People • Science • Regulation

PDA Letter

Volume XLVII • Issue #8 www.pda.org/pdaletter September 2011

Reduce Your Deviations: Implement a Quality Near Hit Program

20

The Parenteral Drug Association presents...

PDA's 6th Annual Global Conference on Pharmaceutical Microbiology & TRI Courses

Challenges Facing Pharmaceutical Microbiology in the 21st Century

Just Confirmed:
Dennis E. Guilfoyle, PhD, Pharmaceutical Microbiologist International Expert, *ORA, FDA* (Keynote Presenter) & **Judith Noble-Wang**, PhD Lead, Environmental and Applied Microbiology Team, Clinical and Environmental Microbiology Branch, *CDC*

October 17-19, 2011
EXHIBITION: October 17-18 | **COURSES:** October 20-21
Bethesda North Marriott Hotel | Bethesda, Maryland

PDA's 6th Annual Global Conference on Pharmaceutical Microbiology & TRI Courses will feature two keynote addresses. Daniel Fung, PhD, Industry Professor, Food and Science, Kansas State University, is confirmed to speak on "Global Developments of Rapid Methods and Automation in Microbiology: A Thirty Year Review and Predictions into the Future." This talk should be of interest to anyone who currently utilizes or is considering the utilization of rapid methods for microbial detection. Our second speaker is from the FDA, who has been invited to speak on "Challenges Facing Pharmaceutical Microbiologists to Define and Control Objectionable Microbes."

Other planned sessions include discussions on:

- Microbiologist of the Future – Emerging Leaders Panel Discussion
- Ask the Regulators Panels Discussion
- New Technologies
- Microbiological Issues Associated with Reconstitution, Administration, and Holding of Products
- Urban Myths
- Impact of Objectionable Organisms on the Industry and Patient Safety.

This conference will offer an excellent opportunity to meet and interact with global leaders in pharmaceutical microbiology.

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

For details and to register, visit
www.pda.org/2011microbiology

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Cover

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Departments

News & Notes

People

Science

Regulation

Programs & Meetings — North America

Programs & Meetings — Europe

TRI — Education

Contents

Features

PDA Mourns Influential Scientist Ted Meltzer

Maik W. Jornitz, Sartorius Stedim Biotech

On Saturday July 30, we lost **Dr. Theodore H. Meltzer,** a giant of our industry, an expert of filtration, separation and water purification.

Ultimately, as one of the most influential people when it came to understanding the science of sterilizing grade filtration, a pioneer of accumulating the knowledge bits and pieces to a must-use compendium (*Filtration in the Pharmaceutical Industry* by Theodore H. Marcel Dekker, ed., New York, NY, 1986), as well as unbiased ambassador for and to the industry, he never rested and continued to publish, even very recently. This accumulated in the publication of over 150 scientific papers, 12 books and numerous book chapters. He has been an influential PDA member and active volunteer for 40 years, faculty of the PDA TRI, task force member and interest group leader. His accomplishments

The late Ted Meltzer with his wife Xavier in Annapolis, Md. in 1994

to the industry and regulations are too numerous to list, but will resound for years to come.

Having said this, his major contribution to all of us was his humility, sense of humor and focus on science instead of politics. Anybody who ever talked to him or had the privilege to work with him will never forget how special he was as a person. Though, even when one has not met him, one was influenced by his works, his words and professionalism. He embraced people as he embraced life.

Ted was an ambassador to all of us. His legacy will continue as he laid a solid foundation in the field of pharmaceutical science. We can rely and will build on it. He will be missed dearly.

We would also like to thank **Kathryn Anne Robinson,** his niece, who took care of Ted over 15 years. Her tireless support has been invaluable.

Donations can be made to:

Congregation Beth El of Montgomery County
General Fund
8215 Old Georgetown Road
Bethesda, MD 20814

The TRI Biotechnology Lab was dedicated to Ted (center) in 2009. Maik Jornitz (left), Bob Dana, John Shabushnig and Richard Johnson presented Ted with a plaque.

Ted was recognized as an Outstanding Scientist in 2006

"The Gold Sheet"

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- **Ready for every single new development in FDA and other regulatory enforcement?**
- **Absolutely confident in your operation's GMP compliance?**
- **100% prepared for every inspection?**
- **Fully briefed on every promising new manufacturing, supply chain and documentation practice?**

It's a new year ... with new regulatory developments ... new problems ... and new chances for you to improve your performance over last year's with *"The Gold Sheet,"* the biopharma industry's most respected source for comprehensive QA/QC reporting, analysis and guidance.

GET ALL THIS FROM *"The Gold Sheet"*

- **Analysis of developments in FDA regulations and policies**

  It looks like chaos, and it might as well be for QA/QC pros: FDA's twists, turns and complex logic makes staying ahead of inspectors a nightmare. But ***"The Gold Sheet's"*** experienced analysts are trained to make sense of it all and deliver it to you in concise, plain language.

- **State-of-the-art production and quality techniques**

  You can't be everywhere around the globe, but ***"The Gold Sheet"*** can. You get reports straight from manufacturing facilities worldwide on successes and failures, so your own processes stay current and error-free.

- **Trends in quality control practices**

  It's easy to deliver headlines and soundbites. ***"The Gold Sheet"*** goes above and beyond that to uncover the trends and big picture guidance that help you be pro-active in keeping your operations fully compliant.

- **Best practices in supply chain integrity**

  With the global economy making mincemeat of supply chains, many a formerly clean operation has fallen drastically foul of FDA standards. Make sure it doesn't happen to you by reading ***"The Gold Sheet's"*** detailed reports on these issues and guidance in avoiding disaster.

- **In-depth reports on a vast range of GMP issues**

  Micro issues such as sterility, microbial controls, validation, laboratory data integrity, cross-contamination, out-of-spec (OOS) results and stability testing can be create macro problems. Let ***"The Gold Sheet"*** drill into the data and on-the-ground realities to keep these details from escaping you.

- **Drug recall and warning letter data**

  Count on ***"The Gold Sheet"*** to deliver exactly what QA/QC professionals need to know, not just general news reports aimed at executives with no quality responsibilities.

- **Early warning of new directions in FDA enforcement policy**

  "The Gold Sheet" has its ear to the ground and a large staff of reporters in the trenches around the industry who keep you one step ahead of an evolving FDA.

- **Insights from peers on ensuring quality from contract suppliers and service providers**

  Thanks to ***"The Gold Sheet's"*** global contacts, you get bulletproof guidance from the most experienced QA/QC pros in the business, making you look like a hero to your supervisor and shareholders.

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WHO to Establish International Standard for Mollicutes NAT

Micha Nuebling, PhD, PEI

In October 2010, the World Health Organization (WHO) Expert Committee on Biological Standardization (ECBS) initiated a project to establish a WHO International Standard (WHO IS) for *Mollicutes* ("Mycoplasma") Nucleic Acid Amplification Techniques (NAT). The Paul-Ehrlich-Institut, as one of the WHO Collaborating Centers for in vitro diagnostic devices, was asked to conduct this project.

An international reference material for Mollicutes NAT is expected to be an important tool for the standardization of different nucleic acid tests designed for the detection of Mycoplasma contamination of biological materials and/or for diagnosis of Mycoplasma infections. Mycoplasma NATs are increasingly playing a bigger role in the safety testing of biological materials used for the production of biological products, including biological medicines. Furthermore, regulatory authorities in different regions of the world increasingly accept Mycoplasma NATs as replacement of (or in combination with) culture-based Mycoplasma detection methods.

The WHO IS for Mycoplasma NAT should be useful for:

- Standardizing NAT assays of different design with a common material
- Performing validation of different methods with the use of a common material
- Reporting quantitative test results by different assays in a common unitage (International Units/ml)
- Expressing analytical parameters (e.g., limit of detection) in a common unitage

In order to evaluate different candidate materials to determine the current consistency of result reporting by different assays and to investigate the suitability of a future WHO IS the Paul-Ehrlich-Institut is asking for volunteers (users or manufacturers of a Mycoplasma NAT) to participate in a feasibility study (set to be published in the autumn/winter 2011).

Participants will receive the panel free of charge and should commit to voluntarily perform and finish the testing in six weeks

NAT assays for this study should be designed to detect a variety of different Mollicutes species (including e.g., *M. pneunomiae, M. fermentans, M. orale* and *A. laidlawii*) which may be included as members of the feasibility panel. Participants will be sent three replicate panels comprising of 12–15 coded members, including lyophilized or liquid frozen Mollicutes preparations as well as negative controls. Each panel should be tested on a three different days in an assay run on each occasion with testing performed in duplicate, if possible. A detailed protocol will be sent with the materials.

Participants should be aware that that the materials are potentially infectious and should be dealt with accordingly. Participants will receive the panel free of charge and should commit to voluntarily perform and finish the testing in six weeks. An evaluation report of the feasibility study will be circulated among participants for comments prior to communication of the results of the study to the WHO ECBS and potential publication. Participants will not be linked to test results or specific assays.

Dependent on the linear range of quantitative assays and/or the limit of detection of qualitative assays dilution of some of the materials might be necessary. The diluent to represent the usual test matrix (e.g., cell culture supernatant) of the participating lab. The diluent will therefore not be provided by the study organizers.

WHO is interested in including different assays in the study and ensuring that there is global representation of participating laboratories. Therefore, it may not be possible for all interested laboratories to participate.

Laboratories interested in participating in the feasibility study were originally asked to notify **Micha Nuebling** from the PEI at micha.nuebling@pei.de by the end of August, but the deadline has been extended to the end of September.

When applying to the feasibility study, please remember to include the following information:

- Name of the participant
- Name and address of the laboratory/organization/company
- Name of the NAT assay
- Commercial assay (manufacturer)/in-house developed assays
- NAT technology (e.g., real-time PCR)
- Detection of Mycoplasma DNA or RNA
- NAT target region (e.g. 16S rRNA encoding region)
- Features of the NAT assay (current result reporting (CT values, copies/ml…), linear range, limit of detection, sample volume for extraction etc.)

The PDA Mycoplasma Task Force has been working with Dr. Nuebling and others on this project since 2009. If there are any questions about the PDA Task Force projects or Mycoplasma, **Barbara Potts,** the leader of the mycoplasma TF, can be contacted at barbarajpotts@comcast.net.

Cast Your Vote at the PDA/FDA Joint Regulatory Conference PDA Booth #65

Calling All Active PDA Members Vote Now!

Online Voting Opens September 5th for the 2012 PDA Officers & Board of Directors Election

PDA members, online voting will open on September 5th for the 2012 **PDA Officers & 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 25, 2011 are eligible to vote**. Voting for this election will close at **11:59 p.m. EST on November 11, 2011**. 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.

PDA Partners with CMC-Vaccines Working Group

Industry Consortium Investigates QbD Potential for Vaccines

Richard Levy, PhD, and Jim Lyda, PDA

PDA entered into a partnership in late May with a consortium of vaccine manufacturers to support and publicize the development of an industry case study designed to demonstrate the potential value of QbD-based scientific data in setting manufacturing processes. The CMC-Vaccines Working Group (CMC-VWG) consists of technical and regulatory representatives from five major vaccine manufacturers: GlaxoSmithKline, MedImmune, Merck, Pfizer and Sanofi Pasteur. The management consulting firm PRTM has been asked by the CMC-VWG to facilitate and manage the overall project.

The goals of the CMC-VWG are to use a case study to:

- Explore and demonstrate how QbD can/should be applied leveraging science-based risk approaches within vaccine development
- Define a vision that will help promote QbD, its concepts and benefits
- Establish a common platform to stimulate discussion related to challenges, expectations and improvement areas among regulated industry, regulators/health authorities and other interested parties

The partnership will allow the CMC-VWG and PDA to effectively promote the scientific content of the case study through conference presentations, training and scientific/technical articles

Tim Durst, PRTM, and PDA's Richard Johnson recognize the PDA/CMC-VWG Partnership at MedImmune's Gaithersburg, Md. location as members of the Vaccines Working Group look on.

At a recent CMC-VWG meeting, held at the MedImmune campus in Gaithersburg, Md., PDA President **Richard Johnson,** accompanied by **Richard Levy,** PhD, PDA's Scientific & Regulatory Affairs Sr. VP., met with PRTM Director **Tim Durst** to sign the non-binding, non-financial agreement during a break in the group's deliberations.

The partnership will allow the CMC-VWG and PDA to effectively promote the scientific content of the case study through conference presentations, training and scientific/technical articles. It is anticipated that once the case study is completed, in late 2011 or early 2012, PDA will host a workshop or related activity to allow the full public exposition of the study and its scientific content. The case study will also be made freely available in the public domain to further sponsor scientific ferment and discussion. It is understood that the case study is not intended to create any new policy or to develop a "gold-standard" for submissions

These efforts should provide benefits to the industry and the health authorities by:

- Making the scientific rationale in regulatory submissions more transparent
- Bringing safe and effective vaccines to the market more quickly
- Making reviews more efficient and decreasing post-approval supplements
- Creating a forum for talking "scientist-to-scientist"

Stay tuned to the *PDA Letter* and PDA's website for further developments on this exciting and unique project.

Good Distribution Tech Reports Available Now

PDA members can download the documents for free until Sept. 30

PDA has published Technical Report 52 and Technical Report 53—available to all PDA members for free download until Sept. 30.

Technical Report No. 52: Guidance for Good Distribution Practices (GDPs) for the Pharmaceutical Supply Chain provides high-level guidance on GDPs, particularly in the areas of stability, distribution control management, performance management and supply chain partner management. The document features a Good Storage and Shipping Practices checklist that can be used immediately.

PDA Guidance for Good Distribution Practices for the Pharmaceutical Supply Chain Task Force Members

Maryann Gribbin, Johnson & Johnson (Task Force Co-Leader)

David Ulrich, Abbott Laboratories (Task Force Co-Leader)

Rafik H. Bishara, PhD, PDA Pharmaceutical Cold Chain Interest Group Leader

Stephanie Bradley, Siemens Healthcare Diagnostics

Bella R. Cohen, PhD, Abbott Laboratories

Emily Badraslioglu, Department of Health and Human Services

Larry A. Gordon, Cold Chain Technologies

Karl I. Kussow, FedEx Custom Critical

Gerry Marasigan, SNC Lavelin Pharma

Elaine Merritt, Johnson & Johnson

Arminda O. Montero, Abbott Laboratories

Johan Nordenberg, Envirotainer

Jeff Seeley, JLS Distribution Packaging

Elyse Smith, Meridan Consulting

Technical Report No. 53: Guidance for Industry: Stability Testing to Support Distribution of New Drug Products delves deeper into the stability studies needed to address the risks that face drug products in the distribution process.

PDA Stability Testing to Support Distribution of New Drug Products Task Force Members

Arminda O. Montero, Abbott Laboratories (Task Force Co-Leader)

Robert H. Seevers, PhD, Eli Lilly and Company (Task Force Co-Leader)

Rafik H. Bishara, PhD, PDA Pharmaceutical Cold Chain Interest Group Leader

Fabian S. de Paoli, GlaxoSmithKline

Maryann Gribbin, Johnson & Johnson

Paul Harber, Eli Lilly and Company

Ian G. King, Pfizer

David Ulrich, Abbott Laboratories

Erik J. van Asselt, PhD, Merck, Sharp & Dohme

Sally S. Wong, Merck and Company

The PDA Pharmaceutical Cold Chain Management Interest Group is driving these reports, and anticipates producing more to cover the seven pillars of GDP:

Stability	Distribution Control Management	Performance Management	Supplier Chain Partner Management	Qualification/ Validation	Continuous Improvement	Import/Export Compliance
Storage Temperature Shipping Temperatures Stability Testing to Support Distribution	Qualification and Training of Personnel Premises and Equipment Material Handling Storage and Inventory Control Transportation Product Disposition and Distribution Product Protection Returns Management Exception Management	Performance Measurement and Reporting Self Inspections Management Review Meetings	Partner Selection Quality Audit Quality Agreements Business Review Meetings	Ambient Temperature Profiles Passive Shipping Systems Active Shipping Facility Qualification Warehouse Management System Validation Distribution Validation Master Plans	Industry Trends Regulatory Trends Requalification	Customs Release Documentation Control Product Tracking

These technical reports are part of a series begun with Technical Report No. 39 (Revised 2007) on cold chain management and Technical Report No. 46 (2009) on the last mile of distribution. Both are available for purchase at the PDA Bookstore, www.pda.org/bookstore.

2010 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 *2011 Annual Meeting* in April, and they will be highlighted in each *PDA Letter* until next year's event. This month we're highlighting 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 Stephen Brown, PhD; Ursula Busse, PhD; Lee Kirsch, PhD; David Matsuhiro; and Kevin Trupp.

Stephen W. Brown, PhD

Brown has been highly committed to PDA. He has been the co-chair of the Biopharmaceutical Development and Manufacturing Conference; subgroup leader for the Facility and Process section of the Biotech IG; and a member of the Single Use Systems Technical Report Task Force.

Ursula Busse, PhD

Busse has participated in many PDA meeting planning committees, moderated many sessions and participates in several task forces. Recently, she has been involved with PDA's Paradigm Change in Manufacturing (PCMO[SM]) Initiative.

Lee E. Kirsch, PhD

Dr. Kirsch served on the Science Advisory Board and his knowledge of industry helped him deftly managed the duties of the PDA *Journal of Pharmaceutical Science and Technology* Editor for nearly a decade (2000-2008).

David K. Matsuhiro

Matsuhiro has a high level of commitment and dedication as the lead instructor for PDA's Training and Research Institute's Aseptic Processing Course, which takes hundreds of hours-per-year. In emergencies, he steps up and fills in as a substitute instructor.

Kevin D. Trupp

Trupp was a key participant with *PDA Technical Report No. 1, Revised 2007, Validation of Moist Heat Sterilization Processes Cycle Design, Development, Qualification and Ongoing Control* and designed and conducted moist heat sterilization research at Hospira in support of the Equilibration Concept discussed in the technical report. He also helped prepare Steam-in-Place training slides for PDA's Training and Research Institute in 2010, was on multiple workshop planning committees and has been a frequent speaker over the past three years. Trupp is also the chair of the Steam-in-Place Task Force.

The Parenteral Drug Association presents...

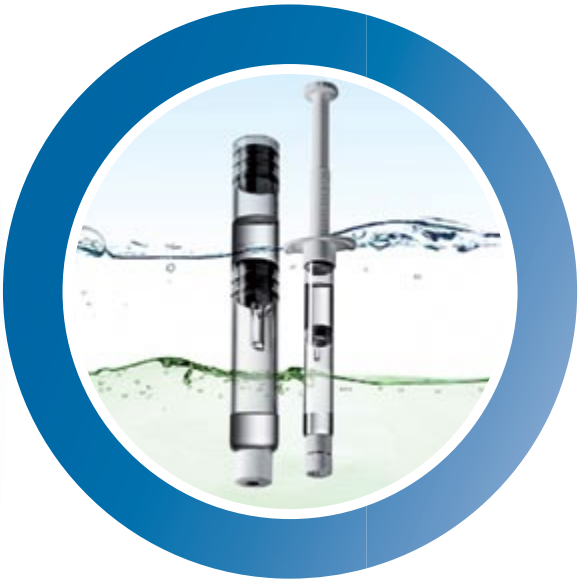
2011 PDA Europe

The Universe of Pre-filled Syringes and Injection Devices

Device Usability and Compliance

Now the Agenda is Posted!

- Daily User Experiences, Challenges and Drivers of Future Trends
- Regulatory, Technical and Marketing Updates
- Factors Influencing Selection and Design of an Injection Device
- Advances in Pre-filled Syringe Development, Manufacturing and Technologies
- Final Container Testing
- Decontamination of Ready-to-Use PFS Systems
- Healthcare, Devices and Materials



Additionally, we are offering our pre-conference workshop:
The Future of Glass as Parenteral's Primary Packaging
and two training courses: **Quality of Glass Containers**
and **Development of a Pre-filled Syringe**

7-11 November 2011

Congress Center
Basel, Switzerland

sponsored by

BaselArea DATWYLER TERUMO SCHOTT glass made of ideas Roche West UNILIFE ONdrugDELIVERY

CONFERENCE 8-9 Nov | **EXHIBITION** 8-9 Nov | **WORKSHOP** 7 Nov | **TRAINING COURSES** 10-11 Nov

https://europe.pda.org/Prefilled2011

Volunteer

Piet Christiaens, Scientific Director, Extractables & Leachables Laboratory, Toxikon

PDA Join Date: 2005

Interesting fact about yourself: My busy agenda during the year necessitates me to build in control-alt-delete moments in my life to help me keep the balance between my professional and personal life. These moments can be spent escaping with my whole family and friends to the French Alps or the North Italian Lake region to do some hiking. I also enjoy stormy evenings in the fall drinking a good glass of wine, listening to some good music and enjoying the warmth of the fireplace.

Why did you join PDA? In 2005, I wanted to know more about the parenteral applications we were testing from an extractables /leachables (E/L) perspective. Attending PDA events and reading scientific articles in the *PDA Journal of Parenteral Science and Technology* also helped me better understand the business we are in.

Of your PDA volunteer experiences, which have you enjoyed the most? I have been volunteering as a speaker since I joined PDA, and I enjoy both the smaller intimate workshops as well as the larger PDA conferences. However, there are two experiences that are at the top of my list: the *2007 PDA Universe of Pre-filled Syringes and Injection Devices* in Berlin which gave me the opportunity to explain more about E/L programs for pre-filled syringes for an audience of more than 400 people! My second favorite experience was the PDA Parenteral Packaging Conference in March 2011, where I was asked—as part of the program planning committee—to organize the "safety assessment" session. As I am not an expert in this myself, I needed to rely on the commitment of other experts wanting to share their expertise in this field (**Dennis Jenke, Steve Beck** and **Carsten Senholt.** Thanks again!).

How has volunteering in PDA benefited you professionally? Volunteering for PDA has helped me to feel the pulse of the pharmaceutical industry and their suppliers working on parenteral applications. It has helped me to understand the business, the sensitivities and future trends in the industry. As a PDA volunteer, the contacts with regulators also helped me to understand their line of thinking which helps us—as a CRO—in designing compliant E/L-testing strategies. During my period as a PDA Volunteer, I also got the opportunity to meet and interact with world class experts in the E/L field, such as **Dennis Jenke, Diane Paskiet, Doug Ball** and many others. These contacts are invaluable!

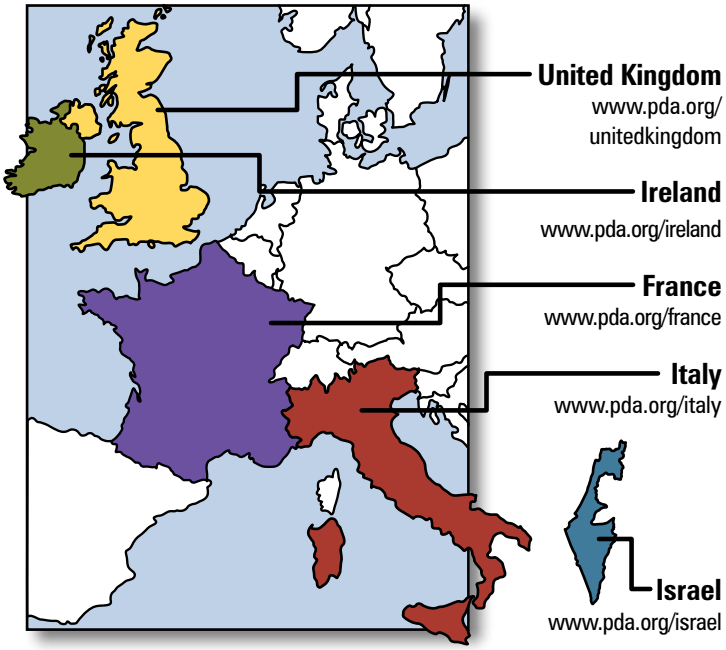
Which PDA conference/training course is your favorite? I have participated as a speaker at many PDA conferences. PDA Europe (**Georg Roessling, Ailyn Kandora, Katharina Keisers-Engstfeld** and all others: congratulations for a terrific job!) does an outstanding job of always getting the top speakers for each subject they want to address in the conference/training course. For me, it is a great honor to be able to contribute as a volunteer to these events. Also, the flawless organization of each event is really remarkable! Out of all the events PDA organizes, *The Universe of Pre-filled Syringes and Injection Devices* is a world-class event. However, although it was the first time it was organized, I think the *Parenteral Packaging* Conference earlier this year could become a successful re-occurring event.

What would you say to somebody considering PDA membership? Do not hesitate. In addition to all the PDA events which will give you the opportunity to interact with peers, the *PDA Journal of Parenteral Science and Technology* gives you online access to a world of excellent scientific articles!

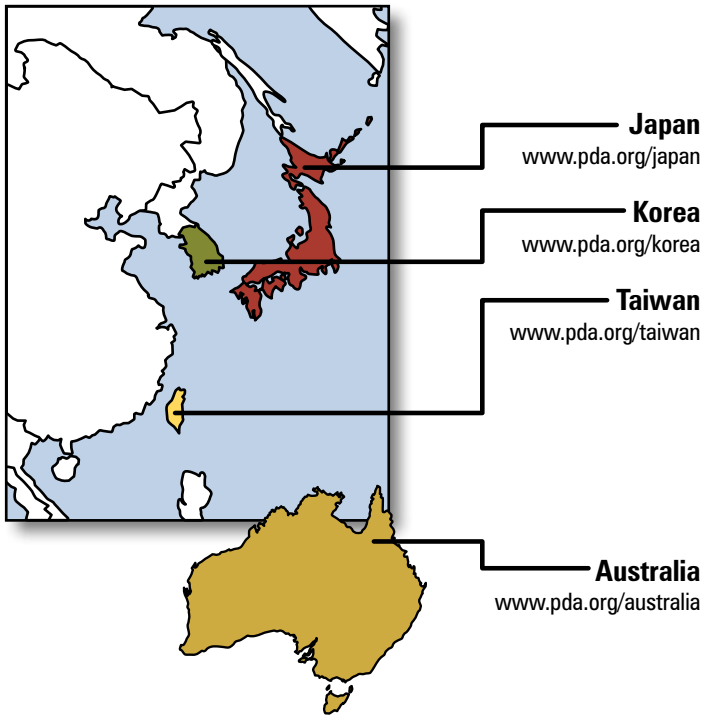
PDA Chapters

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

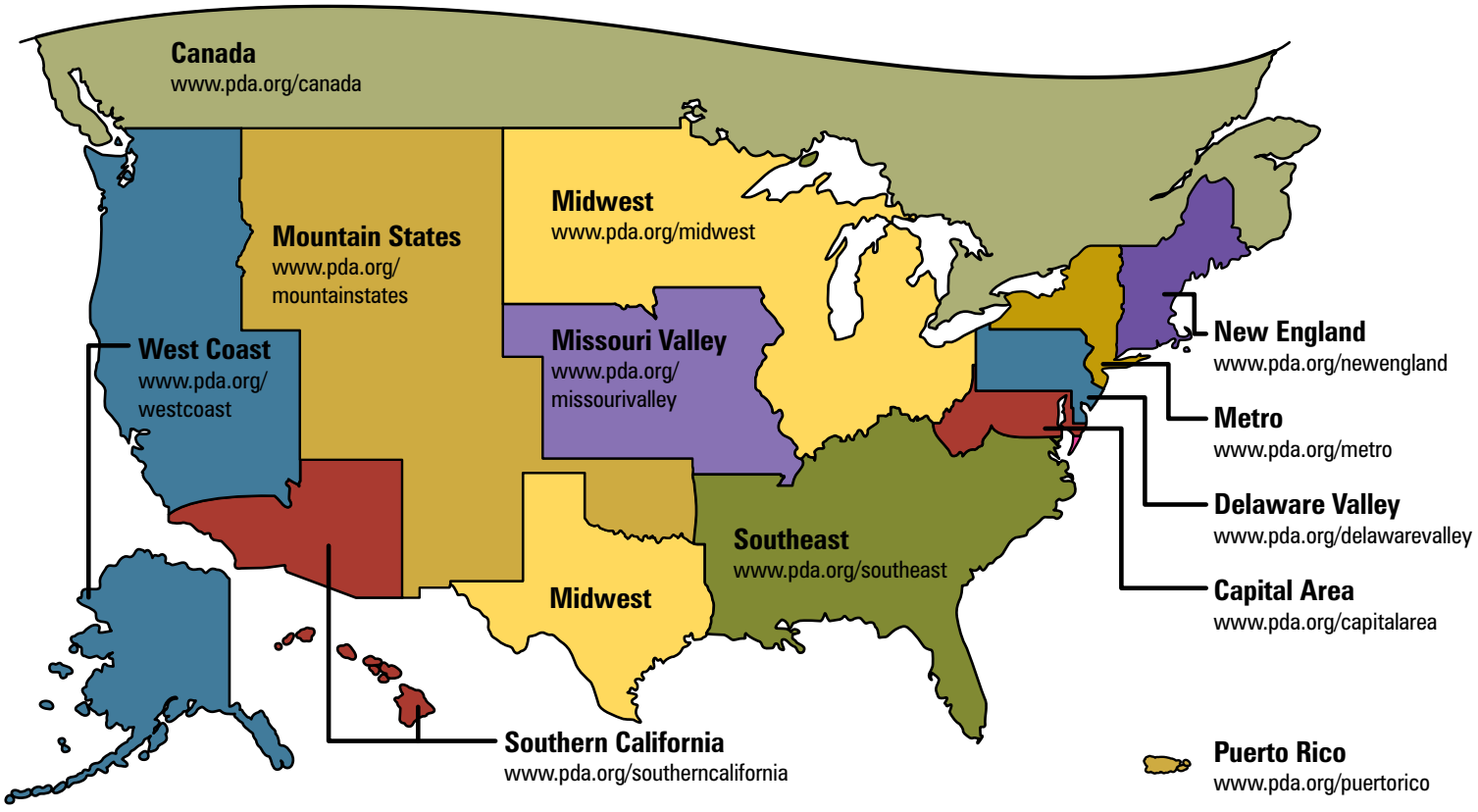
EUROPE

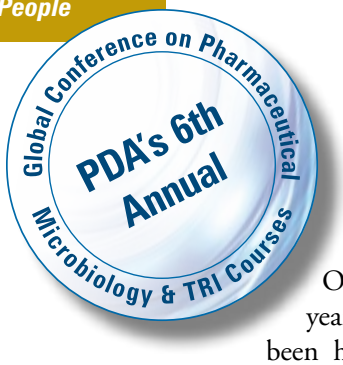


ASIA-PACIFIC



NORTH AMERICA





Breakfast Session Highlights Emerging Leaders

Bethesda, Md. • October 19 • www.pda.org/2011microbiology

Osama (Sam) Elrashidy, Bayer Healthcare

Over the past six years, PDA has been hosting the annual global conference on pharmaceutical microbiology, the only global meeting that is really dedicated to the topics and issues related to pharmaceutical microbiology. The meeting has become the main source of new information and technologies that are mainly focused on pharmaceutical microbiology and one where attendees can meet and discuss similar issues related to their daily work with other microbiologists.

As the number of attendees increase year after year, there is a noticeable increase in junior- and middle-level management individuals attending.

It is clear from this increase that there is an immediate need to extend a hand and serve this new generation of brilliant microbiologists with their daily challenges by establishing a new platform where they can exchange ideas and show their expertise.

This year, for the first time, PDA will dedicate a whole breakfast session to discover and to shed light on these emerging leaders.

This "Microbiologist of the Future" session will present four emerging leaders in the pharmaceutical industry who will be able to share their ideas and views on some of the most current topics and the challenges that they face daily in their own labs.

It is wonderful to have others share how they are are dealing with the same issues we face routinely!

The following speakers will share their experiences with us during the "Microbiologist of the Future" session.

- **Kimberly Wilson-Lamarre,** Manufacturing Quality Scientist, Pfizer, will speak about being a quality scientist in a manufacturing department.
- **Jeanette Skaluba,** Supervisor, Microbiology, Laboratory Systems, Meda Pharmaceuticals, will give a presentation about identifying contaminants.
- **MaryEllen Usarzewicz,** Senior Research Scientist 1, Analytical Research & Development, Bristol-Myers Squibb, will talk about what to do when you see a growth on a negative control.
- **Cheryl Moser,** Research Fellow, Pharm R& D, Merck, will explain how to play hide and seek with endotoxins.

An open discussion will follow these presentations.

By holding a session like this, PDA is not only helping to identify emerging leaders and offering them the opportunity to develop their careers, but also giving them the opportunity to be speakers or poster presenters in future meetings as well as members of PDA task forces.

It is the responsibility of senior management in the pharmaceutical industry to identify junior leaders who should attend this session and prepare and encourage them to participate in future conferences.

It is also a great opportunity for all of us to put our heads together and build our future.

It is the responsibility of senior management in the pharmaceutical industry to identify junior leaders who should attend this session

Fill Out a Survey and Win!

By Participating You Can Make a Dynamic Change at PDA as well as Entering to Win an iPad 2

As a member of PDA, you have the opportunity to help us improve the services that have been tailored to meet your needs. Our goal is to create even greater value for PDA members by focusing on what is important to you.

In order to get your input, we have created a 20 question survey that will take only 10 minutes to complete.

Please fill out the survey by September 30 to be entered into a drawing to win an Apple iPAD 2 and include all of your contact information in response to the first question.

Your PDA membership should provide you with valuable benefits and experiences, and we can't do that without your input. Visit www.surveymonkey.com/s/pdamember to take charge of your association.

The days of comparing apples to apples are over!

Introducing Universal Mycoplasma Detection.

Universal Mycoplasma Detection from ATCC —

a new PCR-based kit for the routine detection of mycoplasma DNA from the leader in cell culture. When it comes to screening cell lines for possible mycoplasma contamination, we know what you're looking for; we designed the Universal Mycoplasma Detection Kit with your needs in mind:

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- **Confirmed Specificity:** Does not detect *E. coli* or mammalian genomic DNA
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snapshot

Popular Micro "Urban Myths" Session Returns

Bethesda, Md. • October 18 • www.pda.org/2011microbiology

Richard Levy, PhD, PDA

By popular demand, we are again offering an "Urban Myths" session at *PDA's 6th Annual Global Conference on Pharmaceutical Microbiology & TRI Courses.*

As this session has been offered for three years, there were many ideas about what should be addressed. I must say, the competition for topics and the three speaking slots was high. Nevertheless, I am pleased to announce our 2011 speakers and their topics.

The session will start with a presentation that focuses on a perennial favorite of our conference attendees, the application of rapid microbiological methods and the challenges we face implementing those methods in a regulated environment. When justifying the use of such methods versus existing microbiological methods, the discussion inevitably gravitates to what is fact and fiction related to the benefits of moving to such rapid methods. So, to help us separate fact from fiction, we have asked the co-chair of the inaugural global pharmaceutical microbiology conference and a continuing conference planning committee member, **Michael Miller,** PhD, President, Microbiological Consultants, to give a presentation on "Debunking the Myth's Surrounding Rapid Microbiological Methods and Their Impact on Pharmaceutical Manufacturing and the Quality of Medicinal Products."

Our second presentation will address an area which has always been a point of fascination for me—the process of microorganism isolation, culturing, preservation and reconstitution post-preservation. We always talk about the number of "passages" and microorganism "recovery" as we strive to repeatedly use both the right organism as well as the one "closest" by several relevant measures to our original isolates. To help us understand what we are really up against in this pursuit, we went to one of the most recognized companies in this area, ATCC, and to long-time PDA member, **Liz Kerrigan,** Director, Standards and Certification, to help us better separate fact from "Myths Surrounding the Preservation, Propagation and Storage of Microorganisms."

And last but not least, following the 2010 publication of *PDA Technical Report No. 51, Biological Indicators for Gas and Vapor-Phase Decontamination Processes: Specification, Manufacture, Control and Use,* there has been considerable discussion about what are the best practices related to the application of biological indicators (BI). And any time best practices are mentioned, the subject of what's fact and fiction surfaces as we try our best to separate what's science from what's not. To help us better understand our use of BI's, we have asked **Dave Adams,** Engineering Specialist, Sterility Assurance, Baxter Healthcare to discuss the "Myths about the Manufacturing, Application, and Use of Biological Indicators in the Verification of Sterilization Processes."

As your session moderator for the second year in a row and as past speaker in this session myself, I anticipate an insightful and informative session with plenty of time for questions immediately following the talks as well as later in the conference. Please join us in October.

Technology *Trend*

AstraZeneca to Remove 1,200 Metric Tons of Greenhouse Gas Annually

Emily Hough, PDA

In June, AstraZeneca announced that it had installed 7,300 solar panels at its Wilmington, Del. campus.

The solar panels will produce energy equivalent to about 10% of the campus' office building electricity use.

AstraZeneca's objectives for the solar project were to increase the use of renewable energy sources, reduce the cost of energy and reduce greenhouse gas emissions globally.

The 1.7 megawatt system will remove about 1,200 metric tons of greenhouse gas emissions annually, the equivalent annual emmissions of 300 cars.

"Producing green electricity is a significant step toward reducing the impact we have on the environment globally," said **Rich Fante,** President, AstraZeneca U.S. & CEO, North America. "AstraZeneca is committed to doing its part to create a cleaner, more energy-efficient Delaware."

This project is the third solar powered project on the Wilmington campus. In 2004, AstraZeneca installed a 20 kW solar energy system and in 2008, it installed a 10kW solar energy system.

AstraZeneca plans on to continue with their energy initiatives in the future.

A look at AstraZeneca's 7,300 solar panels that were installed in June at its Wilmington, Del. campus

Journal *POV*

Wish You Were Here!

Maik Jornitz, Sartorius Stedim Biotech and Govind Rao, PhD, UMBC and Journal Editor

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

PDA excels at "Connecting Science, People and Regulation." We write this from the *2011 PDA Annual Meeting* in San Antonio, Texas, where around 700 members have gathered to exchange ideas and knowledge to move our unique blend of regulatory science ahead. **Maik Jornitz** kicked off the meeting with an anecdote about his recent (mis)adventure in changing a kitchen faucet—suffice it to say, a lack of process knowledge turned a 10 minute job into a messy 1.5 hour affair. The same can be experienced in our day-to-day professional capacities where processes go much smoother and end up meeting defined quality metrics provided there is ready availability of process and product knowledge.

Capturing this expertise is something we are very conscious about. PDA has numerous meetings and task forces that continuously produce authoritative Technical Reports to guide practitioners in our field. For the majority of the 10,000 or so members who cannot attend the annual meeting, we will strive to capture as many of the scientific advances, case studies, and technology reports presented at this meeting in the PDA Journal. We are encouraging presenters to actively consider submitting the work they presented at the meeting for publication in the journal. This will allow us to more effectively capture the tremendous knowledge that PDA members collectively possess. Along these lines, the steady transformation of the PDA Journal to an all-electronic format will facilitate this process. The ability to post comments and/or blog about papers will create and preserve an archive of data, information, and higher level knowledge.

However, this will only work with your involvement. *You,* as a member, are the key to the success of this endeavor. PDA is a society with a very high volunteerism rate and proactive, involved culture—please do contribute actively to the journal. Your feedback and participation are critical.

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Reduce Your Deviations:

Implement a Quality Near Hit Program

John Parrish, Donna Steele, Erin Sorrell, and Jane Keene, Grifols

What if you can preempt quality and compliance problems by training employees to be aware of potential deviations that occur throughout their day and, going further, document them and take proactive corrective measures? Sound a little bit like a Quality version of *Minority Report?* Well, this is exactly what we have done at Grifols Clayton site (formerly Talecris), and the results are noteworthy.

As a continuous improvement initiative, the Clayton site implemented a "Quality Near Hit" (QNH) Program as part of the internal audit process. The program asks employees to take ownership in recognizing potential deviations and proactively take corrective measures to ensure deviations do not occur. This empowers employees by reporting possible issues to management, who further support the program by ensuring corrective/preventative actions are enforced and shared throughout the organization. This program has saved the company time, money and resources.

Objective of QNH: Reduce Deviations

What is a deviation at Grifols? Deviation is defined as an event that represents risk to a product, process or system (the process is out of the normal process/procedure) and is captured in the Incident Tracking System. When pharmaceutical companies refer to deviations certain situations come to mind. A few examples are out of norm, not following standard operating procedure or batch records and out of specification results. At the Clayton site, like most manufacturing sites, deviations are a concern, and we always strive to reduce the number of deviations. In the perfect world (it is our quest), potential deviations would be identified in a Near Hit state.

What is a Near Hit? An unmitigated risk to a process, a product or to compliance:

- An event or error prevented due to detection or recovery
- A system weakness which could cause adverse consequences or risk
- An error caught just before being made
- An error or potential error identified and corrected before becoming a deviation

The tool for employees to use is to ask "*what if*" questions to easily identify QNH situations. Example: "*What if* mislabeled material had been added to a batch?"

The Difference Between Deviation and QNH

A deviation actually occurs and may affect products, processes or systems. Investigating a deviation's cause is reactive (in that it is a reaction to the resulting problem). In a QNH observation, the deviation is prevented because an employee notices a potential problem before it affects products, processes or the systems. Investigating and mitigating the potential cause of a QNH is a proactive quality activity.

Build Upon Existing Programs

The Development Team did not want employees to label this training as another "flavor of the month" training program that may not be continually and fully supported by the organization. The team decided to build upon existing training programs already in place.

The FOCUS training program provided the foundation for QNH.

FOCUS stands for:

Focus on the job

Organize our work

Check the procedures (SOPs, BPRs)

Use the right tools and equipment

Sum it up before moving on to the next step

The QNH Program complements several components of the training system because employees must be FOCUSsed on their tasks and surroundings to observe QNHs.

The organization already had a Safety Near Hit Program in place, so employees were already familiar with the Near Hit concept for safety. The company's Environmental Safety Security Department established the Safety Near Hit Program, so the Development Team met with them to discuss lessons learned, which included the following:

1. All Near Hits carry the same weight. All observations had to be investigated no matter how small the issue might seem, and all employees are given an equal voice in reporting QNHs.
2. The program was not for punitive purposes. Employees submitting a Near Hit could remain anonymous, and those who performed a task incorrectly were not punished.
3. Employees preferred to submit electronically into a database.

Development

The Development Team facilitated meetings with the Manufacturing, Quality and Engineering groups to identify potential QNHs examples. These early meetings provided support and buy-in to the new program. From the expanded meetings with stakeholder departments, the team wanted to produce a training module with video examples of frequent QNHs. The training module would help employees ask "what if" questions from QNH situations.

After the meetings the Development Team realized there were recurring examples that were common to all areas. Some of those examples were reenacted in the video portion of the training to show how to identify events in a Near Hit state. For example, in the video scenario:

An employee goes to the stock room and obtains a bottle of reagent. He notices it is expired and was not removed during the weekly inventory review. That is a QNH. He saved the company time and money and saved himself work by not using the expired reagent and discarding the expired reagent and obtaining new reagent. By identifying, and reporting the QNH, he raised awareness among others to look for expired chemicals.

This reinforces the common concept that all areas have to continually verify chemicals are not expired before use.

Implementation Tools

The Development Team ensured department leaders would encourage their areas to submit QNHs. The importance of computer availability was discussed, and the QNH database was deployed through our intranet which is easily accessible to all employees. Our intranet site was updated by the Information Solutions Department to locate QNH database alongside the Safety Near Hit database making the intranet site user-friendly.

The Development Team also created submission cards to place in common areas, like break rooms, for employees who preferred paper submission.

Video Production

The Development Team contracted a

consultant group for video production. The Development Team determined filming locations and the initial script was written. The script was reviewed three times with stakeholders.

Total Project Time and Cost

The initial program required approximately four months of development effort from concept to delivery of finished training module.

The Development Team provided 80 person hours of effort for video production.

The 10 minute video production cost approximately $35,000.

Program Format

The program format was designed to be provided in one hour sessions. The session was designed to be an interactive employee training which included a video, facilitated group discussion throughout the video and followed up with a hands-on exercise.

Initial Rollout Training

Management and Supervision were trained and the Train-the-Trainer sessions were completed. During the initial 45 day rollout of the program to manufacturing and support employees, six trainers provided 29 sessions, training 1133 personnel. Implementation challenges included a 12 hour rotating shift schedule, logistics, as well as three different company locations.

Examples of QNH discussed in the training:

- Dropping gaskets (or material) on floor
- Placing a clean part in coveralls
- Using leaking pipettes
- Acknowledging nuisance alarms

Reinforcement

To keep the training fresh in the employee's mind, pens and process reminder cards were distributed to employees. QNH were monitored as a Key Performance Indicator. QNHs submitted are announced on our site broadcast so all employees are made aware of issues reported. Employees are notified directly when they report a Near Hit to let them know a quality partner is investigating the situation. Names of employees who submit QNHs are put in a monthly drawing for a gift card.

Furthermore, our first video was deployed in July 2009. Two months later, in September submitted QNHs were reviewed. The script for the second training module was based on Near Hits situations submitted. The second training module with video was deployed three months after the first module in October 2009. At the end of the video employees were thanked for submitting QNHs and making the program a success.

Part three was deployed one year after the first module in July 2010. The program was expanded to encourage supervisors to discuss QNHs submitted from all areas to raise awareness of similar issues.

Logistics of Program

The Near Hits submitted are reviewed by the Director of Quality. If it is defined as a Near Hit, it is assigned to a Quality Partner for that area. If it is defined as a deviation, it is addressed in our Incident Tracking System. The Quality Partner will work with the affected department to resolve the QNH and ensure corrective and preventive actions are taken. Departments must respond to the QNH within 30 days.

Time spent on this process from the Quality Department is averaged at eight hour per-week. The affected department's time requirements vary depending on the complexity of the Near Hit.

Results

Results of the program are quite significant. QNH observations have saved product. We estimate product saving accumulated to $7.76 million (USD) since the start of project in mid-2009 through the end of 2010.

These savings are based on the QNH implementation at two sites, one with 130 employees and a larger site of 2000 employees. Through the end of 2010, the QNH program has resulted in over 400 reports: 125 QNH reports in six months of 2009 and 282 QNHs reports in 2010 (with 100% of manufacturing and 90% of support groups participating in the program).

Other observations of the program are:

- Management trended similar issues to proactively communicate between departments.
- Employees requested procedure changes with exact information for change and reason why.
- Performance Development deployed modified Level III Evaluation (surveyed employees' behavior change) one year after rollout.
- Employees enter QNHs when issues were observed.
- Employees discuss QNHs with other employees.
- Employees are receptive to this direct communication to improve processes.

Conclusion

The QNH program is a successful program at the Clayton site saving an estimated $7.76 million (USD) in 18 ➤

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months. Employees know their observations are being addressed and they are making a positive impact. The quality of QNHs is increasing. This initiative is having a positive impact on production, improving processes, and reducing product write off. The company continues to support the QNH program by deploying it to other smaller sites, developing additional training modules, and following up and trending the QNHs reported.

Questions? Readers can contact Donna Steele via email: donna.steele@talecris.com.

About the Authors

John Parrish is the Director of Quality Operations at Grifols (Clayton site). He has been in this position since 2004. He started his career at the Clayton site in 1980. He has worked in multiple roles which include manufacturing, technology transfer, planning/scheduling, and quality. John graduated from Appalachian State University with a Major in Biology and Minor in Physics.

Donna Steele is the Performance Development Manager at Grifols (Clayton site). For the last 18 years, she has managed and developed employee training programs, seven years at Grifols (formerly Talecris Biotherapeutics) and 11 years at Wyeth. Donna has a Masters in Adult Education from Virginia Commonwealth University. She is also an ASQ certified Engineer, Auditor, and Manager.

Erin Sorrell is a member of the Performance Development Team at Grifols (Clayton site). In this role she worked with various functional areas to assess, design, deliver, and evaluate the QNH Program as well as other training initiatives. She has worked at the Clayton site since 2000 in various rolls which include validation and sterile fill manufacturing. Erin obtained her BS in Animal Science form North Carolina State University and is also an ASQ Certified Quality Auditor, and ASQ Certified Manager of Quality and Organizational Excellence.

Jane Keene is employed by Grifols (Clayton site) as a Performance Development Training Specialist. In her current role, Jane develops, designs, and facilitates numerous courses in GXP. Since 2001, she has worked in various positions from manufacturing to engineering support. She holds a Bachelor's of Science Degree from Mount Olive College in Management and Organizational Development.

About the Development Team

The Development Team was sponsored by John Parrish, Quality Operations Director and Donna Steele, Performance Development Manager. Performance Development is the Technical Training Unit at Clayton.

The Development Team was led by Erin Sorrell, Technical Training Specialist and Jane Keene, Technical Training Specialist.

Video consultant and production was contracted through Dave Gallup of the Training and Communication Group.

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IV/IM Micro Quality: Whose Responsibility is It?

Cheryl Moser, Merck

Drug manufacturers go to great lengths to assure the sterility of their pharmaceutical and biological/vaccine products that are administered intravenously/intramuscularly (IV/IM), but cannot account for the additional manipulations performed by healthcare professionals on the sterile product in preparation for administration to the patient. This is true of even the simplest IV administration bag.

Oftentimes, product preparation manipulations can be complex and require skills in aseptic technique and environmental control to prevent accidental contamination. Any breach of the container-closure system carries a risk of accidental contamination that could potentially threaten the safety of the patient.

Currently, it is unclear whom is responsible for the prevention of accidental contamination and risk assessment of the potential product spoilage at the point of use. What is the product manufacturer's responsibility beyond the recommendations in the package insert in assuring that accidental microbial contamination and proliferation of microbes in the product are minimized should accidental contamination during product use occur? What are the health professionals' responsibilities in assuring patient safety and prevention of accidental product contamination?

The issue gets further complicated with increasing at-home medications. What responsibilities do both the health professionals and product manufacturers have to educate and assure that patients understand the tasks, risks and appropriate storage requirements of their at-home medications? What are the special challenges and difficulties in maintaining microbial quality of products that are distributed and administered in areas of the world where sanitization is poor, environmental control is nonexistent and temperature control cannot be achieved?

Despite the paucity of guidance, the goal of industry, regulatory agencies and health professionals is to assure that no patient is harmed by the use a contaminated product

The regulatory expectations have been evolving. It is important to design experiments demonstrating that an evaluation of the risks of microbial proliferation are understood and that the antimicrobial preservation, storage temperature and holding times for the products are justified with scientific data. Yet, there currently are no official guidelines for pharmaceutical and biological manufacturers to refer to for issues of assessing microbial proliferation risks during preparation, holding and administration of sterile products. The USP chapter <797> *Pharmaceutical Compounding-Sterile Preparations* provides guidance to healthcare professionals involved in sterile compounding. It describes low-, medium- and high-risk preparation operations. This chapter, however, is not applicable to product manufacturers, as they have no direct control over how the health care professionals carry out the instructions for admixing, reconstitution, hold times, storage and administration. Nevertheless, it is important for the manufacturers to know and understand the preparation practices. Knowledge of these practices will aid the health care professionals in carrying out their responsibilities with minimal risk.

Despite the paucity of guidance, the goal of industry, regulatory agencies and health professionals is to assure that no patient is harmed by the use of a contaminated product. Understanding the microbial proliferation risks of the product are important to develop scientific data for regulatory approval supporting label instructions and storage claims. The information is also important to understand the risks to patient safety. Manufacturers will be able to improve/optimize the admixing and reconstituting ➤

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practices, consider drug formulations carrying lower microbial risk, and consider how drug/device design can help to minimize accidental contamination events.

For this reason, a session of the upcoming *6th Annual Conference on Pharmaceutical Microbiology & TRI Courses* is dedicated to this serious issue. It is designed to provide objective information for assessing the risks of microbial contamination which may accidentally ingress into a parenteral drug during admixing or reconstitution activities. Three knowledgeable speakers representing the U.S. FDA, World Health Organization (WHO) and industry will present current expectations and experiences for addressing these questions.

The first speaker will be **John Metcalfe,** PhD, Sr. Microbiology Reviewer, CDER, U.S. FDA. He will present "Microbiological Quality of Drug Products after Penetration of the Container System for Dose Preparation Prior to Patient Administration." The second speaker will be **Rudolf Eggers,** PhD, Group Leader, Immunization Services Strengthening, WHO. His presentation will be about the "Policy on the Revision of Multi Dose Vial Policy by WHO: The Use of Non-Preserved Multi Dose Vaccines." The final speaker for this session will be **Edward Tidswell,** PhD, Senior Director, Research Sterility Assurance Technology Resources, Baxter Healthcare who will give a presentation on "Microbiological Risks Quantified during IV Drug Delivery System Preparation."

About the Author

Cheryl Moser has been with Merck & Co. for 26 years. She currently works in the research and development division where she is responsible for the microbiological quality control of pharmaceutical and biological/vaccine products for all research areas. She is experienced with the compendial microbiological assays as well as evaluating rapid technologies. She is also considered a subject matter expert in endotoxin testing. If you have any questions for Cheryl you may reach her at Cheryl_Moser@Merck.com.

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Solutions for Longer Shelf Life and Cost Savings Explored

Emily Hough, PDA

What would it mean to your company if you could find a way to drive down costs and keep drug products fresher longer?

Three speakers at the *2011 PDA Pharmaceutical Cold Chain Management Conference* told the audience how they would do that by implementing a dynamic cold chain system, modifying a "traditional" stability budget, and shipping at broader temperature ranges.

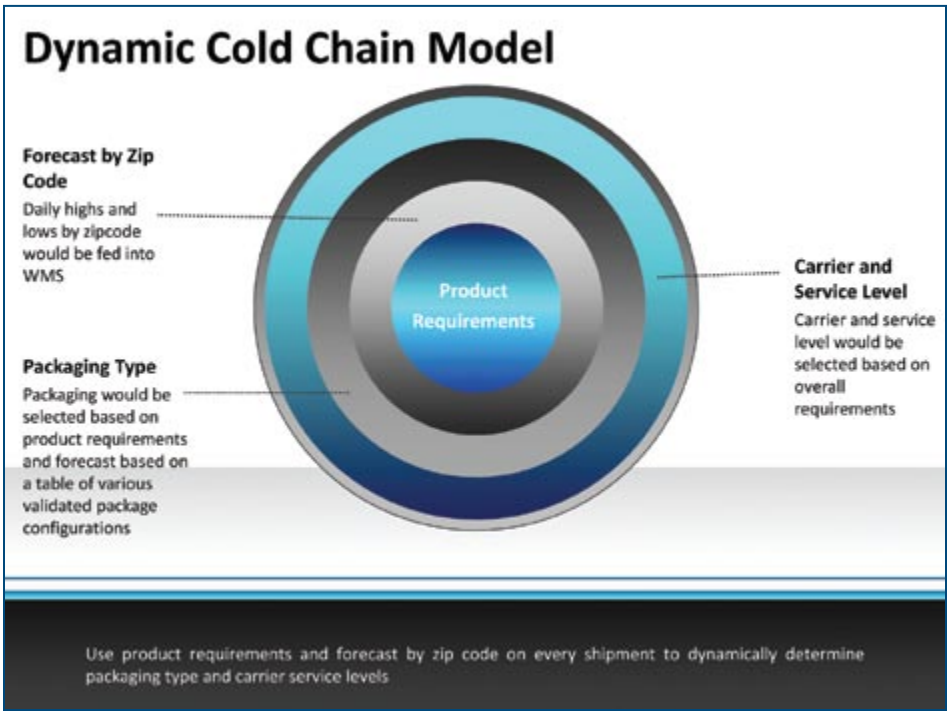
Developing a Dynamic Cold Chain Model

Denise Odenkirk, VP, OM HealthCare Logistics, told audience members, "The way we are handling cold chain management [now] couldn't be more expensive and less sustainable. The cost of shipping temperature sensitive materials has never been higher, and using one-time solutions are not good for the economy."

Odenkirk gave an example of how Wal-Mart has established a system that bases itself on the climate or weather of a particular place and uses two different packing solutions based on those climates to drive down costs. A sterile thermal management solution system used for Alaska and Hawaii allows Wal-Mart to maintain a certain temperature over a three day period. The second solution entails cold chain products shipped in a green box inflator pack for the rest of the United States

According to Odenkirk, "This is an example of a company that because they are trying to drive down costs, they have recognized they a different solution for different locations. So, Alaska and Hawaii are getting treated differently."

To build a similar system establishing how cold chain products are shipped, collaboration with IT, Operations and Packaging to determine the specific requirements for each of a firm's products. It is also important to understand the products' permissible temperature requirements and excursions and to identify different packaging and temperature alternatives. This is ensuring that the basic infrastructure of the system can be put into place.



Odenkirk's presentation gave attendees an example of how a cost-effective cold chain shipping system could be implemented.

Odenkirk said that after the basic infrastructure has been put into place, to practically implement this model, forecast data is needed. Using data from a weather service, carrier and packaging type can be set in a warehouse management system each day by inputting the data.

For example, for every shipment that drops to the warehouse management system, forecast data for the zip codes in the shipment route would be looked at. The forecast data and product specifications would determine, at that point in time, the appropriate carrier mode and packaging.

Odenkirk stressed that it would be wise to set up a task force across packaging and transportation groups to come up with creative solutions for each of the company's products and to lower cost as a number of solutions can be implemented, rather than continuing with expensive solutions across all seasons of the year: "Maybe it is using more expensive validated shippers over a 4-6 week period in the coldest months or the hottest months of the year rather than 365 days of the year. The goal is to meet the temperature requirements without driving a lot of cost in the supply chain."

As many components can be changed or fine-tuned, not only will firms' packaging systems not change overnight, but some companies might not know where to start. To begin a more focused approach to this system, focus on products that have the highest costs or transportation delivery and try to drive those costs down by building in the capabilities of the system. ➤

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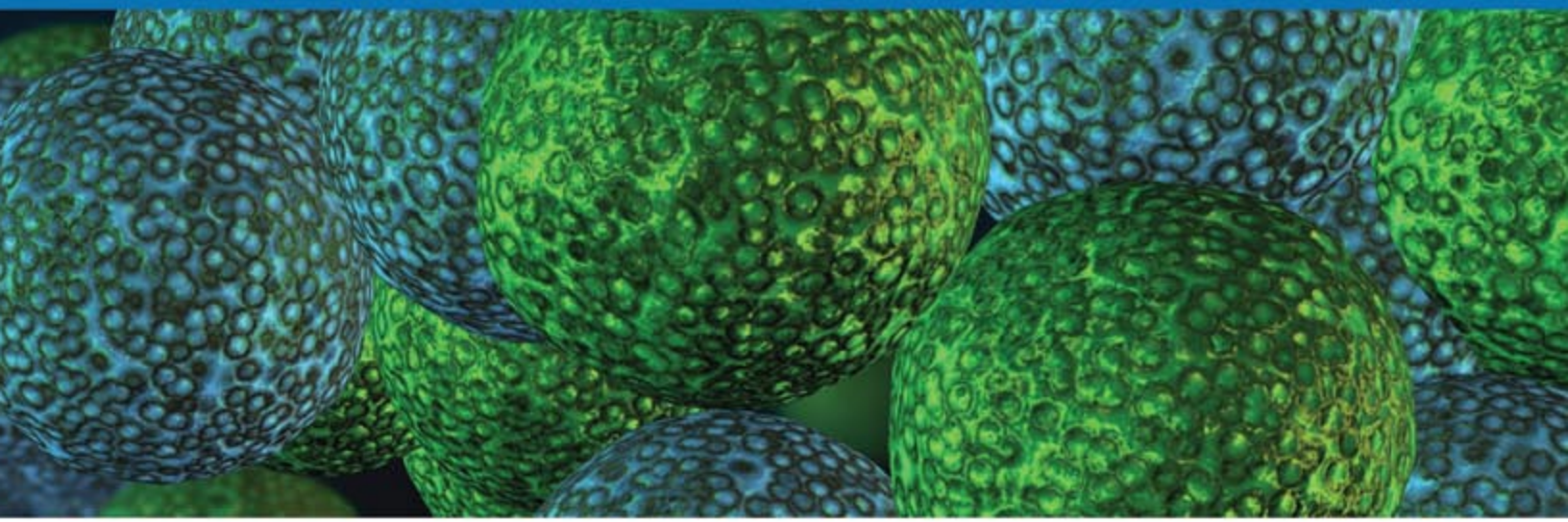

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Poster Presentation:

Tracking the Untrackable Microbes - The Use of SLST and MLST in Environmental Monitoring Programs

Modifying a "Traditional" Stability Budget

Paul Harber, Modality Solutions (with Eli Lilly at the time), gave a presentation about the need for firms to adjust their processes so that patients would have the product longer and have to worry less about expiry dates. "We can't go out and speak to specific sub-lots of product and advise [patients] to shorten the expiry date and cross that off and take a month off. We are going to have to adjust our processes to make sure we are not impacting anything that is going to have an effect on that expiry dating."

He said that the commonly accepted scope and application of iso-thermal exposure under quiescent conditions occurs in distribution centers, warehouses, pharmacies, and end-user facilities. To determine iso-thermal exposure, data from stability monitoring to refine stability estimates (extend dating) should be used. But, Harber said, now inspectors are starting to take an interest in the entire chain of custody to verify that exposures, such as shipping hazards, inherent to the supply chain do not shorten the expiry date of the product

But where does this data end up? Harber said that there is no consensus and some companies and regulatory agencies are encouraging companies to write the data into the NDA/BLA. Other companies will have the data available for onsite review. Harber said it is important to build the expected thermal exposure into the stability program and set the design space to reflect reality and then demonstrate that the CQAs can be maintained.

Building an effective design space and stability program into a company's process is important to ensure that a patient has as much time with the product as necessary, since the products are being built for the end-user: the patient.

Temperature Control Shipping Strategies

Rebecca Gentile, Sr. Stability Coordinator at Merck, spoke about her firm's experiences with shipping at broader temperature ranges.

While some countries are open to scientific justification for a qualified shipping temperature range outside of the label storage condition if there is appropriate stability data and shipping qualification and the information is physically filled in within the applicable product licenses, Gentile said that some countries require shipments strictly within the label conditions.

Merck's basic shipping at broader temperature ranges strategy for cold chain products is based on the stability research phase findings of the product. For example, with a product that would need to be controlled between 2-8°C, lower temperature ranges below 2° and higher temperatures above 8° would be studied for short periods. Products that could be frozen would be studied at lower temperatures, such as -20°C.

To do this for each cold chain product, Merck's stability group identifies an acceptable shipping temperature range and time duration based on the available time out of storage; stability data is used to identify time out of storage. The packaging technology group then identifies an appropriate pack out container configuration that it chooses based on performance qualification testing.

However, Gentile said, when Merck places temperature monitors on these shipments, there are still potential temperature excursions. If an excursion occurs, to determine if the product is to be discarded to ensure safety and efficacy for the patient, Merck's quality groups evaluate whether the excursions are supported by the stability data or they retest it.

While some countries' regulatory authorities aren't supportive about products shipped out of label storage conditions, others are more interested in shipping practices for pharmaceutical companies, but are looking at the stability data to support these practices. The key, Gentile said, is for "communication between regulatory authorities and company representatives. [This] is essential for understanding true requirements and practical limitations."

About the Experts

In 2008, **Denise Odenkirk** joined O&M to lead the company's OM HealthCare Logistics business unit as its Vice President. Denise was the Vice President of Operations and Information Services with Bracco Diagnostics. In addition, she brings over 20 years of experience developing and implementing information technology process solutions in the life sciences and consumer package goods industries from her work experience with Pfizer (formerly Warner-Lambert), Sanofi-Aventis, and the Application Consulting Group.

Paul Harber left Eli Lilly as an Engineering Consultant after 30 years of service. He has over 15 years of experience in Cold Chain Distribution and has worked with internal development groups as well as CRO/CMO partners to assure safe shipment of high/high value pharmaceutical products. In addition, he has worked on the Steering Committee of the PDA Pharmaceutical Cold Chain Interest Group and is a contributing author to *PDA Technical Report No. 39, Revised 2007, Guidance for Temperature-Controlled Medicinal Products: Maintaining the Quality of Temperature-Sensitive Medicinal Products Through the Transportation Environment.* Currently, Paul works as a Principal at Modality Solutions.

Rebecca Gentile works as the Senior Stability Coordinator at Merck. She began her career in the Merck Research Labs in 1996. Today, she is responsible for defining stability strategies for new and in-line vaccines. She has spent the past four years defining Merck's distribution strategy for pharmaceutical and vaccine products from a stability perspective.

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Harmonizaton *Report*

Discussions from June ICH Meeting

Dr.-Ing. Stephan Rönninger, PhD, and Sabine Scheitlin, F. Hoffmann-La Roche, with Jim Lyda, PDA

This article reports on the current, general discussions on quality topics in the International Conference of Harminisation (ICH) environment at the time of the June 2011 meeting in Cincinnati, Ohio of the Steering Committee and Expert and Implementation Working Groups.

During the meeting the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) and ICH regulators had a fruitful discussion acknowledging the issues the industry faces in implementing new guidance or regulations.

Unlike ICH there is no formal process for inclusion of industry perspectives into the PIC/S decisions at this time. Therefore, ICH is a good framework for joint workshops for authorities and industry to enhance communications in emerging markets. It would be helpful if collaboration among authorities and industry going forward can be institutionalized rather than just on select programs. The role of ICH in the emerging markets, which is centered on inspections and assessment, should continue with the involvement of PIC/S in terms of inspections and its expanded role to key emerging markets.

The following guidelines were also addressed at the meeting:

- **ICH Q3D** (Guideline for Metal Impurities): The scope for the Guideline for Metal Impurities will remain on biotechnology-derived drug products and excipients. Conventional vaccines will be excluded from the guideline.
- **ICH M7** (Assessment and Control of DNA Reactive [Mutagenic] Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk [genotox impurities]): The scope of this guideline will be refined and aligned with ICH Q3D and ICH Q11 as appropriate.
- **ICH Q11** (Pharmaceutical Development-APIs): The draft ICH Q11 guideline on Development and Manufacture of Drug Substance (Chemical Entities and Biotechnological Entities) reached step 2 and has been published for comments in all three regions **(Note:** comment deadlines for Europe and the United States were September 1; For Japan, it was August 15. PDA will prepare comments on the draft Q11 guideline, with the effort coordinated by the PDA Regulatory Affairs and Quality Advisory Board (RAQAB).**)**
- **"Points to Consider" documents supporting Q8, Q9, and Q10:** The Quality Implementation Working Group has been created to support the implementation of ICH Q8, Q9 and Q10 by the industry and the health authorities. The Q-IWG recently released to the public three "Points to Consider" documents:
  1. *Criticality of Quality Attributes and Process Parameters*
  2. *Control Strategy*
  3. *Level of Documentation in Enhanced (QbD) Regulatory Submissions*

These documents provide supplementary information to the previously completed IWG Q&A's and training materials and should be considered together with these related documents.

Based on questions raised during the ICH Q-IWG training workshop sessions in the three regions they are intended to assist both industry and regulators and to facilitate the preparation, assessment and inspection related to applications filed for marketing authorization. (For more information, visit the following site: tinyurl.com/3fxf64q)

The development approach for a particular product should be adapted based on

continued on page 36

Volunteers Exchange Viewpoints on EMA Biological IMP Draft Guideline

Jim Lyda, PDA

As a not-for-profit, membership-based scientific association, PDA relies on members from around the world to contribute expert knowledge and experience to support our mission. It is the intellectual property of the membership that makes PDA a trusted and responsive organization by serving as a neutral platform for scientific discussions.

There are special times when PDA members take volunteerism a step further and participate in real-time scientific discussions with health authorities.

Some of PDA's volunteers recently had an occasion to exchange scientific viewpoints with European regulators in a formal consultation discussion at the European Medicines Agency (EMA) in London on June 16 about a draft guidance, entitled, *Guideline on the Requirements for Quality Documentation Concerning Biological Investigational Medicinal Products in Clinical Trials (EMA/CHMP/BWP/534898/2008, 18 February 2010)*

Daniela Kasulke, PhD, Regulatory CMC, BP Quality & Compliance, Boehringer Ingelheim, with the support of **Ruhi Ahmed,** PhD, Director, RA, Regulatory Affairs, BioMarin Pharmaceutical, and **Roland Guenther,** PhD, Group Head Biotech, Global Regulatory CMC, Novartis, led the PDA presentation for this scientific discussion with comments that were submitted by PDA on August 31, 2010.

All were active in the drafting of, or support for, PDA's original comments on this critical guideline. The group was supported and accompanied by **Jim Lyda,** Director Regulatory Affairs, Europe, PDA.

The following members of the Biologics Working Party (BWP) guideline drafting group led the discussions:

Brigitte Brake, PhD, Head of Pharmaceutical Biotechnology, BfArM and Chair of the drafting group

Hartmut Krafft, PhD, Head, Clinical Trials Unit, Paul-Ehrlich-Institut

Ilona Reischl, PhD, Manager, AGES PharmMed, BASG and member of the BWP

Kowid Ho, PhD, Quality Assessor, Biologicals/Biotechnology Unit, AFSSAPS and member of the BWP

Other members of the drafting group also attended, and members of the EMA staff were present including Scientific Administrator, **Katerina Bursikova.**

PDA's delegation to the BWP stakeholder meeting. (L-R seated): Ruhi Ahmed, BioMarin; Daniela Kasulke, Boehringer Ingelheim; Roland Guenther, Novartis. Standing: Jim Lyda, PDA

Stakeholders from the European Federation of Pharmaceutical Industries and Associations (EFPIA) and European Generics Association (EGA) presented at the meeting. Also stakeholders from the Association of Clinical Research Organizations (ACRO), European Biopharmaceutical Enterprises (EBE), European Industrial Pharmacists Group (EIPG), EuropaBio, European Vaccine Manufacturers (EVM) observed the meeting.

The meeting lasted from 10:00 a.m. to 3:30 p.m. at the EMA headquarters with much open and stimulating discussion. The PDA group felt that the meeting was very helpful and that the BWP panel was completely open and responsive to the discussions that came up during the day. There will be an effort to finalize the guideline by the end of 2011.

continued on page 38

Harmonization Report continued from page 34

the complexity and specifics of the product and process. For this reason, applicants are encouraged to contact their regulatory authorities regarding specific information to be included in their application. Using the Quality by Design (QbD) approach does not change regional regulatory requirements but can provide opportunities for more flexible approaches to meet these requirements. In all cases, GMP compliance is expected.

The document on *Criticality of Quality Attributes (CQA)and Process Parameters (CPP)* provides an understanding of the factors that will ensure the quality, safety and efficacy of a specific product for the patient. This also serves as a starting point for identifying the CQAs. Considerations for identifying and documenting CQAs and CPPs and the relationship of criticality to Control Strategy are described.

The second document focuses on control strategy. The following points have to be considered: Lifecycle of the control strategy, suitability of control strategy at different scales, specifications and Certificate of Analysis for real-time release testing (RTRT) and process for a batch release decision.

The description of the level of documentation in enhanced (QbD) regulatory submissions provides suggestions on the type of information and the level of documentation appropriate to support a proposal for an enhanced Quality by Design approach. For submissions containing QbD elements (e.g.,RTRT, design space), it is helpful for regulators to have a statement by the applicant describing the proposed regulatory outcome and expectations.

It is important to realize that not all the studies performed and/or data generated during product development need to be submitted. The subsections describe examples of background information that can be considered by both companies and regulatory authorities to assure scientific risk-based regulatory decisions. These include risk management methodologies, design of experiments and manufacturing process description.

In order to facilitate harmonized understanding, the ICH training workshops will be repeated in collaboration with Health Canada. In Ottawa, Canada, training will be held on September 26-27. Training with the Global Cooperation Group will take place October 4-5 in Seoul, South Korea.

Readers are advised to monitor and track ICH developments for official decisions and guidance at the ICH website, www.ich.org.

Pharmacopaial Harmonization

ICH has finalized the Pharamcopoeial Harmonization guideline ICH Q4B and its annexes in recent years. The Pharmacopoeial Discussion Group (PDG) still meets now outside ICH and considers proposals made by industry for harmonization of requirements by the European Pharmacopoeia, US Pharmacopeia and the Japanese Pharmacopoeia as well as the International Pharmacopoeias within WHO. They include general methods and excipient monographs in the PDG working program.

Background and Role of ICH

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use mission is to achieve greater harmonization to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner. ICH is bringing together the regulatory authorities and pharmaceutical industry of Europe (EC/EMA and EFPIA), Japan (MHLW/PMDA and JPMA) and the U.S. (FDA and PhRMA). The purpose is to discuss scientific and technical aspects of pharmaceutical drugs and the common information needed for their registration. In addition, the Global Cooperation Group (GCG) is the means of sharing the benefits of international harmonization beyond the three ICH regions.

Its members include the following alliances: Asia-Pacific Economic Cooperation (APEC), Association of Southeast Asian Nations (ASEAN), Cooperation Council for the Arab States of the Gulf (GCC), Pan American Network for Drug Regulatory Harmonization (PANDRH) and the Southern African Development Community (SADC) as well as individual member authorities from Australia, Brazil, China, Chinese Taipei, India, Republic of Korea, Russia and Singapore.

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Volunteers Exchange Scientific Viewpoints on EMA Biological IMP Draft Guideline continued from page 35

Common understandings based on discussions were:*

> ***Caution to Readers:*** *The following summary is based on discussions in the meeting and are understood to be correct by the author. Readers should review the final guideline or any summary prepared by the authorities before making any regulatory decisions related to this topic.*

- The scope of the IMP Guideline only covers therapeutic biologics; it will not to be extended to vaccines.
- For early phase products, and products with limited development experience, product characteristics without established acceptance criteria can be reported as "for information only."
- Acceptance criteria and details for in-process control will not be required for early stage (phase I and II). It was generally accepted that it is normally not possible to establish critical process steps in early development phases.
- For shelf life dating, companies can extrapolate using supportive data (per ICH guidelines. This is possible up to two times of the real time/real temperature data, but not more than plus 12 months). Supportive data may be based on representative development batches, data from previous manufacturing processes and use of databases derived from other comparable substances (if justified).
- Shelf life extension criteria should be specified in a stability protocol submitted in the IMP Dossier (if so, the sponsor does not need to file a substantial amendment for expiration date extension).
- Process validation documentation for aseptic processing will be required in the IMP Dossier. This requirement "raises the bar" for documentation compared to current industry practice and may be inconsistent with requirements in other regions.
- The guideline does not exclude the use of platform data, but justification is needed so data is representative of actual development batches.

Additional topics of discussion:

- In early phases of development, batch analyses data for all batches available, including the proposed clinical batch(s), will be expected to be provided in the IMP Dossier.
- Although a list of changes which can be treated as non-substantial amendments would be very useful to industry, at this time it appears the drafting group is not prepared to provide such a list in the guideline.

The PDA group regretted that the chair of the PDA task force, **Hannelore Willkommen,** PhD, Managing Director, Directorate, RBS Consulting, could not be present for this stakeholder meeting.

PDA is grateful to Drs. Kasulke, Ahmed and Guenther for their support. We also recognize and thank all the volunteers and members who participated in preparation of our official comments in 2010, but who could not join the delegation.

Finally, we extend a sincere "Thank You" to Dr. Brake, to members of the BWP, the guideline drafting group and to members of the EMA staff for hosting these consultations in a professional, responsive and open way.

Want to Know More?

For the latest European developments on Clinical Trial Materials and IMPs be aware of the PDA conference on Clinical Trial Materials that will be held in Basel, Switzerland on February 7-8, 2012. For more information visit europe.pda.org

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- **From Genomic Platform to Bio Industry**
  Dominique Rollin, *Directeur Scientifique Centre Génomique Fonctionnelle Bordeaux (CGFB)*
- **ICH Q11: Impact on Biopharmaceuticals**
  Pierrette Zorzi, *Former Head of Biological Evaluation of AFSSAPS*
- **Industry Perspective on Partnership with Authorities and the Status of the Paradigm Change (Quality by Design)**
  Georges France, *Pfizer*
- **Single-Use-Systems: Implementation and Supplier Qualification**
  Steven Brown, Vivalis
- **Compatibilities, Extractable & Leachable Strategies, SFSTP Commission**
  Natacha Sehnal, *SFSTP/Sanofi*
- **Extractable and Leachable Studies for Stoppers and Elastomers: How to Set-up the Right Testing Strategy?**
  Piet Christiaens, *Toxikon*
- **Application of QbD Principles for Innovation and Compliance**
  Irwin Hirsh, *NovoNordisk*
- **From Process Validation to Continuous Verification, Following the EMA Guideline**
  Véronique Davoust, *Pfizer*
- **Cleaning Validation: Case Study in the Vaccine Industry**
  Anne Rigoulot, *Sanofi Pasteur*

Please view the agenda on our web site for the other presentations!

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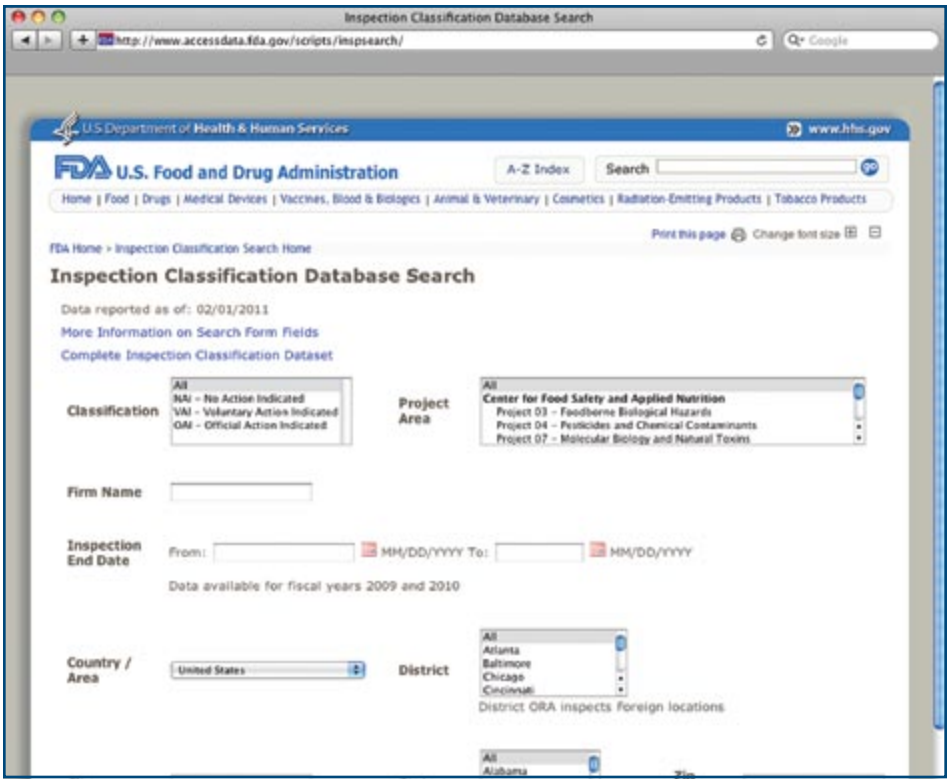
https://europe.pda.org/BioPharma2011

U.S. FDA Compliance Data Easily Accessible Through Web Portal

Emily Hough, PDA

As part of Phase II of the Agency's Transparency Initiative, the U.S. FDA launched a new portal in May that makes enforcement and compliance activities more easily accessible online via a searchable database. The database includes the names and addresses of inspected facilities, inspection dates, type of FDA-regulated products involved and final inspectional classification.

Disclosing firms' compliance status will also help provide the public with a rationale for the Agency's enforcement actions and will also encourage compliance. The FDA plans to specifically disclose the final classification for inspections of clinical trial investigators, institutional review boards, and facilities that manufacture, process, pack, or hold an FDA-regulated product that is currently marketed.



Phase I: FDA Basics

The first phase is intended to provide the public with basic information about the FDA and how it does its work. In early January 2010, the FDA launched the web-based resource, "FDA Basics." This resource now includes:

- Questions and answers about the FDA and the products it regulates
- Nine short videos that explain various Agency activities
- Conversations with 10 Agency officials about the work of their offices

Each month, senior officials from FDA product centers and offices host online sessions about a specific topic and answer questions from the public. Each session is announced on the FDA website.

Phase II: Public Disclosure

The second phase relates to the FDA's proactive disclosure of information it has, and how to make information about its activities and decision-making more transparent, useful, and understandable to the public, while appropriately protecting confidential information. As required by the Administration's Open Government Directive, the Task Force inventoried the information that is not currently available to the public and considered whether the public health would benefit from disclosing some of this information.

In May 2010, the FDA released a report containing 21 draft proposals about disclosing additional information while maintaining confidentiality of trade secrets and individually identifiable patient information.

Phase III: Transparency to Industry

The third phase will address ways that the FDA can become more transparent to regulated industry to foster a more efficient and cost-effective regulatory process. The FDA is also progressing significantly in implementing the Action Items in the Phase III Report, issued in January.

According to FDA spokesperson **Lisa Kubaska,** the FDA is not only exploring ways to better present that information, but is thinking of ways to send out other information to the public. "By the end of 2011, we are also hoping to begin disclosing additional information about FDA evaluations of filers, expanding disclosure of untitled letters and in appropriate situations, disclosing information about what products are not subject to a recall to better support industry recall efforts," she said.

FDA Commissioner **Margaret A. Hamburg,** MD, launched the FDA's Transparency Initiative in June 2009 in response to the Obama administration's commitment to openness in government.

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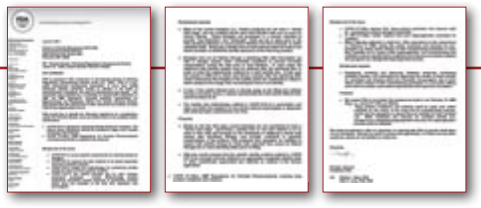
PDA Finds Biologics, Finished Pharma Regs. "Outdated"

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



June 27, 2011

Division of Docket Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Periodic Review of Existing Regulations; Retrospective Review under E.O. 13563; Docket Number FDA-2011-N-0259

Dear Sir/Madam,

PDA is pleased to offer comments on the Periodic Review of Existing Regulations; Retrospective Review under E.O. 13563. PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by a committee of experts with experience in CMC and GMP regulations, including members representing our Biotechnology and Regulatory Affairs and Quality Advisory Boards. PDA appreciates the opportunity to offer comments and wishes to thank FDA for the opportunity to do so.

PDA would like to identify the following regulations for consideration under this Periodic Review, since we believe them to be outdated and/or burdensome:

- 21CFR 610.12 regulations regarding sterility testing for biologics. We believe these regulations should be modified to apply only a subset of biologic bulk material.
- 21CFR 211.94(c); GMP Regulations for Finished Pharmaceuticals covering drug product containers and closures

Background of the issue:

- 21CFR 610.12 covers specific requirements for sterility testing for biologics
- 21CFR 610.12 requires the bulk material to be tested separately from final container material
- 21CFR 610.12 details the methodology for performing sterility testing for bulk and final container material
- 21CFR 610.12 was drafted decades ago for older biologic production processes. Current biotechnology product production processes include advances in production controls which were not available at the time this regulation was promulgated.

Burdensome aspects:

- Many of the current biologics (i.e., biotech products) do not have a "sterile bulk stage" and are rendered sterile upon final filtration with one or more 0.2 micron filter(s). These biologics are processed in a manner intended to provide "low bioburden" and "bioburden" limits are put in place prior to the final sterilizing filtration to assure sterile filtration into final container is within validated limits. Requiring a sterility test on bulk material where the bulk is not sterile provides no additional sterility assurance of the final drug product.
- Biologics that can be filtered through a sterilizing filter after formulation are held in storage vessels under controlled conditions to prevent microbial contamination during the step prior to final filtration. In such cases the additional bulk sterility sample must be obtained after the sterilizing filter in order to meet the requirements outlined for a bulk sterility test. In this case the sample is difficult to obtain and taking a sample after the sterilizing filter could compromise the integrity of the system given the complexity to obtain a sterile sample at this stage, thus increasing the risk of non-sterility.
- In fact, if the sterile filtered bulk is directly going to the filling line without having a receiving vessel, a sample representing the entire sterile filtered bulk, cannot be taken at all.
- The sterility test methodology outlined in 21CFR 610.12 is prescriptive and does not foster the adoption of new sterile method technologies or alignment with pharmacopeia requirements over time.

Proposal:

- Based on the fact that many current biologics are not considered to have a "sterile bulk stage", performing a sterility test on the bulk material is of no value in this case and because of the complexity of obtaining a sterile bulk sample after sterilizing filtration may actually contribute to potential contamination of the product, PDA proposes this regulation be modified to require bulk

sterility testing for those bulk materials that cannot be filtered through one or more sterilizing filters prior to filling.

- PDA also would propose that the specific sterility method outlined in 21CFR 610.12 be removed and that reference to appropriate compendia sterility tests or other scientifically supportable test methods as outlined in the license application.
- 21CFR 211.94(c); GMP Regulations for Finished Pharmaceuticals covering drug product containers and closures

Background of the issue:

- 21CFR 211.94(c) requires that "drug product containers and closures shall be…processed to remove pyrogenic properties."
- 21 CFR 211.94(c) further requires that such depyrogenation processes be validated.
- When originally published in draft form, PDA commented on this requirement on February 15, 2008, noting that certain containers and closures are non-pyrogenic by nature and/or design of their manufacturing processes or have been qualified not to require active depyrogenation, and recommending that validation only be required when containers and closures are actively rendered non-pyrogenic by a designated depyrogenation process.

Burdensome aspects:

- Developing, reviewing and approving validation protocols, conducting validation studies, and reviewing and approving the results of these studies for containers and closures which are inherently non-pyrogenic due to their nature and/or design of their manufacturing processes is a non-value adding work which increases costs without significantly reducing risk to the patient.

Proposal:

- We request FDA to reconsider the proposal we made in our February 15, 2008 letter; i.e.; reword 211.94(c) as follows:
  - "Drug product containers and closures shall be clean and, where indicated by the nature of the drug and its manufacturing process, sterile and non-pyrogenic to assure they are suitable for their intended use. When containers and closures are rendered actively non-pyrogenic by a designated depyrogenation process, the depyrogenation process shall be validated."

We would be pleased to offer our expertise in a meeting with FDA to provide clarification of our comments. Should you wish to pursue that opportunity, or if there are any other questions, please do not hesitate to contact me.

Sincerely,

Richard Johnson
President, PDA
CC: Robert L. Dana, PDA
Rich V. Levy, PhD, PDA

Regulatory Briefs

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

North America

U.S. FDA Draft Report Released Clarifying CDER's Science and Research Needs

The U.S. FDA has released a draft report identifying the Center for Drug Evaluation and Research's (CDER) science and research needs. The report identifies current priorities in regulatory science related to the mission of CDER and will guide strategic planning of internal research efforts. Comments are due on the report by September 26.

U.S. FDA Holding "Town Hall" Meeting with the Director of CDRH in California

The U.S. FDA is holding a public meeting with the Director of the Center for Devices and Radiological Health and other senior Center Management in San Francisco, Calif. on September 22.

Advance registration is required.

U.S. FDA Releases Draft Guidance About Requirements for Pre-market In-Vitro Diagnostic and Radiology Devices

A draft guidance describing the U.S. FDA's intent of how they will enforce premarket notification [510(k)] requirements for certain in vitro diagnostic and radiology devices has been released to the public.

Comments on the draft guidance, entitled, *"Enforcement Policy for Premarket Notification Requirements for Certain In Vitro Diagnostic and Radiology Devices"* are due October 11.

U.S. FDA Releases Draft Guidance on In-Vitro Companion Diagnostic Devices

The U.S. FDA has released a draft guidance intended to assist sponsors planning to develop a therapeutic product that depends on the use of an in vitro companion diagnostic device or an in vitro diagnostic device that is intended for use with a corresponding therapeutic product and included in the instructions for use in the labeling of those products.

Entitled, *In-Vitro Companion Diagnostic Devices,* the draft guidance describes certain statutory and regulatory approval requirements relevant to therapeutic product labeling that stipulate concomitant use of a companion diagnostic device to ensure safety and effectiveness of the therapeutic product.

Comments are due to the Agency by September 12.

U.S. FDA Proposes Removal of Sec. 203.50(a) of PDMA

The U.S. FDA is proposing to remove the section of the Prescription Drug Marketing Act (PDMA) regulations that requires an unauthorized distributor to provide the purchaser with "a statement identifying each prior sale, purchase, or trade of such drug" starting with the manufacturer, because a recent district court's decision to issue an injunction against enforcing the rule.

Unauthorized distributors have long argued that the rule was impossible to meet when purchasing material from authorized distributors, who are not legally bound to provide pedigree information back to the point of manufacture.

Comments are due to the Agency by September 12.

U.S. FDA Releases Two Draft Guidances on its Approaches to Product Classification

The U.S. FDA has released two related draft guidances on the Agency's current thinking on approaches for classifying products as drugs and devices, certain additional product classification issues and the interpretation of the term "chemical action" under the Food, Drug & Cosmetic Act.

Comments on the *Draft Guidance for Industry and FDA Staff: Classification of Products as Drugs and Devices and Additional Product Classification Issues and Draft Guidance for Industry and FDA Staff : Interpretation of the Term 'Chemical Action' in the Definition of Device Under Section 201(h) of the Federal Food, Drug and Cosmetic Act* should be submitted by September 19.

Key Regulatory Dates

Comments Due:

September 12 — U.S. FDA Proposes Removal of Sec. 203.50(a) of PDMA

September 19 — U.S. FDA Draft Guidances on Approaches to Product Classification

U.S. FDA Sterility Test Requirements for Biologics

September 22 — U.S. FDA Town Hall Meeting

September 26 — U.S. FDA Draft Report Clarifying CDER's Science and Research Needs

October 11 — U.S. FDA Enforcement Policy for Premarket Notification Requirements for Certain In-Vitro Diagnostic and Radiology Devices

November 14 — U.S. FDA Premarket Benefit-Risk Determinations of Medical Devices

December 31 — EMA's Revised Draft Guideline on GDP of Medicinal Products for Human Use

U.S. FDA Proposes Changes to Sterility Test Requirements For Biologics

The U.S. FDA has proposed changes to the current sterility test requirements for biological products.

According to the Agency, the proposed changes will provide manufacturers of biological products greater flexibility and encourage use of the most appropriate and state-of-the-art test methods for assuring the safety of biological products.

Comment by September 19.

U.S. FDA Draft Guidance Released on Medical Device Premarket Review Benefit-Risk Determinations

The U.S. FDA has released a draft guidance on factors to consider when making benefit-risk determinations in medical device premarket review.

The recommendations in this guidance are intended to provide greater clarity on FDA's decision making process with regard to benefit-risk determinations in the premarket review of medical devices.

Comments are due by November 14.

U.S. FDA Reports Progress of Drug Inspection Collaboration

The U.S. Food and Drug Administration, together with its European and Australian counterparts, released two reports detailing the results of pilot programs focused on increasing international regulatory collaboration among the agencies so that drug quality and safety can be enhanced globally.

These pilot programs are part of the FDA's global strategy to ensure the safety and quality of imported products. The new strategy builds on efforts that are currently underway at the FDA.

U.S. FDA Revises 2006 Guidance on Bar Code Label Requirements

The U.S. FDA has published a revised Q&A guidance about bar code label requirements.

The revised guidance, published in question and answer form, amends a response of a 2006 guidance with the same title. The revised response addresses the ability of vaccine manufacturers to use alternative coding technologies to the linear bar code requirement.

Europe

EMA and U.S. FDA Collaborate Together on Biosimilar Medicines

The European Medicines Agency and the U.S. FDA have identified biosimilar medicines as an area of common interest and will be working together to increase their degree of interaction and will begin with a kick-off meeting to discuss the group's activities.

This biosimilar "cluster" is the latest step in the two agencies' ongoing collaboration on regulatory issues under their confidentiality arrangements, which they first signed in 2003. The degree of interaction between the EMA and the FDA has increased significantly since then, to the current stable level of around 55 interactions per month, according to a report issued by the two agencies.

Public Consultation Open on EMA's Revised Draft Guideline on GDP of Medicinal Products for Human Use

The European Medicines Agency has opened public consultation on the revised guideline on good distribution practice of medicinal products for human use.

The guideline was revised to take into account developments in the storage and distribution of medicinal products in the European Union and to meet new requirements for wholesale distributors and brokers established in the new Directive 2011/62/EU on falsified medicines.

Comments are due by December 31.

Asia-Pacific

Australian TGA to Regulate Biologicals Separately

The Therapeutic Goods Administration (TGA) has decided to regulate biologicals separately from other therapeutic goods, such as blood and blood components.

According to the TGA, this move will

- Ensure the level of regulation applied matches the level of risk posed by specific biologicals by classifying them into four risk-based classes
- Provide a more flexible framework to respond to changes in technology than has been the case under previous arrangements
- Provide regulatory requirements that are unique for biologicals, because the arrangements for medicines or devices may not be appropriate, particularly in exceptional circumstances
- Reduce the ambiguity about what was included or excluded from regulation through the use of consistent terminology
- Increase international harmonization of therapeutic goods regulation

Australian's TGA to Release Online Forms for Medical Device Adverse Events

Australian's Therapeutic Goods Administration (TGA) will be releasing new online reporting forms for medical device adverse events soon.

The forms will provide a TGA reference number upon submission and support the attachment of electronic documentation.

Danish Medicines Agency Updates Guidelines to Facilitate Electronic Submissions

The Danish Medicines Agency has devised new guidelines for marketing authorizations, variations, updates to Mutual Recognition Procedures, renewals, follow-up and referrals to the coordination group.

The new guidelines are intended to facilitate electronic submission and processing.

Send us your news briefs!

If you follow the Regulatory News in your country or region, send your briefs to hough@pda.org; we might post them online, the PDA Connector and/or in the *PDA Letter.*

Challenges Facing Pharmaceutical Microbiology

Bethesda, Md. • October 17-21 • www.pda.org/2011microbiology

Amy McDaniel, PhD, Pfizer

Whether you are a seasoned microbiology professional or a new analyst just starting out, and regardless of your company's specific product or production process, as microbiologists in the 21st century, we all face certain challenges. These may include keeping current with the latest industry and regulatory trends, improving testing by implementing new technologies, and improving quality by avoiding contamination by "objectionable" microorganisms. The PDA program committee of this year's *6th Annual Global Conference on Pharmaceutical Microbiology & TRI Courses* has incorporated these challenges into a far-reaching and engaging program with something that should benefit everyone!

The theme of this year's conference is focused on *Challenges Facing Pharmaceutical Microbiology in the 21st Century.*

The conference will kick off with keynote speaker, **Daniel Fung,** PhD, Professor, Animal Sciences & Industry, Kansas State University, who will give a presentation on "Global Developments of Rapid Methods and Automation in Microbiology: A Thirty Year Review and Predictions into the Future." This should provide an entertaining and thought-provoking look at how far we've come, and where we might still go in the future. The second keynote speaker, **Dennis Guilfoyle,** PhD, Pharmaceutical Microbiologist, ORA, U.S. FDA, will give a presentation on Tuesday morning on "Challenges Facing Pharmaceutical Microbiologists to Define and Control Objectionable Microbes."

Incorporated into the 2½ days of the conference are a series of concurrent sessions designed to maximize specificity while allowing a greater diversity of topics. Sessions focusing on container closure, preservation for non-sterile, multi-dose products and new technologies will be presented alongside sessions on risk assessment, challenges in radiation sterilization and contamination control. I'm sure that it will be tough to choose!

The conference provides an excellent opportunity to network with other microbiologists and vendors

The keynote presentations as well as one plenary session each day will bring the entire audience together on topics of general interest, including objectionable organisms, and microbiological issues associated with reconstitution of products.

The conference provides an excellent opportunity to network with other microbiologists and vendors at the poster sessions and in the exhibit hall, where case studies including the use of risk assessments for environmental monitoring during open manufacturing operations, and the design of a test chamber for the development and validation of a rapid technology will be displayed. Even if you "network" too late into the night, you won't want to miss the two unique breakfast sessions: "USP Update" and "Microbiologist of the Future-Future Leadership Panel Discussion." You will be sure to wake up as recent revisions to the USP are being discussed and emerging microbiology leaders speak about the issues they currently face.

Finally, the "Urban Myths" and the "Ask the Regulators" sessions will be back by popular demand, where speakers will focus upon scientific reality versus current microbiological practices and representatives from the FDA and WHO will participate in a panel discussion formal answering questions posed by the audience.

We look forward to seeing you at the conference; it is a great way to meet new people, re-establish relationships and learn from other professionals in our industry. Who knows, maybe you will even discover a new way to overcome a 21st century challenge or two of your own! For more information and to register, go to www.pda.org/2011microbiology.

Go to page 60 to read more about the microbiology courses that will be offered by the Training and Research Institute following the conference.

Can you spot the 1,962,523 differences?

Harmful microorganisms are too small to see, yet too dangerous to ignore. Confidently detect these contaminants before they can do any real damage. For pharmaceutical manufacturers, quality control testing is critical. To help ensure your product safety, we deliver microbiology solutions for sterility testing, microbial limits testing, and media fill trials – along with the quality control microorganisms required. Just like yours, our testing is designed to meet or exceed the official requirements of the United States Pharmacopoeia (USP). These stringent standards include testing growth promotion properties to minimize false positive results and testing to determine whether products are free of bacterial and yeast contamination. Rely on reproducible results with our microbiology product solutions. After all, what you do impacts lives. **Learn more at remel.com/pharma.**

Visit us in Booth #2 at PDA's 6th Annual Global Conference on Pharmaceutical Microbiology.

remel

Part of Thermo Fisher Scientific

Visual Inspections Discussed at Conference

Washington D.C. • October 3-6 • www.pda.org/visualinspection2011

Deborah Shnek, Amgen and John Shabushnig, Pfizer

Inspection of finished injectable products continues to be a challenge to us in the pharmaceutical and biopharmaceutical industry due to limitations in the technologies and methods available and evolving regulatory expectations.

High product quality is ultimately assured by a combination of a good visual inspection process to detect defects and good manufacturing controls to prevent them. Detection and control of intrinsic versus extrinsic particulates especially in biopharmaceuticals along with the impact of incoming component quality continue to test drug product development.

The *2011 PDA Visual Inspection Forum & TRI Course,* held annually and rotating between the United States and Europe, provides a forum to discuss these and other issues associated with the fundamentals of visual inspection practice. It also provides attendees with the most up-to-date regulatory trends driving changes in inspection process design. For example, the medical impact of visible particulate matter will be highlighted along with a presentation from the U.S. FDA on current concerns with visual inspection performance. Developing standards for visible particulates in parenterals will also be presented to stimulate further discussion on the definition of "essentially free from visible particulates."

Successful inspection implementation requires understanding critical parameters such as lighting, timing and sampling plans that affect manual and automated inspection. Case studies on best practices to create and use defect challenge sets to develop and maintain a well characterized inspection process that meets global requirements are planned. This conference will also provide current industry case studies on manual inspection "hot topics" such as six sigma implementation, defining baseline inspection performance and how to demonstrate control of inspection processes.

Additional sessions will complement quality requirements with real world challenges to detect defects in drug products and cover new equipment for automating the inspection process as well as new approaches to defect detection using automated inspection. Emerging technologies such as inspection of lyophilized drug products using x-ray imaging have been included in the program. Also, inspection solutions for specific glass defects, such as glass lamellae, related to component preparation showcase difficult inspection scenarios will be discussed.

During the conference, there will be adequate time for discussion and networking with leaders in the field of visual inspection. This conference brings together professionals from quality, process development, manufacturing and validation to focus on current practices in visual inspection.

Developing standards for visible particulates in parenterals will also be presented

The highly acclaimed PDA training course, "Introduction to Visual Inspection" will immediately follow the conference. Taught by **John Shabushnig,** PhD, Sr. Manager/Team Leader, Quality Systems and Technical Services, Pfizer; **Ronald Leversee,** Operational Manager II, Finishing, Baxter Healthcare; and, **Matt Ostrowksi,** Injectable Filling Supervisor, Pfizer, this course will cover the fundamentals of visual inspection and their application to injectable products. The combination of lecture/discussion and hands-on laboratory exercises will help participants develop and practice practical inspection skills applied to both manual human inspection and automated machine inspection.

Don't make the mistake of thinking the Visual Inspection Meeting doesn't pertain to your job; because, in reality, you can't afford to miss it. Remember, everyone from the manufacturer, through the healthcare professional to the patient, is an inspector.

For more information and to register, visit www.pda.org/visual2011

The Parenteral Drug Association presents...

2011 PDA Visual Inspection Forum & TRI Course

October 3-4, 2011

EXHIBITION: October 3-4 | **COURSE:** October 5-6
Hyatt Regency Bethesda | Bethesda, Maryland

The *2011 PDA Visual Inspection Forum & TRI Course* will provide an opportunity to present and discuss new developments in the field of visual inspection, including contributions to a basic understanding of the sampling and inspection process, practical aspects of manual and automated methods.

This forum will have seven plenary sessions each with three to four presentations on topics like:

- Medical and Regulatory Concerns with Particulate Matter
- Special Considerations for the Inspection of Biotherapeutics
- Supplier Quality and Component Defects
- Good Practices in Manual Inspection
- Good Practices in Automated Inspection
- Case Studies – Emerging Inspection Technologies

Immediately following the conference, the PDA Training and Research Institute (PDA TRI) will be hosting a stand-alone course, *Introduction to Visual Inspection* on October 5-6.

For details and to register, visit
www.pda.org/visualinspection2011

Photo Credits: John G. Shabushnig, Ph.D., Quality Systems and Technical Services, *Pfizer* / Eisai

Virus Detection Methods Evaluated at Adventitious Workshop

Rockville, Md. • November 2-4 • www.pda.org/adventitious2011

Adventitious Program Planning Committee

The *PDA/FDA Adventitious Agents and Novel Cell Substrates: Emerging Technologies and New Challenges* workshop is currently being organized in order to evaluate the benefits and potential applications of broad virus detection technologies, for safety testing and characterization of biological products, and to facilitate safety testing of novel cell substrates.

This workshop is intended to provide an engaging forum for the participants and the audience to discuss and integrate current and emerging strategies for controlling virus contamination and enhancing product safety. It is also designed to encourage discussions between industry, testing labs and regulatory agencies with respect to:

1) Adventitious agent testing and the gaps that can be filled by emerging test methods
2) Quality and safety issues related to novel insect, plant, and animal cell substrates
3) Controlling adventitious agents in source materials and raw materials
4) Gaps in our current ability to detect, control, and clear adventitious viruses

Johannes Löwer will give a keynote presentation on safety concerns regarding different types of cell substrates and the key issues related to use of novel cell substrates. He will also discuss the development of new adventitious virus detection assays to meet the challenges of using novel cell substrates for product development.

Day one sessions will focus on emerging technologies for adventitious virus detection and the application of such technologies to the evaluation of biological materials. The sessions will include a broad talk on Next–Gen sequencing platforms by **David Munroe** as well as first-hand accounts of the practical use of massively parallel or deep sequencing by **Matt Friedenberg,** PhD and **John Kolman,** PhD. **Charles Chiu,** MD, will speak about virus microarrays and the use of the PLEX-ID in an industrial setting will be presented by **Houman Dehghani.**

Day two will open with a talk on retroelements by **Marcie McClure,** an expert on molecular evolution of retroid agents and complexities of genome analysis. Day two sessions will include discussions on the potential safety and quality issues related to novel insect, plant, and mammalian cell substrates. Speakers for that session will include **Vivadi Yusibov,** PhD, who will address issues associated with plant cell substrates; and **George Rohrmann,** PhD, will speak about baculoviruses and insect cells.

The third day will focus on virus risk mitigation of source and raw materials with a talk from **Ivar Kljavin,** PhD, on identifying source materials of reagents.

In addition, each day the workshop ends with a panel discussion affording a unique opportunity for audience participation.

On day one, there will be specific panel discussions on issues related to emerging technologies. The discussion will include assay standards by **Marc Salit,** PhD, challenges in assay validation and bioinformatic analysis by **David Onions** and **Tom Slezak.**

On day two, the panel will discuss the risks associated with the use of novel cell substrates with particular focus on product development in insect cells and plants. Finally, the workshop will end with an "expert panel" that will focus on discussing the key challenges in virus detection methods and forward directions for addressing novel cell substrate safety concerns. Participants will have an opportunity to raise any outstanding issues that need additional discussion.

The PDA/FDA Adventitious Agents and ➤

Program Planning Committee

Co-Chair **Arifa Khan,** Senior Investigator, CBER, U.S. FDA

Co-Chair **Kathryn King,** Biologist, CDER, U.S. FDA

Co-Chair **Anthony Lubiniecki,** Senior Fellow, Large Molecule, Portfolio Management, Centocor R&D

Howard Anderson, Biologist, U.S. FDA

Kurt Brorson, PhD, Biologist, U.S. FDA

Jason E. Brown, Senior Programs Manager, Parenteral Drug Association

Houman Dehghani, Director, Amgen

James (Jim) Gilbert, Associate Director, Global QC Virology, Biogen Idec

Pawan Jain, PhD, Biologist, U.S. FDA

Rich Levy, PhD, Senior Vice President, Science and Regulatory Affairs, PDA

Robert McElwain, Consumer Safety Officer, U.S. FDA

Wanda Neal, Senior Vice President, Programs & Meetings, PDA

David Onions, Chief Scientific Officer, BioReliance

Mark Plavsic, Senior Director and Corporate Biosafety Advisor, Genzyme (Sanofi Aventis)

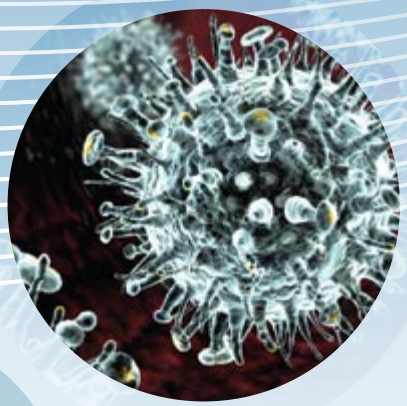
Jose Varghese, Vice President, Process Science, Merrimack

Zenobia Taraporewala, CMC Reviewer, U.S. FDA

Michael Wiebe, President, Quantum Consulting

Hannelore Willkommen, Directorate, RBS Consulting

Vidadi Yusibov, PhD, Executive Director, Fraunhofer USA Center for Molecular Biotechnology



The Parenteral Drug Association Presents...

Register By September 22 - The Second Registration Savings Deadline!

PDA/FDA Adventitious Agents and Novel Cell Substrates: Emerging Technologies and New Challenges

November 2-4, 2011

EXHIBITION: November 2-3

Hilton Hotel | Rockville, Maryland

This event is being organized in response to the need to evaluate the benefits and potential applications of emerging broad virus detection technologies for safety testing, characterization of biological products and to facilitate safety testing of novel cell substrates.

The *PDA/FDA Adventitious Agents and Novel Cell Substrates: Emerging Technologies and New Challenges* event will provide an engaging forum for all participants to discuss and integrate current strategies for controlling virus contamination and enhancing product safety.

Plenary sessions at this year's conference include:

- Risks Associated with Cell Substrates and Other Biological Materials and Product Safety
- Adventitious Agent Testing and Emerging Methods Part I and Part II
- Technologies and Application to Evaluation of Biological Materials Part I and Part II
- Panel Discussion – Technical Challenges of New Methods
- Retrotransposons and Retroviruses
- Insect, Avian and Mammalian Cell Substrates Part I and Part II
- Potential Safety and Quality Issues Related to Plants and Plant-based Products
- Adventitious Agents and Raw Materials Part I and Part II
- Two Expert Panel Discussions

For details and to register, visit
www.pda.org/adventitious2011

"This workshop was very useful for vaccines business. I highly appreciated the quality of the talks and speakers and the format for gathering regulators and manufacturers is great. Sharing experience and views from manufacturers and regulators is major."
Past Attendee from Sanofi Pasteur

Participants will have an opportunity to raise any outstanding issues that need additional discussion

Novel Cell Substrates: Emerging Technologies and New Challenges Workshop Program Planning Committee has planned an information-packed workshop and all participants from industry, testing labs, suppliers, regulatory agencies, and academia should find the discussions engaging and relevant to current events. For more information, visit www.pda.org/adventitious2011.

PDA Who's Who

Charles Chiu, MD, Director, Viral Diagnostics and Discovery Center, UCSF-Abbott

Houman Dehghani, Director, Amgen

Matt Friedenberg, PhD, Senior Director, Engineering, Gen-Probe

Ivar Kljavin, PhD, Associate Director, Product Quality Management, Genentech

John Kolman, PhD, Senior Director, BioReliance

Johannes Löwer, President, International Alliance for Biological Standardization (IABS) and past president, Paul-Ehrlich-Institut

Marcie McClure, Professor, Department of Microbiology, Montana State University

David Munroe, PhD, Director, Technology Development, SAIC-Frederick

David Onions, Chief Scientific Officer, BioReliance

George Rohrmann, PhD, Professor, Microbiology, Oregon State University

Marc Salit, PhD, Group Leader, Biochemical Science, National Institute of Standards and Testing

Tom Slezak, Associate Program Leader, Lawrence Livermore National Laboratories

Vivadi Yusibov, PhD, Executive Director, Fraunhofer USA CMB

Help Advance Your Career: Attend the Annual Meeting

Phoenix, Ariz. • April 16-20, 2012 • www.pda.org/annual2012

Program Planning Committee Member Marsha Hardiman, Dendreon

The *PDA Annual Meeting* is the one meeting each year dedicated to advancing the careers of pharmaceutical and biopharmaceutical professionals. This signature event focuses program content on science and technology innovation as well as optimized performance, offering extensive formal and informal networking opportunities. It also provides a forum to contribute to and influence the advancement of science and regulation in the industry.

As the manufacturing of quality products is a keystone of our industry, the *2012 PDA Annual Meeting's* theme is *Manufacturing Innovation: Achieving Excellence in Sterile and Emerging Biopharmaceutical Technology.*

With the emergence of new technologies, our program will feature a one-day track on personalized medicine focusing on challenges in manufacturing and quality assurance/quality control of these products. The program will also feature sterile biopharmaceutical manufacturing with a focus on manufacturing innovations and new technologies as well as regulatory perspectives on biopharmaceuticals. Properly planned and performed process design, development, validation, sourcing, process control, contamination control, testing, handling, product and supply chain security, distribution, and manufacturing all drive product quality and essentially positive business results. Use of innovation and new technologies helps to ensure success of these processes. This conference will bring together experts from academia, industry and regulatory agencies from around the world to discuss current practices and opportunities in sterile and emerging biopharmaceutical manufacturing.

This meeting, which will be held from April 16-20, 2012 at the JW Marriott Desert Ridge Resort in Phoenix, Ariz., is an opportunity to participate in presentations, case studies and initiate discussions on manufacturing innovation, productivity in large scale sterile manufacturing and contract manufacturing, automation and new technologies, such as personalized medicine and cellular therapeutics. In addition, the meeting will offer a track for biopharmaceutical foundations to focus on the basics and fundamentals of industry practices. This track is intended for those who are new to the industry or who have a new focus in their career and will cover topics such as contamination control, quality control testing, process control, validation and supply chain.

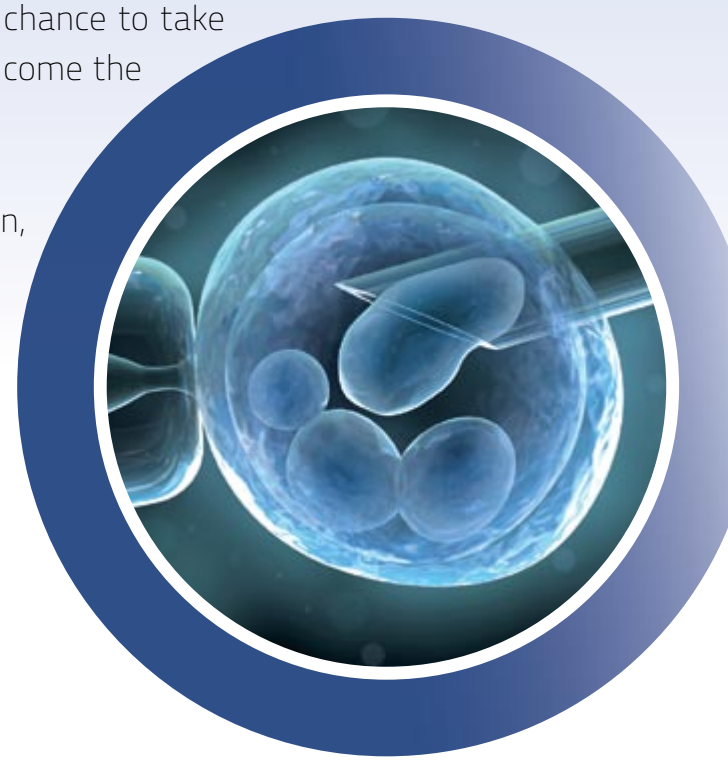
2011 PDA Europe Workshop on Advanced Therapy Medicinal Products

7-8 June, Helsinki | Finland

Audio Recordings Available for Purchase

The conference was opened by the Director General of Fimea, Dr. Sinikka Rajaniemi. In her introductory talk, Dr. Rajaniemi highlighted the advances in molecular and cell biology and biomaterial technology that have created the foundation for a new era in medicine. The conference brought together 148 ATMP experts from academia, industry and regulatory bodies from 20 countries around the world. All aspects of ATMP development were discussed, including CMC issues, non-clinical and clinical development, as well as the recent scientific results, novel technologies and regulatory advances concerning ATMPs. The high quality agenda was appreciated by the participants and the workshop met all the expectations of both the organizers and the attendees. Subsequent to this year's conference, we are now offering presentations with voice-over commentary. Session recordings will provide those who could not personally attend the conference a chance to take part in the lectures and allows the people who did come the chance to hear sessions that they missed.

If you are interested or would like more information, please email or call Antje Petzholdt at **petzholdt@pda.org** or **+ 49-33056-2377-10**



https://europe.pda.org/ATMP2011

Learn the Principles of ICH Q10

Arlington, Va. • October 4-6 • www.pda.org/q10

Co-chairs David Cockburn, EMA and Rick Friedman, U.S. FDA

The *Pharmaceutical Quality System (ICH Q10) Conference* will not just tell attendees what is in the guidance, it will also offer practical, real-life case studies on how a company can go about implementing the guidance. It will show attendees how senior management commitment and involvement is vital.

This conference offers a unique opportunity for 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 are reaping the benefits that come from establishing and maintaining a state of control, continual improvement, enhancing regulatory compliance and meeting quality objectives everyday.

You should attend this conference if you are a decision-maker at mid-level or senior level, or a professional working at site or corporate level

You should attend this conference if you are a decision-maker at mid-level or senior level, or a professional working at site or corporate level in the following areas:

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

Who Should Attend This Conference?

If you are a leader or decision maker in a pharmaceutical manufacturing business and want to maintain a sustainable business, and can only attend one conference in 2011, make it the *Pharmaceutical Quality System (ICH Q10) Conference.*

The Parenteral Drug Association presents...

Pharmaceutical Quality Systems (ICH Q10) Conference

Co-sponsored by FDA and Supported by EMA

A Practical Approach to Effective Lifecycle Implementation of Systems and Processes for Pharmaceutical Manufacturing

October 4-6, 2011 | Crystal Gateway Marriott | Arlington, Virginia
November 14-16, 2011 | Sheraton | Brussels, Belgium

This is an essential conference for all involved in product development, quality, manufacturing and regulatory affairs.

Do you want to enhance quality and reduce costs? Are you capitalizing on the benefits to quality and compliance that accrue from adopting a robust quality system?

PDA, ISPE, FDA and EMA have created a unique conference dedicated to the successful implementation of ICH Q10. Adoption of the Q10 model for a pharmaceutical quality system should facilitate innovation, continual improvement and strengthen the link between pharmaceutical development and manufacturing activities.

Join leading regulators and industry experts to learn how to implement a robust pharmaceutical quality system according to ICH Q10 that will enable you to reap the benefits of establishing and maintaining a state of control, continual improvement, enhancing regulatory compliance and meeting quality objectives.

For details and to register, visit
www.pda.org/Q10

Co-Chairs, Program Planning Committee:
David Cockburn, *EMA*
Richard L. Friedman, *CDER/OC, FDA*

Regulator, Industry Perspectives Aired at MaB Workshop

Rich Whitworth, BioPharm International and Pharmaceutical Technology Europe

The intimate atmosphere at the fully attended *4th PDA Europe Workshop and Exhibition on Monoclonal Antibodies* (MaBs) "fostered a feeling of closeness and networking," according to **Richard Levy,** PhD; and indeed it did. There was great opportunity for industry peers and regulators to mix and continue discussions initiated in presentations. Perhaps if it had been any bigger the sense of community would be lost. Basel served as the perfect host to this meeting, on June 7-8.

The workshop kicked-off with a wonderfully candid and standout presentation by **Nanna Kruse,** M.Sc.Pharm. Her presentation focused on the regulatory perspective of a control strategy in the QbD paradigm, and gained the full attention of all attendees. Not least the statement that shifting quality control upstream as part of a risk-based control strategy could, in theory at least, mean an end to product release testing—something that, Kruse said, might come as a surprise, even to regulators.

There was a call for more openness and transparency in application dossiers. The situation was likened to an iceberg, of which the tip represented release tests (specifications) and the actual contents of the dossier, and where the bulk of the iceberg was hidden underwater: extended characterization, process controls (procedures, materials, in-process testing, monitoring, validation)—all information and knowledge within the company not routinely included in the dossier and yet some parts of which are accessible at inspections. The message was made quite clear: companies cannot provide too much information about process knowledge gained in terms of control strategy.

A fascinating question that raised interest was: how do we determine critical quality attributes (CQAs) in terms of control strategy? Of course, this has no straight answer, but the message was that it may change over time as knowledge is gained or if even small changes are made to the production process. From regulatory experience, it seems that the definition and understanding of CQAs is clear in dossiers, but the rationale is often lacking or absent.

The second presentation of the day from **Stephanie Schnicke** also focused on control strategy, putting forward strategic considerations for design. Roche has addressed the difficulty of determining CQAs and non-CQA by assigning an "impact score" to all attributes using a risk-based approach, which takes into account four impact areas: pharmacokinetics/dynamics, biological activity, safety and immunogenicity. The latter of which caused debate for the entire conference.

Throughout the post-presentation discussions (and to certain extent within the presentations) it was clear that regulatory bodies had limited experience (by their own admission) in QbD applications, put down to the simple fact that so few "full-blown" applications have been seen. European regulators have looked to FDA for advice and example, where the QbD paradigm shift has far more momentum.

Questions over what should or should not be included in dossiers is clearly a sensitive issue for companies who feel the need to protect certain information for future process flexibility and these questions will no doubt continue between regulators and industry.

Sequence Variants

In addition to regulatory challenges, the conference also addressed some common technical issues, sequence variants among them. The session was introduced by **Kathleen Francissen,** who asked: "What is acceptable and what is not?"; as analytical methods approach the inherent "error rate" of biosynthetic processes, and the actual risk of sequence variants is somewhat unknown, the answer to that particular question is a moving target.

The first presentation on sequence variants by **John Stults** considered both angles: detection and subsequent risk assessment. Detection of sequence variants, which are unintended amino acid substitutions caused by mistranslation or mutation, is not new. But traditionally, detection has occurred at the cell line development stage during sequence-variant screening (if a sequence variant is detected, the cell line is abandoned). Importantly, detection capability is increasing so Stults' firm, Genentech has implemented earlier systematic sequence variant analysis on both normal and extended cell age samples to avoid discovery and subsequent issues in late phase development. If a sequence variant is discovered during extended characterisation, risk assessment is performed by a cross-functional team based on several principals, not least risk of immunogenicity.

There are several issues with measuring immunogenicity risk though. One is the limited scope of in silico assessments or animal models; another is the inability to measure low frequency immune responses in the small patient groups of Phase I/II studies.

So what is the regulatory perspective? **Chris Holloway,** PhD, provided some extreme examples. In one instance, a client was considering the impact of a sequence variant discovered at Phase II. They were told it was certainly a concern—especially as the variant ➤

The Parenteral Drug Association presents...

2011 PDA Europe Workshop on

Single-Use-Systems for Pharmaceutical Applications

The workshop addresses the vital role that Single-Use-Systems play in pharmaceutical development and manufacturing. Guided by the PDA Technical Report learn the advantages, disadvantages and when to use Single-Use-Systems. Benefit from applicable case studies, discussions with regulators and a tour of the GE Healthcare´s manufacturing facility for Single-Use-Systems.

Join our Site Visit!

29-30 November 2011
Uppsala, Sweden

WORKSHOP 29-30 November | **EXHIBITION** 29-30 November

https://europe.pda.org/SingleUse2011

Navigating a legacy product through new regulations and process changes should be viewed as an opportunity to drive "better science"

occurred at a level of 45%! Holloway pointed out that there exists very little data relating to the actual impact of sequence variants. But whether the risks are real or perceived, impurities are a fundamental quality attribute, and batch-to-batch consistency is crucial.

In concluding, Holloway stressed the need to start the analytical methodology early on to detect sequence variants. Along with a long list of recommendations to reduce regulatory risk, he stated that perhaps the single most important point was the need to fully investigate all factors that could conceivably affect sequence variant levels during process development. A last key recommendation, backed by a case study, was to secure retained samples for future discoveries; it could alleviate regulatory concerns if a new variant is retroactively discovered in a legacy product.

In the panel discussion that followed, there was more debate yet few solid answers over the risks of immunogenicity. But what everyone appeared to agree on was that if any level of sequence variant is found, extensive investigation is required; regulators will demand that sufficient data are presented to mitigate risks—whether real or perceived.

Life Cycle Management

The second day of the workshop primarily focused on post-approval process changes and management of legacy products.

Pascal Venneugues delivered a very insightful presentation that centred on post-approval change management protocols (PAMPs), which allow companies to describe changes that they wish to make throughout the life cycle of a product and how those changes will be verified, using a risk-based approach. Changes that can be included in the protocol depend on product and manufacturing process complexity, as well as the amount of scientific knowledge gained. Examples include changes to manufacturing sites (when GMP status is already confirmed), changes to suppliers of raw material, and changes to analytical methods.

However, in cases where non-clinical or clinical data are required to determine similarity of the pre- and post-change product, change management protocols are not an option. Once again, QbD during development aids in process understanding and thus extends the ability to predict the impact of future changes. Indeed, the whole idea of PAMP is to adapt to ICH concepts. When asked "how does this save time and money?" the speaker cited faster implementation of changes, especially those of a repetitive nature. In Q3 of this year, a final Q&A on PAMP will be published by the EMA with the intention of it becoming a "living" document.

There were several presentations on legacy product changes; all noted that huge changes in the regulatory landscape had demanded a different way of thinking about product management. Complex global supply chains and different regulatory requirements around the world have made such management difficult and the key phrase here was "holistic approach," perhaps not by choice but by necessity. But the main takeaway was that navigating a legacy product through new regulations and process changes should be viewed as an opportunity to drive "better science"—something that I think everyone can agree on.

EU GMP Annex II

Daniel Müller offered an overview of upcoming changes to Annex II for biologicals, a revised version of which, we were told, will be available soon. The revision increases the scope of Annex II and provides much more information over an additional 19 pages. Cell-bank establishment is included along with a number of different product types, such as monoclonal antibodies and gene therapies, set in a separate guidance section.

Müller went on to discuss another hot topic: single-use disposables (SUD) and noted a lack of detailed requirements in GMP guidelines; companies should create their own specifications, he suggested, based on the European Pharmacopoeia, USP, and EMA notes for guidance. He pointed out that risk assessment for a move to SUD was the responsibility of the system owner, who must also fully evaluate the impact of single-use components on product quality. Special attention was drawn to the distinction between true single-use, multi-batch (one product) and multi-product systems with a call to question companies' internal definitions. Müller also offered examples of regulatory issues at inspection, including some surprising basics, such as "insufficient clean room qualification" and "no clear cleaning strategy." The presentation ended with the notion that you never get a second chance to make a good first impression; companies would be wise to heed this particular advice.

There were several other excellent presentations, sadly too many to mention here, but the open-mindedness and spirit of debate endured for the highly packed two days. One message rang out: understanding the different perspectives of industry and regulators is key to moving forward successfully and with direction.

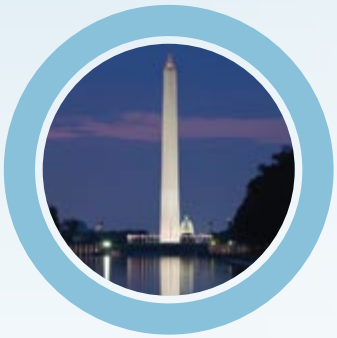
Hot topics that may appear in the fifth iteration of the workshop (planned for June 2012) are how to successfully make QbD submissions; biosimilars and the implication of sequence variants; and expansion on risk-assessment strategies. No doubt there will be an abundance of highly informative yet informal discussion to boot. Co-Chairs for the 2012 workshop are **Steffen Gross,** PhD, and **Mike Defelippis,** PhD.

See you next year.

continued on page 60

Parenteral Drug Association Training and Research Institute (PDA TRI)

Upcoming Laboratory and Classroom Training for Pharmaceutical and Biopharmaceutical Professionals



October 2011

Hosted in conjunction with the *2011 PDA Visual Inspection Forum & TRI Course*

An Introduction to Visual Inspection
October 5-6, 2011 | Bethesda, Maryland | www.pda.org/visualinspection2011

PDA's 6th Annual Global Conference on Pharmaceutical Microbiology & TRI Courses
October 20-21, 2011 | Bethesda, Maryland | www.pda.org/2011microbiology

Course Series:

- Environmental Control and Monitoring for Regulatory Compliance - *New Course* (October 20)
- Rapid Microbiological Methods: Overview of Technologies, Validation Strategies, Regulatory Opportunities and Return on Investment (October 20)
- Auditing for Microbiological Aspects of Pharmaceutical and Biopharmaceutical Manufacturing (October 21)
- Microbiological Issues in Non-Sterile Manufacturing (October 21)

PDA TRI Filtration Week
October 24-28, 2011 | Bethesda, Maryland | www.pdatraining.org/filtrationweek

- Filters and Filtration in the Biopharmaceutical Industry - Basics Course (October 24-25)
- Filters and Filtration in the Biopharmaceutical Industry - Advanced Course (October 26-28)

Save 10% when you register for both courses!

November 2011

Quality and Compliance Management for Virtual Companies - *New Course*
November 1-2, 2011 | Bethesda, Maryland | www.pda.org/virtualcompanies

Preparation of Virus Spikes Used for Virus Clearance Studies - *New Course*
November 7-8, 2011 | Bethesda, Maryland | www.pda.org/viruspikes

Validation of Biotechnology-related Cleaning Processes - *New Course*
November 8-10, 2011 | Bethesda, Maryland | www.pda.org/validation

December 2011

Quality Systems for Aseptic Processing
December 1-5, 2011 | Bethesda, Maryland | www.pda.org/qualitysystems

Laboratory Courses

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

All 2011 Aseptic Processing Training Program Sessions are sold out. The 2012 schedule will be available soon.

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

Broad Scope Covered with TRI's Micro Courses

Bethesda, Md. • October 20-21 • www.pda.org/2011microbiology

Stephanie Ko, PDA

A spectrum of micro issues will be covered in the lecture courses offered at *PDA's 6th Annual Global Conference on Pharmaceutical Microbiology & TRI Courses.* So, whether or not you're attending the conference, take the opportunity to sign up for one, or even two, of our four training courses from October 20–21.

These courses will cover:

- Rapid Microbiological Methods (October 20)
- Environmental Control and Monitoring–New Course (October 20)
- Microbiological Issues in Non-sterile Manufacturing (October 21)
- Auditing for Microbiological Aspects of Pharmaceutical and Biopharmaceutical Manufacturing (October 21)

Participants who sign up for the "Rapid Microbiological Methods: Overview of Technologies, Validation Strategies, Regulatory Opportunities and Return on Investment," will receive a very thorough and holistic approach to understanding the scientific basis for RMMs across many different technological platforms. By the end of the course, students will understand how RMMs can be validated as alternatives to traditional microbiological applications, what the regulatory expectations are, and how to develop a business case in support of an implementation strategy. This is the most complete and comprehensive rapid methods training program currently available, and is taught by one of the original subject matter experts and advocates for RMMs within the pharmaceutical and biopharmaceutical industries, **Michael J. Miller,** PhD, President, Microbiology Consultants.

If your focus is to maintain a compliant environmental monitoring program, consider taking the training course, "Environmental Control and Monitoring for Regulatory Compliance." Dunning this course you will learn about the tools, techniques, methods, and best industry practices to employ when performing environmental monitoring. Instructor **Frank Kohn,** PhD, President, FSK Associates, will give valuable insights into potential contamination issues and problems. Participants will understand how the use of various trending methods and risk analysis demonstrates a quality systems approach to improving environmental monitoring.

Kohn also teaches "Auditing for Microbiological Aspects of Pharmaceutical and Biopharmaceutical Manufacturing." In this course, students will learn key auditing concepts to identify microbial problems in production. Current FDA and global regulatory authority GMP regulations will be reviewed. Participants will use various auditing tools to analyze and discuss actual manufacturing case studies and develop a scientific justification for their current quality systems programs.

Finally, we're pleased to offer a popular course, "Microbiological Issues in Non-Sterile Manufacturing." Taught by **Barry Friedman,** PhD, Consultant, this course is designed to give attendees an enhanced appreciation of the various concerns surrounding non-sterile manufacturing. Friedman will define elements and issues associated with non-sterile manufacturing that do not occur within the aseptic environment. Issues such as water activity, impact of incoming microbial content of raw materials, and "specified" microorganisms are explained as to how they impact the outcome of the final product. A case study will be included.

Take the opportunity to sign up for one, or even two, of our four training courses from October 20–21

For more information on these TRI courses or to register, visit www.pda.org/2011microbiology.

Regulator, Industry Perspectives Aired at MaB Workshop continued from page 58

PDA's Who's Who

Mike Defelippis, PhD, Research Fellow, Biopharma R&D, Eli Lilly

Kathleen Francissen, Associate Director, Genentech

Steffen Gross, PhD, Deputy Head, Monocolonal and Polyclonal Antibodies, Paul-Ehrlich-Institut

Chris Holloway, PhD, Group Director, Regulatory Affairs, ERA Consulting Group

Nanna Kruse, M.Sc.Pharm, Sr. Biological Assessor, Danish Medicines Agency

Richard Levy, PhD, Sr. Vp., Scientific and Regulatory Affairs, PDA

Daniel Müller, GMP Inspector, Regierungspräsidium

Stephanie Schnicke, Director, Regulatory Affairs, Roche Diagnostics

John Stults, Director, Protein Analytical Chemistry, Genentech

Pascal Venneugues, Scientific Administrator, Q-Sector, EMA

About the Author

Rich Whitworth graduated from the University of Leicester (UK) in Medical Biochemistry, spent five years in the publishing industry in Tokyo and Japan, and is now Editor of *BioPharm International and Pharmaceutical Technology Europe.*

Filtration Course Series Offered at TRI

Bethesda, Md. • October 24-28 • www.pda.org/courses

Stephanie Ko, PDA

In alignment with its mission, PDA's Training and Research Institute (TRI) is offering a brand new course series on filtration.

Our members and students, through their feedback, have helped TRI create the series, and we are happy to offer it for the first time.

"Filters and Filtration in the Biopharmaceutical Industry"—Basics Course will take place from October 24–25. This course will give participants a fundamental understanding of biopharmaceutical filtration and filters that will allow participants to apply knowledge of filter properties and perform key filtration operations for the manufacture of aseptic products. This is a highly interactive lecture course, focusing on practical applications and experiences of filter usage, economics and performance of systems designs, integrity test methods and importance, process validation of filter devices, and more!

Immediately after, **"Filters and Filtration in the Biopharmaceutical Industry"—Advanced Course** will take place October 26–28. This course consists of 30% lecture and 70% hands-on training. Time in the laboratory includes group work that will determine the optimal filter combination in particular case studies. Integrity tests for liquid and gas filters will be performed, including trouble shooting to determine reasons for integrity test failures and counter measurements. Product wet integrity test limits will be determined in another segment of the hands-on training to be able to establish the correlation between product and water wet integrity test limits.

Both courses will be taught by **Maik W. Jornitz,** Sr. Vice President, Marketing & Product Managemen, Sartorius Stedim Biotech and by **Wayne Garafola,** Field Application Specialist Biotechnology Division, Sartorius Stedim Biotech.

Jornitz has said that this course series is essential "to keep the training of the filter user up-to-date and enhance knowledge with a broader base of training topics...."

If you would like more detailed information on these or any course that TRI offers, visit www.pda.org/courses.

Editor's Message

The End of an Era

It is our sad duty to report that **Theodore Meltzer** has passed away. Ted has a long history of, imparting his experience to newer members through his books, lecture courses and presentations. In 2006, Ted was honored as one of PDA's Outstanding Scientists during the PDA 60th Anniversary Celebrations, and in 2009, he was further honored with the dedication of the biotechnology lab in PDA's Training and Research Institute. Through his advice, he will live on in our hearts and minds. Ted's long-time, close associate, **Maik Jornitz,** has written a tribute to Ted befitting his legacy (see page 6).

Elsewhere in this issue, we present a novel blueprint on how companies can proactively reduce the number of quality deviations in their operations. In the article, "Reduce Your Deviations: Implement a Quality Near Hit Program" (page 20), a group of authors from Grifols (formerly Talecris) discuss how their firm is training its employees to take proactive corrective measures based on potential deviations by documenting "near hits" that occur throughout the day. The team first presented the case study at the *2010 PDA Biennial Training Conference* in Baltimore, Md.

The *PDA Letter* Editorial Committee (PLEC) *loved* this case study, and we are really proud to present it to you. Here are a few examples of PLEC's comments:

"This article adds value in demonstrating proactive compliance vs. reactive. Good case study with demonstrable results."

"This article applies best to large organizations that make many products. Small companies would not need such an extensive program, but the underlying theme is still relevant; everyone should be recognizing potential deviations and proactively take action."

"Excellent article, simply written, with real metrics and cost savings detailed. A great example of the Cost of Quality concept."

If you attend *PDA's 6th Annual Global Conference on Pharmaceutical Microbiology & TRI Courses,* you'll also pick up some great ideas to bring back to your firm. In this issue, we have highlighted a few key sessions from the upcoming conference: Breakfast Session II: Microbiologist of the Future - Emerging Leaders Panel Discussion (page 16); P4: "Urban Myths" (page 18); Session P2: Microbiological Issues Associated with Reconstitution, Administration, and Holding of Products (page 26); a conference overview (page 46); and a comprehensive look at the Training and Research Institute's Micro Courses (page 60).

A report from the *2011 PDA Pharmaceutical Cold Chain Management Conference* highlights three speaker's presentations that examined solutions for a longer product shelf life and potential for cost savings with a dynamic cold chain model.

Make sure you participate in the World Health Organization's feasibility study, and read about PDA's partnership with the CMC-Vaccines Working Group in the "News and Notes" section. Also, please be aware of the PDA Officers & Board of Directors Election. You can cast your vote at eBallot4.votenet.com/pda if you are a current PDA member.

Thank you for taking time to read my second Editorial Column. This month I'm pinch-hitting for **Walter Morris,** Director of Publishing, as he and **Katja Yount,** Publication Design Specialist, are busy wrapping up the 65th Anniversary Book, which will be available in September. They both have done a great job of going through archives and digging up some fantastic pictures and almost-forgotten information about PDA. **—Emily Hough**

PDA Letter

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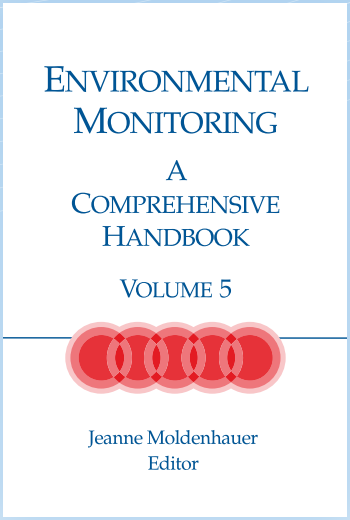

The Much Anticipated 5th Volume of Environmental Monitoring a Comprehensive Handbook is Now Available!

Jeanne Moldenhauer, along with fourteen expert authors discuss the requirements and establishment of an environmental monitoring program for the quality control microbiology laboratory.

This comprehensive handbook address key topics such as environmental trending and the reports needed for manually trending data, how to present environmental data to both internal and external stakeholders, details regarding the development of an identification laboratory at your site, and the latest technology for performing identifications.

Chapters include:

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- Malidi-Tof Method for Identification of Microbial Isolates
- Microbial Identification Laboratory in Support of an Environmental Monitoring Program
- Environmental Monitoring and the Microbial Control Strategy
- Fungal Contamination and Disinfection
- Emerging Technology for Fungal Contamination Control
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This book is a welcome addition to any Environmental Monitoring collection.

Learn more at www.pda.org/em5

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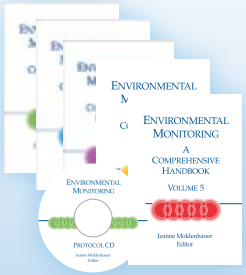

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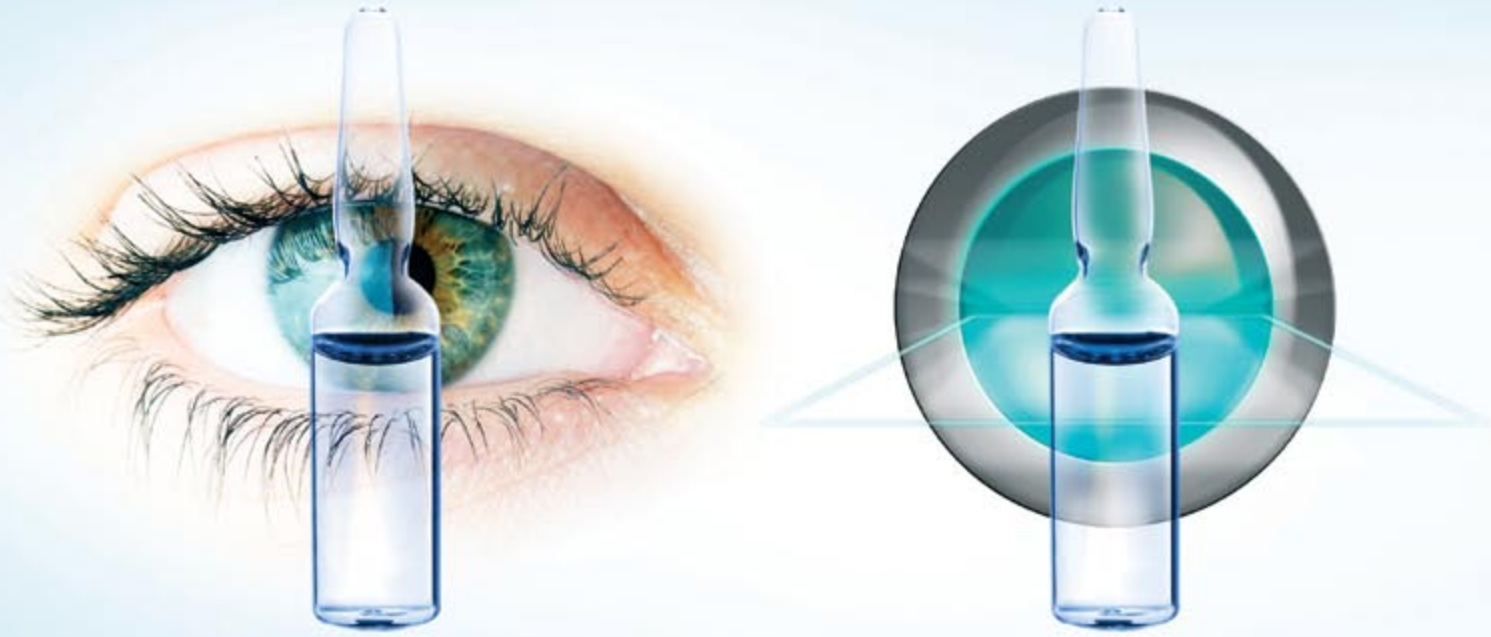

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