People • Science • Regulation

PDA Letter

Volume XLVIII • Issue 9 www.pda.org/pdaletter October 2012

Industry Asks FDA to Look to EU for Biosimilar Regulations

24

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

PDA®
Parenteral Drug Association

The Parenteral Drug Association presents...

2012 PDA/EMA Joint Conference

Compliance: A Prerequisite for Availability of Medicinal Products

- Falsified medicines regulation and it's impact to regulators and industry
- Ensure availability and quality of drugs in a challenging environment
- Risk management to control product shortage due to manufacturing quality problems; business continuity plans
- New trends in manufacturing and controls
- Closing plenary: The regulatory and industry environment 2020

Four Interest Group Meetings:

EU Inspection Trends
Stephan Rönninger, *F. Hoffmann-La Roche*
EU Regulatory
Barbara Jentges, *PhACT*
Quality Systems
Lothar Hartmann, *Crucell*
GMP Links to Pharmacovigilance
John Ayres, *Eli Lilly*

PDA-PIC/S Training: GMP for APIs (ICH Q7)

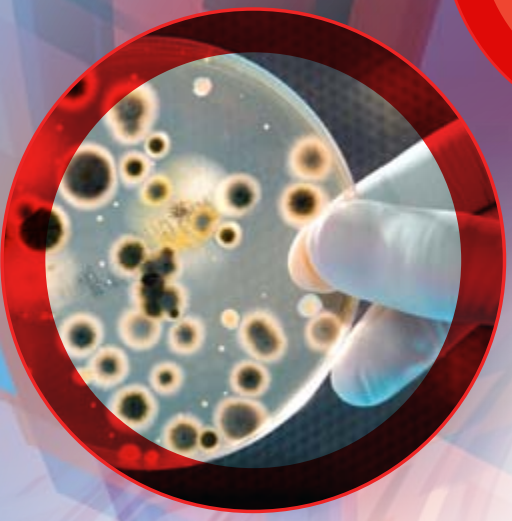
4-7 December 2012

Hotel Cascais Miragem
Lisbon (Cascais) | Portugal

CONFERENCE 4-5 DEC | **EXHIBITION** 4-5 DEC | **TWO-DAY TRAINING COURSE** 6-7 DEC

https://europe.pda.org/PDAEMA2012

Just Added!
New half-day post conference workshop: Understanding the Requirements for Cleanrooms Workshop



The Parenteral Drug Association presents...

PDA's 7th Annual Global Conference on Pharmaceutical Microbiology

Everyday Microbiology – It's All About Control!

October 22-24, 2012

Bethesda North Marriott Hotel | Bethesda, Maryland

Bring back valuable first-hand knowledge on the role of microbiology, contamination control, risk management in manufacturing, requirements in maintaining sterility of products and services, strategies for maintaining a non-sterile manufacturing environment, and more.

This year, experts in the microbiology field will share with us their visions and expertise, suppliers will introduce their latest equipment and devices that will help us in our daily activities and scientists will present their latest research findings. Hear directly from experts, such as:

- **Matthew J. Arduino,** Dr. PH, Lead Microbiologist, Chief Clinical and Environmental Microbiology Branch, *Centers for Disease Control and Prevention (CDC)*
- **Ebony Arrington,** Scientist, QC Microbiology, *Pfizer, Inc.*
- **Thuy Bui,** QC Microbiology Senior Supervisor, *Pfizer, Inc.*
- **Anthony M. Cundell,** PhD, Director, Analytical Sciences Microbiology, *Merck Research Laboratories* and Vice-Chair, *USP General Chapters-Microbiology Expert Committee*
- **John Metcalfe,** PhD, Senior Microbiology Reviewer, CDER, *FDA*
- **Brandye Michaels,** PhD, Principal Scientist, Biotherapeutic Research, *Pfizer, Inc.*
- **Kalavati Suvarna,** PhD, Consumer Safety Officer/ Microbiologist, CDER, *FDA*
- **Anders Vinther,** PhD, Vice President, Roche Quality Biologics Operating Unit (PTQB), *Genentech, Inc.*

Don't miss the ***Biotechnology Interest Group Session*** led by **Vince Anicetti,** Adjunct Professor, *Keck Graduate Institute/ PDA* Fellow, Science and Regulatory Affairs—an informative and interactive session including an update and panel discussion with PDA authors of the *Bioburden and Biofilm Management* technical report team.

Immediately following the conference, PDA's Training and Research Institute (PDA TRI) will be hosting five courses on October 25-26.

Visit **www.pda.org/microbiology2012**
for more information and to register

Exhibition: Oct. 22-23 | Cleanrooms Post-Conference Workshop: Oct. 24 | Courses: Oct. 25-26

PDA Letter

Volume XLVIII • Issue 9 www.pda.org/pdaletter

Cover

Cover Art Illustrated by Katja Yount

Departments

News & Notes

People

Science

Regulation

Programs & Meetings

Contents

Features

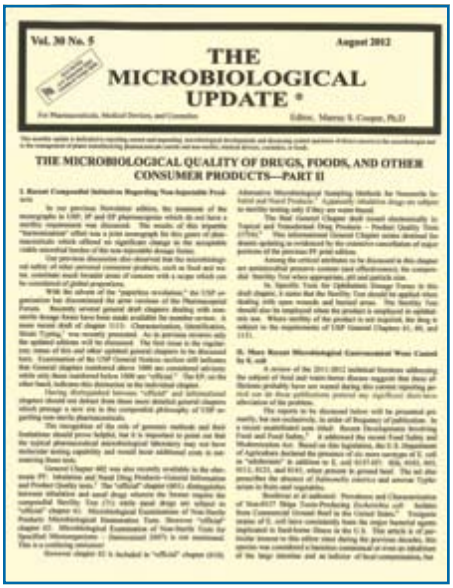
PDA Mourns Passing of Dr. Murray Cooper

It is with great sadness that we inform you of the passing of **Dr. Murray Cooper, a** long-time PDA member since 1983 and editor of The Microbiological Update, on July 29, 2012 in Miami, Fla. He was 89 years old. As a microbiologist and pharmaceutical consultant, Dr. Cooper helped develop and produce key vaccines and diagnostic tests.

In 1950 he received his PhD in Microbiology, following his service in World War II. Until his retirement in 1982, he worked for Lederle Laboratories, now a division of Pfizer. After retiring, he established a consulting service, Microbiological Applications, Inc. and began publishing The Microbiological Update, one of the few recurring industry sources of information on pharmaceutical microbiology.

Additionally, for over 30 years Dr. Cooper served as an active member of the U.S. Pharmacopeial Convention and was inducted as a permanent member in 2000 in recognition of his contributions.

A memorial website for Dr. Cooper will be posted eventually at www.microbioupdate.com.


Vol. 30 No. 5 August 2012

THE MICROBIOLOGICAL UPDATE

THE MICROBIOLOGICAL QUALITY OF DRUGS, FOODS, AND OTHER CONSUMER PRODUCTS—PART II

A copy of the August 2012 *The Microbiological Update* edited by Murray Cooper

Plenty of Opportunities to Connect with Regulators in the Fall

Regulatory Speakers Headline Many Of PDA's Fall Meetings

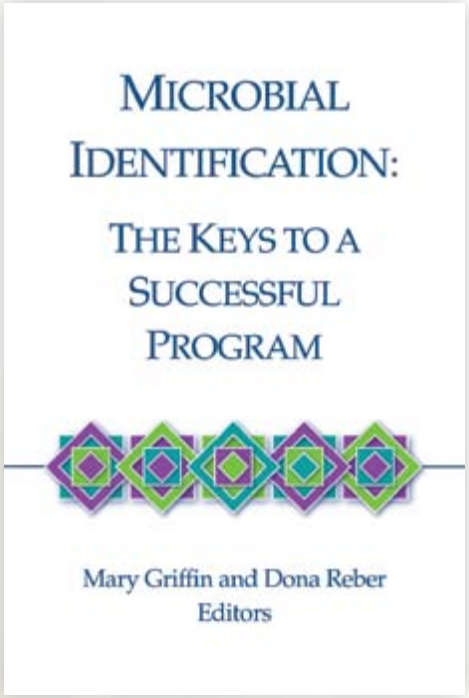
Five U.S. FDA officials will speak at *PDA's 7th Annual Global Conference on Pharmaceutical Microbiology* (Oct. 22 – 24). They are **Julie Bailey,** PhD (CVM), **Cynthia Jim** (ORA), **John Metcalfe,** PhD, (CDER), **Rebecca Rodriguez** (ORA), and **Kalavati Suvarna,** PhD (CDER). **Matthew Arduino,** a Lead Microbiologist with the U.S. Center for Disease Control and Prevention's Clinical and Environmental Microbiology Branch will also speak. At the follow-on workshop, *Understanding the Requirements for Cleanrooms* (Oct. 24), CDER's **David Hussong,** PhD, will speak.

The PDA *Pharmaceutical Quality System (ICH Q10)* Conference in Tokyo, Japan (Nov. 5 – 6) includes presenters from the FDA, Europe (invited) and the Japanese MHLW (invited). FDA's **Rick Friedman** (CDER), who served as a planning co-chair for the event, will provide FDA's perspective.

The *PDA/FDA Pharmaceutical Supply Chain Conference* includes six speakers representing regulators in Europe and the United States. **Gerald Heddell** (MHRA) will join with FDA's **Ilisa Bernstein,** PharmD, JD (CDER), **Fredericke Fricke** (ORA), **Valerie Jensen** (CDER), **Connie Jung** (CDER), and **Greg Goneconto** (OCI) to provide industry the latest regulatory views on this pressing topic.

The planning committee for the *PDA/FDA Vaccines Conference* recently confirmed the participation of FDA's **Michael Havert,** PhD (CBER) and **Michael Pfleiderer,** PhD, of the Paul-Ehrlich-Institute, Federal Agency for Vaccines and Biomedicines.

New Release at the PDA Bookstore



Microbial Identification: The Keys to a Successful Program

Edited by **Mary Griffin and Dona Reber**

Here, in one volume, is a unique compilation rich with vital information. **Mary Griffin** and **Dona Reber** have assembled a team of subject matter experts who share their expertise in this thoughtfully edited volume. This invaluable book on microbial identifications (ID's) includes details about:

- Regulatory and compendia guidance
- Recent regulatory findings
- Viral and mycoplasma ID methods
- Challenges and case studies on fungal ID's
- ID's for pharmaceuticals and biopharmaceuticals
- Use of science-based risk assessment for objectionable organisms
- Maintenance and use of control cultures and facility isolates
- Microbial ID's for medical devices and cosmetics
- Validation of ID systems
- Knowledge management
- The future QC ID laboratory
- The role of rapid micro ID methods
- And much more

www.pda.org/microbialid

The PDA Bookstore's Top 5 Best Sellers

1 GMP in Practice: Regulatory Expectations for the Pharmaceutical Industry, Fourth Edition, Revised & Expanded
By James L. Vesper
Item No. 17269
PDA Member
$225
Nonmember
$279

2 Environmental Monitoring: A Comprehensive Handbook, Volume 6
Edited by
Jeanne Moldenhauer
Item No. 17304
PDA Member
$335
Nonmember
$419

3 Practical Aseptic Processing: Fill and Finish, Volume I and II
Edited by
Jack Lysfjord
Item No. 17283
PDA Member
$425
Nonmember
$530

4 Microbiology in Pharmaceutical Manufacturing, Second Edition, Revised and Expanded, Volume I and II
Edited by
Richard Prince, PhD
Item No. 17280
PDA Member
$375
Nonmember
$465

5 Cleaning and Cleaning Validation, Volume I
Edited by
Paul L. Pluta, PhD
Item No. 17288
PDA Member
$335
Nonmember
$419

www.pda.org/bookstore | Tel: +1 (301) 656-5900 | Fax: +1 (301) 986-1361

PDA Adds to Popular Shipping/Distribution TR Series

Download *PDA Technical Report No. 58: Risk Management for Temperature-Controlled Distribution* Now!

The Risk Management for Temperature-Controlled Distribution Task Force has produced a comprehensive Technical Report that will help manufacturers and distributors apply risk management to distribution practices.

PDA Technical Report No. 58: Risk Management for Temperature-Controlled Distribution is meant to complement ICH Q9: Quality Risk Management, and is part of the series of good distribution technical reports produced by the PDA Pharmaceutical Cold Chain Interest Group, which has developed Technical Reports No. 39 (Cold Chain), 46 (Last Mile), 52 (GDPs) and 53 (Stability Testing).

The goals of risk management in the temperature-controlled distribution of pharmaceutical products, are to:

- Preserve the quality, safety and efficacy of the product
- Understand the distribution process
- Reduce risk
- Understand residual risk
- Improve the effectiveness of the process

Technical Report No. 58 provides specific guidance on the identification, assessment, evaluation, control and review of risks in the distribution process, such as receipt, storage, handling and shipping of bulk, intermediate and finished pharmaceuticals, biological medicinal products and medical devices. It also provides guidance for handling incidents, like temperature excursions, that occur during the distribution process.

The Appendix includes examples of five executed FMEAs for the distribution of products in temperature-controlled containers and thermal packouts and a description of Incoterm definitions.

Authors

Task Force Leader: Erik J. van Asselt, Ph.D., Merck, Sharp & Dohme B.V (MSD), PDA Pharmaceutical Cold Chain Interest Group Leader (EU Branch)

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Olav Berkelmans, Penske Logistics B.V

Rafi k H. Bishara, Ph.D., PDA Pharmaceutical Cold Chain Interest Group Leader (U.S. Branch)

Boriana Cavicchia, PRTM Management Consultants

Bent Christensen, Novo Nordisk A/S

Kelvin M. Chuu, Abbott Laboratories, Inc. (Task Force workgroup leader)

Margaret Clayton, Envirocooler (Task Force workgroup leader)

Mel Drews, Agility Logistics (Task Force workgroup leader)

Herbert Ernst, Ph.D., Sensitech (Task Force workgroup leader)

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Geoffrey Glauser, Health and Human Services, ASPR

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Ian King, Pfizer

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Helena Sjöström, Envirotainer AB

Carsten Thiemt, Arvato Services Healthcare (Bertelsmann AG)

Arno van Klaveren, Air France KLM Cargo

Niels van Namen, DSV Solutions

Tony Wright, Ph.D., Exelsius

PDA Members can download Technical Report No. 58 for free until October 31, 2012. Go to www.pda.org/bookstore

Improve your strike rate

With enhanced Bioavailability for your successful final drug

Developing drugs often seems like scoring a goal that is all boarded up. While your API is innovative and safe, it still may fail. Bioavailability is one key to success. With drug targeting, increased solubility, PK/PD modifiers, and optimized formulation, we help you to bring APIs out of the pipeline and improve your life cycle management. Suddenly, that goal is wide open. Find out how to improve your strike rate at

www.emdmillipore.com/bioavailability

EMD Millipore is a division of Merck KGaA, Darmstadt, Germany

Volunteer

William J. Nichols, Senior Project Manager, PAREXEL

PDA Join Date: 2009

Interesting fact about yourself: My background is in electrical engineering. I started out as an electrician in the late '50s and then went to night school and worked for a few years as a technician at electronic companies in the early '60s. I was fortunate to have been working at ITEK corp. when they had the Lockheed sub-contract to develop the camera module for one of the first satellites launched by our country. This was for the Strategic Air Missile Observation System project. I was the person who wired these camera satellites. It didn't seem like much of a deal then but now 50 years later I can look back and realize that, hey, this was space pioneering work, just before the Mercury program, and the records will show that they never had any malfunctions due to wiring. So, I feel good about having that opportunity.

By the late '60s I was a senior engineer doing electrical design at Raytheon Company. For the next 20 years I worked at several companies as a consultant designing control systems for automated equipment. My last design projects were at the Fluor Corporation. This is where I was first introduced to pharmaceutical validation. Those days we had very few guidelines for qualifying computers as the industry was just learning how to. I recall following guidelines produced by Paul Motise, of the U.S. FDA Drug Quality Compliance Division, and reports by Dr. Ronald Tetzlaff, also of the FDA, for developing validation plans, writing qualification test procedures and for documenting test results.

In the early '90s I was recruited by Kemper Masterson, Inc. where Dr. Clarence Kemper was very active with PDA and was the PDA Chairman in 1995. In the '90s KMI was regarded by many as the experts in the computer validation process, and they were developing many new guidelines and test procedures. As such, Dr. Kemper chaired the development of *PDA Technical Report No. 18: Validation of Computer Related Systems*. By the time KMI was purchased by Paraexel International in the late '90s, Dr. Tetzlaff and a whole staff of retired FDA investigators all worked for KMI as compliance experts. We at SCPDA have been very fortunate to have Dr. Tetzlaff give presentations for us at our meetings on such subjects as "Process Validation–Key Issues Leading to FDA-483's and Warning Letters," "Computer Validation, Then and Now," "Perspectives on Dr. Hamburg's 1st 500 Days as FDA Commissioner," and more.

Areas of Volunteerism: Southern California Chapter: Board (Treasurer) and Business Leaders (lead master), a local organization of small businesses.

Why did you join PDA? I was a member of PDA when I worked at PAREXEL and dropped my membership when I retired in 2001. I moved to California in 2007. The president of the SCPDA, Saeed Tafreshi, recruited me in 2008 to help out in the treasurer position for SCPDA on a temporary basis. The next year I rejoined PDA when the board asked me to take on the treasurer's job more permanently. Saeed and I have a history that goes back a few years as he used to work for me at PAREXEL as a contractor where we completed several validation projects together.

Of your PDA volunteer experiences, which have you enjoyed the most? I have had a chance to get re-acquainted with many people I worked with before retirement, and I have made new professional friends.

How has volunteering in PDA benefited you professionally? You would think that since I am retired there would be little benefit. But that is far from the case. I have made new friends and I have learned about current challenges the industry is facing. Through PDA I feel that I am playing a small part to help the industry meet those challenges. I have also had offers of work through PDA connections.

Which PDA conference/training course is your favorite? I particularly enjoyed taking my son (a sailor and manager for a hospital computer applications group) along on the PDA conference cruise from Newport Beach, CA where he learned new perspectives on FDA requirements.

What would you say to somebody considering volunteering with PDA? DO IT! Don't even think about it. Just do it. You meet the best people and the experts in their respective fields. It's worth every bit of time and effort. I stay in touch with Saeed, Ron and new friends I have made through PDA. You learn what dedication is when you see these experts spending hours of their personal time with their only rewards being the satisfaction of knowing they are working to facilitate improvements in drug manufacturing. If you are in any facet of drug manufacturing you want to be working elbow to elbow with these professionals.

2011 Honor Awards Recipients

The PDA Honor Awards are bestowed on members who provide exceptional leadership and service to the Association, and have been awarded at the Annual Meeting since 1958. The 2010 award winners were announced at the *2012 Annual Meeting* in April, and they will be highlighted in each *PDA Letter* until next year's event. This month we highlight the Distinguished Service Award.

Distinguished Service Award

Distinguished Service Award: This award is given in recognition of special acts, contributions or service that has contributed to the success and strength of PDA. This years recipients for the award were Scott Bozzone, PhD, Lothar Hartmann, PhD, Edwin Rivera Martinez, Vince Mathews, Michael Wiebe, PhD.

Scott Bozzone, PhD

Scott Bozzone is a Senior Manager in Quality Systems and Technical Services-Validation for Pfizer in New Jersey. He has been at Pfizer for 25 years in Quality Operations and Research-Process Development, spending over four years in the Global Employee program. Prior to Pfizer, Scott worked at Revlon Health Care Group (Armour/USV) for several years.

In his current position he is responsible for site support and guidance concentrating on cleaning and process validation, and leads Pfizer's global Validation Community of Practice.

Lothar Hartmann, PhD

Head of Knowledge Management for the Global Quality Department of F. Hoffmann – La Roche.

Lothar has served as Plant Manager and in numerous functions such as Auditing, Quality Systems and External Relations in the Global Quality Department since 1988.

He has spent nearly 10 years as Vice Chairman for the Board of APIC/CEFIC. In this function, he was nominated for the ICH Q7a Expert Working Group. Lothar is currently a member of PDA's Scientific Advisory Board and the PDA Board of Directors.

Edwin Rivera Martinez

Rivera Martinez has been with Sanofi since January 2012 in Global Quality. He serves as the focus point between Chief Quality Officer, the FDA, professional associations and internal quality entities in the United States and ensures alignment of the Sanofi-Aventis Quality System with the evolution of regulations and guidances. Before joining Sanofi, he worked with PAREXEL as a Vice President, providing cGMP compliance services to clients in the United States, Europe and Japan. Previously, he worked with the U.S. FDA for 33 years.

Vince Mathews

Vince is a member of the 2008 Joint PDA/FDA Regulatory Conference Planning Committee and is the leader of the PDA Clinical Trial Materials Interest Group.

He is a Quality Consultant in the Development QA organization at Eli Lilly and Company. In his current role he is involved in the establishment of corporate quality standards for the development and manufacture of investigational new drugs, provides support for an API clinical trial material manufacturing site, provides internal direction on corporate quality matters, and is active in pharmaceutical industry groups.

Michael Wiebe, PhD

Dr. Wiebe is Founder and President of Quantum Consulting based in Redwood City, California. His consulting practice is focused on biotechnology development, biosafety, manufacturing, quality assurance and GMP compliance. He has more than 25 years of experience in the CMC aspects of biotechnology and has held positions at Genentech, BioReliance, IDEC Pharmaceuticals, Biogen Idec, Chiron, and Novartis. Earlier in his career Dr. Wiebe held positions at Duke University Medical School, Cornell University Medical College and the New York Blood Center. He received his PhD in Microbiology from the University of Kansas.

Please Welcome the Following Industry Leaders to the PDA Community

Tayo Adebiyi, Pharmaceuticals

Betsy Anda-Harris, Ortho-Clinical Diagnostics

Adam Angel, Hospira

Addis Arega, MedImmune

Yoshio Arino, Baxter Limited

Jose Arroyo, ARTEK Inc.

Golnaz Badie, Grifols

Sarah Baer, Safety Syringes, Inc.

Jenny Banh, Genentech

Yun Bao, PALL Corporation

Charles Barton, Safety Syringes, Inc.

Suchitra Basu

Timothy Bell, U.S. ARMY

Eileen Benham, Genzyme

Rajesh Beri, Lonza

Adam Bianchi, Cutting Edge Information

Jonathan Blackie, BioMarin Pharmaceutical, Inc.

Kathryn Boino, Shire, HGT

Grant Bomgaars, Baxter Healthcare

Thomas Brady, Elanco

Vicky Breeze, BioMarin

Robin Bruns, Gallus BioPharmaceuticals

Akshay Buch, Aerpio Thearpeutics

Katherine Burri, Shire

Jose Caamcho, Bristol Myers-Squibb

Brian Cameron, 3M

Austin Caudle, NSF International

Alfred Chan, Health Canada

Caifu Chen, PALL Corporation

Lorie Cook, Ben Venue Laboratories

Jean Cookinham, Teva Pharmaceuticals Industries Ltd.

James Courtemanche, AMRI

Glenn Courtney, Otsuka America Pharmaceutical

Casey Coy, NSF-DBA LLC

Stuart Curbishley, University of Birmingham

Philippe De Raeve, Quality Assistance

Prashant Desai, Zydus

James Dey, The Tungsten Shield Group

Deonarain Dikshit, Ranbaxy Laboratories Limited

Jose Dorbecker, Becton Dickinson

Nicole Droste, Becton Dickinson

Philippe Ducarme, Promethera BioSciences

Julia Eatmon, Boehringer-Ingelheim Pharma GmbH & Co. KG

Kurt Ebenhoe, Becton Dickinson

Michelle Eldridge, Genzyme

Zein Elkelany, EIMC United Pharma

Michelle Ellwanger, BD

Dexter Evans, Covidien

Dell Farnan, Genentech

Thomas Fink, Pharmaceutical Manufacturing

Carlos Flores, Bristol-Myers Squibb

Neuza Fukumori, National Commission of Nuclear Energy - IPEN-CNEN/SP

Dereck Gallo, Hospira

Laure Giraud

Stefany Goldman, NSF Pharmalytica

Marie Graves, Sangart

Ashley Greene, Human Genome Science

Sunil Gupta, Bayer Health Care LLC

David Guy, Lonza Biosciences

Nel Alpuerto-de Guzman, Bayer HealthCare

Joseph Haepers, Lantheus Medical Imaging

Jeffrey Hall, Hospira

James Hamilton, JE Hamilton & Associates

Cora Haney, Ben Venue Laboratories

Tomoko Hareyama, Hitachi

Scott Haymond, Evonik Degussa Corporation

John Haynes, Merck (MSD)

Richard Herling, Genentech

Blake Herr, GSK Vaccines

Lauren Hickey, PolyOne

David Holland, Class Biologically Clean, Ltd

Bethany Hoover, BioMarin

Amy Hoskinson, Merck & Co.

David Houck, Pharmakey LLC

Tetsuya Ishihara, Japanese Red Cross

Fay Jarmolowicz, Ben Venue Laboratories

Noriaki Jizou, Mochida Pharmaceutical Co.

Michael Johnson, Entegris Inc.

Steven Junker, Janssen Supply Group

Cara Kaufhold, Alkermes

Xing Yi Kek, Roche

Roger Kelley, Alcon

Nelson Kent, Hospira

Victor Khachatourians, Paxvax

Kim Killackey, Baxter Healthcare

Kathy Kirksey-Wilson, ProPharma Group, Inc.

Jeff Kisslinger, Steris Corporation

Stewart Kohnberg, TSI

John Kolman, BioReliance

Satoshi Komaki, Baxter Limited

Timothy Kotyla, Anterios Inc.

Marie-Alice Lalo, Laboratoire AGUETTANT

Didier Latty, Baxter Healthcare Corporation, Bioscience

Mary Latza, Merck & Company, Inc.

Cris Lebrilla, Amgen

Allen Leduc, AWL Consulting

Edmond Lee, Boehringer Ingelheim Fremont

Cathryn Lemkuil, Scientific Protein Labs

Ying Li, Bayer Heathcare Pharmaceuticals

Celine Liew, National University of Singapore

Carine Logvinoff, Sanofi Pasteur

Ellen Losciuto, Meridian Medical Technologies, a Pfizer Company

Robert Lowery, Hospira

Carolina Lundquist, Envirotainer

Bruce MacKay, MacKay & Associates Consulting, LLC

Alyce Maksoud, Therapeutic Goods Administration

Justine Mann, Hospira

Anne Marie Mannion, A.M. Mannion Pharmaceutical consultants

Djikolngar Maouyo, Lonza

Jay Marshall, Amgen

Brunilda Melendez, ECHO Consulting Group

Robert Melton, Evonik

Dawn Merdaa, Microtest Laboratories

Jennifer Mitchell-Chard, Eden Biodesign Ltd.

Ritchie Mooney, Veltek Associates Inc.

Elodie Muller, CONFARMA France

Yoshinobu Murai, Baxter Limited

Kellie Nadeau, OrganoGenesis

Dustin Neiman, Upsher-Smith Laboratories Inc.

Larry Nelson, ProPharma Group, Inc.

Michael Neu, Abbott

Register by **October 23rd** to receive the final registration discount!

The Parenteral Drug Association presents the...

PDA/FDA Vaccines Conference

Challenges and Opportunities for Providing Vaccines to the World

December 3-4, 2012

Bethesda North Marriott Hotel | Bethesda, Maryland

While advances in science and technology are leading to the research and development of a wide array of new vaccines and novel manufacturing approaches; technical, logistical and regulatory challenges continue to face the vaccine industry, especially in developing countries.

This conference will include industry, regulatory and vaccine experts from non-governmental organizations such as the World Health Organization, PATH and the National Vaccine Program Office along with many FDA speakers such as:

- **Vladimir Chizhikov,** Chemist, CBER, *FDA*
- **Konstantin Chumakov,** PhD, Associate Director for Research, CBER, *FDA*
- **Bruce Gellin,** MD, Director, *National Vaccine Program Office*
- **Marion Gruber,** PhD, Director, OVRR, CBER, *FDA*
- **Arifa Khan,** PhD, Senior Investigator, CBER, *FDA*
- **David Wood,** PhD, Coordinator, Quality, Safety and Standards Team, *World Health Organization*

Highlights of this two-day event include:

- Plenary Sessions on:
  - Global Responsibilities and Challenges
  - Global Regulatory Challenges – Manufacturing in and for Developing Countries
  - Standardization and Testing in a Global Environment
- Vaccines Interest Group Session
- Roundtable Sessions:
  - Quality by Design
  - Rapid Test Methods
- And much more!

Immediately following the conference, PDA's Training and Research Institute (PDA TRI) will host three new courses on December 5-6.

If you are involved in the manufacture and testing of vaccines for preventative and therapeutic purposes, this is a must-attend event.

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

Exhibition: December 3-4 | Courses: December 5-6

The Parenteral Drug Association presents...

2013 PDA Europe

Parenteral Drug Development

A good product development ensures less manufacturing problems and reliable product quality. The topics at the meeting deal with:

- Workshop on VHP decontamination: Risks to development and product stability
- Process issues
- Phase appropriate validation
- Future of clinical trial manufacturing
- Regulatory inspections of clinical manufacturing sites

Including a Site Visit at Boehringer Ingelheim

Register by 14 Dec 2012 and SAVE!

11-13 February 2013

Maritim Hotel
Ulm | Germany

WORKSHOP | CONFERENCE | EXHIBITION

https://europe.pda.org/ParDrug2013

Brett Newswanger, Xeris Pharmaceuticals

Nidia Noel, EZEM Canada

Nobutaka Okada

Elizabeth Olcay, Covidien

Tina Ovbude, Medtronic

Priyabrata Pattnaik, Merck Pte Ltd

Kelly Patton, Ben Venue Laboratories

Leonard Pauzer, Integrated Project Services

Sahran Pegram, Shire

Jody Peraino, Pfizer

Jennifer Perrin, Ben Venue Laboratories

Laura Pflug, Insmed

Melissa Porazzo, Biogen

Jochen Probst, IDT Biologika GmbH

Degalahal Reddy Dr Reddy's

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Virve Reiman-Suijkerbuijk, MPA Medical Products Agency

Anna Risse, Sanofi Pasteur

Tomas Rivera, Boehringer Ingelheim

Marc Rogers, Steris Corporation

M Sarkari, Cephalon

Ben Sauer, Parnell Laboratories Pty Ltd.

Sandra Schinzel, F. Hoffmann – La Roche Ltd

Ramnath Seetharam, Shoram Technical Consultants LLC

Tina Self, Genzyme

Vishal Sharma, Vienni Training and Consulting LLP

Sunil Singh, Ranbaxy Laboratories Limited

Sanjay Singh, Aurobindo Pharma

Melissa So-Brixey, Hospira

Jannette Soto, Bristol-Myers Squibb

Andy Stribling, Aptalis Pharma

Tony Stuckwisch, Kremers Urban Pharmaceuticals Inc.

Shirley Suarez

Tokuhito Sugiyama, Dainippon Sumitomo Pharma

Oleksii Sukhomlynov, Ukrainian State Administration of Medicinal Products

Steven Tackach, Otsuka America Pharmaceutical

Hiroaki Tajiri, Baxter Limited

Kenneth Tan, Baxter Healthcare Corporation, Bioscience

Chin Bin Tan, Merck Pte Ltd

Qiana Thomas, Covidien

Marianne Thompson, Immunogen

Martin Tilly, Envirotainer

Vyacheslav Timokhin, Astecpro

Leyla Toksoy, Alexion

Ivy Tran, Dynavax Technologies

Lorey Trier, Baxter Healthcare Corporation

Robert Tweedy, Hospira

Chris Vallery, Hospira

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Rolando Vega, BMS

Romain Veillon, GSK Vaccines

Steve Voelz, Kremers Urban Pharmaceuticals Inc.

Cristie Vollmar, Cook Pharmica, LLC

Atsushi Watanabe, Hach

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North American Interest Group Leader
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snapshot

Task Force *Corner*

AMD Task Force to Include QbD in Tech Report

Rebecca Stauffer, Emily Hough, and Walter Morris, PDA

The Analytical Methods Development (AMD) Task Force is currently working to include QbD concepts within the method development and qualification framework in their upcoming technical report, along the lines of the Analytical Target Profile concept.

The inclusion of QbD elements is a "hot topic" that touches on all aspects throughout the analytical methods development technical report, according to task force co-leader **Melissa Smith**, MJQuality Solutions.

The task force has been charged with covering the analytical method lifecycle from design/development through qualification for intended use within the overall method lifecycle framework in the technical report. The document will have major sections on development, qualification and method transfer, along with a chapter on the deliverables for validation.

The AMD Task Force worked in cooperation with the Analytical Methods Validation (AMV) Task Force, which published *PDA Technical Report No. 57: Analytical Method Validation* in July (see the July/August *PDA Letter,* p. 6). "The AMD Task Force is harmonized with the AMV Task Force report," Smith explained. Though the AMV report was published first, Smith said that "it relies on the deliverables from the AMD Task Force report to ensure that the method proposed to enter the validation phase of the lifecycle has the appropriate foundation for intended use. So the two Task Forces are linked with the AMV Task Force starting first and then the AMD starting later, with common members on both teams to ensure the two reports are harmonized."

Together the task forces addressed "unique challenges during each stage of the lifecycle," Smith added. "One challenge which seems on the surface to be a fairly simple challenge, but in reality took some time to tackle, was to define well what the term 'qualification' means with respect to a method, its place in the lifecycle and its role, and to have that definition be realistic, appropriate, and best practice." Defining the elements of qualification and deliverables for validation were areas of additional challenge.

"Of course, the inclusion of the QbD elements within the development and qualification lifecycle likely is the most 'hot topic' that touches on all aspects of the AMD report," Smith stated.

As for other elements of the report, Smith said, "we are also working with a method example to use from inception-design through qualification so that there is a common example with a sufficiently detailed data set that will work well to illustrate concepts throughout the document."

Smith also mentioned some other hot topics affecting the task force, including "issues with equipment qualification and potential impact on validation as well as substantive investigations for OOS occurrences are things which are ultimately connected to the analytical method lifecycle and how complete/in-depth the approach to the AMD-AMV lifecycle has been.

"These are matters of some concern," she added. "Also, how well methods are kept up-to-date with the times, the needs of the laboratory, and the current state of the art-and how well the validated method performance is monitored, and what triggers a revalidation--these are all important topics in our industry."

Continued at top of page 20

Technical Report *Correction*

In the final proofing stages for *PDA Technical Report No. 56: Application of Phase Appropriate Quality Systems and CGMP to the Development of Therapeutic Protein Drug Substance,* Task Force member **Renita Johnson-Leva's** name was mistakenly removed from the Task Force list at the front of the document by PDA staff. Task Force co-leader Amnon Eylath discovered the error, and PDA made the appropriate correction and posted the corrected Technical Report on the PDA Bookstore website. Renita and the entire Task Force were provided electronic copies of the corrected version. Renita was an instrumental member of the Task Force, and PDA regrets the error.

Tech *Trends*

Challenges of Manufacturing Cell Therapy Products

Rebecca Stauffer, PDA

Recently, researchers at the University of Sheffield published a paper in *Nature* describing how implanted human stem cells restored the ability to hear in previously deaf gerbils ***(1).*** Another recent study indicates the potential for stem cells to improve mobility in paraplegic rats ***(2).*** Human embryonic stem cells also show the potential to serve as therapies for human patients suffering from spinal cord injury, liver failure, heart disease, macular degeneration, and a host of other ailments.

In fact, the number of applications for investigational new drugs utilizing cell and gene therapy products has increased significantly over the past few years. Yet the burgeoning field also presents unique challenges when it comes to meeting manufacturing regulations.

The *2012 PDA/FDA Joint Regulatory Conference* included the session "Cell Therapy Innovations" that featured three experts on cell therapy and regulation: **Kimberly Benton**, Phd, Deputy Director of the Division of Cellular and Gene Therapies at the U.S. FDA, **Jean Stanton**, Director of Research and Development Compliance, Johnson & Johnson, and **Alice Varga**, Vice President Regulatory Affairs and Quality Assurance at OXiGENE.

The FDA regulates the manufacturing of cellular therapies within the Division of Cell and Gene Therapies, part of the Office of Cellular, Tissue and Gene Therapies. The two review branches within this division are: cell therapy and gene therapy. Somatic cell therapies are regulated as biologics if they meet the following criteria: they are more than minimally manipulated, they are combined with another article other than a storage agent, they are used in a way that is not homologous to their normal function, or they have a systemic effect and are dependent on the metabolic activity of living cells. Based on these factors, FDA regulates clinical development of these products under Investigational New Drug premarket approval.

Examples of cell therapy products include the aforementioned human embryonic stem cells along with stem-cell derived products, such as cord blood, cancer vaccines, immunotherapies, and xenotransplantation products. The latter are cell products that have undergone ex vivo contact with live nonhuman animal cells, tissues, or organs. An example of this would be human embryonic stem cells that have been grown on a mouse feeder layer. Other animal research involving xenotransplantation products has included using pancreatic islets from pigs to treat diabetes, transplantation of ovarian tissue into mice to analyze the development of ovarian follicles, and using porcine cells to treat liver failure.

Continued at bottom of page 20

Journal *POV*

PDA Opposes Mandatory Sterilization Integrity Testing

Rebecca Stauffer, PDA

In the September-October issue of the *PDA Journal of Pharmaceutical Science and Technology*, PDA published the Association's recommendation regarding pre-use/post-sterilization integrity testing of sterilizing grade filters. Ultimately, PDA believes that it should not be mandatory to perform a pre-use/poststerilization test. Instead, it should be up to the discretion of the sterilized filter user based upon a documented risk-based analysis that adheres to ICH guidelines. Ultimately, pre-use testing of a sterilized filter has the potential for adding an additional layer of residual risk to the quality of the product as pre-use integrity testing requires the manipulation of the sterilized filtrate side.

These manipulations which involve wetting and venting when atmospheric conditions provide the potential for microbial contamination present a considerable elevation in risk. It is PDA's perspective that any damage to an integral filter during sterilization is usually caused by exceeding the manufacturer's recommended pressure and temperature parameters. In the event such damage occurred, it would ostensibly be observed in the post-use integrity test. Any product that fails this post-use integrity test must be rejected.

The PDA Pre Use/Post-Sterilization Integrity Test Task Force came to this conclusion in response to the following EU regulation in Annex I, paragraph 113 stating: "The integrity of the sterilised filter should be verified before use and should be confirmed immediatelv after use by an appropriate method such as bubble point, diffusive flow or pressure hold." The task force felt that this wording did not take into account risk evaluation of pre-use/post-sterilization integrity testing in light of the potential for microbial contamination.

To view the September/ October issue of the PDA Journal visit journal.pda.org

snapshot

Task Force Corner continued from page 18

The task force also considers method monitoring, method replacement, revalidation, and supportive elements such as critical reagent control other topics of concern.

According to Smith, the task force is currently organizing the subject matter expert reviewer panel for the next stage of the report process, which it hopes will begin by the end of the year.

About the Expert

Melissa Smith, Founder and Principal Consultant, MJQuality Solutions, has over 30 years experience in quality control, quality assurance, analytical development, qualification and validation for biologics, and devices.

Analytical Methods Development Task Force Members

Melissa J. Smith, Task Force Leader, MJ Quality Solutions

Phillip Ramsey, Task Force Co-Leader, SAIC-Frederick, Inc

Florence Baudoux, GlaxoSmithKline Biologicals

Marta Germano, Pharming

Joachim Leube, PhD, Crucell Holland B.V.

Sheila Magil, PhD, BioProcess Technology Consultants, Inc.

Carl Gustav-Millinger, Swedish Orphan Biovitrum

Dwayne Neal, SAIC-Frederick, Inc.

Michael Rooney, PhD, BiotechLogic

Zoran Sosic, Biogen Idec

Jane Weitzel, Quality Analysis Consultants

Earl K. Zablackis, PhD, Sanofi Pasteur

Tech Trends continued from page 19

As far as regulation, the FDA applies existing rules for drugs and biologics to regulate cell therapies. This represents some challenges due to the unique characteristics of cellular products. For example, Benton noted there is often a limited amount of material that can be used for lot release testing, especially patient-specific lots. Other concerns include timing of manufacturing, testing, and administration as many cellular products cannot be cryopreserved and need to be administered as soon as possible after harvesting. Another issue involves challenges regarding reproducibility due to patient variability and sterility testing as cell therapy products cannot be terminally sterilized.

Still, despite these challenges, the field continues to grow despite being only a decade old.

"We're seeing an increase in maturity in some areas of the cell therapeutic field that we expect to continue," said Benton. "This is an exciting time."

Stanton provided more detail as far as some of the regulatory challenges from an industry perspective.

"There's been some success out there but we've obviously had more fires than success," she said. "I think that the common link you'll notice is in two areas: characterization, both in product and in process, and reproducibility."

She explained that this is due to the lack of experience and knowledge within the industry as these are new products. Other risk factors within industry include the quality of the sourced cells, the variability and complexity of the components used to generate the final product, contamination and cross-contamination, non-cellular components (raw materials, excipients, ancillary materials, etc.), and the specific use and mode of administering the final product.

Stanton identified many of the same manufacturing challenges that Benton cited—storage and distribution, product sterilization, raw materials, and selection of clinical sites. She also noted that the number of suppliers within the industry is very limited. This can present a challenge for companies who may find themselves locked in with a less-than-adequate supplier due to lack of competition.

Donor eligibility of cell sourcing is another issue and has its own set of regulations concerning the testing of donors, specific physician qualifications, and retention of records for traceability.

To alleviate some of the onsite challenges, Benton recommends educating personnel about the differences between cell therapy drugs and more traditional medicines. Since academic researchers are also involved in developing cell therapies, she recommends a "tech transfer" between academics and commercial personnel as there can be a lack of knowledge among academic researchers concerning commercial expectations. Such a "tech transfer" would leverage the strengths and expectations of both industry and academic, noted Stanton.

Varga wrapped up the session by providing a case study of her experience at Geron which conducted clinical trials of a product derived from human embryonic stem cells for patients with spinal cord injuries. As with traditional medicines, the company submitted an IND to the FDA with a CMC review. For testing of cell therapies, CMC's can be complex. Most cell therapy products require aseptic fill and finish; some require cryopreservation and storage under vapor phase LN2. The differentiation process can be labyrinthine due to the heterogeneity of the cells. Plus, little is ➤

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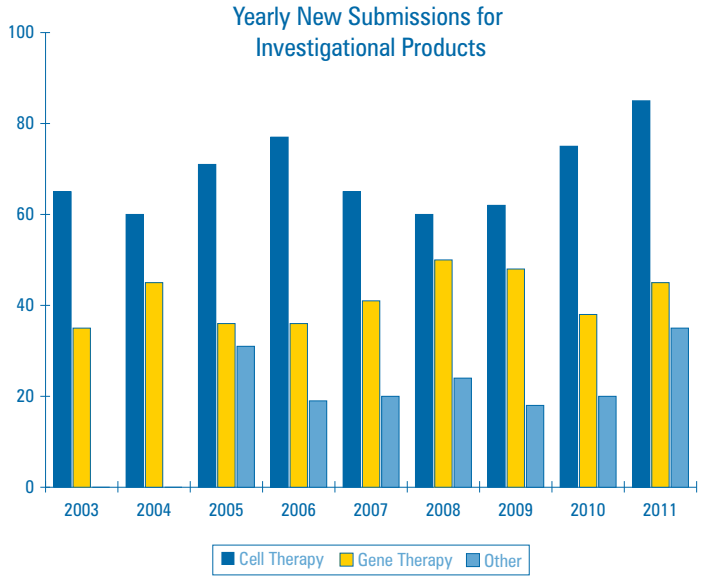

From Kimberly Benton's presentation "Regulation of Cellular Therapy Products: US FDA Perspective"

known how chromosomal variations during the manufacturing process can affect the product.

Based on her experience, Varga recommends treating each product individually and adhering to the somatic cell guidances put forth by the Agency. Regulatory advice, she noted, will also differ depending on the types of cell used. And she urges manufacturers of cell therapies to meet early and often with officials in the Office of Cellular, Tissue and Gene Therapies during the initial testing phases.

Despite the challenges of manufacturing cell therapies, the field shows significant promise as highlighted by the University of Sheffield study. As cell therapies provide the potential to cure serious illness and injury—not just treating symptoms—industry and regulators will need to collaborate on finding solutions to the unique demands of manufacturing these products.

References

1. W. Chen et al. Restoration of auditory evoked responses by human ES-cell-derived otic progenitors. *Nature*. doi:10.1038/nature11415
2. P. Lu et al. Long-Distance Growth and Connectivity of Neural Stem Cells after Severe Spinal Cord Injury. *Cell*. **2012,** *150*,1264-1273.

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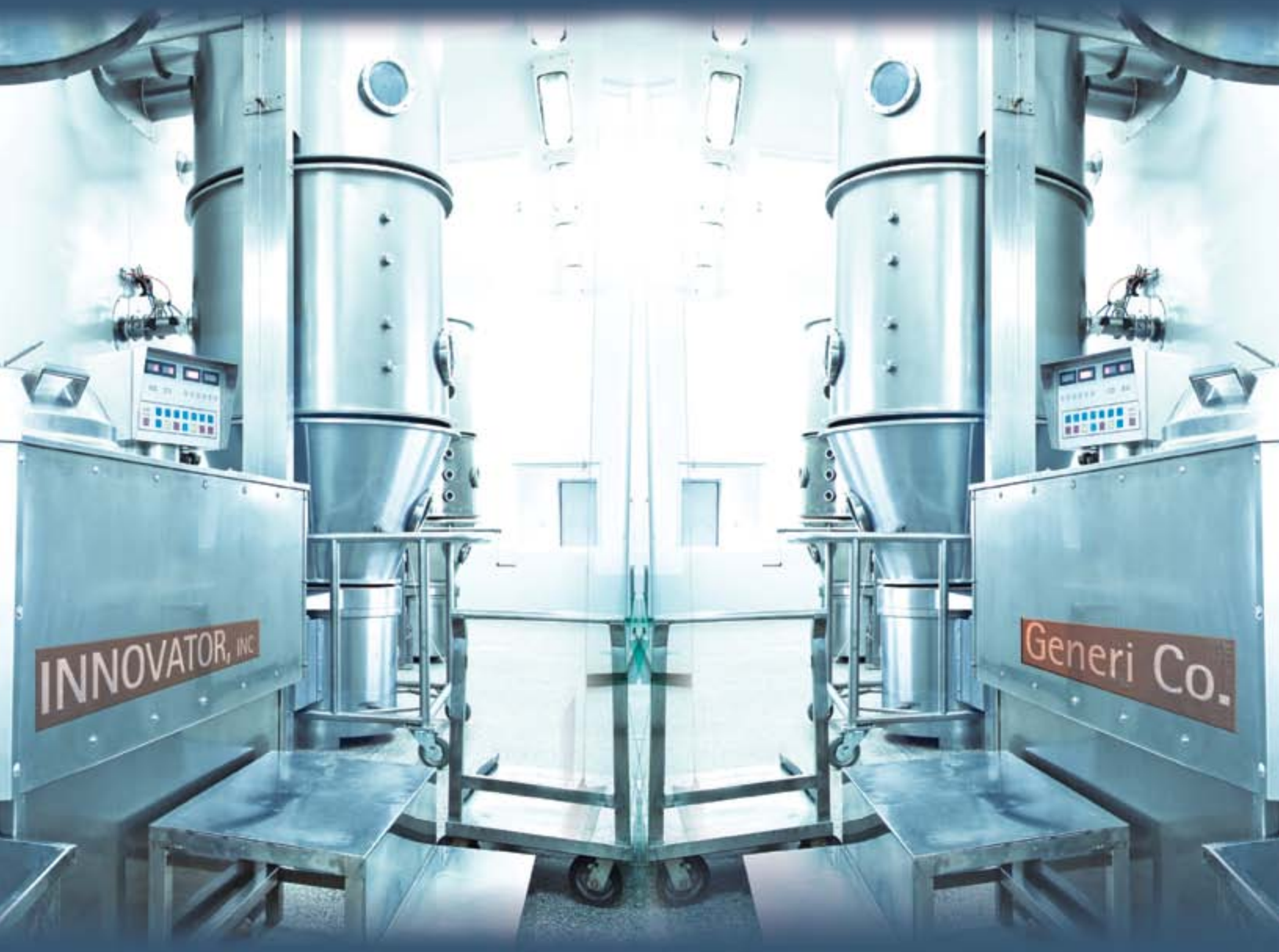
Industry Asks FDA to Look to EU for Biosimilar Regulations

Kathleen E. O'Sullivan, Becton Dickinson and Company



The information contained herein is a synopsis of the key themes that emerged during the course of the public hearing; they are not the opinions of the author.

On May 11, the U.S. FDA held a public hearing at its White Oak Campus in Silver Spring, Md., to obtain input on three recently issued draft guidances relating to the development of biosimilar products. FDA released the draft documents on Feb. 9 as part of its efforts to implement the Biologics Price Competition and Innovation Act (BPCIA) of 2009.

BPCIA established an abbreviated licensure pathway for biological products that are demonstrated to be biosimilar to, or interchangeable with, a reference product. FDA issued a guidance on the scientific considerations and the quality considerations of biosimilar development. The third document is a questions and answers guidance on the implementation of BPCIA.

The goal of the hearing was to offer interested parties an opportunity to raise their concerns and air comments to FDA for consideration in the finalization of these guidance documents. The format of the meeting included a presentation by interested party of eight minutes and a five minute opportunity for questions from a panel of FDA officials from the Office of Chief Counsel (OCC), Office of the Commissioner (OC), Office of Special Health Issues (OSHI), CDER and CBER. The Presiding Officer of the panel was **Rachel Sherman,** MD, CDER. **Leah Christl,** PhD, CDER, OMPT, **Denise Esposito,** JD, CDER, **Steven Kozlowski,** MD, CDER, **Diane Maloney,** JD, CDER, **Heidi Marchand,** PharmD, OC, OSHI, **Maryll Toufanian,** JD, OC, OCC,and **Robert Yetter,** PhD, CDER, CBER also served on the panel. The audience was not invited to ask questions due to time constraints.

Speakers represented pharmaceutical innovator companies, generics, patient advocates, trade organizations, regulators and academia, spoke with a view to raising important issues to FDA in an attempt to influence the anticipated final guidance documents. A number of common themes emerged with presenters voicing their support or opposition on particular topics, such as:

- Clinical studies, extrapolation of data, PK/PD studies
- Patient protection and safety
- Reference of non-U.S.approved products for biosimilarity claims in the United States
- Freedom of medical practice for medical professionals
- Prescribing choices influenced by payors or pharmacist
- Interchangeability, definition and clarification
- Inherent complexity of biological products; potential impact of minor changes
- Innovation, stifle vs. stimulate
- Protection of trade secrets
- Naming conventions; product mix-up avoidance and track and trace
- Communication campaigns and education
- Pre- and postmarket surveillance and the global supply chain
- Europe's established therapy-specific guidances and existing practices
- Totality of the evidence risk-based approach

One of the speakers, **Robert Yapundich** of Alliance for Patient Access and a practicing neurologist, spoke on a number of the aforementioned themes, including the importance of preserving the physician-patient relationship and the physician clinical decision-making process. He went on to discuss the need for physicians, not insurers or other third parties, to safely prescribe powerful therapies such as biosimilars. Yapundich also elucidated the need for unique proprietary names and lot numbers to ensure a robust tracking system to allow very precise tracking of each dose of product to the specific manufacturer in the event of an adverse event.

Representing the Colon Cancer Alliance, Chief Executive Officer **Andrew Spiegel** said that "patients have the right to know exactly what is being put in their bodies. One way to do this would be a unique naming system that includes nonproprietary names for biologics and biosimilars so that physicians, patients, and regulators can easily differentiate products."

He also asked FDA to mandate clinical testing of biosimilars to ensure that they are as safe and as effective as approved products that are already on the market.

On behalf of the Global Healthy Living Foundation, **Alexey Salamakha** stated that because biosimilars are comprised of living, unique, and complex structures, they are not easily replicated; minor changes in producing biosimilars have the potential to help or hurt a patient. He believes it should be openly communicated to patients and stakeholders that biosimilars are not identical to the innovator drug.

Salamakha also spoke out on the crucial need for clinical trials to demonstrate safety and efficacy of biosimilar products. Additionally he said that "as a society, we have to decide whether we want physician-based or profit-based care," and recommended against payer initiated automatic substitution and interchangeability while advocating for keeping biosimilars names and distinctive labels so physicians can make informed decisions and regulatory bodies can track any quality or safety issues.

Marcia Boyle, President and Founder of the Immune Deficiency Foundation, specifically requested exclusion of immunoglobulins from the biosimilars pathway because of the fragility of the class of medicines. She cited the worldwide voluntary withdrawal of an immunoglobulin product in 2010 by a major manufacturer due to increased reports of

Article At a Glance

- The U.S. FDA seeks feedback on three guidances developed under Biosimilar Act
- Industry and patient advocacy groups stressed the importance of unique, noproprietary names for innovator and biosimilar products to avoid mix-ups
- Adoption of existing European standards advocated

thromboembolic events thought to be caused by a minor change in a manufacturing process approved by the FDA. To reinforce her request she revealed the fact that the EMA opted to exclude immunoglobulin from its regulatory pathway for biosimilars.

Representing the interests of the National Kidney Foundation, **Dolph Chianchiano** described an incident surrounding patients suffering pure red cell aplasia as a result of changes in the manufacturing and/or packaging of EPREX, and stated that the kidney community has been especially cautious about the development of an approved pathway for biosimilars and of substituting or alternating between reference drugs. Chianchiano asked the Agency to clarify in greater detail their thoughts around post-marketing safety monitoring in the finalized guidance.

From the Alliance for Safe Biologic Medicines, **Richard Dolinar,** MD, a practicing endocrinologist, presented his organization's objective of ensuring that patient safety is at the forefront of biosimilars policy. Dolinar stated that a way of obtaining this assurance would be through track and trace mechanisms and naming provisions. He urged that "it is absolutely critical that different nonproprietary names be used for the biologic and also for the biosimilar drugs."

Also speaking on the naming conventions of biosimilars, **Marcie Bough, PharmD**, from the American Pharmacists Association, presented on the need to avoid confusion at pharmacy as related to naming of biosimilars. She requested that the guidance should clearly indicate approval of the biosimilar to a reference product, as well as labeling to indicate approval or lack thereof of interchangeability with reference products. Bough recommended avoiding the use of suffixes because of potential errors and complexity in the pharmacy systems.

She also advocated for education and outreach related to biosimilars focusing on "interchangeability, terminology, processes, and logistics to prescribe and dispense biologics and importantly, those that are determined to be interchangeable, differences from current generic process, and necessary resources that are available to health care providers and patients."

Michelle Rohrer, PhD, VP, U.S. Regulatory Affairs, Genentech Roche, spoke on the need for unique naming, labeling considerations, including data and promotion guidance for biosimilar and interchangeable products. Rohrer indicated that "having unique names will avoid unintended substitutions, minimize risk of medication errors, allow for essential elements of pharmacovigilance such as traceability and follow-up of adverse drug reactions, as well as facilitate prescriber-patient decision making".

He urged that "it is absolutely critical that different nonproprietary names be used for the biologic and also for the biosimilar drugs."

She continued that labels should be required to be clear about which indications are supported by clinical trial data and which were granted based on extrapolation from solely the referenced product data. She also recommended that biosimilar labels should state that there is a risk to switching or substituting and should acknowledge that there may be differences between biologic product and that prescribing decisions should be based solely on information in the labeling.

Abbott attorney **Neal Parker,** requested FDA implement the BPCIA in a manner that both increases access to biotherapies for a greater number of patients but also preserves **incentives** for companies like Abbott to continue to discover, study, and get approved new **innovative** biologic products.

His comments focused on two areas, the use of non-U.S. comparator products in biosimilar applications and also protection of reference product sponsor trade secrets during FDA's review of biosimilar applications.

The guidance discusses the potential use of data comparing a proposed biosimilar product to a non-U.S. licensed product to demonstrate that the proposed biosimilar is highly similar to the U.S. licensed reference product.

"Our position is that data from studies involving a foreign comparator product cannot be considered pivotal if the foreign comparator is different than the U.S. reference product," he said.

He then indicated that there would be inherent difficulties in comparing a proposed biosimilar to a foreign non-licensed, non-U.S. reference product and then trying to compare that non-licensed, non-U.S. comparator product to the U.S. reference by adding a third and a different product into the mix possibly increasing residual uncertainties.

On the topic of the protection of trade secrets and the notion of subconscious bias, Parker said "specifically, we think safeguards are needed to ensure that the Agency doesn't unintentionally, inadvertently, but nevertheless, impermissibly use or disclose to a biosimilar applicant an innovator's trade secrets."

Another presenter, **Joseph Miletich,** PhD, MD, Sr. VP, Research and Development, Amgen, said his firm believes it is essential that FDA adopt policies that facilitate the attribution of adverse events and foster manufacturer accountability, conduct a communication campaign about biologics and biosimilars and foster supply chain stability.

Sumant Ramachandra, PhD, MD, Chief Scientific Officer and Head of Research Development Regulatory and Medical Affairs Hospira, the only U.S.-based company with biosimilars on the market in Europe and Australia, indicated support of the FDA's totality of the evidence and stepwise approach to ➤

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approval of biosimilars. He highlighed the value of using non-U.S. reference product with appropriate scientific data bridging ability to reduce the preclinical and clinical requirements using bioanalytical characterization, extrapolation with scientific justification, and the ability to incorporate product differentiation that does not affect clinical safety or efficacy.

This would "enable biosimilar development in a cost-effective and timely manner without compromising quality or safety," he said.

Momenta is an innovative biotechnology company that is focused on the development of analytical tools and methods to advance the science of thorough product characterization. Their technology has enabled the development of generic versions of complex drugs such as enoxaparin, and glatiramer and the company has a strong interest in utilizing the 351(k) pathway.

Roach voiced his support for the allowance of non-U.S.licensed product data to support biosimilarity with appropriate bridging data and stated that "clinical trials should be designed and conducted to provide supportive evidence to the existing structural and functional data set, rather than to be conducted to independently establish safety and efficacy".

Ulm then recommended some changes to the draft guidances based on European biosimilars experience from the past five years

In his presentation, **Jay Sigel, MD**, Chief Biotechnology Officer and Head of Global Regulatory Affairs for Janssen, the pharmaceutical companies of Johnson & Johnson, highlighted three areas of focus: the biosimilarity standard, interchangeability and extrapolation of indications and their relationship to avoidable risk. Regarding his concerns on extrapolation he stated that there "is the possibility that there could be differences between the biosimilar and reference products, differences that haven't been excluded non-clinically that may not manifest in the first indication studied but might be clinically meaningful in another indication".

He asked FDA to prohibit biosimilars from being the opportunity to claim that a biosimilar has attributes that make it better than the innovator.

Momenta Pharmaceuticals Sr. VP of Development/Chief Medical Officer **Jim Roach,** MD supported the FDA's totality of the evidence risk-based and stepwise approach that permits development to proceed and the flexibility for the science to dictate additional requirements, if any, following review of structural and functional characterization data.

Representing the Novartis group, **Mark McCamish,** PhD, MD, pointed out to FDA that "patient access to biologics is increasingly limited by high costs and increasing demand, that high quality clinically-proven biosimilars can fulfill this unmet need" and stated the need for a science-based standard for comparing all biologics.

McCamish indicated that the Novartis group has 50 million patient days' experience in 50 countries with biosimilars. He recommended that FDA not spend a lot of time creating novel guidance on biosimilars, since EMA already has existing product-specific technical guidelines on which to capitalize. He suggested that FDA instead focus on the interchangeability issue and also perhaps work with EMA on establishing a legitimate scientific approach to using a non-U.S. or non-EU reference product.

He also raised the topic of the benefits of conducting analytical and physicochemical characterization in order to negotiate reduced clinical trial requirements and the outcome of this possibly encouraging innovation by means of available health care dollars for the purchase of innovative products.

Speaking on behalf of the European Generic Medicines Association, **Cornelia Ulm** indicated an appreciation of the FDA's draft guidances. She said EGA considers them a "big step forward to global biosimilar development as it now allows sponsors to obtain coherent advice globally".

Ulm credited the guidances for several positives: prepared using sound science; focus on similarity and the totality of evidence; acceptance of non-U.S. licensed reference product, if adequately justified; the possibility of extrapolation of indications; and the acknowledgment of the value of human PK/PD studies to demonstrate biosimilarity. She also acknowledged an appreciation of the fact that clinically irrelevant differences in formulations and container/closure systems may be acceptable if justified.

Ulm then recommended some changes to the draft guidances based on European biosimilars experience from the past five years. Using Europe's definition of the requirement for interchangeability and reconsideration of the need for review of active ingredients were two of her recommendations. Further, she advocated for the use of the same nonproprietary name for biosimilars as reference products, regardless of their interchangeability status.

Kristin Van Goor, PhD, of The Pharmaceutical Research and Manufacturers of America, addressed exclusivity and the need to protect this provision in order to encourage innovation in that it is the basis for investment decisions made by biopharmaceutical companies.

She also discussed naming of biosimilars and the need for nonproprietary names that differentiate a biosimilar from a reference product and other biosimilar products. This lends to post-marketing safety monitoring and to error prevention in the prescribing, dispensing and

Continued at bottom of page 45

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2012 PDA UPCOMING EVENTS

OCTOBER EVENTS

8-11
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www.pda.org/biennial2012

9-10
Developing and Validating a Contamination Control, Cleaning and Disinfection Program
Bethesda, Maryland
www.pda.org/contamination2012

9-10
Pharmaceutical Cold Chain Management & Good Distribution Practice
Berlin, Germany
https://europe.pda.org/ColdChain2012

11-12
PDA Good Temperature-Controlled Management Practices
Berlin, Germany
https://europe.pda.org/TCColdChain2012

15-19
The Universe of Pre-filled Syringes & Injection Devices Conference and Course Series
Las Vegas, Nevada
www.pda.org/prefilled2012

15-19
2012 Aseptic Processing Training Program – Session 5 Week 1
(Week 2: November 5-9)
Bethesda, Maryland SOLD OUT
www.pda.org/2012aseptic

22-26
PDA's 7th Annual Global Conference on Pharmaceutical Microbiology and Course Series
Bethesda, Maryland
www.pda.org/microbiology2012

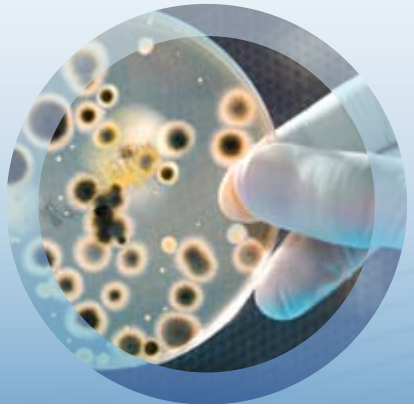
30-1
Validation of Biotechnology-related Cleaning Processes
Bethesda, Maryland
www.pda.org/biotechnology2012

2
Steam in Place
Bethesda, Maryland
www.pda.org/steam2012

6-7
Parenterals 2012 – Contribution of Biologics to Public Health
Barcelona, Spain
https://europe.pda.org/Parenterals2012

8
Recommended Practices for Manual Aseptic Processes
Barcelona, Spain
https://europe.pda.org/RecPrac2012

8-9
Process Validation and Verification: A Lifecycle Approach
Barcelona, Spain
https://europe.pda.org/ProcessVal2012



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8-9
Implementation of Quality Risk Management for Commercial Pharmaceutical and Biotechnology Manufacturing Operations
Barcelona, Spain
https://europe.pda.org/QualityRisk2012

12-14
PDA/FDA Pharmaceutical Supply Chain Conference and Course Series
Bethesda, Maryland
www.pda.org/supplychain2012

13-14
DoE Basics for Validation by Design
Bethesda, Maryland
www.pda.org/doe2012

14-15
Single-Use Systems for Manufacturing of Parenteral Products
Bethesda, Maryland
www.pda.org/suscourse2012

15-16
2012 Pharmaceutical Cold Chain & Good Distribution Practice Conference
Bethesda, Maryland
www.pda.org/coldchain2012

27-29
Risk-Based Qualification of Sterile Drug Product Manufacturing Systems – *New Course*
Bethesda, Maryland
www.pda.org/riskbased2012

DECEMBER EVENTS

3-6
PDA/FDA Vaccines Conference and Course Series
Bethesda, Maryland
www.pda.org/vaccines

4-5
Risk Management in Aseptic Processing
Bethesda, Maryland
www.pda.org/riskmanagement

4-5
PDA/EMA Joint Conference – Compliance: A Prerequisite for Availability of Medicinal Products
Lisbon, Portugal
https://europe.pda.org/PDAEMA2012

6-7
PDA-PIC/S Training: GMP for APIs (ICH Q7)
Lisbon, Portugal
https://europe.pda.org/GMP2012

Next Gen Microbiologists Need to Broaden Their Knowledge of Pharma Business

Rebecca Stauffer, PDA

Preparing the workforce of the future for the pharmaceutical industry is an ongoing challenge industry-wide, but is particularly challenging with respect to specialized experts like microbiologists due to the dominance of other areas of expertise, particularly chemistry. Today, there are close to 4,000 microbiologists working in manufacturing in the pharmaceutical industry, compared to over 13,000 chemists ***(1).*** Ultimately, microbiologists make up just over 8% of the scientific staff employed within the industry.

The pool of microbiologist talent is not getting any bigger, and the proportion of students training to be microbiologists compared to chemists is smaller than in the industry. The number of students graduating with degrees in microbiology has remained unchanged for the past 25 years. In 2010, 2,449 students received bachelor's degrees in microbiology compared to over 12,000 in chemistry according to the Department of Education's National Center for Education Statistics ***(2).***

With almost five times as many chemists as there are microbiologists in the industry and even fewer specializing in microbiology at the academic level, it will become ever more vital to accelerate development of the next generation of pharmaceutical microbiologists, especially as the older generation heads closer to retirement.

At PDA's seventh annual *Global Conference on Pharmaceutical Microbiology,* three speakers will address how to train and lead the future microbiology quality control workforce to ensure that industry knowledge is not lost as the workforce transitions to a new generation. This session, "Preparing the QC Micro Workforce of the Future" (Tuesday, October 23 at 10:15 a.m.-12:15 p.m.) will be moderated by **Ed Balkovic,** Phd, Principal Microbiologist, Genzyme. Later that afternoon, **Kevin Luongo,** Sr. Quality Control Analyst, Shire Human Genetic Therapies, will present his "Top Ten Lessons for a New QC Micro Supervisor" at the "Future Leaders" session.

The *PDA Letter* recently spoke with Lu-

ongo and the other three speakers about the challenges and solutions of leading the new generation of quality control microbiologists.

Neal Machtiger, a consultant with Microbiology Solutions, sees challenges beginning at the academic level as universities shift resources away from microbiology programs.

"In all too many departments, the microbiology program and coursework has been integrated into a biochemistry program," he said. "There are no longer freestanding microbiology programs."

He believes this is due to lack of funding allocated for the field.

"The field is becoming more and more molecular so therefore the money goes where the money goes."

Even well-established microbiology departments at universities are not immune to these challenges.

"Training in classical microbiology is becoming a minor consideration for departments that previously had strong microbiology departments," he added. "I've done a survey of about ten or 12 major universities that have or had true microbiology programs and in a number of cases, I was surprised to learn that some have a course in microbiology and that's it. Boom!"

During his presentation, Machtiger will summarize microbiology programs and courses at about ten major universities and evaluate the strengths of these programs. Then he will relate this information to recommendations from the American Society of Microbiology.

"We're going to make it as interactive as possible because you're going to have the points of view of trade-practicing microbiologists. But we want input from other people who are similarly employed and similarly credentialed so we can get a true picture of what the world looks like out there."

For those microbiologists already working in the field, **Dona Reber,** Sr. Manager, Laboratory Operations, Pfizer, recommends that the existing workforce take the lead with showing new microbiologists the ropes.

"New microbiologists can learn a lot from those that have already been on the bench too," she said. "The technologies are changing rapidly in the micro lab, yet the basic knowledge of organisms cannot be forgotten."

Additionally, she said that new microbiologists will need to gain a more holistic picture of how their work fits in with product development.

"One of the most important skills for the workforce is knowledge of the products and processes that the microbiology lab supports. By going beyond the walls of the microbiology lab, visiting and learning about the manufacturing area, the ➤

microbiologist will add more value to the facility they support."

As far as specific training of microbiologists within a company, **Patrick Spain,** Manager of Technical Training at Genzyme, will touch on his experiences setting up training programs for microbiologists. Although manager of technical training at Genzyme, he began his career in the quality control laboratory. While in this position, he took on a number of training tasks.

"In that time I did a lot of training," he said. "Taking everything that I learned from being a teacher's assistant all through college and applying that to the biotech world."

He then took on a full-time training role within the company.

"The materials that I started bringing into Genzyme, I always did with a micro focus in mind," he said. "I've actually designed an on-the-job training program with an on-the-job training checklist that combines the best of everything I've seen in the industry. I'll be sharing the outline for that and giving everyone that wants a copy."

His presentation will focus on examples of training involving endotoxin and bioburdens testing. He will also discuss how academic training in microbiology differs from on-the-job training.

"Honestly, everything in school is an experiment," he said. "The difficulty is translating everything you learned in school to how to run an assay."

Not surprisingly, leadership within the microbiology field will need to adapt to meet the training challenges of the new quality control workforce. Luongo's presentation at the "Future Leaders" session will cover what he considers the most important skills for managerial microbiologists. These skills are not necessarily technical; in fact, soft skills in customer service and communication will be some of the areas he will touch on.

"Microbiology departments usually have the most dynamic relationships in a QC organization. As a supervisor, you need to develop positive and successful partnerships with customers throughout the business. In some cases you end up spending some time to repair these relationships and because of this, the need for developing and utilizing effective people skills is essential," he said. "To be successful long term, you also need to identify and develop lab staff in this role by having them attend meetings to sit, listen, observe and learn on a regular basis with you."

Additionally, microbiologists in management roles will need to wear two hats—one as a scientist and the other as a business manager

Additionally, microbiologists in management roles will need to wear two hats—one as a scientist and the other as a business manager.

"As a supervisor, I am tasked to run a lab like a business. The challenge is in the case of most microbiologists, like me, we never took a business class in college so the learning curve can be rather dramatic in the beginning," he said. "It is critical for supervisors to gain an in-depth understanding of the day-to-day metrics of a microbiology laboratory from sample testing throughput to cost-per-test. With the advent of lean lab operations, it's more common that financial justification now trumps scientific justification when it comes to capital purchases, headcount, etc."

The U.S. Department of Labor projects the number of microbiologists will increase by 13 percent between 2010 and 2020. The Agency specifically cited the pharmaceutical and biotechnology industries as contributing significantly to the growing demand. Considering that currently there are five chemistry graduates for every one microbiology graduate, the next generation microbiology quality control workforce may prove highly competitive. The four speakers highlighted here will hopefully provide microbiology leadership the tools needed to attract, train, and retain the next generation of microbiologists within the industry.

References

1. Occupational Employment Statistics, Bureau of Labor Statistics: May 2011, data.bls.gov/oes/
2. Digest Of Education Statistics, National Center for Education Statistics: February 2012, nces.ed.gov/programs/digest/index.asp

About the experts

Kevin Luongo is a supervisor in the Quality Control Microbiology laboratory at Shire HGT in Lexington, MA. In this role, he oversees the product testing and microbial identification workflows of the laboratory. Additionally he provides subject matter expertise in microbiological contamination response/control as well as evaluating, validating and implementing microbiology methods and technologies. Mr. Luongo holds a Bachelor of Science in Microbiology from the University of New Hampshire, and has worked in the biopharmaceutical industry for over ten years including time at both Wyeth and Pfizer.

Neal Machtiger, PhD, owns Microbiology Solutions, an independent consulting company providing guidance for applying microbiological control processes for clients in the personal care, paint and coatings, and other consumer products industries. Before becoming a consultant, he worked as a quality control microbiologist for Richardson-Vicks and Procter and Gamble, Colgate Palmolive, International Specialties Products, and Rohm & Haas, a division of Dow Chemicals. He is an active member of the American Society for Microbiology, the Society for Industrial Microbiology, and the Microbiology Committee of the Personal Care Products Council.

Dona Reber is currently Senior Manager of Microbiology and Aseptic Support, Global Quality Operations for Pfizer involved in assessing

Continued at bottom of page 42

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Audit-Sharing Can Lead to Fewer Supply Chain Headaches

Helena Champion, Drug Quality Assurance. LLC

Drug and device companies are often resource-constrained, which can lead to limited resources for auditing contractors and suppliers. While auditing of drug substance and drug product contract manufacturing organizations is a heavy focus, less attention is often given to other materials, such as excipients and chromatography resins, especially during early clinical development. There are, however, safety risks with some commodity excipients and materials (e.g., glycerin and gelatin capsules, to name some recently adulterated materials that made headlines), and there is no way of knowing what material may be adulterated next. It makes sense to use shared resources that are available from independent organizations to help qualify material suppliers and to monitor supply chain issues.

Most adulterated products come from supply chains unknown to the drug or device manufacturer. The European Directive 2011/62/EU (the falsified medicine directive ***(1)***) requires drug manufacturers to verify compliance by manufacturers and distributors of active substances with GMP and GDP by means of onsite audits. For excipients, the Directive requires drug manufacturers to verify that GMPs are followed, but not necessarily by onsite audits.

The U.S. FDA has indicated that industry should know the full supply chain for materials at risk, and Agency investigators are now reviewing supplier qualification more carefully during inspections. The FDA Safety and Innovation Act ***(2)*** passed in July 2012 addresses many aspects of drug safety and supply chain security, including requiring identification, facility identifier and point of contact email addresses of all establishments used in the production of excipients used for some listed drugs. This is a big change, since information on all establishments used in the production of excipients is currently difficult for drug and device manufacturers to obtain.

Supplier qualification of any one material is multifaceted and difficult for a number of reasons:

- Qualification of a supplier is specific to a single manufacturing location and for specific materials and manufacturing operations performed at that location.
- The actual site of manufacture of a chemical or component may be different from the site where it is packaged in small quantities for the customer.
- Often a number of distributors and brokers are involved with the supply of a chemical or component.
- Some suppliers to the pharmaceutical industry get their materials from brokers who may change material sources at any time to reduce costs. The FDA does not require brokers of excipients to register, and very few of them have ever been inspected. How can the supply chain be verified?
- It is usually not clear on the certificate of analysis where testing was performed.

It requires considerable quality expertise and resources to establish an effective supplier qualification program, to perform supplier audits and to discover and verify the full supply chain for materials.

How can we do our best to avoid adulterated and low quality materials?

Risk assessment is useful to decide and prioritize which materials suppliers require more attention. Drug and device companies must purchase materials from suppliers that deal with high quality manufacturers, distributors and brokers ➤

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Third party audits are accepted by the EMA and FDA, as long as they are relevant

who know and monitor the entire supply chain to avoid risk of adulteration That is easier said than done.

How do firms find out the supply chain and whether a supplier really monitors the supply chain, other than by audit after extensive confidentiality negotiations? The effort involved can be significant, therefore it makes sense to share the work with other companies using the same materials. This is best done by using available independent industry resources that help facilitate the use of well-qualified suppliers for pharmaceutical and device materials. A good independent resource is the various audit-sharing programs that have evolved over the last decade or so. Shared audits could obtain and audit detailed supply chain information for excipients that are part of the audit.

Third party audits are accepted by the EMA and FDA, as long as they are relevant. "Relevant" means the audit and report must relate to a particular supplier facility and to materials made at that facility that are used by the drug or device manufacturer and the report needs to be recent.

For example, take audits reports from the International Pharmaceutical Excipients Auditing, Inc. ***(3),*** a subsidiary of the International Pharmaceutical Excipients Council-Americas. Based on recent experience of the author, one can expect IPEA audit reports to cover essential topics, to be well-written, and to be unbiased and truthful. I have seen an IPEA audit report that said the targeted excipient manufacturer did not audit their suppliers—not good news by any means! There are a host of organizations working to facilitate the exchange of reliable audit reports.

IPEC–Americas has offered a number of shared audit reports over the past few years. The organization has about 67 members, mostly raw materials producers and finished drug product manufacturers. IPEA has launched a program to provide IPEA Certification of Conformance with Excipient GMP's. So far seven excipient GMP Conformance Certification Audit Reports are available. Ten other recent audit reports are available, some of which cover multiple excipients made at a particular facility. The IPEA audits evaluate compliance with the NSF 363/ANSI American National Standard for Excipient GMP. IPEA reports can range in cost from $750–$1500 (USD).

Rx-360 ***(4)*** is an organization focused on pharmaceutical supply chain security that currently offers shared audit reports—19 at last count—each covering a particular supplier facility and named materials (raw materials, excipients, chromatography resins, APIs, etc.). The group says they have 378 audit requests, which should result in a large number of useful audit reports in the future. Rx-360 was founded in 2009 by volunteers from the pharmaceutical and biotech industry and their suppliers, with members including 25 drug product manufacturers, 31 suppliers and various associations and auditors. Their website is a useful resource for current supply chain issues. Rx-360 is pricier than IPEA, charging nonmember organizations $5000 (USD) for reports and members $2500.

EXCiPACT™ ***(5)***, plans to offer independent third party certification and supply chain assessment of manufacturers, suppliers and distributors of pharmaceutical excipients worldwide. EXCiPACT™ was founded in 2012 by volunteers from IPEC–Europe, IPEC–Americas, European Fine Chemicals Group and others, to provide independent third party certification of manufacturers, suppliers and distributors of pharmaceutical excipients worldwide. Certification will be to an ISO 9001 GMP Annex, similar to IPEA excipient GMP certification. IPEC–Europe has about 76 members (mostly excipient and drug manufacturers).

The Active Pharmaceutical Ingredients Committee ***(6)*** is a European group (with about 60 members) that offers third party API audit reports. They have conducted three third-party GMP Audits in Germany recently and are likely to do many more in the near future, considering the European Directive to prevent falsified medicines requires on-site audits. You can buy a copy of an audit report for €1500, provided that you purchase an item covered by audit from the supplier and sign a secrecy agreement with the supplier.

In Europe, the QP Association ***(7)*** facilitates the planning of shared audits by providing a database, called QPSHARE, to enable QP's to identify other QP's interested in the same suppliers. Currently this database comprises 284 API and Excipient Suppliers, chiefly in Germany, India, China, France and Italy.

USP has a Verified Pharmaceutical Ingredients program ***(8)*** and so far 15 ingredients and excipients made by companies in the United States, India and Turkey have been verified.

The organizations providing shared audits offer various cost sharing models, and the information is available on their respective websites.

The planned publicly accessible European Union database required by the Directive showing the compliance status and certificates of GMP and GDP issued for entities inspected by Member States will also be a very useful resource to those buying API's.

Pros and cons

There are pros and cons for third party audits. Third party audits are useful for drug product and device manufacturers, particularly smaller companies, start ups and for development programs that don't have the purchasing clout to get an audit at all—the vendor is likely to be cautious about refusing IPEC or a similar organization. Some drug product and device manufacturers may want more extensive information for their particular needs, and it may be necessary for them to ask additional questions from the supplier, but this should still be more efficient


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than doing the audit themselves.

Supplier companies that participate in these various shared audit and certification or verification programs will gain the benefit of fewer client audits, which saves them a lot of effort and expense. In addition suppliers can reduce the inadvertent sharing of information on their equipment and process, which is inevitable when people are physically present in a facility.

I personally believe that supplier companies that participate in these various shared audit and certification or verification programs will gain credibility, since participation conveys a message of genuine commitment to quality. As one who helps companies select and qualify suppliers, I am certainly more inclined to consider qualifying a material supplier named in an audit report done by a reputable independent organization.

It is well worth your time to find out if there are shared audits available for materials and suppliers used for your drug substance and drug product manufacturing and to review any databases that may be available on supplier compliance status and certification. These options will save you time and effort that you can spend on your other materials suppliers that are not evaluated by an independent organization.

I am certainly more inclined to consider qualifying a material supplier named in an audit report done by a reputable independent organization

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About the Expert

Helena Champion, MS, MBA, is Principal Consultant with DRUG QUALITY ASSURANCE, LLC., USA.

Helena has over 25 years of international experience in pharmaceutical and biotechnology manufacturing and testing, medical devices and product development. She was Quality Assurance Director at Wyeth Biotech External Supply /Pfizer and before that held senior positions at Biogen Idec, Genzyme, Millipore and Cambridge Isotope Laboratories/ Otsuka.

Her areas of expertise within manufacturing quality include API (traditional and biotech), aseptic processing of biotech drugs, parenterals, oral liquids/solids, and inhalation products. Auditing and compliance are also areas she works in.

Helena can be contacted at drugqualityassurance@gmail.com or www.drugqualityassurance.com.

Next Gen Microbiologists Need to Broaden Their Knowledge of Pharma Business continued from page 34

aseptic processing facilities, micro-related risk assessments, troubleshooting and investigations, and is a Subject Matter Expert for training on micro related topics including aseptic behaviors. She has a number of publications in the area of microbial identifications systems, microbiology lab training and microbiology risk assessments.

Patrick Spain is the manager of technical training at Genzyme, a Sanofi Company. He began working for the company in 2002 in the chemistry and microbiology quality control laboratories. While in this role, he was the lead trainer on various QC assays, enabling him to move into a training role full time.

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FDASIA Aims to Fund Foreign FDA Inspections

Rebecca Stauffer, PDA

The 2012 Food and Drug Administration Safety and Innovation Act (FDASIA) will allocate new user-fee revenue from generic drug and biosimilar user fees to foreign GMP inspections. Previously, user-fees were not collected on generic medicines and biosimilars, but FDASIA included the Generic Drug User Fee Act and Biosimilar User Fee Act.

Ultimately, the allocations from the new user-fees will enable U.S. FDA inspectors to visit foreign drug manufacturing facilities every two years using risk-based methodologies. Without these user-fees, FDA only has the resources to inspect foreign facilities once every seven to 13 years.

The Agency's risk modeling for inspections will focus on the following areas: the plant's compliance history, record and nature of recalls linked to the site, inherent risk of the processes in place, whether the plant has been inspected in the preceding four years, and whether it's been inspected by a foreign agency. Beginning in 2014, these inspections will be compiled and reported each year to Congress by Feb. 1 of each year.

The FDA is also required to issue a guidance within a year following enactment of FDASIA to define which circumstances constitute denying or limiting inspection, including delays on the part of the manufacturer.

At the same time, the new law allows for the FDA to utilize inspection information acquired from foreign governments or agencies. Another requires all drug manufacturers to register every foreign and domestic site. Each site will then receive a unique facility identifier that must be provided to the Agency along with point-of-contact email addresses. The Agency will be responsible for developing the unique identifier system for facilities and is tasked with developing an electronic database for collecting registration information within two years of developing the unique identifiers.

In fact, since the law requires that all all prescription, generic, and biosimilar applications be submitted electronically, the Agency also plans upgrade certain features of its IT systems.

Related provisions require establishments to submit certain identifying information for excipient manufacturers when submitting product listing information for drugs.

FDASIA also clarifies information requirements from foreign manufacturers importing drugs into the United States. These manufacturers must demonstrate the regulatory status of the drug, provide proof of facility registration with the FDA, and meet CGMP requirements, export regulations, as well as other certifications. The Agency can use its discretion to destroy imported drugs that are not in compliance and valued $2,500 or less. This provision, however, will not take effect until the Agency develops regulations around due process and other areas. These regulations must be issued within two years of enacting FDASIA.

Commercial importers must also register with the agency, including a unique identifier for the associated establishment. For now, this requirement will not take effect as the Agency must develop these regulations within three years as well as provide a reasonable time frame for manufacturers to comply with good importation practices.

The law touches on other areas of the industry besides foreign inspections. Another key provision concerns drug shortages. Manufacturers must now notify the Agency at least six months before life-saving medications are suspended, either temporarily or permanently, from production. This provision comes after the FDA identified 250 drug shortages in 2011. The law requires that by the end of 2013, the Agency submits a report to Congress on drug shortage statistics and actions addressing these shortages; the Agency will then deliver similar reports to Congress no later than the end of each following calendar year. Ultimately, the Agency will form a task force with a specific goal of developing and implementing plans for regulatory actions on this topic.

FDASIA also extends the the opportunity for manufacturers to take advantage of the ability for the Agency to consider single enantiomer drugs as new chemical entities for exclusivity to October 1, 2017.

Additional provisions pertinent to the industry include authority granted to the FDA to review and amend current penalties for drug counterfeiting, changes to the review process for medical devices (including an expedited appeals process), expansion of research into regulation for medications using nanotechnology, modification to language in the Risk Evaluation and Mitigation Strategies provision which allows for manufacturers to submit minor REMS changes without a full reassessment, and accelerated approval requirements for drugs fitting the description of "breakthrough therapies." For the latter, the FDA must issue a draft guidance regarding the expediting the review process for breakthrough therapies within 18 months following enactment of the law. Then, the Agency has to issue final guidance within one year after the comment period on the draft guidance ends.

The Agency will also be required to develop a "strategic integrated management plan" for the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research. This will entail developing a culture of efficiency for both divisions, using results-oriented, outcome-based metrics.

With the passing of FDASIA, the new user fees are expected to increase funding for the FDA by $3.2 billion between 2013-2017. The requirement to subject generics and biosimilars to user fees, reflects a market that is significantly

increasing the usage of generic drugs, according to a report by PricewaterhouseCoopers.

The *PDA Letter* will continue to follow up on FDASIA and keep readers apprised of how industry is responding to changes in the law as well as any additional FDA guidelines and comments.

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Industry Asks FDA to Look to EU for Biosimilar Regulations continued from page 28

administration of biologics.

PhRMA additionally recommends that "evaluation of biosimilars to demonstrate the absence of the clinically meaningful differences should include comparative molecular evaluations of physical chemical and functional properties, as well as preclinical and clinical testing."

Conclusion

While the various speakers represented the interests of their specific organization on the issues, not many failed to mention the overarching goal of patient safety and wellbeing.

This meeting was an invaluable opportunity to air concerns by a variety of stakeholders, to broaden understanding of the proposed regulations as well as to provide input to FDA on the biosimilars guidance and implementation of BPCIA in the United States.

About the Author

Kathleen O'Sullivan has been working at BD Medical-Pharmaceutical Systems for over two years in medical device Regulatory Affairs. Prior to working at BD, she worked in the pharmaceutical industry for 20 years, ten of which were at Wyeth Pharmaceuticals working in both the Medical Research Division and in the vaccine business with responsibility primarily for the Asia/Pacific region. Kathleen has also worked in Regulatory Affairs for both generic and brand pharmaceutical companies. She has provided regulatory consulting services to the pharmaceutical industry and clinical research organizations.

Challenges and Opportunities for Providing Vaccines Globally

PDA/FDA Vaccines Conference • Bethesda, Md. • Dec. 3-4, 2012 • www.pda.org/vaccines

Anthony M. Luttrell, Luttrell Consulting Group, LLC

After the success of the inaugural *PDA/FDA Vaccines Conference* in 2010, we are inviting all to join us at our second Vaccines Conference in Dec. 2012. The conference will focus on both our responsibility to provide vaccines to the world as well as the regulatory and technical challenges to effectively produce and supply these needed medicines. The conference will include industry, regulatory and vaccine experts from the World Health Organization, PATH and the National Vaccine Program Office, along with many U.S. FDA officials. This important event will provide a great venue to both hear about and actively discuss the many important vaccine development, manufacturing and regulatory issues we face today.

While advances in science and technology are leading to the research and development of a wide array of new vaccines and novel manufacturing approaches, technical, logistical and regulatory challenges continue to face the vaccine industry. This is especially true for vaccines needed in developing countries and other international markets. Come hear about novel industry approaches to supply vaccines along with international regulatory approaches to manufacturing and distribution issues, all discussed by industry and regulatory subject matter experts.

This two day event includes many information-packed sessions, vital for today's vaccine professional. Here are just some of the sessions that will be of high interest:

- Learn about global responsibilities and challenges from distinguished speakers from the WHO and the National Vaccines Program Office.
- Discuss global regulatory challenges for manufacturing in and for developing countries with **Cathy Hoath** from Merck along with **Akira Homma,** PhD from Bio-Manguinhos/ Fiocruz (Brazil).

The conference will focus on both our responsibility to provide vaccines to the world as well as the regulatory and technical challenges to effectively produce and supply these needed medicines

- Discover how to navigate the multiple regulatory requirements and guidances for adventitious agent testing and cell substrate characterization with **Arifa Khan,** PhD, from CBER, FDA and **Laurent Mallet,** PhD, of Sanofi Pasteur, Ltd.
- Discuss high-profile supply chain problems and proposed strategies to solve them with **Jeffrey Jones,** Senior Director of Manufacturing Operations, Emergent BioSolutions and **Charles Nicholls,** Jr., Senior Director of Supply Chain Operations, MedImmune.
- Explore the challenges of assuring consistent supply of high-quality excipients and controlling the end product supply chain with real world examples and case studies from recent industry experience.
- Investigate emerging trends in vaccine manufacturing with **Vidadi Yusibov,** Executive Director, Franhofer USA – Center of Molecular Biotechnology and **John E. Butler,** PhD, Global Project Leader, Bayer Innovation.
- Review global regulatory challenges with **Marion Gruber,** PhD, Director, the Office of Vaccines Research and Review, CBER, FDA by understanding the regulatory environments around the globe including licensing requirements, immunizations schedules, lot release, and pharmacopeial specifications.

Please join us for these topics and more! This is a must-attend event for all involved in the manufacture and testing of vaccines for preventive and therapeutic purposes. Pharmaceutical and biopharmaceutical professionals with responsibilities in development, manufacturing, preclinical, quality assurance, quality control and regulatory affairs are encouraged to participate.

TRI will also hold two one-day courses on December 5 and 6 following the conference.

Join Global Movement for Safe Drug Supplies

Pharmaceutical Supply Chain Conference • Bethesda, Md. • Nov. 13-14, 2012 • www.pda.org/supplychain2012

Steve Wolfgang, PhD, FDA, and Lucy Cabral, Genentech, Inc., Conference Co-chairs

Breaches in integrity at various points in the global pharmaceutical supply chain and drug shortages continue to make headlines. Regulators and the pharmaceutical industry continue to work diligently toward assuring the availability and security of the U.S. drug supply. Looking back, much progress has been made to secure the use of safe drugs and components. However, we still have a ways to go before systems for prevention and detection become fully operational. Amid these concerns, legislators have acted in the United States, Europe and China, and regulators and manufacturers are increasingly gaining traction against acts of drug diversion and counterfeiting. New authorities, such as the European Falsified Medicines Directive and Food and Drug Administration Safety and Innovation Act (FDASIA), promise to empower regulators to better oversee the movement of pharmaceuticals in the supply chain. As stated in section 711 of FDASIA, the statutory requirements for good manufacturing practices now emphatically include the implementation of principles of quality risk management throughout the supply chain.

Advances in information (e.g., cloud) and analytical technologies, including the ability to rapidly obtain and share emerging information among stakeholders, also promise to empower manufacturers and regulators to better manage and perhaps avoid risks. Tools implemented by manufacturers to promote and manage drug availability and integrity likewise will prevent patients from being unduly exposed to unsafe or substandard products.

Cooperative efforts between suppliers, manufacturers, distributors and global regulatory agencies are of paramount importance to the success of detection and preventive programs to eliminate adulteration and counterfeiting of medicines. Global supply chain integrity is a shared responsibility.

On behalf of the program planning committee we would like to invite you to attend the *2012 PDA/FDA Pharmaceutical Supply Chain Conference* and join forces to be part of the this global movement: the shared responsibility of integrity and protecting the Global Pharmaceutical Supply Chain.

Focus Continues on Temperature-Controlled Products

Pharmaceutical Cold Chain & GDP Conference • Bethesda, Md. • Nov. 15-16, 2012 • www.pda.org/coldchain2012

Program Co-chair Rafik Bishara, PhD, Leader, *Pharmaceutical Cold Chain Interest Group*

Recently regulators are focused on controlled room temperature products particularly in the following countries: Canada, Israel, Ireland, EU, Turkey, Saudi Arabia, and South Korea. In addition, there is an increased emphasis to expand from the traditional "cold chain" (2-8°C) supply chain temperature management to controlled room temperature products as well as the increased /expanding emphasis on active pharmaceutical ingredients, bulk finished goods, intermediates, critical excipients and critical raw materials to be part of the "end-to-end" supply chain temperature control.

The ongoing increase in the number of temperature-controlled medicines and vaccines is requiring greater global control during the last mile of the supply chain. It is imperative that the industry, their partners and service providers cooperate to ensure that the quality, integrity, potency and efficacy of pharmaceuticals are not compromised during the various handlings until they reach the patient.

The ongoing increase in the number of temperature-controlled medicines and vaccines is requiring greater global control during the last mile of the supply chain

In its seventh consecutive year, the *2012 PDA Pharmaceutical Cold Chain Management Conference* will focus on the various challenges, solutions and case studies regarding the global partnership for handling the temperature controlled supply chain. Representatives from the U.S. FDA, United States Pharmacopeia, industry, academia and cold chain solution providers and partners will discuss, review and debate many of these cold chain issues that pertain to the global cold chain GDP requirements. Migration from cold chain to temperature-controlled GDP and how to make data-based quality decision for ensuring the integrity of the temperature controlled pharmaceuticals in the supply chain will also be discussed.

With the overwhelming number (and volume) of GDP regulations and guidelines from both industry and ministries of health, a special session has been designed to outline/summarize a clear understanding of what is expected and how may the participants prepare their companies for these new requirements. A special focus will be given to global serialization.

For the first time, we have planned a session with members of the Steering Committee of the PDA's Pharmaceutical Cold Chain Interest Group so that participants may ask questions, propose projects and volunteer to serve on current activities. A special working luncheon with many of the exhibitors or sponsors will also take place.

We have designed a session on supply chain integrity and security. This will help attendees learn about some of the current security solutions as well as how to protect their products in the domestic and international supply chain. Presentation and round table discussions have been planned for maintaining chain of custody through real-time supply chain visibility.

Discussions, debates and case studies are scheduled to stimulate and enhance the knowledge of the conference delegates. These will include topics on:

- Quality agreement
- Stability budgets
- Evaluating risk of humidity exposure during distribution
- Risk to drug product quality from shock, vibration and pressure during transportation
- International ambient profile
- Cold chain packaging

On behalf of PDA and Program Planning Committee, I am extending a personal invitation to you and your colleagues to join us for what is promising to be an informative, stimulating and engaging conference!

Register for the *2012 Pharmaceutical Cold Chain & Good Distribution Practice Conference* and receive $250 off attendance to both.

The Parenteral Drug Association presents the...

PDA/FDA Pharmaceutical Supply Chain Conference

Global Supply Chain Integrity – A Shared Responsibility

November 13-14, 2012

Bethesda North Marriott Hotel | Bethesda, Maryland

Counterfeiting, product diversion and economic adulteration are on the rise. We are all aware that these illicit acts can occur at any point in the extended pharmaceutical supply chain. Functional organizations, regulatory agencies and industry must band together in an open and collaborative manner for the sake of patient safety worldwide.

At the *PDA/FDA Pharmaceutical Supply Chain Conference*, you'll hear from experts such as:

- **Ilisa Bernstein,** PharmD, JD, Acting Director, Office of Compliance, CDER, *FDA*
- **Jean-Marc Bobee,** Director, Industry Anti-counterfeiting Strategy & Transformation, *Sanofi Industrial Affairs*
- **John Clark,** Vice President and Chief Security Officer, Global Security, *Pfizer, Inc*
- **Allan Coukell,** Director, Medical Programs, *Pew Health Group*
- **Frederick Fricke, Jr.,** Director, Forensic Chemistry Center, ORA, *FDA*
- **Gregg Goneconto,** Special Agent, Senior Operations Manager – Drug Investigations, Office of Criminal Investigations, *FDA*
- **Gerald Heddell,** Director, Inspection Enforcement & Standards Division, *MHRA*
- **Captain Valerie Jensen,** Associate Director, Drug Shortage Program, CDER, *FDA*
- **Captain Connie Jung,** PhD, Acting Associate Director for Policy and Communications, Office of Drug Security, Integrity and Recalls, *FDA*
- **David Ulrich,** Director, QA, Distribution Global Pharmaceutical Operations, *Abbott Laboratories*
- **Steven Wolfgang,** PhD, Acting Associate Director, Risk Science, Intelligence and Prioritization, CDER, *FDA*

Immediately before the conference, the PDA Training and Research Institute (PDA TRI) will be hosting a one day course, *Developing a Robust Supplier Management Process*, on November 12th.

Visit **www.pda.org/supplychain2012** for more information and to register

Exhibition: November 13-14 | Course: November 12

2013 Annual Meeting to Look at Modern Manufacturing

2013 PDA Annual Meeting • Orlando, Fla. • April 15-17, 2013 • pdaannualmeeting.org

Maik W. Jornitz, Co-chair, Sartorius Stedim Biotech

In our ever evolving industry, information, networking and the recognition of technology trends are key. This probably is more so, when one has to decide upon, design or optimize manufacturing processes to meet quality requirements as well as supply and economical needs. At the same time, modern manufacturing equipment, unit operations, process designs and site implementation are being rapidly developed, introduced and adopted. The pharmaceutical and biopharmaceutical industry is recognizing the challenges and market pressures and actively seeks for more flexible, swiftly deploying and scalable manufacturing solutions.

PDA, as in the past, is supporting this recognition and need for knowledge for modern manufacturing of sterile products. The theme of the 2013 PDA Annual Meeting *Modern Sterile Product Manufacturing – Exploring Best Practices and Seeking New Approaches* shows once again PDA's commitment to support the industry and be the interface of knowledge exchange.

The 2013 Annual Meeting program will be of highest quality addressing the current issues of our industry. As a snapshot here is a sampling of some of the topics that will be presented:

- There will be six keynote speeches given on major topics, like drug shortages, counterfeiting, future technologies and trends. Patient advocates will remind us, why we work so diligently in our profession; finding, developing and delivering cures.
- There will be over 30 talks given in three tracks. The topics are manifold and range from new facility designs, implemented QbD, biosimilars, root cause analysis to novel sterilization techniques. These talks are designed to provide information and knowledge to the attendees, but also to stimulate discussion and the exchange of ideas on topics related to manufacturing technologies and quality approaches. During the sessions, there will be ample opportunity to ask questions, pose problems, and present ideas.
- Fourteen of the PDA's Interest Groups will provide interactive forums for discussion on the most recent developments and trends in their respective subject matter expert areas. The Interest Groups are the place to work directly with colleagues to explore new ideas and develop initiatives, which will be the basis of future efforts to educate, guide, and improve our industry. As such it is a unique opportunity to be a part of the solution, rather than just a recipient of its benefit.
- Fundamental tracks on virus filtration, single-use technologies, visual inspection, process validation, steam-in-place and statistics will be given. These fundamental tracks serve as a glance into the courses held at PDA's Training & Research Institute.
- Following the conference, TRI offers in-depth training courses, which will meet your needs and requirements and enhance your knowledge base.
- Finally and perhaps most importantly, this conference will provide us with the opportunity to meet and network directly with industry professionals, your peers. This is the time to talk, agree, and disagree on questions, approaches and answers.

Patient advocates will remind us, why we work so diligently in our profession

I would also like to take the opportunity to thank the program committee of the 2013 Annual Meeting and PDA team for their tireless support and hard work. If you want to become a program committee member or active volunteer, please do not hesitate to contact PDA or myself. We would like to have you in the teams.

Join us at the Annual Meeting I am looking forward to see you there!

Case Studies Show Best Practices for Quality ICH Q10 Implementations

Pharmaceutical Quality System (ICH Q10) Conference • Tokyo, Japan • Nov. 5-6, 2012 • www.pda.org/japanichq10

Conference Co-Chairs Junko Sasaki, Dainippon Sumitomo Pharma and Masashi Imamura, Nichi-iko Pharmaceutical

Attendees at this year's Pharmaceutical Quality System (ICH Q10) Conference can expect to see real-life case studies on to implement the guidance in addition to learning the specifics of the guidance.

The conference will also show that senior management commitment is key.

Supported by PDA, the U.S. FDA, the Japan Pharmaceutical Manufacturers Association, and the Japanese Ministry of Health, Labour and Welfare, this conference offers a unique opportunity for members of the industry to learn the principles of ICH Q10 from companies that have implemented a pharmaceutical quality system across the product lifecycle according to the ICH Q10 model. These companies now reap the benefits that come from establishing and maintaining a state of control, continual improvement, enhanced regulatory compliance that come from meeting quality objectives every day. Mid-level to senior level decision-makers as well as professionals working on site or at the corporate level in the following areas are invited to attend:

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

Editor's Message

Introducing Rebecca Stauffer, *PDA Letter's* New Writer/Editor

It is my pleasure to introduce new writer/editor **Rebecca Stauffer,** who joined our team September 4. Rebecca is an experienced writer and editor, and also has some publication design experience (most recently with *International Pharmaceutical Quality*). Her background includes interviewing IT executives about banking IT systems and writing about regulations governing pensions.

Rebecca lept right into the fire, conducting interviews of speakers from the upcoming *PDA 7th Annual Pharmaceutical Microbiology Conference* to write an article on the future of microbiologists in the industry. She also helped shepherd a number of additional articles to completion.

Next, Rebecca traveled to the *2012 PDA/FDA Joint Regulatory Conference* to begin the process of familiarizing with PDA's particular areas of interest and establishing contacts with members from industry and government. She also had a chance to meet several members of the *PDA Letter* Editorial Committee who were at the conference.

At the meeting, I asked Rebecca to learn everything she could about the supply chain expectations for the U.S. FDA as outlined in the new FDASIA law. A few days after the meeting, she produced an article on the subject which is included in the Regulatory department of this issue.

As to the rest of the issue, this is second one in a row that includes a feature article related to career advancement/training. These fit nicely with the "Tools for Success" articles we have been publishing for a number of years (sponsored by the PDA Career Center). The *PDA Letter* has received feedback from members that this kind of article is desired, so please provide feedback: morris@pdaa.org.

PLEC member **Kathleen O'Sullivan** submitted the cover story on the hearing FDA recently hosted on the biosimilar act and related guidances. The comprehensive report was well-received by her colleagues on the committee, and the editors feel is extremely helpful to our community.

Finally, **Helena Champion** provided us with the third feature article on third-party auditing. This article is extremely timely. I cannot say how many times I heard speakers mention the importance of third-party auditing during the *2012 PDA/FDA Joint Regulatory Conference*, but it came up quite a bit. Champion's piece provides valuable insight into the topic.

PDA Letter

The PDA Letter is published 10 times per year, exclusively for PDA members.

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2013 PDA ANNUAL MEETING

Modern Sterile Product Manufacturing – Exploring Best Practices and Seeking New Approaches

April 15-17, 2013
The Peabody Orlando
Orlando, Florida

"It certainly was a great meeting. The flow of sessions, vendor booths, and posters ran smoothly and provided opportunity for interesting discussions and interactions."

C. Denoya, *Pfizer, Inc.*

www.pda.org/annual2013

Exhibition: April 15-16 | Workshop: April 17-18 | Course: April 18-19

Calling All Active PDA Members Vote Now!

Online Voting Opens September 10th for the 2013 PDA Board of Directors Election

PDA members, online voting will open on September 10th for the 2013 **PDA Board of Directors Election**, we encourage you to take a moment and vote for your candidates of choice.

To vote is easy, just follow the instructions below. You will need your PDA Member ID and last name to log in.

All PDA members in good standing as of **midnight on August 31, 2012 are eligible to vote**. Voting for this election will close at **11:59 p.m. EST on November 11, 2012**. All votes cast after this date and time will not be accepted.

If you need assistance please contact the PDA Membership Service Department at +1 (301) 656-5900 ext. 119 or howe@pda.org.

Thank you for being a valued PDA member and voting!

Instructions for Voting:

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

Thank you for your participation in this important election process.

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

October 2012

The Universe of Pre-filled Syringes and Injection Devices Course Series
October 18-19 | Las Vegas, Nevada
www.pda.org/prefilledcourses2012

- Combination Products: Principles, Regulations, Current Issues and Solutions (October 18)
- Technical Development of Pre-filled Syringes, Autoinjectors and Injection Pens (October 18)
- Syringes and Elastomers: Understanding the Effects on Quality and Demonstrating the Production Process, Influences and Needs (October 19)

PDA's 7th Annual Global Conference on Pharmaceutical Microbiology Course Series
October 25-26 | Bethesda, Maryland
www.pda.org/microcourses2012

- Alternative Methods for Mycoplasma Testing – New Course (October 25)
- Biofilms – New Course (October 25)
- Evaluation, Validation and Implementation of Alternative and Rapid Microbiological Testing Methods – New Course (October 25)
- Microbiological Issues in Non-Sterile Manufacturing (October 26)
- Investigating Microbial Data Deviations – New Course (October 26)

Validation of Biotechnology-Related Cleaning Processes
October 30-November 1 | Bethesda, Maryland
www.pda.org/biotechnology2012

November 2012

Steam in Place
November 2 | Bethesda, Maryland
www.pda.org/steam2012

2012 PDA FDA Pharmaceutical Supply Chain Conference Course Series
November 12 | Bethesda, Maryland
www.pda.org/supplychaincourses2012

- Developing a Robust Supplier Management Process (November 12)

DoE Basics for Validation by Design
November 13-14 | Bethesda, Maryland
www.pda.org/doe2012

Single-Use Systems for Manufacturing of Parenteral Products – New Course
November 14-15 | Bethesda, Maryland
www.pda.org/suscourse2012

Qualification of Pharmaceutical Systems – New Course
November 27-29 | Bethesda, Maryland
www.pda.org/pharmasystems2012

December 2012

Risk Management in Aseptic Processing
December 4-5 | Bethesda, Maryland
www.pda.org/riskmanagement

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

Laboratory Courses

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