified in relation to their identity, history or source pose serious risks to public health. In reaction to an alarming increase of falsified medicines and in order to prevent falsified medicines entering the legal supply chain of medicinal products, the EU Falsified Medicines Directive 2001/62/EC ***(1)*** was released in 2011.

Falsified medicines usually contain "substandard or falsified ingredients, or no ingredients or ingredients, including active substances, in the wrong dosage" ***(1).***

In order to prevent non-GMP-compliant APIs from being processed in medicinal products, a number of measures have been taken. **[Author's Note:** API and drug substance are used in this article as synonyms**.]** The EU Falsified Medicines Directive 2011/62/EU has introduced additional requirements applicable to the manufacturer of the medicinal product with respect to verify GMP-compliance of drug substances, e.g., the need to additionally verify the compliance with good distribution practices for active substances, check that "manufacturers, importers or distributors (…) are registered with the competent authority of the member state which they are established," and ascertain the "authenticity and quality of the active substances and the excipients" ***(1).***

Additionally, EU member states are required to "take appropriate measures to ensure that manufacture, import and distribution on their territory of active substances including active substances that are intended for export comply with good manufacturing practice and good distribution practice for active substances" ***(1).***

The Falsified Medicines Directive obliges the EU Commission to adopt GMP for active substances through the *Delegated Act on the Principles and Guidelines of Good Manufacturing Practice for Active Substances in Medicinal Products for Human Use* ***(3).*** Once finalized and released, the delegated act* will strengthen the legal force applicable to both the drug product manufacturer and the EU member states to respectively verify and ensure that GMP compliance for drug-substances are implemented. As outlined in the concept paper, this is planned to be realized by amending the scope of the current GMP Directive for medicinal products to GMP for active substances.

With the recently published concept paper for the delegated act ***(3),*** the Commission has initiated the discussion on how to initiate GMP for APIs. While the GMP guidelines for APIs themselves (Eudralex Volume 4, Part II (ICH Q7) ***(5)*** will remain the same that the industry is already familiar with, the concept paper ***(3)*** proposes to elevate the legal status of "GMP for APIs" by amending and extending the scope of the existing EU GMP-Directive 2003/94/EC

Article at a Glance

- It is proposed that EU GMP-Directive 2003/94/EC and Directive 2001/83/EC will be amended and extended to cover active substances
- The status of GMP for APIs will be elevated from "guidelines only" (as adopted by Dir 2001/83/EC) to "legally enforced" by the *Delegated Act On The Principles And Guidelines Of Good Manufacturing Practice For Active Substances In Medicinal Products For Human Use*
- No legal difference will made between the requirements to comply with either GMP for medicinal products or GMP for APIs in the future

PDA will comment on the concept paper and will suggest a separate and distinct GMP directive for active substances with a unambiguous reference to the already existing GMP guidelines for APIs

(6), which is currently applicable for medicinal products and investigational medicinal products. As a consequence, no legal difference will made between the requirements to comply with either GMP for medicinal products or GMP for APIs in the future.

However, while a medicinal product manufacturer (and holder of a manufacturing authorization) is being inspected by the regional authorities, the GMP compliance of drug substance manufacture needs to be verified by the qualified person (QP) of the manufacturing authorization holder of the drug product. Apart from a number of exemptions where API manufacturers are inspected by authorities (e.g., suspicion of non-compliance with GMP and based on a risk-analysis), GMP-compliance needs to be verified via audits conducted at the manufacturing and distribution sites of the manufacturers and distributors of active substances either directly by the drug product manufacturer or via a third-party. A respective "QP declaration" needs to be provided when applying for a marketing authorization within EU/EEA. Thus, the planned directive will put more (legal) pressure on the QP of the manufacturing authorization holder of the drug product as they will take on the duties associated with verifying GMP compliance for APIs.

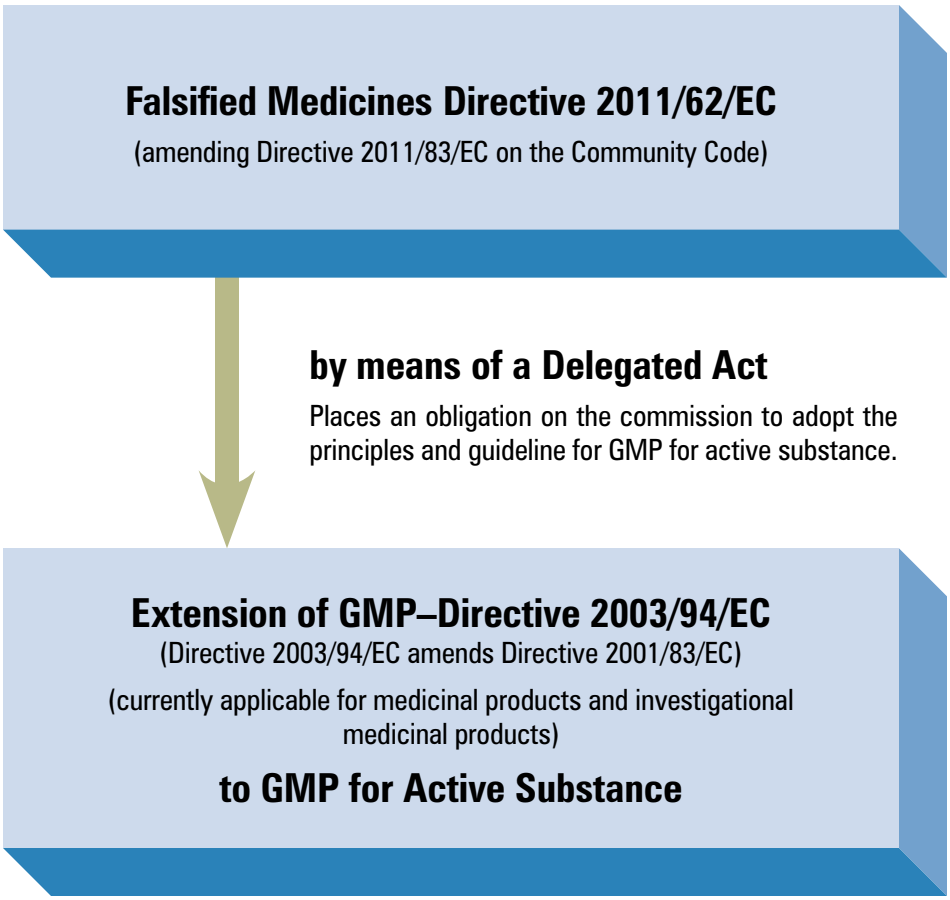
PDA will comment on the concept paper and will suggest a separate and distinct GMP directive for active substances with a unambiguous reference to the already existing GMP guidelines for APIs. If, however, the Commission chooses to go the route of extending the Directive 2003/94/EC, then PDA suggests that the scope section needs to clarify that there will be two parts (Part I for GMP for medicinal products and Part II for GMP for APIs) in accordance with the requirements set out in Eudralex Volume 4. These two distinct parts in Directive 2004/93/EC would allow the requirements for medicinal products to remain unaltered. It also would appropriate requirements to be clearly laid out for active substances, which would essentially match ICH Q7.

The consultation phase will end on April 20 and the adoption of the delegated act is planned for 2013.

References

1. Directive 2011/62/EU, *European Commission*, ec.europa.eu/health/files/eudralex/vol-1/dir_2011_62/dir_2011_62_en.pdf
2. Directive 2001/83/EC, *European Commission,* ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_cons2009/2001_83_cons2009_en.pdf
3. Delegated Act on the Principles and Guidelines of Good Manufacturing Practice for Active Substances in Medicinal Products for Human Use, *European Commission,* ec.europa.eu/health/files/gmp/2012_01_20_gmp_cp_en.pdf
4. European Union Legal Acts, *Europa*, europa.eu/legislation_summaries/institutional_affairs/treaties/lisbon_treaty/ai0032_en.htm
5. EudraLex-Volume 4: Good Manufacturing Practice (GMP) Guidelines – Part II–Basic Requirements for Active Substances Used as Starting Materials, *European Commission,* ec.europa.eu/health/files/eudralex/vol-4/2007_09_gmp_part2_en.pdf

Directive 2011/62/EC obliges the Commission to adopt GMP for APIs



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The Benefits and Challenges of Targeted Drug Delivery

Martha Folmsbee, Pall

In the 16th century, Philippus von Hoehenheim (Paracelsus) is credited with pointing out (in German): "Alle Ding' sind Gift, und nichts ohn' Gift; allein die Dosis macht, daß ein Ding kein Gift ist, which means: "All things are poison, and nothing is without poison; only the dose permits something not to be poisonous."Clearly, this is still true today.

The clinical utility of a medicine is inevitably limited by toxicity. It is a significant challenge to deliver some drugs at the dosage required for effective treatment without harming the patient in the process. However, targeted drug delivery that allows precise release of the desired drug to the exact location where it is needed is rapidly progressing.

The focus of this essay will be limited to liposomes and closely related delivery systems.

In addition to the significant design challenges facing the pharmaceutical industry when developing and constructing these drug delivery systems, regulatory and manufacturing challenges also arise

Benefits of Targeted Drug Delivery

The benefits of targeted drug delivery are clear and can be simplified to two major categories:

- Protection of the patient from collateral damage when the drug attacks sites other than the targeted site
- Protection of the drug from breakdown or removal, until it is delivered to its exact destination to perform its job.

Additionally, the ability to facilitate removal of the by-products of drug activity would also be beneficial (even if not yet feasible).

Table 1 shows what idealized targeted drug delivery can do.

Targeted Drug Delivery Systems

Generally speaking, targeted drug delivery involves the use of micelles or liposomes as the delivery vehicle or a closely related nanosuspension. This is an emulsion of suspended particulates of a very tiny size.

[Editor's note: The *PDA Letter* published an article on drug delivery called, "A Look into the Future: Nanocarriers, Nanomachines, and Micropharmacies" on page 12 in the June 2008 issue.**]**

Both micelles and liposomes are colloidal dispersions constructed from amphiphilic molecules such as lipids, which have a hydrophilic "water-loving" head and a hydrophobic "lipid-loving" tail (see **Figure 1).** The exterior surfaces of micelles and liposomes are composed of hydrophilic groups which face outward and interact with the surrounding water environment. However, the interior environment of micelles and liposomes differs significantly.

The interior of the micelle is comprised of the lipid tails of the amphiphilic molecule and generates a hydrophobic core. In contrast, the interior of a liposome is aqueous, generating a hydrophilic core. This difference is due to the distinct construction of the liposome. A liposome is constructed with a lipid bilayer, similar in concept to the lipid bilayer of a cell (see **Figure 2** on page 34), which makes it possible for the liposome to contain a watery core.

Micelles can be used to carry poorly water soluble drugs in their hydrophobic core and liposomes can carry crystallized or water soluble drugs in their core or lipid soluble drugs in their lipid bilayer. Micelles tend to be small (< 100 nm in diameter) and liposomes can be much larger (even larger than a micron) ***(1).***

A significant advantage of these delivery systems (other than protecting the drug during drug delivery) is that their exterior can be modified so that they can attach to specific cells and improve penetration at the targeted site. Their interior can also be modified to protect and deliver the drug as desired with the environmental conditions required. Of course, none of the modifications are necessarily easily-made ,but the possibilities are exciting.

Doxirubicin is used to treat several cancers and has been successfully (even it passively) delivered in a liposome system ***(2,3,4)***. In this delivery system, doxorubicin has a longer circulation time and is less susceptible to removal by the immune system and more of the drug reaches the targeted tumors.

Cancer chemotherapy, most notorious for toxic side-effects, is an obvious candidate for controlled delivery in a liposomal (or similar) system. But, other drug treatments can

Article at a Glance

- It is a significant challenge to deliver some drugs at the dosage required for effective treatment without harming the patient in the process
- Targeted drug delivery that allows precise release of the desired drug to the exact location where it is needed is rapidly progressing
- A significant advantage of the micelles or liposomes delivery systems (other than protecting the drug during drug delivery) is that their exterior can be modified so that they can attach to specific cells and improve penetration at the targeted site. Their interior can also be modified to protect and deliver the drug as desired with the environmental conditions required

also be improved with more targeted drug delivery. A liposomal delivery system for antibiotics could potentially allow for gradual and sustained release at the site of the infection maintaining a steady assault on the pathogen and minimizing the generation of resistant strains ***(5).*** Isoniazid, Rifampicin, Amikacin and Ciproflaxin are examples of liposomal antibiotic candidates for targeted drug delivery in the treatment of tuberculosis.

Challenges of Targeted Drug Delivery

Many informative reviews can be found in the literature addressing recent advances in drug delivery which provide a wealth of information and describe exciting advances ***(1, 2, 6,7).***

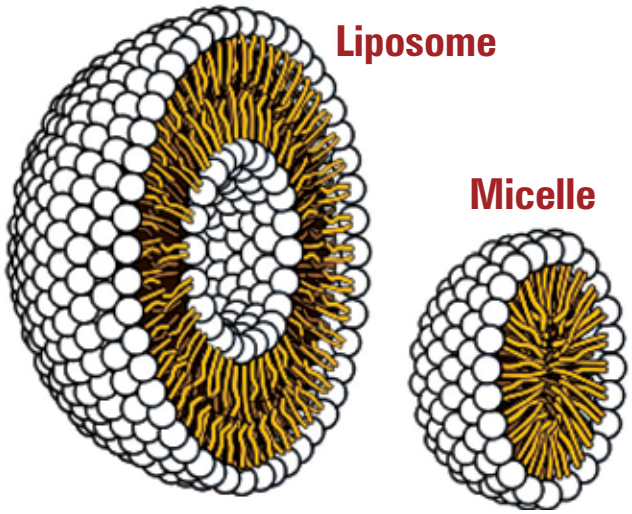
One of the initial hurdles to the practical use of liposomal (and related) drug delivery systems was the susceptibility of the delivery vehicle to quick removal via the reticuloendotheial system. Such removal led to unfavorably short circulation times and low accumulation of the drug at the desired site. One way this limitation has been overcome is by coating the surface with polyethylene glycol (PEG) which slowed removal and resulted in improved circulation time. This has often led to an improved accumulation of the drug at the targeted site ***(2,3)***. However, a PEG coating can also reduce tumor cellular uptake, in some cases, by serving as a barrier between the drug and the target cell. This illustrates the disadvantage of a delivery system dependant on passive drug delivery. In a passive drug delivery, the drug is circulated throughout the body without preference for any one site. As a result, it may accumulate equally well at non-target and target sites.

Fortunately, due to the tendency of many tumors to be heavily vasculated (well supplied with blood vessels), even passive drug delivery can result in accumulation at the tumor. However, if the targeted site is not heavily vasculated or if it is poorly vasculated, passive drug delivery may not be adequate. In those cases, active drug delivery clearly is preferable. Active drug delivery may also reduce negative side effects by avoiding (or reducing) accumulation at non-target sites. This is clearly beneficial to the patient.

Active drug delivery can be accomplished by adding surface ligands which preferentially bind the drug delivery system to the targeted cell. Even so, it is still necessary to ensure that the drug exits the delivery system and enters the cell once it has arrived. At the site, an additional step may be required. For example, active delivery can be further enhanced with the use of photochemical treatment, such as UV exposure, potentially allowing control of the rate and location of drug release.

Progress on improved (active) targeted delivery of doxorubicin has been made, allowing it to specifically target breast cancer cells ***(8)***. Active delivery was achieved by attaching a ligand to the liposome surface that would bind to an integrin, which is over-expressed in some cancer cells. With the liposome vesicle preferentially binding to cancer cells, accumulation and delivery of the cancer

Figure 1 Structure of micelle vs. Structure of a liposome

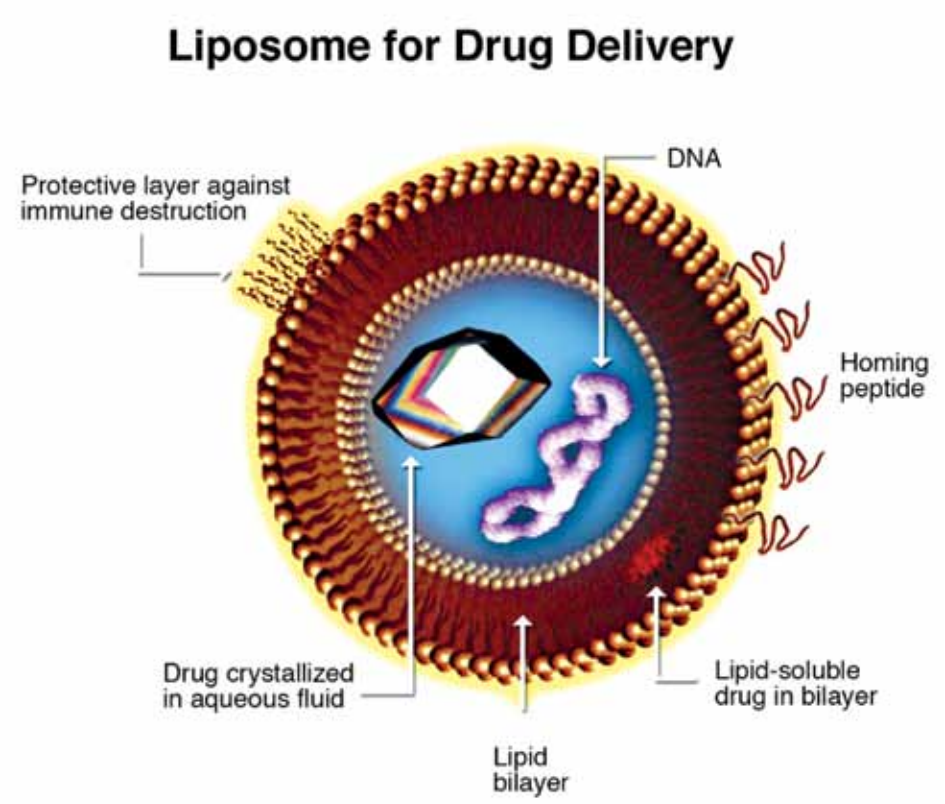


The basic structure of a micelle compared to that of a liposome. The circles represent the hydrophilic head group of the amphoteric molecules and the small tubular structures represent the hydrophobic tails. The head group faces an aqueous solution, internally or externally.

Table 1 Idealized Drug Delivery Benefits

Protect the Patient	Protect the Medicine
Prevent collateral patient cell damage (in the event it occurs, due to toxic side effects)	Prevent premature removal/excretion and generate a longer circulation time (if appropriate)
Actively deliver to targeted cell site (delivery is limited to desired site)	Prevent exposure of the drug to unfavorable environmental conditions at any point in the delivery system
Enhance target cell damage once at the site	Control environmental conditions so as to provide conditions for optimal drug efficacy at the site
Provide rapid "clean-up" of the site when the job is done (facilitate removal of degradation by-products, both of the drug and targeted cells)	Allow for controlled timing of drug release

Figure 2 A stylized depiction of an idealized liposome drug carrier



The outside of the liposome is water soluble and protected from immune destruction with a layer of a protective compound such as polyethelyene glycol (PEG). The outer surface also has a protein tag that will allow it to preferentially attach to the target site (thus accumulating at the target site and limiting drug delivery to that site). The medicinal component can be carried in the internal aqueous compartment or in the lipid bilayer surrounding that compartment (the drug may be in solution or crystallized as a "nanoparticle"). As illustrated, even nucleic acids or genes could be delivered this way in the form of DNA.

drug to the tumor is further improved.

Active delivery was also recently demonstrated with the controlled release of the cancer drug, methotrexate ***(9)***. In this example, the rate of drug release varied in response to several parameters, including light wavelength, exposure time and the pH of the drug environment. Overall, it is evident that successful development of these drug delivery systems is extraordinarily challenging. However, the benefits make it well worth the effort, and the future looks promising.

In addition to the significant design challenges facing the pharmaceutical industry when developing and constructing these drug delivery systems, regulatory and manufacturing challenges also arise.

A summary was recently published on drug delivery systems and their current scientific and regulatory challenges ***(6)***. Some of those challenges include:

- A lack of safety protocols and trained manufacturing personnel
- A lack of specific regulatory guidelines
- Challenges with regard to contamination control (both of the product and the manufacturing environment)

Post-formulation sterilization is a significant challenge and requires careful testing and extra planning to ensure final product sterility. Due to the nature of many drug delivery systems (or the drug itself) terminal sterilization with heat is often not possible or not practical. The large size of liposomes can also make filter sterilization difficult, if the liposomes are removed or altered in the course of the filtration. Qualification of sterile filtration of liposomal fluids, even if the liposome vesicle is not overly large can still be demanding ***(10)***. Successful sterile filter qualification will possibly require several filter qualification trials and careful consideration of the specific characteristics of the drug, the filter and the preferred process parameters.

Most importantly, all these elements must be balanced early in the process design by the various teams developing the drug delivery system.

Given the complex nature of targeted drug delivery systems, these challenges are not surprising. However, with the potential for improved disease treatment and greatly-reduced negative side effects during drug treatment, it is clearly well worth the effort. Scientists, engineers, manufacturing experts, regulatory leaders and medical personnel can work out the solutions to overcome these challenges.

Table 2 Examples of liposome delivery systems currently in use or in development

Drug or Drug group	Target
Doxurubicin	Various Cancers
Topotecan	Cancer
Mitoxantrone	Various Cancers
Amphotericin	Fungal infections
HepaXen	Hepatitis B vaccine
Anitibiotics	Tuberculosis

This has been modified from Elbayoumi and Torchelin, 2010 and Drulis-Kawa and Dorotkiewicz-Jach, 2010 ***(1,5)***

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References

1. Elbayoumi, T. A., and V. P. Torchilin, "Current Trends in Liposome Research." In V. Weissig (ed.), *Liposomes; Methods and Protocols, 2010,* Humana Press, New York.
2. Cattel, L., M. Ceruti, and F. Dosio, "From Conventional to Stealth Liposomes: A New Frotier in Cancer Chemotherapy." *Tumori*, 2003, 89:237-249.
3. Gabizon, A. A., "Pegylated Liposomal Doxirubicin: Metamorphosis of New and Old Drugs into a New Form of Chemotherapy." *Cancer Investigation*, 2001, 19:424-436.
4. Musacchio, T., and V. P. Torchilin, "Recent developments in Lipid-based Pharmaceutical Nanocarriers." Front Biosci, 2011, 16:1388-1412.
5. Drulis-Kawa, Z., and A. Dorotkiewicz-Jach, "Liposomes as Delivery Systems for Antibiotics." *International Journal of Pharmaceutics*, 2010, 387:187-198.
6. Hock, S., Y. Ying, and C. Wah, "A Review of the Current Scientific and Regulatory Status of Nanomedicines and Challenges Ahead." *PDA Journal of Science and Technology,* 2011, 65:177-195.
7. Malam, Y., M. Loizidou, and A. Seifalian, "Liposomes and Nanparticles: Nanosized Vehicles for Drug Delivery in Cancer." *Trends in Pharmacological Sciences*, 2009, 30:592-599.
8. Shroff, K., and E. Kokkoli, "PEGylated Liposomal Doxorubicin Targeted to α5β1 Expressing MDA-MB-231 Breast Cancer Cells." *Langmuir* epub, Jan 23, 2012.
9. Choi, S., M. Verma, J. Silpe, R. Moody, K. Tang, J. Hanson, and B. JR., "A Photochemical Approach for Controlled Drug Release in Targeted Drug Delivery." *Bioorg Med Chem*, Dec 20, 2011.
10. Onraedt, A., M. Folmsbee, A. Kumar, and J. Martin, "Sterilizing Filtration of Adjuvanted Vaccines: Ensuring Successful Filter Qualification." *BioPharm International*, October 2010.

About the Author

Martha Folmsbee, Sr. Staff Scientist, Pall, works in the Scientific and Laboratory Services department with a focus on bacterial retention testing of sterilizing grade filters. She is primarily concerned with sterile filtration of liposomes and related fluids and mycoplasma removal in a broad range of customer applications.

Rx Distribution Licenses: A Matter of State continued from page 26

Once it has been determined that a particular state requires the manufacturer to be licensed, the next step is to figure out which type of license to get

According to the author, there is no one resource available to discover all the requirements. A comprehensive reference section at the end of PDA Technical *Report No. 46: Guidance for Good Distribution Practices for Pharmaceutical Products to End Users* includes references to distribution laws in the fifty U.S. states.**]**

References

1. The Board of Pharmacy wields this regulatory authority in approximately 40 States. Others have assigned it to a program housed within a different entity, such as the Department of Health (*e.g.*, Texas, New Jersey) or the Department of Agriculture (*e.g.*, North Carolina).
2. VAWD is operated by the National Association of Boards of Pharmacy. The states in which current VAWD accreditation is a condition of licensure are Indiana, North Dakota and Wyoming.

About the Author

Joanne S. Hawana, Associate, Arent Fox, focuses her practice on government oversight of foods, drugs, and devices, as well as wholesale distribution and pharmacy activities regulated by the states. She frequently works with manufacturer and distributor clients regarding their licensing obligations at the state and local level.

EU Directive to Thwart Noncompliant APIs continued from page 31

6. Directive 2003/94/EC, *European Commission,* ec.europa.eu/health/files/eudralex/vol-1/dir_2003_94/dir_2003_94_en.pdf

About the Authors

Barbara Jentges, PhD, Senior Regulatory Affairs Professional and Managing Director, PhACT. She also teaches at ETH Zurich/Switzerland (Swiss Federal Institute of Technology) and at the University of Applied Sciences and Arts in Northwestern Switzerland. Additionally, she chairs the Regulatory Europe Affairs Interest Group and is member of PDA's Regulatory Affairs/Quality Advisory Board (RAQAB).

Karen Ginsbury, CEO, PCI Pharmaceutical Consulting, has 25 years hands-on experience of setting up, implementing and maintaining GMP compliant pharmaceutical quality systems, Karen Ginsbury has her own consultancy firm and provides services to small and large pharmaceutical companies in the field of QA and GMP compliance. Karen is the past president of the Israel Chapter, Chairperson of the Investigational Medicinal Products taskforce, the Chair of the *PDA Letter* Editorial Committee and currently serves on PDA's RAQAB.

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Interest Group *Corner*

PCMO[SM]/QRM Interest Group Contributes to Four Technical Reports

Interest Groups have a long history of bringing together experts in the PDA community to discuss important topics. Several task forces that produced technical reports were created in response to IG proposals. Once in a while, the members of an IG can coalesce around the development of a technical report and provide input.

Participants of the Quality Risk Management Interest Group (QRMIG) have gone even further, having actively contributed to the development of four new technical reports, one of which just was published by PDA. These reports are intended to educate PDA members and the industry at large on how to integrate QRM in the manufacturing process, and will provide case studies on applying risk assessments to manufacturing processes for bulk biologics, pharmaceuticals, and packaging operations. Each report is being produced by task forces under the PDA Paradigm Change in Manufacturing Operations (PCMO[SM]) program.

PCMO Technical Report No. 54: Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations is the first technical report published through this combined effort. It was released by PDA in March in is available free to PDA members until April 9 (*see related article, p. 6*).

The QRMIG group is tentatively planning a workshop at the *2012 PDA/FDA Joint Regulatory Conference* on its technical reports. A training session on R01 sponsored by TRI will be held this month (April 19-20) following the 2012 PDA Annual Meeting.

Since 2009, **Jeffrey Hartman**, Validation Manager, Validation Quality Assurance, Merck, and Dr. **Mike Long**, MBB, Director, Consulting Services, ConcordiaValSource, have served as the co-leaders of the QRMIG, which seeks to help industry build on its knowledge of risk management.

Hartman and Long told the *PDA Letter* that advancing this knowledge within the industry is very important, and, as such, they see the IG continuing to serve an important role in advancing such knowledge.

Recently, there has been new regulatory focus on QRM. Long said that regulatory agencies have been going to firms and asking them to provide evidence of QRM infrastructure—when inadequate, the facilities have received observations. Hartman explained that QRM is more than just executing risk assessments, the information and knowledge gained must be assimilated into one's quality systems. For example, a recent regulatory guidance from the U.S. FDA, *Process Validation: General Principles and Practices,* includes QRM as one of the cornerstones for building a validation lifecycle process.

Long said that it is imperative that you can justify the manner in which you have structured your risk management program itself, as well as the individual risk assessments performed within the program. He continued, " A good rule of thumb in risk management is the structure and output should be commensurate with the level of risk being evaluated."

Though risk management is nothing new, the co-leaders said that still not everybody is implementing it correctly. The co-leaders said that there needs to be better understanding that not every issue, question or concern that surfaces in the pharmaceutical industry requires a full formal risk assessment, such as an FMEA. While decisions using risk need to be documented, this can be done with a memo or within the existing quality system (CAPAs, change control, etc). In practice, companies need to be careful about overdoing or underdoing risk management.

One of the other troublesome points for industry is knowledge management of QRM. Much time and resources are invested in performing risk assessments, but effectively documenting and efficient retrieval of this information is critical. The need is for one to connect quickly to other quality systems such as change control, deviation management, validation, etc. and be able to review, and perhaps update information as required easily and efficiently.

The better the system design, the more a company will gain from their QRM program. Hartman said, "QRM should be focusing on integration; one needs to design with the end in mind to ensure that information/data is managed efficiently and readily accessible."

About the Experts

Jeffrey Hartman has over 25 years experience in the pharmaceutical industry, supporting API, pharmaceutical and vaccine manufacturing. Currently, Jeff is a Validation Manager in divisional Validation Quality Assurance, Merck. His responsibilities include development of Merck Manufacturing Division guidelines/policies, Quality System requirements and support of validation activities worldwide. With hands-on, consulting, and publication experience, he is considered a leading Subject Matter Expert within Merck.

Mike Long, MBB, Director, Consulting Services, ConcordiaValSource, has two decades of experience leading product, process development and validation efforts on a wide range of pharmaceutical, medical device and combination products. He is a frequent speaker/writer on topics such as Risk Management, Quality Systems, Quality By Design, Process Validation, and Process Robustness. He is an active member on industry committees including the PDA's Science Advisory Board and the *PDA Letter* Editorial Committee.

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U.S. FDA IDs Solutions to Drug Shortages

Early Notification is "Key" to Avoiding Drug Discontinuation

Emily Hough, PDA

The U.S. FDA announced at a Feb. briefing that it has identified solutions that could decrease the chance of future drug shortages.

Margaret Hamburg, MD, Commissioner, U.S. FDA, stated that early notification of manufacturing or quality problems to critical drug products is one important way to avoid a drug shortage or discontinuation. FDA needs enough time to make the appropriate arrangements to keep stable supplies—including outreach to overseas firms and allowing unapproved versions—to keep the supplies at necessary levels.

Hamburg told the audience that members of FDA's Drug Shortage Program have already experienced both these situations with the chemotherapy drugs methotrexate and doxil.

For methotrexate, FDA asked alternative manufacturers to ramp up their supply of the drug product months before the primary manufacturing plant voluntarily shutdown its facility. This action helped keep this product available for patients.

In the case of the doxil, Hamburg mentioned that FDA is allowing a temporary overseas importation of a substitute. According to the Commissioner, "the substitute remains unapproved by the FDA for the US market, but when a critical drug is unavailable and the substitute can produce a comparable outcome and has been evaluated by us for quality and for safety, we use our enforcement discretion to allow for its temporary and limited use."

While volunteer reporting has decreased drug discontinuation of critical drug products like in the cases above, Hamburg said there needs to be legislation to create "a broader reporting framework." The Agency believes this "will have real benefits in an ongoing institutionalized way, so we support that going forward," she said.

While volunteer reporting has decreased drug discontinuation of critical drug products like in the cases above, Hamburg said there needs to be legislation to create "a broader reporting framework."

A draft guide published on February 27 in the *Federal Register* recommended protocols that should be followed prior to a prescription drug or biological product shortage. The draft guide, *Notification to FDA of Issues that May Result in a Prescription Drug or Biological Product Shortage*, clearly describes the actions a manufacturer must take. It specifies who is required to notify the Agency, what information to report and when and how to notify the Agency.

Hamburg stated that FDA needs "additional authority to be able to truly work effectively in a global landscape." However, she mentioned that FDA has effectively prevented 195 drug shortages in 2011. She said that 114 shortages have been prevented since October 31, 2011, the date that an executive order directed FDA to use all available administrative tools to expand efforts already underway to combat drug shortages.

In December of 2011, FDA issued an interim final rule that required manufacturers that are the only producer of certain critical drugs to report to the Agency all interruptions in manufacturing that could lead to potential disruptions of supply.

"At the present time," she said, "we are seeing a fairly significant increase, a six-fold increase, in notifications to the FDA as a result of voluntary reporting from companies about potential shortages or disruptions in the supply chain. So we know that early notification matters and we're encouraged by the voluntary participation we've seen so far."

FDA has been working closely with the Generic Pharmaceutical Association, the Pharmaceutical Research and Manufacturer's Association of America and Biotech Industry Organization as well as with the three largest drug wholesalers to discuss the development of strategies to prevent and to reduce drug shortages.

The Agency has also increased its staff in its Drug Shortage Program. The staff has developed a tracking database for drug shortages and shares information with the Justice Department about "stockpiling, gray markets and exorbitant pricing of drugs that are in short supply."

Drug shortages, according to Hamburg, "stems from an interconnected series of factors, including demand outpacing supply and maintaining high quality manufacturing practices and other economic and legal issues." But, the issue ultimately boils down to "…getting people the treatments they trust, they need and that they rely on."

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Regulatory Briefs

Regulatory briefs are compiled by PDA member volunteers and staff directly from official government/compendial releases. Links to additional information and documentation are available at www.pda.org/regulatorynews.

North America

U.S. FDA to Amend 21 CFR Part 5, Subpart M

On April 1 the U.S. FDA amended 21CFR Part 5, subpart M to reflect organizational change in the Agency and to make other conforming changes.

The action is editorial in nature and is intended to improve the accuracy of the Agency's regulations. The alterations will not result in any substantive changes to the regulations themselves.

U.S. FDA Draft Guidance on IND Applications for PET Drugs Available

A U.S. FDA draft guidance on investigational new drug (IND) applications for positron emission tomography (PET) drugs is now available.

The draft guidance is intended to assist manufacturers of PET drugs in submitting IND applications. The draft guidance summarizes the IND process for PET drugs, makes recommendations for how to submit an IND, provides advice on expanded access options for investigational PET drugs, and describes the process for requesting permission to charge for an investigational PET drug.

Comment by May 14.

U.S. FDA Releases Q&A Draft Guide on PET Drug Products

The U.S. FDA has released a draft guidance, entitled, *FDA Oversight of PET Drug Products—Questions and Answers.* The draft guidance provides questions and answers that address nearly all aspects of the FDA approval and surveillance processes for PET drug products, including application submission, review, compliance with good manufacturing practices, inspections, registration and listing, and user fees.

Comment by May 29.

U.S. FDA Releases Draft Guidance about Drug Shortages

The U.S. FDA has announced the availability of a draft guidance for industry entitled, *Notification to FDA of Issues that May Result in a Prescription Drug or Biological Product Shortage.*

This draft guidance relates to the Federal Food, Drug, and Cosmetic Act, which requires sole manufacturers to notify FDA of discontinuance of certain drug products and to the President's Executive Order 13588 of October 31, 2011, directing FDA to use all available administrative tools to expand the Agency's efforts to combat the problem of drug shortages.

Comment by May 29.

Available U.S. FDA Draft Guide on Phthalates

The U.S. FDA has released a draft guidance, entitled, *Limiting the Use of Certain Phthalates as Excipients in CDER-regulated Products*.

The draft guidance provides CDER's current thinking on the potential human health risks associated with exposure to dibutyl phthalate and di(2-ethylhexyl) phthalate. In particular, the draft guidance recommends that the pharmaceutical industry avoid the use of these two specific phthalates as excipients in CDER-regulated drug and biologic products, including prescription and non-prescription products.

Comment by May 31.

USP Chapter on Supply Chain Integrity Proposed

The USP's *Pharmacopeial Forum* has announced that a new general information chapter, called, <1083> Good Distribution Practices—Supply Chain Integrity has been proposed.

The chapter will be a part of a series of informational chapters describing various aspects of the pharmaceutical supply chain. Specifically, <1083> will describe a set of recommended practices for helping to ensure supply chain integrity for drug components and drug products.

Comment by May 31.

Key Regulatory Dates

Comments Due

May 14 — U.S. FDA Draft Guidance on IND Applications for PET Drugs

May 29 — U.S. FDA Q&A Draft Guide on PET Drug Products

U.S. FDA Draft Guidance on Prescription Drug and Biological Product Shortages

May 31 — EMA Draft Guideline on the Use of Near Infrared Spectroscopy

U.S. FDA Draft Guide About the Use of Phthalates

USP Chapter on Supply Chain Integrity

Europe

EMA Draft Guideline on NIRS Released

A draft guideline on the use of near infrared spectroscopy (NIRS) by the pharmaceutical industry and the data requirements for new submissions and variations has been released by the EMA.

The guideline describes the regulatory requirements for marketing authorization applications and variation applications submitted for medicinal products for human or veterinary use, which include the use of NIRS. It also outlines the requirements for applications in which NIRS is used for qualitative and quantitative analysis or where it is used as a process analytical technology for monitoring and controlling drug substance synthesis and finished product manufacturing processes.

Comment by May 31.

The Parenteral Drug Association presents...

2012 PDA Europe

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Science Translating into Cures

See the Highlights

Cell-based products

- cancer immunotherapies
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GMP related issues

- GMP for clinical trials and commercial production
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Challenges and advances of ATMP development

- quality and CMC issues
- non-clinical and clinical challenges
- constraints in commercialisation

4 June Pre-Conference Workshop on GMP for ATMPs

WORKSHOP 4 June | **CONFERENCE** 5-6 June | **EXHIBITION** 5-6 June

https://europe.pda.org/ATMP2012

Don't Be Left in the Cold: Attend PDA's GDP Conference

Bethesda, Maryland • November 15-16 • www.pda.org/coldchain2012

Rafik H. Bishara, PhD, RHB Technical Advising

In its seventh consecutive year, *the PDA Cold Chain Management/Good Distribution Practice Conference* will focus on the various challenges, solutions and case studies regarding integrated supply chain management and Good Distribution Practices. Regulators and representatives from the United States Pharmacopeia, industry and cold chain solution providers have been invited to discuss, review and debate many of these cold chain issues as it pertains to the distribution in light of PDA *Technical Report No. 39, Revised 2007, Guidance for Temperature-Controlled Medicinal Products: Maintaining the Quality of Temperature-Sensitive Medicinal Products Through the Transportation Environment,* PDA *Technical Report No. 46, Last Mile: Guidance for Good Distribution Practices for Pharmaceutical Products to the End User* as well as the recently published PDA *Technical Report No. 52, Guidance for Good Distribution Practices (GDPs) For the Pharmaceutical Supply Chain* and PDA *Technical Report No. 53, Guidance for Industry: Stability Testing to Support Distribution of New Drug Products*

A special session has been designated to detail the migration from cold chain to good distribution practices of temperature-controlled products. This will allow the presenters to cover the concerns about refrigerated, frozen, ambient and controlled room temperature products thus covering all spectrum of temperature-sensitive shipments.

Regulatory approaches to stability studies to support distribution of temperature-controlled products will be reviewed by regulatory and industry representatives. Firms have used the idea of a stability budget to assign permissible time out of storage for packaging and labeling operations for refrigerated drug products for some time. This concept has been expanded in TR-53 to include storage and distribution as well. It is intended to complement existing guidance on stability studies and maintaining the quality of pharmaceuticals during distribution.

With the overwhelming number (and volume) of GDP regulations and guidelines from regulators, a special session will address 30+ GDP world-wide regulations, guidelines and position papers on good distribution practices and will outline and summarize clearly what is expected. Topics including temperature management, supply chain integrity and information control/sharing will be discussed.

Risks to product quality from moisture during handling, storage and transportation will also be debated by experts with the intention to determine pragmatic solutions.

On behalf of the program planning committee, I would like to extend a personal invitation to you and your colleagues to join us on November 15-16 in Bethesda, Md. for what is promising to be an informative, stimulating and engaging conference.

For more details on the conference, agenda and to register online, please visit www.pda.org/coldchain2012.

Learn About Virus and TSE "Hot Topics"

Bethesda, Md. • May 15-18 • www.pda.org/virustse2012

Dayue Chen, PhD, Eli Lilly and Brian Hubbard, PhD, Amgen

The *PDA/FDA Virus & TSE Safety Conference* provides an excellent opportunity for real time discussion between industry and regulatory agencies. Over the years, it has evolved into the major and most popular event in the field of Virus & TSE safety. The conference rotates between United States and Europe and will be held this year on May 15–17 in Bethesda, Md. The program planning committee has put together an exciting and well-balanced agenda on hot topics such as Quality by Design, Hepatitis E Virus (HEV) epidemiology and advances in the TSE in vitro assay.

The first day will focus on two major topics: modular approaches for viral clearance and QbD approaches for viral clearance studies. You will learn of case studies on how companies have used in-house data and prior experience to support modular claim for specific unit operations. In addition, you will learn how to use appropriate tools to apply QbD concepts in viral clearance studies.

The epidemiology of HEV, control of raw materials and model viruses used in virus clearance studies are in the spotlight the second day. The potential risks and challenges posed by HEV are discussed in the context of products safety, detection methods and control strategies. In addition, speakers from industry, consulting firms and regulatory agencies will share their thoughts, experiences and case studies on risk mitigation strategies for raw materials, new technology for virus detection and the importance of model viruses for virus clearance studies.

The third day of the conference will focus on risks associated with TSE in biotechnology and vaccine products. Contamination of TSE agents can occur from a variety of sources ranging from cell ➤

If you are in Operations or an Executive Leader in the Pharmaceutical/ biopharmaceutical industry, this is the single most relevant conference for you as it relates to Health Authorities current Quality expectations of management and why some companies are struggling with GMP compliance.

2012 PDA ICH Q10 Workshop:

Expectations of Operations & Executive Management

September 12-13, 2012

Baltimore Marriott Waterfront Hotel
Baltimore, Maryland

Has your company faced stock-outs due to quality problems in the past couple of years? Have you experienced different and stricter regulatory Health Authority dialog recently? Are you considering how deviations and failures in your operations can be reduced and how the product supply can become more reliable and predictable?

During this workshop, participants will meet and learn from other industry leaders on how ICH Q10 can be used as an incredibly efficient and powerful way to drive improvements within your company.

In a span of just two days you will be able to:

- Better understand the recent changes in regulatory compliance trends including warning letters and consent decrees
- Explore FDA's expectations for operations and executive management Summarize Current Expectations for Incoming Glass and Pharmaceutical Product Packaging
- Understand how the PQS can be used to align the company across multiple sites and drive the right quality culture
- Examine how ICH Q10 can be used as an incredibly efficient and powerful way to drive improvements within your company.

www.pda.org/ICHQ10

culture reagents to a proposal that spontaneous development of TSE infectivity can occur in PrP-expressing cell lines. Day three will discuss the experimental and regulatory approaches to address the risks associated with TSE. Mechanisms of TSE infectivity, susceptibility of cell substrates to TSE agents and the challenges and requirements of developing in vitro infectivity assays that have the potentially to serve as replacements for in vivo assays will be discussed.

Immediately following the *PDA/FDA Virus and TSE Safety* Conference, TRI will host two courses on May 18. To learn more about "Viral Contamination and Remediation" and "Basic Virology as it Applies to the Biopharmaceutical Industry," visit www.pda.org/virustse2012.

We look forward to your attendance at the PDA/FDA Virus & TSE Safety Conference on May 15-17.

CMC Workshop Explores QbD Implementation

Bethesda, Md. • May 14 • www.pda.org/cmc2012

2012 CMC Program Planning Committee

The primary focus of the A*pplying QbD Principles in Vaccine Development: PDA/FDA CMC Workshop* will be to explore and understand the application of QbD principles in vaccines development and post-licensure changes. The basis for the discussions will be drawn from the A-VAX case study that was developed by a consortium of vaccine manufacturers to facilitate further discussion moving the implementation of QbD approaches in product development into the biologics arena.

The workshop will start by examining factors involved in developing the control strategy and in defining the critical quality attributes for a model vaccine product.

The second and third session of the day-long program will focus on post-licensure changes that benefit from a defined design space and the enhanced process knowledge gained from using QbD during product development.

In the second session, a representative of the U.S. FDA has been invited to focus on the application of QbD product development and will share how to incorporate this information in an investigational new drug application. The industry presentations in the second session will focus on downstream processing and drug substances. The speakers will also provide examples of how scientific data supporting a process might be used to manage change throughout the product lifecycle, including some examples that might be encountered during process development prior to commercial approval.

The third session of the day will focus on the application of QbD approaches to drug product manufacturing. The authors of the drug product section of the A-VAX case study will be discussing strategies and experimental results that support post-licensure change of scale for drug product manufacturing.

The workshop will conclude with two additional presentations examining regulatory and implementation challenges followed by a panel discussion that will include FDA representatives and pharmaceutical industry experts discussing the merits of a QbD approach to vaccine development with full audience participation.

Please join us for this exciting opportunity to continue the dialogue examining the barriers and opportunities in implementing QbD approaches in biological product development.

For more information or to register, visit www.pda.org/cmc2012.

Learn About Current Glass Quality Expectations

Washington, D.C. • June 4-7 • www.pda.org/glass2012

Chair Martin VanTrieste, Amgen

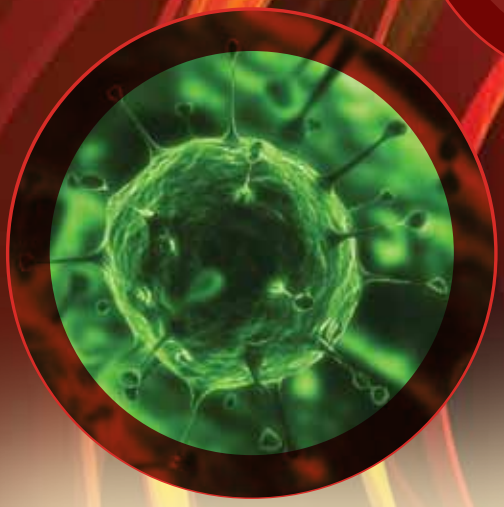
On behalf of the program planning committee, I would like to invite you to the second co-sponsored conference by PDA and the U.S. FDA on the important topic of glass quality. As you are aware, there have been several recalls and increasing concerns about pharmaceutical glass packaging, both with regard to defects and/or incompatibilities with finished product over the shelf life.

Standards, glass supplier reliability and pharmaceutical manufacturer handling and distribution best practices are all necessary elements to maintain container integrity and product sterility assurance throughout the product lifecycle of sterile injectable pharmaceutical and biopharmaceutical products.

Pharmaceutical manufacturers, regulators and glass suppliers all share a common goal of assuring the highest quality products (including packaging) for patients. This meeting will discuss these issues, best practices to preventing and/or detecting at-risk glass packaging and review current expectations to ensure that recalls are avoided and container closure integrity is assured.

If you are involved in the selection and quality assurance of glass packaging, manufacture of products packaged in ➤

Register for this Conference and the Pre-Conference Workshop on CMC and Save!



PDA/FDA Virus and TSE Safety Conference

Proactive Approaches to Mitigate Virus & TSE Risk

May 15-17, 2012

Hyatt Regency Bethesda | Bethesda, Maryland

The *PDA/FDA Virus and TSE Safety Conference* starts next month! Don't miss out on your chance to attend one of the most popular events in the field of Virus & TSE Safety. The program planning committee has put together an exciting and well-balanced agenda focusing on hot topics such as:

- Quality by Design
- HEV epidemiology
- Regulatory Update: Biopharmaceuticals
- Advances in the TSE in vitro assay

At the conference you will learn methods and strategies that are applicable to your own job function. In addition, you will be able to network with renowned worldwide regulators in the field of Virus/TSE safety, such as:

- **Howard Anderson**, *FDA*
- **David Asher**, MD, *FDA*
- **Johannes Bluemel**, *Paul-Ehrlich-Institut*
- **Kurt Brorson**, PhD, *FDA*
- **Martin Groschup**, PhD, *Friedrich-Loeffler-Institut*
- **Yashurio Kishioka**, PhD, *PMDA*
- **Marc Martin**, PhD, *AFSSAPS*
- **Pedro Piccardo**, *FDA*
- **Suzette A. Priola**, PhD, *NIH*
- **Jack Ragheb**, *FDA*
- **Captain Rebecca Sheets**, PhD, *NIH*
- **Jeffrey Skene**, *Health Canada*

Join PDA for this important meeting discussing viral safety for biopharmaceutical and plasma derived products. Reserve your spot today.

For more information and to register visit
www.pda.org/virustse2012

Pre-Conference Workshop: May 14 | Exhibition: May 15-16 | Courses: May 18

The PDA is conducting a benchmarking survey to understand glass quality and your perceptions of glass quality and glass suppliers. This survey applies to manufacturers who use glass to package sterile injectable drug products.The results of this survey will be compared with the 2011 survey and shared with all survey respondents and with the attendees at the *PDA/FDA Glass Quality Conference.*

Please note, the identity of respondents will not be revealed in any publication or presentation of the results of the survey. Even though we are asking questions about specific glass suppliers, these results will be blinded and reported as Supplier A, Supplier B, Supplier C, etc.

Visit www.surveymonkey.com/s/B2ZLHH7 to take the survey today!

glass or deal with glass suppliers, this is the meeting to attend to find out what the pharmaceutical and glass industry are doing to make it better.

PDA will also be hosting an exhibition of glass, packaging and glass inspection companies throughout the conference, and two TRI courses will be offered immediately following the conference on June 6–7.

Join us at the *PDA/FDA Glass Quality Conference* held in Washington, D.C. on June 4–7.

Sterility Assurance for Aseptic Processes

Chicago, Ill. • June 18-21 • www.pda.org/steriletechnology2012

2012 Program Planning Committee

The 2012 sterilization program planning committee would like to invite you to attend the *2012 PDA Innovation & Best Practices on Sterile Technology Conference* June 18 -19 at the Conrad Chicago in Chicago, Ill. The focus and theme of the conference is: *Sterility Assurance for Aseptic Processes and Terminal Sterilization*. The conference will concentrate on the state of sterile product manufacturing for the healthcare industry including updates on regulatory expectations, innovative technologies, process design and decision making methods and sources of valuable knowledge.

The conference will feature speakers from: Baxter Healthcare, Bayer Healthcare, Eli Lilly, Excellent Pharma Consulting, Genzyme, Hosperia, Merck Sharp & Dohme, ValSource, West Pharmaceuticals and many others.

By attending this important conference, you will be provided the opportunity to meet other sterile processing industry experts and regulators and obtain answer to your sterile product questions on such topics as:

- The practical application of quality risk management principles to design effective aseptic processing and product sterilization programs
- Methods to identify, control and remediate bioburden, biofilm and other sources of microbiological contamination

The conference will showcase a series of new and revised PDA technical reports on sterilization and aseptic processing

- The selection and use of evolving, novel and alternate sterilization methods
- New sterile product manufacturing facilities, utilizing innovative technologies and approaches
- Regulatory requirements, expectations and trends

In addition, the conference will showcase a series of new and revised PDA technical reports on sterilization and aseptic processing, a brief update on USP's Sterilization Chapters and the rewrite of USP's <1207> *Sterile Product Packaging Integrity*.

This conference will provide attendee's with a unique opportunity to meet with task force members and discuss the content and basis of the principles presented in the reports in an effort to further promote understanding of the technologies, something you definitely don't want to miss out on!

Immediately following the *2012 PDA Innovation and Best Practices on Sterile Technology Conference* PDA TRI will be hosting four courses from June 20-21.

For more information, visit www.pda.org/steriletechnology2012.

We look forward seeing you this June in Chicago, Ill.

On the forefront - Mab developments in Europe

Emerging Trends for Therapeutic Monoclonal Antibodies and Related Products

Considerations for Quality Attributes throughout the Development Continuum and Registration

Session 1: Development for biological IMPs

- What is the appropriate level of quality detail needed for biological IMP dossiers?
- Are acceptance criteria and details for in-process control required for early stages?
- How can an IMP dossier be built based on QbD principles?
- Degree of characterization of IMPs in early drug development?
- To what extent can shelf life dating be based on supportive data?

Session 2: Molecular Approaches to Optimization

- Can certain routine testing be eliminated based on molecule optimization strategies?
- Is it possible to optimize a monoclonal antibody drug substance to the point of having no critical quality attributes related to its molecular properties?
- How should molecule design features be communicated in the market application?
- What are the expectations for in vitro bioassays when more than one cell-killing target is involved?

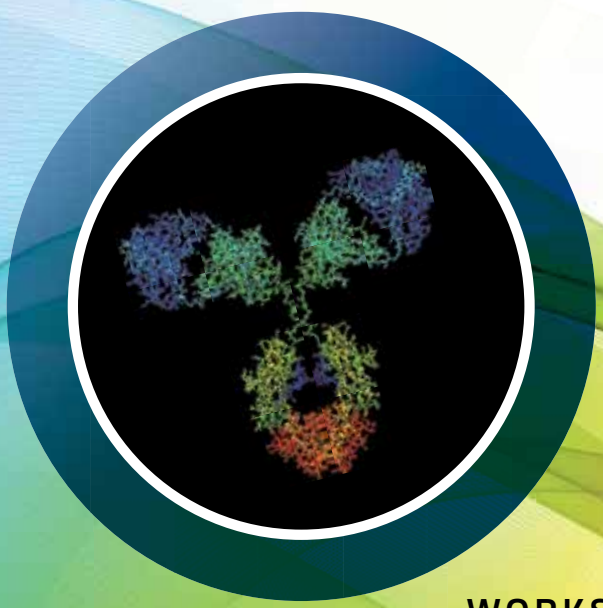
Session 3: Late-stage Process Development

- How is process parameter criticality assessed and confirmed?
- How much can we rely on prior knowledge to support process characterization?
- What are the most frequent questions health authorities ask regarding the control strategy. What are the major missing elements in the dossier?
- What information on the control strategy needs to be provided during an inspection? How far back into process development does the inspector look?

Session 4: Development, Regulatory and Future

- What are Molecular particulars and how are they characterized?
- How do we characterize the starting material used to manufacture the Antibody Drug Conjugate (ADC)?
- What are the test methods used to investigate and quality control ADC and multifunctional antibodies?
- How do we characterize the linker-quality, its mechanism in-vivo and the relevant data requirements?
- What are the unique dossier structure and data requirements for ADC and multifunctional antibodies?

Workshop Co-Chairs:
Steffen Gross, *Paul-Ehrlich-Institut, Germany*
Michael DeFelippis, *Eli Lilly*



Not to be missed: Nathan Ihle, PhD, Seattle Genetics!

12-13 June 2012

Hotel NH Danube City
Vienna | Austria

WORKSHOP 12-13 June | **EXHIBITION** 12-13 June

https://europe.pda.org/Monoclonal2012

Future Leaders Session to Tackle Issues Facing Jr. Managers

Bethesda, Md. • October 22-24 • www.pda.org/microbiology2012

Osama (Sam) Elrashidy, Bayer Healthcare and Richard Levy, PhD, PDA

Over the past six years, PDA has been hosting the annual global conference on pharmaceutical microbiology, the only global meeting that is really dedicated to the topics and issues related to pharmaceutical microbiology.

Last year, for the first time, PDA dedicated a whole breakfast session where four emerging leaders from the pharmaceutical industry shared their ideas and views on some of the most current topics and the challenges that they face day-to-day in their own labs.

The *Microbiologist of the Future* session was very lively and interactive and was well received by all attendee.

The first presentation was given by **Kimberly Wilson-Lamarre**, Manufacturing Quality Scientist, Pfizer. Her presentation was entitled, "Quality Scientist in Manufacturing? To Be or Not to Be." She told audience members during her presentation that a collaborative relationship between the QC Microbiology Laboratory and the manufacturing organization is critical for successful production operations. She also mentioned that traditional organizational structure and physical separation can be a barrier to a successful collaboration and mutual understanding. QC Microbiologists may lack the required manufacturing knowledge to adequately troubleshoot issues and that manufacturing technicians may lack the background to identify microbial/contamination risks and implement improvements. These gaps can lead to delays in identifying root causes and finding corrective actions, so the interaction is a great tool for both.

As a result, embedding a quality scientist within the manufacturing organization allows for a stronger partnership and a greater focus on aseptic technique and microbiology overall, that creates a bridge between the two areas for better communication, trust.

She also mentioned that for a successful and symbiotic relationship with the QC, the quality scientist needs to be familiar with the functions of manufacturing. This partnership will become critical when contamination events and out of specification results occur. Collaboration will allow for a quick return to production.

The second presentation was given by **Jeanette Skaluba**, Supervisor, Microbiology, Meda Pharmaceuticals. She gave two case studies dealing with the presence of *B. cereus.* In the first case study, *B. cereus* was found in a raw material of natural sourcing and in the second, it was recovered from a nonsterile oral product.

(l-r standing) Kimberly Wilson-Lamarre, Pfizer; Osama Elrashidy, Bayer (l-r sitting) Jeanette Skaluba, Meda Pharamecuticals; Mary Ellen Usarzewicz, Bristol Myers Squibb; Cheryl Moser, Merck

In the two case studies mentioned, USP <61> and <62> were followed. No growth was seen on agar plates, but turbidity was seen in the enrichment broth. When it was subcultured and identified, results showed it was B. cereus.

In her risk assessment, she concluded that the source of the contamination was from the raw material that is used in a solid oral dosage. Since the finished product was intended for adults and had a low level of water activity, it was determined the drug could still be used.

Next up was **MaryEllen Usarzewicz**, Senior Research Scientist 1, Bristol-Myers Squibb. She gave a very interesting presentation about getting a growth on a negative control.

It is important, she said, to investigate the material receipt by asking:

- What is your process for sample receipt?
- Was it received in good condition?
- Was it stored properly?

She said it was also imperative to see what type of test that media was used for (EM, MLT, etc.) as well as to see if the material growth was promoted, what personnel training took place and if the autoclave was validated or not. She said it is necessary to contact the vendor to see if they had any other complaints or if anything changed in their process. Finally, it is important to evaluate the results of the investigation and document all findings.

Cheryl Moser, Research Fellow, Merck, gave the last presentation. Entitled, "Playing Hide and Seek with Endotoxin." In her talk, she gave two case studies. In the first, she went over LAL testing in complex biological matrices. She told the audience that measuring endotoxin in aggregate form is difficult as well as vari-

continued at bottom of page 57

Register By **May 18, 2012** and Save up to $200!

The Parenteral Drug Association presents the...

2012 PDA Innovation & Best Practices on Sterile Technology Conference

Sterility Assurance for Aseptic Processes and Terminal Sterilization

June 18-19, 2012 | Conrad Chicago | Chicago, Illinois

Brochure Now Available!

If you are looking for a conference that will help prepare you to better understand and meet the challenges of manufacturing sterile health care products in the modern global technological and regulatory environment, then look no further.

This summer, PDA will host an important conference, the *2012 PDA Innovation & Best Practices on Sterile Technology Conference*, which will help you obtain the knowledge needed to address the challenges and complexities of today's manufacturing.

Highlights of this year's event include:

- Industry experts in sterile processing to present papers, provide case studies, meet with attendees and answer questions
- **HOT Plenary Session:** PDA Technical Report: Answers to Your Sterile Product Questions with presentations on:
  - **Steam-In-Place**
  - **Dry Heat Sterilization**
  - **PDA Technical Report No. 22 (Revised 2011), Process Simulation for Aseptically Filled Products**
  - **Updates on PDA Technical Report No. 30 – Parametric Release (2012 Revision) and the Revision of PDA Technical Report No. 27 – Container Closure Integrity**
- **Closing Plenary Session:** Ask the Experts Panel Discussion – The Future of Sterile Product Manufacture – Trends, Issues and Solutions featuring:
  - **Michael Sadowski**, Director, Sterile Manufacture Support, *Baxter Healthcare Corporation*
  - **Diane Paskiet**, Associate Director, Scientific Affairs, *West Pharmaceuticals*
  - **Edward Tidswell**, PhD, Senior Director, Research Sterility Assurance Technology Resources, *Baxter Healthcare Corporation*
  - **Harold Baseman**, Chief Operations Officer, *ValSource, LLC*
  - **Betty Hannoun**, PhD, Technology Management Leader, Global Engineering Services, *Merck Sharp & Dohme Corporation*
  - **Jeanne Moldenhauer**, Vice President, *Excellent Pharma Consulting*
  - **FDA Representatives**
- And much more!

PDA Technical Reports (TRs) to be discussed at this meeting!

Immediately following the conference the PDA Training and Research Institute (PDA TRI) will be hosting four stand-alone courses on June 20-21.

Visit **www.pda.org/steriletechnology2012** for more information and to register.

Exhibition: June 18-19 | Courses: June 20-21

Photo Courtesy of Sartorius Stedim Biotech

Executive, Senior Management: Attend the ICH Q10 Workshop

Baltimore, Md. • September 12-13 • www.pda.org/Q102012

Co-Chair Anders Vinther, PhD, Genentech

Has your company faced stock-outs due to quality problems in the past couple of years? Have you experienced different and stricter regulatory Health Authority dialog recently? Are you considering how deviations and failures in your operations can be reduced and how the product supply can become more reliable and predictable? The *2012 PDA ICH Q10 Workshop: Expectations of Operations and Executive Management* will cover each of these questions that are targeted directly to executive and senior operations management.

ICH Q10 is the first regulatory guidance that has significantly ventured into the area of expectations outside those of strictly meeting the GMPs. Management now has clear obligations within the pharmaceutical quality system (PQS) in terms of sponsorship and support, allocating adequate resources, setting clear roles and responsibilities and sponsoring continual improvements. Quality is no longer just for the quality professionals. Quality must be owned by all across the technical disciplines in the company from the shop floor to the most senior executive.

This is *the* conference to attend if you in a span of just two days want to learn more about recent changes in regulatory compliance trends including warning letters and consent decrees, the U.S. FDA's expectations for operations and executive management, and how the PQS can be used to align the company across multiple sites and drive the right quality culture.

You will learn from other industry leaders how ICH Q10 can be used as an incredibly efficient and powerful way to drive improvements within your company, including:

- Increasing the predictability of your product supply
- Proactive identification of quality issues
- Selecting the right key performance indicators to drive the right behaviors
- Delivering a culture of accountable leaders across the organization

You should register for this conference if you want "everything quality in one package" as it relates to expectations of operations for executive leaders in our pharmaceutical and biopharmaceutical industry.

This is the perfect conference if you a decision maker at the senior level or a professional working on site or corporate level in the following areas:

- Quality Assurance
- Manufacturing Operations and Engineering
- 6-sigma and Quality Risk Management
- Executive Management
- Senior Operations Management
- Senior Supply Chain Management
- Senior Procurement Management
- Pharmaceutical Development and CMC
- Regulatory Affairs

Global Supply Chain Integrity–A Shared Responsibility

Bethesda, Md. • November 12-14 • www.pda.org/supplychain2012

Edwin Rivera Martinez, Sanofi Aventis

On September 10–12, 2008, PDA and the U.S. FDA co-sponsored the first PDA/FDA Pharmaceutical Ingredient Supply Chain Conference in Washington, D.C. The conference was attended by over 200 professionals from industry, academia and regulatory bodies and is still remembered today by many as the most educational and emotional conference they've ever attended on supply chain security. The conference heightened the importance of supply chain controls in assuring the quality, safety and integrity of pharmaceuticals and the need to act together to address supply chain issues.

In the last 3 ½ years, both regulators and the industry have implemented many initiatives to enhance supply chain security. Yet, much remains to be done. According to a recent report from the European Alliance for Access to Safe Medicines, a frightening 62% of medicines purchased online are fake or substandard. Reuters reports that counterfeit drugs have become a $200-billion-a year business, and the World Trade Organization reports that fake anti-malaria drugs kill an estimated 100,000 Africans a year.

Some progress has been reported in deterring pharmaceutical cargo thefts. According to *FreightWatch International*, cargo theft in the U.S. in 2011 increased by 8.3%. However, last year there were less pharmaceutical thefts. There were only 36 thefts in 2011 which is down from the 49 that occurred in 2010. Also, 2011

In conjunction with the *2012 PDA/FDA Pharmaceutical Supply Chain Conference,* PDA TRI will be hosting "Developing a Robust Supplier Management Process" on November 12. For more information, please visit www.pda.org/supplychain2012.

was the first time on record in which the "pharmaceutical industry did not have the highest value per theft incident."

Fortunately, we have not witnessed another major economically motivated adulteration incident involving pharmaceutical raw materials resulting in patient deaths. However, let's not get too complacent. Most of us recognize that it not a question of whether this will happen again, but rather "when will it happen again?"

Ensuring the quality and safety of products to the patient has become increasingly more challenging in the last several years as the pharmaceutical industry continues to globalize. This has resulted in continued concern and scrutiny of supplier controls and integrity of the pharmaceutical supply chain by regulators and legislative bodies.

In the summer of 2011, FDA Commissioner **Margaret Hamburg** created a new FDA enforcement directorate, the Office of Global Regulatory Operations and Policy that is responsible for strengthening FDA oversight and enforcement of global supplier controls for medical devices, diagnostic equipment, drugs, biologics and nutritional supplements. The European Commission and World Health Organization have both issued recent guidance documents to address supply chain challenges while regulatory agencies around the world are currently reviewing their regulations in an attempt to enhance regulatory controls to assure safe, efficacious drug supply from the manufacturer to final delivery to patients.

The *2012 PDA/FDA Pharmaceutical Supply Chain Conference* builds on earlier PDA-FDA cosponsored conferences and workshops and provides an excellent forum for discussion of best practices and innovative approaches to prevent illicit acts such as counterfeiting, diversion and economic adulteration from threatening the safety of the drug supply.

I strongly encourage you to attend this year's conference to stay abreast of current events and participate in developing new initiatives to ensure the integrity of the global pharmaceutical supply chain. Remember the cry from the September *2008 PDA/FDA Pharmaceutical Supply Chain Conference*—"we have a collective call to action, and we must act together!" Get involved. Be a part of the caring professionals committed to this noble effort.

Solve Pre-filled Syringe and Injection Device Challenges

Las Vegas, Nev. • October 15-19 • www.pda.org/prefilled2012

2012 Program Planning Committee

With tremendous progress in the past decade, drug delivery continues to face challenges meeting the market needs of improving administration, compliance, safety, costs and accuracy by taking an integrated approach to develop prefilled syringes and injection devices for tomorrow's success.

New advances in construction materials, manufacturing processes, injection processes, safety devices and other technology improvements create a dynamic environment in the drug delivery device arena. Regulatory requirements, industry experience and evolving market trends are critical considerations to ensure a complete understanding of the application of pre-filled syringes and injection devices to drug delivery. The challenges of new product introduction and support of existing products require that companies be aware of new developments.

The Universe of Pre-filled Syringes & Injection Devices brings together industry and regulatory experts to share their experiences, new developments, regulatory considerations, challenges and industry trends in this exciting area. The topics will benefit those looking for a basic understanding of pre-filled syringes and injection devices as well as those looking for a more in depth presentation of current challenges and developments. This is a must-attend event for all industry professionals involved in the development, manufacturing, marketing or use of pre-filled syringes and injection devices.

Sessions will cover topics such as:

- Quality Infrastructure and Issues
- New Technologies and Trends in Manufacturing Processes
- Human Factors/Usability
- Injection Devices: Critical Attributes and Risk Management
- Regulatory and Compliance Aspects Such as Combination Products
- New primary Containers, Safety Devices, and Delivery Systems
- Global Market Trends

Immediately following *The Universe of Pre-filled Syringes and Injection Devices,* TRI will be host three courses on October 18-19.

For more information, visit www.pda.org/prefilled2012.

Attend the PDA/FDA Joint Regulatory Meeting in Baltimore

Baltimore, Md. • September 9-12 • www.pda.org/pdafda2012

Bob Dana, PDA

It's not too soon to start making your plans to attend the 21st PDA/FDA Joint Regulatory Conference which will be held from September 9-12. I'm sure that September seems to be a long way away, but the time will go quickly and you do not want to miss this signature GMP conference. In a change of pace this year, the conference is leaving its long-established base in the Washington, D.C. area and is moving 40 miles up the road to Baltimore, Md. The location this year will be the Baltimore Marriott Waterfront Hotel located in Baltimore's Harbor East neighborhood. The hotel sits on the water's edge, and you'll enjoy spectacular views as well as easy access to the city's finest shopping and restaurants.

However good they are though, the shopping and restaurants will be secondary to the conference program itself. Your program planning committee is busy assembling what will be another timely and informative conference, built around the theme of *Compliance Through Quality Systems: Implementing and Advancing a Sustainable Global Quality Culture.* As in the previous 20 years, the U.S. FDA is supporting the conference through active participation on the program planning committee. While it is too early to identify any specific presenters, there is no reason to think we will have anything but the usual high level of quality presenters from both FDA and the industry.

The committee has already identified several topics which will be covered during the conference. Each day there will be plenary sessions where all the attendees can hear presentations on timely topics regarding manufacturing, quality and regulatory functions during product lifecycle. These plenary sessions are intended to focus on emerging themes, such as the importance and challenges of changing the quality culture to meet the demands of the current and future environment.

A trend which has clearly emerged is the increased focus on the use of contract manufacturing operations (CMOs). One of our plenary sessions will focus on the use of CMOs, featuring presentations from both the CMO and the contract giver.

In addition to these podium presentations, all the plenary sessions will include an opportunity to interact with subject matter experts in a Q and A session.

A key benefit of attending the PDA/FDA Joint Regulatory Conference is the opportunity to interact with your peers and representatives from FDA in both formal and informal settings

The *2012 PDA/FDA Joint Regulatory Conference* would not be complete without the always popular *Compliance* and *Center Initiative* sessions that will be held on Wednesday morning. These sessions always play to a full house as FDA representatives provide the attendees with an update of hot topics from a compliance perspective and a summary of upcoming Center-led initiatives. In addition to the presentations, these sessions include lively Q and A sessions. No one should miss the opportunity to take part in these sessions.

Beside the plenary sessions, the conference will have plenty of concurrent sessions that will drill down into more specific topics and themes. These recurrent sessions will focus on both compliance issues as well as topics associated with regulatory submissions, so there will something that appeals to both traditional regulatory affairs professionals as well as those looking for updates on regulatory compliance topics.

We are also currently planning a split-focus concurrent track. This track will help address foundation topics for those looking to develop and build on a solid base of information and best practices for those wanting to ensure they are up to speed with the most current information.

A key benefit of attending the PDA/FDA Joint Regulatory Conference is the opportunity to interact with your peers and representatives from FDA in both formal and informal settings. In fact, these opportunities are sometimes seen as more valuable than the chance to hear the podium presentations themselves. These interactions with fellow PDA members and industry peers often lead to lasting relationships which endure for years after the conference. This year's schedule will ensure there are plenty of opportunities to develop and build on these relationships.

To help attendees further enhance their knowledge, PDA's Training and Research Institute will be offering seven training courses designed to further enhance and build upon what you learn at the conference. For further information on these courses, go to www.pda.org/pdafdacourses or contact **Stephanie Ko**, Senior Manager, Lecture Education, at ko@pda.org.

All in all, the 21st PDA/FDA Joint Regulatory Conference promises to be one of the best ever. Don't miss it! See you in Baltimore, Md.

The 2012 Aseptic Processing Training Program is **SOLD OUT!** Visit **www.pda.org/aseptic** to sign up to receive an email notice when registration opens for the next session.

Parenteral Drug Association Training and Research Institute (PDA TRI)

Upcoming Laboratory and Classroom Training for Pharmaceutical and Biopharmaceutical Professionals

June 2012

PDA/FDA Glass Quality Conference Course Series

June 6-7, 2012 | Renaissance Downtown Hotel | Washington, DC
www.pda.org/glasscourses

- Technical Report 43: Identification and Classification of Nonconformities in Molded and Tubular Glass Containers for Pharmaceutical Manufacturing | June 6
- Selection and Utilization of Glass Containers in Pharmaceutical Packaging | June 7

Preparation of Virus Spikes Used for Virus Clearance Studies – New Course

June 19-20, 2012 | Bethesda, Maryland
www.pda.org/viruspikes

Virus Filtration – New Course

June 21-22, 2012 | Bethesda, Maryland
www.pda.org/virusfiltration

2012 PDA Innovation and Best Practices on Sterile Technology Conference Course Series

June 20-21, 2012 | Conrad Chicago | Chicago, Illinois
www.pda.org/sterilecourses

- Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Validation and Ongoing Control | June 20
- Steam Sterilizers: Getting it Right from the Beginning | June 20
- Validation of Dry Heat Processes – New Course | June 21
- Parametric Release of Pharmaceutical and Medical Device Products Sterilized with Moist Heat – New Course | June 21

Basic Microbiology for the Pharmaceutical and Biopharmaceutical Industries – New Course

June 27-29, 2012 | Bethesda, Maryland
www.pda.org/basicmicro

July 2012

Quality Systems for Aseptic Processing

July 30 - August 3, 2012 | Bethesda, Maryland
www.pda.org/qsaseptic

August 2012

Filtration Week

August 27-31, 2012 | Bethesda, Maryland
www.pda.org/filtrationweek2012

- Filters and Filtration in the Biopharmaceutical Industry – Basics Course | August 27-28
- Filters and Filtration in the Biopharmaceutical Industry – Advanced Course | August 29-31

Fundamentals of an Environmental Monitoring Program

August 29-30, 2012 | Bethesda, Maryland
www.pda.org/environmental2012

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

Laboratory Courses

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

Save Money by Attending TRI Courses

Stephanie Ko and James Wamsley, PDA

TRI has taken measures to optimize your opportunities to attend trainings by holding courses in conjunction with conferences and workshops.

In the next two months, TRI will hold eight courses immediatly after PDA meetings. TRI will also hold four laboratory courses in its training facility which is conveniently located in the Washington Metropolitan Area.

On May 18, in conjunction with the *PDA/FDA Virus and TSE Safety Conference* in Bethesda, Md.,TRI will hold two courses:

"Basic Virology as it Applies to the Biopharmaceutical" will give participants a basic understanding of the viruses that are a threat and the very simple ways that they can be eliminated from the processing of biopharmaceuticals in Industry. Learn to make the correct decisions about raw material sourcing and treatments, footprints for heat treatment or other inactivation devices, risk assessments and contamination response plans.

"Viral Contamination and Remediation" will help firms reduce the risk of viral contamination during the manufacture of biological. Participants will learn to establish strategies to respond to a contamination event event in order to contain spread, efficiently initiate and conduct an investigation, implement corrective action, minimize disruption to production and help ensure minimal impact on company operations.

If you are interested in additional virus courses, join expert instructors **Kurt Brorson**, PhD, Staff Scientist, Division of Monoclonal Antibodies, Office of Biotech Products, CDER, U.S. FDA, and **Scott Lute**, Biologist, CDER, U.S. FDA, for two new laboratory courses on June 19-20 and June 21-22 at TRI in Bethesda, Md.

"Preparation of Virus Spikes Used for Virus Clearance Studies" (June 19-20) and "Virus Filtration" (June 21-22) will teach you the principles and practical applications for the preparation and testing of high quality virus spikes. You will also learn how to control virus spike quality attributes to ensure that they do not perturb unit operation performance during validation studies, how virus filters work, how to select the best filter for various applications, physical and biological/safety characterization of filter test methods, and validation of virus removal.

Two courses will also be held in conjunction with the *2012 PDA/FDA Glass Quality Conference* in Washington, D.C.

On June 6, the "Technical Report 43: Identification and Classification of Nonconformities in Molded and Tubular Glass Containers for Pharmaceutical Manufacturing" course will help students gain valuable knowledge related to the quality of glass containers, including the types of defects associated with glass manufacture, the development of standardized quality criteria and sampling plans for use in the quality decision-making process. The importance of the partnership between glass manufacturers and the pharmaceutical company using the glass containers will be emphasized.

On June 7, attendees will learn to appreciate the methods that both glass suppliers and pharmaceuticals utilize to increase the compatibility of glass with drugs and reduce glass container defects in "Selection and Utilization of Glass Containers in Pharmaceutical Packaging." Attendees will also receive broad overview of the advantages and disadvantages of glass containers based on the interaction of glass with drug products.

Four courses will be held in conjunction with the *2012 PDA Innovation and Best Practices on Sterile Technology Conference* in Chicago, Ill. On June 20, take your pick from two courses on sterilization:

"Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Validation and Ongoing Control" will provide a foundational understanding of sterilization science (microbiology and thermal science) that will then be applied in the selection of a cycle design approach, sterilization process development, process performance qualification and ongoing process control.

"Steam Sterilizers: Getting it Right from the Beginning" will give students an understanding of sterilization processes using steam. Students will also learn how steam sterilizers are designed, specified and qualified with the appropriate loads and cycles.

On June 21, two additional courses will be offered on dry and moist heat processes:

Current industry practices and approaches to validating dry heat depyrogenation processes will be covered in "Validation of Dry Heat Processes." This lecture course focuses on the microbiology and principles for qualification of dry heat sterilization and depyrogenation processes and the general approach to sterilization and depyogenation science in batch and continuous sterilizers (ovens and tunnels). Also included are points to consider in equipment design, equipment verification, process development and performance qualification for new systems and the development and validation of processes for existing systems.

Global parametric release requirements along with best demonstrated practices that can be utilized will be presented in the "Parametric Release of Pharmaceutical and Medical Device Products Sterilized with Moist Heat" course. Topics will include the history of parametric release, limitations of the sterility test, sterilization science (microbiology and thermal science), essential elements of a parametric release program, recommended submission content and a case study on the application of quality risk management.

Want to learn more about contaminates? Join us at our training institute in Bethesda, Md. for the Environmental Mycology Identification Workshop. Taught by TRI's expert instructor **John Brecker**, Senior Mi-

crobiologist, Quality Control, Fleet Laboratories, on May 2-4, this extensive three-day, hands-on workshop will give participants an opportunity to identify environmental isolates of fungi using both macroscopic and microscopic techniques. Hands-on exercises will include Genus and species identification for many common, environmental contaminants that can be found in a manufacturing environment.

John will return to Bethesda on June 27-29 to lead the new laboratory course "Basic Microbiology for Pharmaceutical and Biopharmaceutical Industries." This three-day-workshop that will give participants an opportunity to understand the importance of microbiological testing to assure products meet USP guidelines for consumer safety and product quality. Hands-on exercises in this workshop will give a foundation skill level in the basic techniques of aseptic technique, sampling, testing, identification of microbial contaminants and contamination control.

Since TRI also offers in-house training, the cost of traveling shouldn't deter you from attending one of our courses.

If you want to learn more about the courses mentioned here or any of the courses we offer on nine subject areas, visit www.pda.org/courses.

Future Leaders Session to Tackle Issues Facing Jr. Managers continued from page 50

able and that an endotoxin dispersing agent may be necessary to expose the lipid A portion of the endotoxin molecule for activation of the lysate.

In her second case study, she focused on the impact of slope from a bacterial endotoxins test assay of control standard and native endotoxins. She concluded that a slope of regression line for native endotoxin differs significantly from the control standard.

In the Q&A session, the audience was very interested and pleased with the presentations.

Some of the feedback received about this session:

- I thought this was one of the best sessions. I wish that they had more time to speak.
- This was a great session—there should be more like this
- It allowed new faces on the podium, which brought a different prospective
- It is good opportunity to get the young QC staff to talk about the problems they face routinely

The *Future Leaders* session will address issues facing junior managers from across the industry. These new leaders will discuss their current issues, challenges and the way they were able to resolve them. Managers are encouraged to send their staff to participate in the upcoming meeting. Microbiologists themselves are encouraged to be proactive as well. This is a great opportunity to show your talent and expose yourself to the global microbiology audience.

The Parenteral Drug Association and the PIC/S present...

PDA Parenteral Drug Association

2012 PDA Europe-PIC/S Workshop

GMP Inspection Practices and Trends

Participate to an experiment which is also a challenge:

Join an interactive discussion between inspectors and industry sharing experiences gained in GMP inspections. Come for an open forum where inspectors and the site management will present issues raised during inspections. The results of this workshop will be summarized and published by PIC/S.

Topics to be discussed will include:

- Drivers to a success of a "Pharmaceutical Quality Management System"
- Documentation on manufacturing and batch release procedure
- Personnel issues – training
- Sterility assurance incl. filter integrity test (Annex 1, 113)
- Design and maintenance of facility/equipment (incl. dedicated facilities)
- Root cause analysis for an issue/recall
- Design and maintenance of premises
- Potential for contamination (chemical, physical, microbial) - Cleaning Validation
- Observations at API (biotech) facilities
- Implementation of QRM in manufacturing sites

Workshop Co-Chairs

Jacques Morénas, *Head of Inspections AFSSAPS, former Chair of PIC/S*

Stephan Rönninger, *Head External Collaboration Europe/Japan/CEMA, F. Hoffmann-La Roche*

9-10 May 21012
Geneva | Switzerland

PIC/S

https://europe.pda.org/PICS2012

Editor's Message

Other Layers of Regulation

This month we look at various pharmaceutical regulations. The cover story examines the challenges posed to manufacturers because of the discrepancy in state regulations for drug distribution in the United States. This article drew plenty of discussion among the *PDA Letter* Editorial Committee members. We decided, based on their feedback, to work with author **Joanne Hawana,** Associate, Arent Fox, to publish a follow-up article that will discuss examples of regulatory actions based on state law and a case study or two on implementation of various state laws.

It is for good reason that the various U.S. states, the U.S. FDA, the EMA and regulators around the world want to control drug distribution. PDA and the *PDA Letter* have had an eye on the integrity of the supply chain for years as it stands out as one of the weakest areas of drug product quality and safety in an ever expanding global marketplace. Threats of counterfeiting economically motivated adulteration and substandard drug supplies are serious and can harm consumers and manufacturers alike.

Barbara Jentges, PhD, Senior Regulatory Affairs Professional and Managing Director, PhACT, and **Karen Ginsbury**'s, CEO, PCI Pharmaceutical Consulting, piece on the EU's 2011 falsified medicines legislation examines the implications of the new requirement in the European Union to legally mandate GMPs for APIs. While, as the authors point out, this legislation does not change the expectations for API GMPs, but does elevate their prominence legally—further evidence that governments all over the world are concerned about the integrity of drug product supplies.

We are also pleased to present an article by Editorial Committee member **Martha Folmsbee**, Sr. Staff Scientist, Pall, on the benefits and challenges of targeted drug delivery systems. Evolving drug delivery technologies are important not only to patients, but also to innovator drug manufacturers who can use new delivery systems to extend the lifecycle of their products. As Martha's article points out, the use of liposomes and micelles for drug delivery can help drug developers deliver important therapies that have been stymied in development because of low solubility.

Please check out the Science and Regulatory Snapshots! Each month, PDA provides snapshots of its various activities in science and regulation, including reports on interest groups and task forces. This month, in addition to a Task Force Corner in the Science Snapshot, we preview the March/April PDA Journal and include a Journal POV—the editorial by Journal Editor Dr. **Govind Rao.** Assistant Editor **Emily Hough** provides another installment in the *PDA Letter*'s Green Technology series with a look at Shire's recently licensed single-use facility in Lexington, Mass. In the Regulatory Snapshot, the *PDA Letter* spoke with the leaders of the Quality Risk Management Interest Group, which went above and beyond by contributing directly to the development of several PDA Technical Reports, including recently published *PCMO℠ PDA Technical Report No. 54: Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations*.

Don't forget to read articles online at www.pda.org/pdaletter and submit comments online about what you think!

PDA Letter

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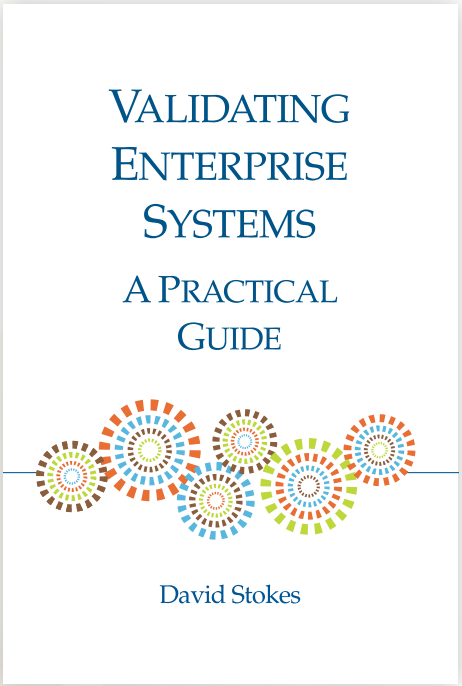

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