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PDA Letter

Volume XLIV • Issue #9

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October 2008

In This Issue:

Online Voting:

PDA Parenteral Drug Association

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Regulator Cooperation on Display at *2008 PDA/FDA Joint Regulatory Conference*

Walter Morris, PDA

Anyone doubting the sincerity of health authorities to harmonize regulations and inspection practices would have been surprised to see an official from the EMEA and the Shanghai Municipal FDA (SHFDA) participating in the opening plenary session of the *2008 PDA/FDA Joint Regulatory Conference.* Of course, it came as no surprise to PDA members that SHFDA Deputy Director **Tang Minhao** and EMEA Inspections Sector Head **Emer Cooke** joined with U.S. FDA Center for Drug Evaluation and Research Director **Janet Woodcock,** MD, and U.S. Pharmacopeia Executive VP and CEO **Roger Williams,** MD, to open a meeting ostensibly held to provide industry and the U.S. FDA a neutral forum for discussion. Harmonization, after all, has been at the forefront of regulatory activities worldwide for over a decade, and PDA members have been active contributors.

After hearing the opening talks, it is obvious that more and accelerated harmonization is on the horizon to keep pace with the global market for drugs and the hazards that accompany it. CDER's Woodcock called the heparin situation a "wake-up call" that "brought home the need for vigilance throughout the supply chain and in all global settings." The situation provides the FDA with the resolve to redouble its harmonization efforts, many of which have been underway since the 1990s.

Woodcock outlined "significant challenges" the Agency is facing:

- Explosion of globalized manufacturing
- Increased complexity of supply chains
- Greater potential for exploitation (e.g., counterfeits, terrorism)
- Global regulatory system still fragmented
- U.S. erosion of inspectional coverage over last several decades
- U.S. lack of modern IT (e.g., registration and listing systems, inspection tracking, imports)

For all its good, globalization of the pharmaceutical industry has placed great strains on the Agency, said Woodcock. The number of drug products manufactured offshore has more than doubled since 2001. Correspondingly, the number of inspections conducted by FDA has increased, but overall coverage has dropped by 37%. The number of imports have doubled (with 312 operable points of entry), while field exams have declined. Growing reliance on generic drugs,

continued on page 14

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Cover art:
Industry leaders from across the globe met in Washington, DC for the 2008 PDA/FDA Joint Regulatory Conference. Photos and photo collage by James Austin Spangle

Coming Next Issue:
Reports from PDA's 3rd Annual Global Conference on Pharmaceutical Microbiology

PDA
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2009 PDA Annual Meeting

The Impact of the Microchip – Application of Modern Technologies in the Development, Manufacture and Testing of Bio/pharmaceutical Products

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Exhibition	April 20-21, 2009
Career Fair	April 20-21, 2009
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Join industry and regulatory colleagues at the *2009 PDA Annual Meeting* to explore some of the most influential factors impacting the current state and future development of the pharmaceutical and biopharmaceutical industry. Built on the theme, *The Impact of the Microchip – Application of Modern Technologies in the Development, Manufacture and Testing of Bio/pharmaceutical Products*, the conference will examine the systems and tools that can help you and your company maximize efficiency and productivity, while consistently delivering safe, pure and reliable drugs to patients.

Complementing the conference are PDA Training and Research Institute (PDA TRI) courses, an exhibition featuring today's leading bio/pharmaceutical companies and service providers, PDA's 5th Annual Career Fair and enhanced networking opportunities that take advantage of all that Las Vegas and the exciting Red Rock Resort and Casino have to offer.

Increase your knowledge, find solutions to every day challenges, make valuable contacts and advance your career at the *2009 PDA Annual Meeting*.

Photos courtesy of Bayer Healthcare and Sartorius Stedim Biotech

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Editor's Message

E is for…PDA Letter

It seems that nowadays every form of media has a great online product, whether it is our favorite magazine, newspaper, television program or book. The availability of online material has enhanced traditional print and broadcast media, and in some cases, supplanted them. In this issue, PDA announces three new online offerings, with the most immediate being the online voting for the board of directors and the next edition of *International Pharmaceutical Quality* (see p. 7 for announcements). In early 2009, the *PDA Journal of Pharmaceutical Science and Technology* will launch an exciting new website with archives and powerful research tools (see p. 10).

While these advances are new and exciting, the PDA Letter has been ahead of the e-curve since 2007, when www.pda.org/pdaletter launched. At this site, members and nonmembers can access three "selected" articles from the most recent issues, and members can click into the membership archive to view entire issues going back to 2001. There are also links to the upcoming editorial themes and other information about the Letter.

It is an exciting time to be working on PDA's publications, and not just because of the transition to electronic publishing. The level of energy and creativity of our members has never been higher, and is manifesting throughout our publications. Each month, the Letter offers timely articles on a variety of topics by members, including the contribution by **Anita Whiteford,** titled "How Does Your Training Measure Up?" in this issue's TRI/Education department (p. 42) and the report on a recent EMEA Biologics Working Party meeting (p. 12) by a group of dedicated PDA members in Europe.

Finally, I want to ask all readers to pay attention to how the Letter is looking. If you are like me, you might focus almost exclusively on the words on the page, but sometimes it is worthwhile to step back from the words and take a look at the pages. I've been doing so recently and like what I see, and I've heard the same from other readers as well. All the credit goes to our Publications Design Specialist **James Austin Spangle**. We are always interested in getting feedback on the Letter, so please send an e-mail to James or me to let us know how you feel about the publication design.

PDA Letter

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Membership Alert: IPQ Now Available Online!

Starting with your November/December issue of the *International Pharmaceutical Quality*® (IPQ®), PDA members will have instantaneous access to all the hot news and incisive analysis provided in each issue. PDA knows that busy professionals require anytime/anywhere access to the information that is most important to them. Digital availability of IPQ will provide readers such access.

The online version of IPQ also will include easy navigation through each issue. Search tools also will allow readers to find specific keywords or phrases in the current issue and to search and access IPQ's archives.

Not only will IPQ continue to operate "Inside the Global Dialogue," but it will contribute to the dialogue with the use of online community-building tools. Such tools enhance creativity, information sharing, collaboration and functionality of websites, which lead ultimately to the evolution of web-based communities.

Offering IPQ electronically is in line with PDA's mission to develop practical information and resources to advance science and regulation. The value of IPQ is in the information offered, not the container in which it is delivered. The move to an electronic format is also in line with the global need to find environmentally friendly methods of doing business.

For those who find value in the hardcopy IPQ, members and subscribers can continue receiving six hardcopy issues each year for an additional $50 (U.S.). To request your hardcopies please contact PDA's Membership Department at info@pda.org or +1 (301)656-5900.

PDA Election Goes Electronic:

Vote online for the upcoming PDA Board of Directors election!

PDA is pleased to announce a new electronic (eBallot) voting process for the upcoming 2009 PDA Board of Directors election in October. PDA members will have the ability to cast their votes quickly and easily online in a secure environment. In addition to the ease and anywhere/anytime voting capabilities, eBallot brings advanced security and voting verification to ensure your vote is counted.

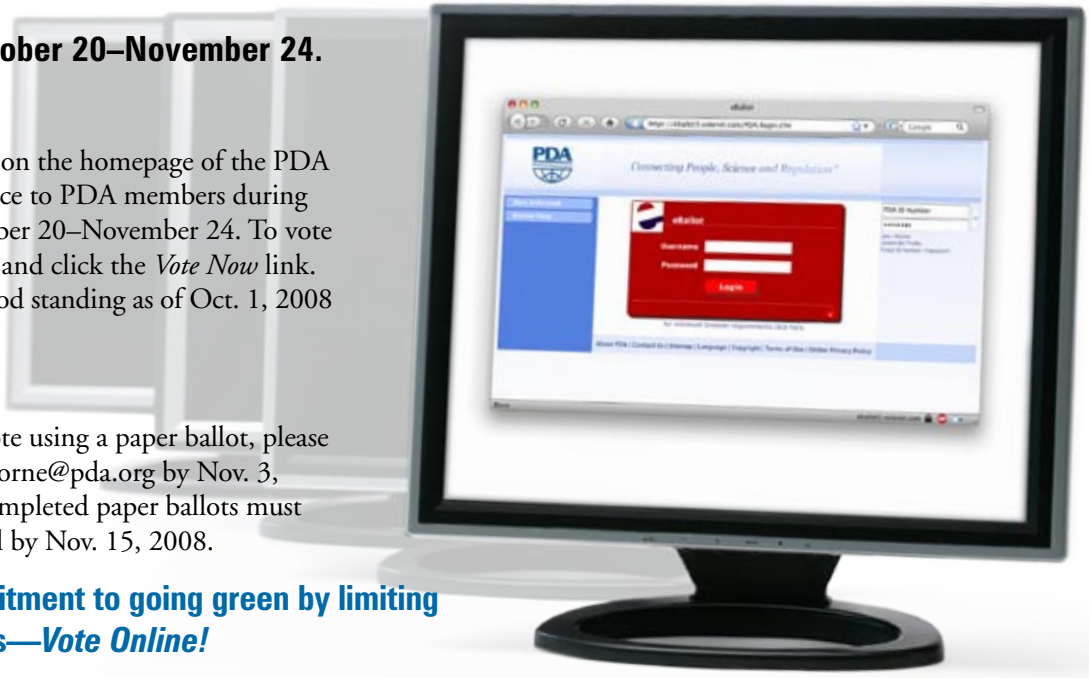
Polls will be open from October 20–November 24.

Voting

Links to the eBallot will be posted on the homepage of the PDA website and in email correspondence to PDA members during the open voting period from October 20–November 24. To vote simply log on to the PDA website and click the *Vote Now* link. You must be a PDA member in good standing as of Oct. 1, 2008 to participate.

Requesting Paper Ballots

If you would prefer to cast your vote using a paper ballot, please contact **Tracie Carthorne** at carthorne@pda.org by Nov. 3, 2008 to request a paper ballot. Completed paper ballots must be returned to PDA via fax or mail by Nov. 15, 2008.



Please support PDA's commitment to going green by limiting printing of election materials—*Vote Online!*

PDA Enters MOU with Shanghai Institute for Food and Drug Safety

PDA and the Shanghai Institute for Food and Drug Safety (SIFDS) signed a Memorandum of Understanding (MOU) at the *2008 PDA/FDA Joint Regulatory Conference* on Sept. 8, 2008, in Washington, D.C.

Moments after the signing, Chinese authorities exchanged gifts with PDA representatives

An observer from the Shanghai Municipal Food and Drug Administration (SHFDA), **Tang Minhao**, Deputy Director, was witness to the MOU signing. SHFDA acknowledges and supports PDA and SIFDS cooperation and establishes SIFDS/PDA Shanghai Joint Development Center (SHJDC). Earlier that day, Minhao was a speaker during the opening plenary session PDA/FDA Joint Regulatory Conference.

Gao Huijun, Deputy, SIFDS, signed the MOU for her organization. The SHJDC will assist PDA in meetings and training. Items where assistance will be provided by SHJDC in China include organizational support, promotion, identification and invitation of Chinese speakers, sponsorships by Chinese industry and general administration.

PDA President **Bob Myers** and Chair **John Shabushnig,** PhD, Pfizer, signed the MOU on behalf of PDA.

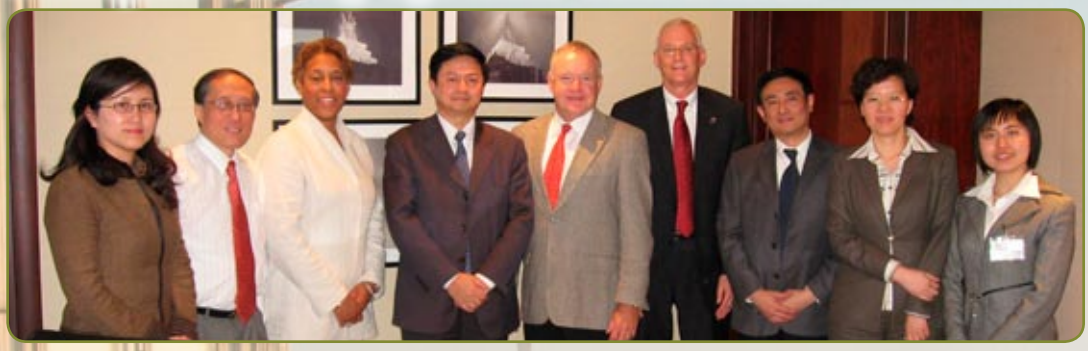
Myers told those in attendance, "The agreement is a major endeavor to enhance quality in China's pharmaceutical manufacturing, to improve pharmaceutical technology and quality control, and to achieve international exchanges on laws and regulations in pharmaceutical manufacturing."

Shabushnig stated that the opportunity PDA and the SIFDS were taking allowed for a safer and effective way to produce medicines. "I hope that the signing today is the start to a long relationship and we can continue to find ways to support our common interests."

The first conference hosted by this joint venture will be held in May 2009 in Shanghai. The content will focus on topics from PDA/FDA meetings in 2008. Training sessions will concentrate on regulations, latest technical standards, and regulatory tools for relevant Chinese government departments or commercial enterprises.

The MOU grew out of PDA's work with Chinese health authority officials to sponsor a conference on quality systems in Beijing and Shanghai earlier this year.

Shanghai Quality Systems Conference



(l-r) Xu Lai, SIFDS; Jinming Bao, Eastbound Synopharma Co.; Wanda Neal-Ballard, PDA; Tang Minhao, SHFDA; Bob Myers, PDA; Rich Levy, PDA; Yan Liang, SHFDA; Gao Huijun, SIFDS; Tian Yifang, SHFDA

The relationship between PDA and the SHFDA has been budding over the past two years, culminating in the MOU signed at the PDA/FDA Joint Regulatory Conference. Pictured on this page are select photos from the Joint Conference on Quality Systems held in Shanghai last May. The conference was the second of two held in China in cooperation with the regulatory authorities, the first taking place in Beijing (see the July/August *PDA Letter,* pp. 56–57).

(l-r) John O' Sullivan, Pfizer; Neil Wilkinson, David Begg Associates; Mike Beatrice, Abbott; Gerald Lohan, Merck

Science & Technology *Snapshot*

Building a Better Journal Online

Walter Morris, PDA

Ever wanted to look up an article from the *PDA Journal of Pharmaceutical Science and Technology* away from your hardcopies? Ever wished the Journal archives were available in a format more convenient than CD-ROM? Do you think you should be able to link from a current Journal article to its references? Ever submitted an article to the Journal and wished it was published faster?

Well, PDA is working to bring you these features and more with our new online version of the *PDA Journal of Pharmaceutical Science and Technology.* After months of careful consideration, we have selected a vendor that currently produces more than 1,100 online journals, reference works, books and other "knowledge environments." By teaming with this experienced online journal facilitator, PDA will build a top-rate online Journal experience that will increase the value of the Journal to all members, authors and subscribers.

Using the latest Web 2.0 tools, the online journals offer powerful research capabilities, which include "most read" and "most cited" listings. The new platform will ensure that the PDA Journal becomes an even more useful tool for researchers and academics, in addition to PDA members and subscribers.

PDA is about to launch the project and expects the online journal to be available by the second quarter of 2009.

Keep an eye on this column for more information on the evolution of the PDA Journal website. Updates will include screenshots and links to other online journals you can visit to test drive the online research tools.

PDA is still reviewing candidates for journal editor. To apply, send resume to **pdajournaleditor@pda.org**

Technical Report *Watch*

In Edit: *After global review, task forces responsible for the TRs consider the feedback received. TRs then undergo final technical editing.*

- ***Points to Consider: Microbial Data Deviations***
- **TR-22 (Revised),** ***Process Simulation Testing for Aseptically Filled Products***
- ***Biological Indicators for Sporicidal Gassing Processes: Specification, Manufacture, Control and Use***

In Board Review: *Following technical editing, TRs are reviewed by PDA's advisory boards (SAB, BioAB). If/when approved, the PDA Board of Directors (BoD) makes the final decision to publish or not publish the document as an official PDA TR. Balloting at each level can take several weeks or longer, depending on the questions posed or revisions required.*

- ***Blow-Fill Seal*** **(BoD)**
- **TR-15 (Revised),** ***Validation of Tangential Flow Filtration in a Biopharmaceutical Application*** **(BioAB)**

In Publication: *TR is approved and ready for publication with next Journal*

- **TR-26 (Revised),** ***Sterilizing Filtration of Liquids*** **(September/October Journal)**
- **TR-41,** ***Virus Filtration*** **(September/October Journal)**

Journal *Preview*

Volume 62, Issue 5 of the PDA Journal contains several notable articles. First off is the two-part article from a team of researchers led by FDA's **Kurt Brorson** on a consensus rating method for small virus-retentive filters. The issue also includes commentary from PDA filtration experts **Maik Jornitz** and **Ted Meltzer,** in cooperation with a group of co-commentators, on points to consider for product-wet integrity testing of sterilizing grade filters. The issue also marks the return of the "conference proceeding" category with articles by **Anurag Rathore** and **Rebecca Devine** from the 2007 PDA conference on QbD for biotech.

The full line up for this issue:

Commentary

- M. W. Jornitz, T. H. Meltzer, V. Chiruvolu, A. Chen, B. Kanoh, C. Connoly, J. Mora, "Product-Wet Integrity Testing of Sterilizing Grade Filters—Points To Consider"

Technology/Application

- Kurt Brorson, et al., "A Consensus Rating Method for Small Virus-Retentive Filters. I. Method Development"
- Kurt Brorson, et al., "A Consensus Rating Method for Small Virus-Retentive Filters. II. Method Evaluation"

Research

- Ajit S. Kulkarni and Manish S. Bhatia, "Design of Floating Bilayer Tablets of Diltiazem Hydrochloride and Lovastatin"
- M. Saeed Arayne, Najma Sultana, S. Shahnawaz Sajid, S. Shahid Ali, "Cleaning Validation of Ofloxacin on Pharmaceutical Manufacturing Equipment and Validation of Desired HPLC Method"

Review

- Sanjay K. Jain, Kavita Rai, Yashwant Gupta, Anekant Jain, "Transfersomes: Self-Optimizing Carriers for Bioactives"

Conference Proceeding

- Anurag S. Rathore and Rebecca Devine, "PDA Workshop on 'Quality by Design for Biopharmaceuticals: Concepts and Implementation'"

Interest Group *Briefing*

New QRM IG Holds 1st Meeting at PDA/FDA

Emily Hough, PDA

The PDA Quality Risk Management Interest Group met for the first time at the *2008 PDA/FDA Joint Regulatory Conference.* The lively session drew over 50 participants who came not only because of their interest in Risk Management, but also because the co-chairs lined up four expert presentations on the topic.

In introducing the IG, co-chair **Mike Long,** Director of Engineering and Product Development, Cooper Surgical, said that the IG's objective was to build a body of knowledge around QRM through published journal articles, case studies, presentations and by working with TRI to establish training courses. PDA board member **Lothar Hartmann,** PhD, Head, External Relations, F. Hoffmann-La Roche, said one aim of the IG was to help industry understand how to proceed in applying QRM in terms of utilizing the correct tools for a responsible risk management system.

Nancy Waites, Biologist, CBER, U.S. FDA, gave the first presentation, qualifying her remarks that she speaking about her own opinions and not those of the Agency. Waites said that when she receives a company's submission on risk management and risk assessment, she would like it clarified as to why the company picked the assessment they did. Also, she said that specific information that defines terms, such as the difference between major or minor impact helps the reviewer, as opposed to the blanket statement, "I have a risk assessment."

Ed Tidswell, PhD, Director, Baxter, underscored the importance of risk management. Using the example of vulnerable patients in the hospital, he said that as a manufacturer of medicinal products, there is "an obligation" to the patient from the development of symptoms until the patient's symptoms have abated.

Rob Piperno, QA, GBSC, said that his company is trying to integrate QRM training into new employee orientation, at least as a basic overview, and bring other training as needed. Piperno advised IG participants to use the QRM as often as possible, saying, "The more we used it, the better we got at it and the more we used it, the more uses we got out of it." He added, "the more you train [using QRM], the better everyone will feel doing it." He said that the core team that has worked on the implementation is moving towards forming a steering committee.

To find out more about this interest group, email either co-chair **Jeff Hartman,** Validation Manager, Merck, at jeffrey_hartman@merck.com or Mike Long at Mike.Long@coopersurgical.com.

Revised EMEA Guideline on Monoclonal Antibody Manufacturing

Report on BWP Scientific Discussion

Anita Derks, F. Hoffmann - La Roche; Hannelore Willkommen, PhD, RBS Consulting; Michael R. DeFelippis, PhD, Eli Lilly; Lynne Krummen, Genentech; Wassim Nashabeh, PhD, Genentech; and Jim Lyda, PDA

On June 18, a delegation of PDA experts met with the EMEA's Biologics Working Party (BWP) for a scientific discussion to support revision of the *Guideline on Production and Quality Control of Monoclonal Antibodies and Related Substances*, draft, (EMEA/ CHMP/ BWP/ 157653/ 2007, 5 April 2007). This discussion was requested by the BWP in light of industry comments on the revised draft of the guideline which was subject to consultation thru Nov. 30, 2007. The BWP invited professional and industry associations to provide scientific input in six broad areas, such as:

- Terminology
- IgG, IgM, IgE, fragments and fusion proteins
- "Platform manufacturing" including viral safety
- Specific analytical methods
- Specifications including glycosylation
- Particulates

The discussion was chaired by **Kowid Ho**, PhD, Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS), the BWP rapporteur for this guideline and was attended by representatives of the BWP. Invited associations included PDA, European Biopharmaceutical Enterprises (a specialized group of the European Federation of Pharmaceutical Industries and Associations) and EuropaBio. The entire discussion was cordial and professional, addressing relevant scientific and technical issues, with all parties able to express opinions and areas of concern.

Current status of guideline and review process: The BWP has redrafted the guideline based on the consultation comments, and many industry suggestions have been adopted. BWP is pleased with this consultation format (external/ industry written comments, followed by scientific discussion). Following the scientific discussion, the guideline will be revised followed by internal EMEA approval. No further external consultation will be invited. Release of the final version will probably be in 2009.

Scope of Guideline: The scope is primarily monoclonal antibodies (MAb), but the principles would also apply for MAb-related proteins. In the future there may be specific annexes for such products. The focus is on marketed products, but the principles should be taken into consideration for MAbs used in clinical trials. Industry suggested that the scope be described clearly in the guideline.

Platform Manufacturing: Submission data may be reduced based on experience with other products. For marketed products, ICH Q5B is the standard but alternate approaches may be possible with appropriate data. Regarding submission procedures, there is recognition of the impact of introducing a platform change affecting several products. The new regulation on variations may offer some possibilities for streamlining the process. The Quality Working Party and BWP are going to discuss and evaluate the possibilities. Industry should appraise the new variation procedures to determine the opportunities.

Specifications: In general, specification tests and acceptance criteria should be included for relevant product attributes. Reference was made to the inclusion of additional testing for pro-inflammatory contaminants. Specifically, the Monocyte Activation Test (MAT) should be considered for characterization purposes due to experience showing interference with the Limulus Amebocyte Lysate (LAL) test. (Binding to the Fc-portion of the MAb was observed, and therefore was not detected in the LAL assay.) Also, the LAL test is specific for endotoxins from gram-negative bacteria. The MAT assay may add assurance that other pyrogens can be detected. There are currently no standardized MAT assay formats available. Current industry practices for pyrogen control have proven to be effective.

Glycosylation: There is a regulatory perception that a glycosylation specification would provide a useful measure of process consistency. There is also recognition that glycosylation might not be a critical quality attribute of a particular MAb. It was agreed that alternative approaches for assuring control of glycan structure might be possible.

Specific analytical methods: In the final version of the guideline, reference to specific methods will be kept to a minimum and cited as examples.

Particulates: Most of the requirements for sub-visible/visible particles are described in several European Pharmacopeia (Ph.Eur.) monographs. As a result, there are legal and regulatory issues associated with requirements which cannot be resolved solely in the guideline. Resolution will require industry action regarding the monographs which can be initiated through the EDQM/Ph. Eur. process.

[Author's Note: This informal summary reflects the substance of the scientific discussions as interpreted by the PDA participants on the date of the meeting. This summary has not been officially approved by the BWP. Readers should use caution making any regulatory or compliance interpretations based on this information. The final version of the guideline will be published by EMEA in the near future. It may or may not reflect discussions in this article.

A more complete article regarding the outcome of this scientific discussion can be accessed at www.pda.org/stnews. Contact PDA's **Jim Lyda** for further information at lyda@pda.org.**]**

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Regulator Cooperation on Display at 2008 PDA/FDA Joint Regulatory Conference, continued from cover

which heavily utilize foreign ingredients, is driving the trends. Finally, the Agency has experienced a "progressive decline" in the number of field investigators devoted to pharmaceuticals since 2003.

To meet these challenges, she said, there needs to be "seamless, effective global regulatory collaboration" to provide a "world-wide safety net" and to "increase the effectiveness of inspectorates in developing countries." In addition, quality and pharmacopeial standards need to be harmonized globally, manufacturing needs to be modernized, supply chain security and integrity needs improvement, and IT systems need to be upgraded to track the global inventory.

It is up to manufacturers, primarily, to take responsibility for pharmaceutical quality and supply chain integrity, said Woodcock. The health authorities, on the other hand, need to:

- Promulgate/adopt quality standards
- Ensure standards are met
- Take action against poor quality
- Enable continuous improvement

The challenges outlined by Woodcock are shared by the EMEA, according to Cooke, and the EU Agency is already well experienced with harmonization among the various member states.

EMEA Pilot Program on Inspections

Cooke noted that the EudraGMP database can help cooperation and communication. The database is the first European source of information on EU manufacturers and on inspections performed by European competent authorities. It facilitates the exchange of information and inspection planning, prevents duplication of inspections and increases transparency. A public version of the EudraGMP system is planned for the end of 2008, said Cooke.

EMEA is looking to go further than sharing inspection information; it is looking to coordinate international inspections among its members to better use resources and increase inspectional coverage outside participating regions. A pilot program for APIs was launched at the end of 2007. Joining the EMEA in the program are the inspectorates for France, United Kingdom, Ireland, Germany, Australia and the United States. The goal is for the authorities to share inspection data.

The pilot program will help determine:

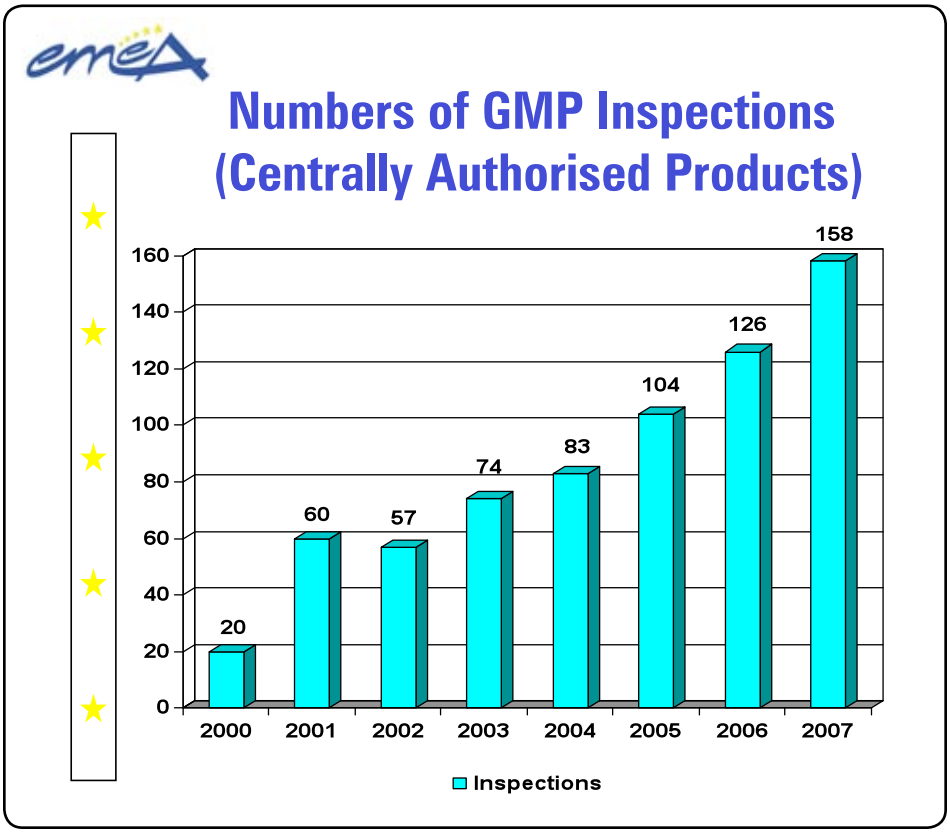
1. If authorities can use the information to avoid its own inspection.
2. If a new inspection meet the needs of several authorities.

And if not,

3. If a joint inspection is possible.

The pilot is expected to get underway by the end of 2008.

The EMEA is hopeful of the pilot's effectiveness in the face of its growing inspection load. The number of GMP inspections for centrally authorized products by the EMEA grew from 20 in 200 to 158 in 2007 (see figure below).



Emer Cooke discussed the rapidly growing workload for the Inspection Sector

Chinese Authorities Cooperating Internationally

SHFDA's Minhao spoke about the impact of globalization on his regulatory agency. Like its counterparts in Europe, the United States and around the world, the SHFDA is facing tremendous growth in the pharmaceutical industry in a short period of time. The value of its pharmaceuticals has grown nearly seven times since 1998. Chemical drug exports have grown 28.2% in that period and imports 32.2%.

The State Drug Administration was established in 1998, and it was reorganized as the State Food and Drug Administration in 2003. In 2007, China boasted 2,692 drug regulatory departments with over 64,000 personnel throughout China. These regulatory departments operate at the provincial, municipal and county levels.

To help manage its growing international role, the Chinese government has signed cooperative agreements and memorandums with the drug regulatory authorities in the United States, Canada, France, the United Kingdom, the European Union, Italy, Australia, Cuba, Brazil, South Korea, Singapore and Thailand.

(l-r) John Shabushnig, Pfizer; John Finkbohner, MedImmune; Janet Woodcock, U.S. FDA; Roger Williams, USP; Tang Minhao, SHFDA

In 2007, China's agreement with the United States was signed covering drugs and medical devices. The agreement established a mechanism of meetings between senior officials of the drug regulatory authorities of the two countries and enhanced the supervision over the export and import of pharmaceutical materials. Through the exchanges, representatives of the FDA visited with the SHFDA.

To improve drug safety monitoring, the SHFDA intends to establish clearer administrative goals, create more rational systems, allocate more effective administrative resources, standardize working procedures and expand transparency.

U.S. and EU Open Door to Simplified Regulatory Procedures for Pharmaceuticals

Emily Hough, PDA

The Transatlantic Administrative Simplification (TAS) initiative has brought the U.S. FDA, the European Commission, and the EMEA together to closely examine administrative procedures that do not contribute to the protection of public health. For example, an EU requirement for retesting of imported medicines and a proposed guidance on dedicated facilities could be impacted as a result of TAS.

TAS is an offshoot of the Transatlantic Economic Council and runs parallel to other efforts to remove regulatory barriers to trade. For example, the International Conference on Harmonisation is a parallel effort to harmonize regulatory requirements. Confidentiality arrangements between EMEA and FDA allow the two agencies to share, among other things, inspection information.

How TAS will impact industry and the agencies was the topic of discussion at a session of the *2008 PDA/FDA Joint Regulatory Conference.* Making sense of it all were **Neil Wilkinson,** PhD, Partner, David Begg Associates; **Emer Cooke,** Inspection Sector Head, EMEA; and **Nick Buhay**, Deputy Director, DMPQ/OC, CDER, FDA. The key take-home message of the three speakers was that through the TAS there is a good chance that certain frustrating and sometimes perplexing administrative regulatory procedures will be revised or removed.

EMEA's Cooke said that the purpose of the TAS was to "draw up a list of opportunities for administrative simplification and then see where those could actually be achieved. The real focus here…was on those that couldn't be addressed in other forums."

In a move towards better responsiveness to industry needs, EMEA and FDA opened up the process of simplification to industry. In November 2007, a Transatlantic Simplification Workshop was co-sponsored by FDA and its counterparts in Europe, including representatives of the European Commission, EMEA and national authorities.

The authorities requested industry participation to help identify target projects. Wilkinson said that the workshop was "very much the first event of its kind, still probably the only event of its kind." Suddenly the industry was asked to identify specific administrative data that did not impact the regulatory systems or healthcare to patients.

The invitation to comment came with three caveats. The first, Wilkinson said, was that industry "was not allowed to purpose areas of change that actually required changes to be made to legislation." It is understood that "changes to regulations in the U.S. and Europe is a very painful, time consuming and expensive process." Another stipulation was that industry should not make proposals that could jeopardize "the overall assurance and coverage of public health protection." The third caveat was that industry's proposals must address areas of true transatlantic or international concern.

Under these conditions, industry offered proposals in the areas of quality/inspections, scientific collaboration, pharmacovigilance and guidelines/format harmonization/ electronic submissions.

Looking specifically at the proposals in the quality and inspections area, the EU grouped them into four different categories as part of a triage system: work done, work in progress, for careful consideration and visionary ideas.

Work in Progress

The following proposals were categorized as work in progress:

Certification of Pharmaceutical Products (CPPs): Wilkinson said that industry would like the FDA to issue CPPs that then can be used by other regulatory agencies around the world as proof that a product has been licensed and registered in the United States, and the same thing applies for those issued in Europe. It was decided that FDA will start to do them and continue to do them for products irrespective of where they were manufactured.

Exchange of inspectional information: Wilkinson said that when industry presented information about all the duplicity of inspections, the regulators saw the light and recognized that there could be a better use of resources.

Cooke said that a plan was in the works for such an exchange to "see whether we could identify sites of interest, avoid duplication, more effectively use our resources and ensure a higher safety level for product coming from countries outside our own territory." Currently, she added, "we've been talking to one or two companies about candidates sites for these joint inspections, obviously they have to be sites where same products are concerned and have more or less same deadlines in both regions. We are hoping that we will be work that inspection together [with the FDA], either by the end of 2008, or if not, very shortly into 2009."

The EU guideline on dedicated facilities: A guideline issued by the EMEA on this topic was recently withdrawn. EMEA is now working with the FDA to see if they can come up with a harmonized guidance. Cooke stated, "This is an area that the EU has been working on for some time. We already have some wording in our current GMPs guide that is open to different interpretation, and have launched an in-depth consideration of, really, how best to ensure the safety ➤

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U.S. and EU Open Door to Simplified Regulatory Procedures for Pharmaceuticals, continued from page 16

of product…where there is a risk of cross contamination within industry facility."

Harmonization via the Pharmacopoeial Discussion Group and Q4b: Wilkinson said that industry strongly supports the concept of mutual acceptance of pharmaceopeial standards.

Careful Consideration

The following proposal was categorized as "careful consideration."

Bilateral cooperation and formalization of inspection information exchange: In this area, Wilkinson mentioned that the regulators want to heighten the level of bilateral cooperation on inspections. He said it would be a great step forward if the regulatory agencies worked together to better understand who they are inspecting, where they are inspecting and the outcome of those inspections.

Visionary

The following "visionary" proposals were labeled as such because they didn't fall into the other project criteria and could be considered in the future.

EU retesting of products on imports: Products imported into the European Union from the United States have to be retested on arrival. According to Wilkinson, industry thinks that, provided inspections of facilities have been carried out, retesting would not be an essential requirement on a case-by-case basis for a site for products it made. (Industry has challenged the retesting outcome, but has yet to hear back from the European Commission.)

A single globalized pharmacopoeia: Wilkinson said that industry should continue to press for mutual acceptance of pharmacopeial standards because in many areas, the multiplicity of testing and standards offers no benefit or added protection to the patient.

Transatlantic Initiatives Working

According to the provisions of the TAS, a roadmap had to be in place by June 2008. Wilkinson said that once the topics had been accepted and prioritized they would be delivered through bilateral work. "We recognized that some of the areas, because we were focusing on areas of trivia, 'blind compliance' (which is a term I like to use a lot), we actually could increase public health protection by changing the focus, not doing some of these activities and then redeploying the resources of both regulators and industry to things that actually mattered in terms of patient safety."

FDA's Buhay said that the ability to work with counterparts in Europe was an important tool for developing communication networks. Since "the entire regulatory process depends on information," he explained, "the more the better."

Wilkinson said the Transatlantic Initiative is very positive. "When we see the European regulators and FDA working together simplifying things like post-approval change, that is a very positive message that everybody is trying to move in the same direction. We really have to support it though, from both an industry perspective and the regulators' perspective. We have to recognize that we have to work together to make this happen, so there is a partnership between regulators and industry—which might worry some people. We have to keep the right distance, but work together in some of these areas. Otherwise, we will not get the value for the patient that we really want."

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Quality & Regulatory Snapshot

An Interview with the Co-chairs of the RAQC

Emily Hough, PDA

PDA Regulatory Affairs and Quality Committee (RAQC) co-chairs **Steven Mendivil** and **Stephan Roenninger** gave an interview to the *PDA Letter* about being the new leaders of RAQC. Steven is the Executive Director of Global Quality, Environment, Health, Safety Compliance at Amgen and is a member of PDA's Board of Directors. Stephan is Global Quality Manager at F. Hoffmann – La Roche. They recently became co-chairs of the PDA RAQC when former chair **Zena Kaufman's** term ended. Zena is the Divisional Vice President of Abbott Quality and Regulatory at Abbott.

PDA Letter: *What do you see as a major development occurring during your tenure as the RAQC Leader?*

Steven: I would expect a number of changes to important guidances from around the world. We are anticipating a revision to the FDA's Validation Guideline anytime, and we know that ICH Q11 is being drafted and would expect this to be available for comment over the next two years. It's a very exciting time as we set ground work for new Quality and Regulatory concepts and process for the future.

Stephan: In addition, the harmonized implementation of the guidance on ICH Q8, 9, 10 & 11 will be a challenge. I hope and think the RAQC community can and will support this for the benefit of the PDA membership and industry. Communications and discussions with regulators is key for me in order to understand their positions and that they understand where industry is coming from.

PDA Letter: *What issues if any would you say have occurred while you were the leader of the RAQC? What do you see happening?*

Steven: The need to formalize our commenting process within RAQC and determine how we can reach out beyond RAQC for comments within PDA on a specific document. PDA has quite a diverse membership and a lot of expertise in a variety of subject matters.

Stephan: I see opportunities where RAQC becomes more global. We already comment on EU requirements. A challenge is to include guidelines that are issued in Asian countries into the commenting process.

PDA Letter: *What do you hope to achieve while you are in charge of the RAQC?*

Steven: Organize and create a robust reviewing and commenting processes that allow us to respond quickly as a scientific body.

Stephan: Motivate our RAQC members to keep the behavior of an active support. In addition RAQC should get more proactive to suggest solutions on questions raised based on science, knowledge of our members, risk assessments and understanding of the GMP based systems, manufacturing and business processes. This hopefully will serve as a base from which regulators do not raise the bars with suggesting additional requirements. All of us should focus on patient needs.

PDA Letter: *What do you think is ahead for RAQC?*

Steven: There is a lot of interest in people wanting to join RAQC. It is up to the leadership and the committee to make sure we have good representation across the geographic as well as scientific disciplines that strengthens the RAQC committee.

Stephan: Nothing to add.

PDA Letter: *What is ahead for you in terms of PDA volunteerism?*

Steven: Not sure, but I have certainly enjoyed volunteering at PDA and working with so many great people to help shape the future of our industry.

Stephan: For me, the scientific discussions focusing on rationalized results developed by a multidisciplinary team inspires me. Based on that, PDA can move things by facilitating open and fruitful discussions at conferences especially with regulatory agencies.

[Editor's Note: We would like to thank Steven and Stephan for their interview and wish them continued luck as the co-chairs of RAQC.**]**

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 http://www.pda.org/regulatorynews.

North America

U.S. FDA Publishes Final Drug GMPs

The U.S. FDA has issued the final rule amending the pharmaceutical cGMPs. The Agency has amended the regulations in order to modernize or clarify some of the requirements, as well as to harmonize them with other FDA regulations and international cGMP standards.

The changes revise the cGMPs primarily in the areas of aseptic processing, process performance verification, and the use of asbestos filters.

The amended cGMPs becomes effective December 8, 2008.

U.S. FDA Releases an Integrated Summary of Effectiveness for NDAs and BLAs

The U.S. FDA has announced the availability of a draft guidance for industry entitled, *Integrated Summary of Effectiveness.*

The draft guidance describes how an integrated summary of effectiveness should be prepared for New Drug Applications (NDAs) and Biologics License Applications (BLAs). The draft guidance is intended to improve the quality of NDAs and BLAs by describing what efficacy information should be submitted so FDA can make a regulatory decision on an application.

When finalized, the draft guidance will supersede Section G, Integrated Summary of Effectiveness Data of the 1988 guidance on Format and Content of the Clinical and Statistical Sections of an Application. The draft guidance incorporates the conceptual framework of Section 2.7.3, Summary of Clinical Efficacy, from the ICH guidance for industry entitled, M4E: The CTD-Efficacy.

New USP Residual Solvents Standards Reinforced in U.S. FDA Draft Guide

The U.S. FDA has published a notice of the availability of a draft guidance entitled, *Control of Residual Solvents in Drug Products Marketed in the United States.*

On July 1, 2008, the USP published a new test requirement for the control of residual solvents; General Chapter <467> "Organic Volatile Impurities" was replaced by General Chapter <467> "Residual Solvents." The FDA draft guidance provides recommendations on how to comply with the USP changes. The change affects all compendial drug products marketed in the United States.

Europe

ICH Q4B Annexes Out for Comment

The U.S. FDA has made available the following annexes to the ICH Q4B Guidance: Evaluation and Recommendation of Pharmacopoeial Texts for use in the ICH Regions: Annex 4A: Microbiological Examination of Non-Sterile Products: Microbial Enumeration General Chapter Annex 4B: Microbiological Examination of Non-Sterile Products: Tests for Specified Microorganisms General Chapter Annex 4C: Microbiological Examination of Non-Sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use General Chapter Annex 5: Disintegration Test General Chapter.

EMEA Guideline Provides Advice on Viral Safety

An EMEA guideline entitled, *Guideline on Virus Safety Evaluation of Biotechnological Investigational Medicinal Products,* provides advice on the viral safety data and documentation that should be submitted in a request for authorization of a clinical trail of a human biotechnological medicinal product. It provides for a harmonized approach throughout the EU, for both sponsors and regulators, with regard to assessment of viral safety of biotechnological IMPs during clinical development. Also, it outlines the viral safety requirements applicable to all stages of clinical development of an IMP.

The guideline is slated to come into effect by February 1, 2009.

EMEA Publishes Proposal for Coordinated Global GMP Inspections

The EMEA has brought together a group of regulators in an international effort to optimize the use of global GMP inspection resources.

Regulators from EU Member States, U.S. FDA and Australian Therapeutic Goods Administration met to discuss simplifying administrative tasks relating to inspections and how to avoid unnecessary duplication of inspection work.

EMEA has published a proposal for the coordination of inspection plans between them.

International Cooperation

Transatlantic Regulators Commit to Shared Cooperation

Meeting in London on September 30 and October 1 ,2008, for the annual review of cooperative activities undertaken under the scope of their confidentiality arrangements, the European Union and United States authorities agreed to expand cooperation in the areas of advanced-therapy medicines and nanotechnology-derived medicinal products, as well as on the exchange of pharmacovigilance information.

Having been in place for five years, both sides concur that the transatlantic cooperation activities continue to be successful in protecting and promoting global human and animal health, reducing the regulatory burden and costs so that innovative medicines can be brought to patients in a timely manner, while also allowing critical safety information about medicines to be shared between the United States and European Union regulatory authorities.

Preliminary Results of U.S. FDA Recall Study Unveiled

Walter Morris, PDA

What really causes recalls? What insights can we gain through a retrospective assessment of recalls and related information? The U.S. FDA Center for Drug Evaluation and Research (CDER) is seeking answers to these questions by evaluating drug product recalls. The project is led by PDA volunteer and TRI faculty member **Lynn Torbeck,** PhD, a statistician and president of Torbeck and Associates. He provided an interim update during the September PDA/FDA Joint Regulatory Conference.

Torbeck started working with FDA on the study in October 2007. The ultimate goal is to provide the agency and industry with greater understanding of recall root causes in order to help prevent product defects.

What sets this study out from others done in the past, according to Torbeck, is its scope. "There have been retrospective reviews of recalls in the past," he stated. "And if you have been in the industry for a while you know that; you've seen those published before. But they have been infrequent and [addressed] one topic at a time. So what we are trying to do now is take on a bigger task of looking at multiple topics and reviewing all of them in kind of a same organized format."

The objective of the study is threefold. The first is to identify what recalls have the greatest impact on the patient. "That is what this is all about," said Torbeck. "How can we reduce the impact on patients relative to safety, efficacy and availability (the drug is no good if it is not there)?"

Second, FDA wants to identify the specific manufacturing root causes that lead to a product quality defect. Finally, the project is meant to feed FDA and industry lessons learned. "So this is where the statistics come in," added Torbeck. "Are there trends and patterns in the data we are collecting that can be used reduce recalls in the future?"

The study is ambitious as it includes all Class I drug recalls since 2000 and all Class II drug recalls in 2006 and 2007. For recall reasons identified as a "focus area" by FDA, the study is looking at the Class II's all the way back to 2000. The focus areas are:

- Out-of-specification (OOS)
- Dissolution
- Content uniformity
- Mislabeling
- Micro contamination
- Container/closures
- API
- Excipients
- Shipping/Distribution
- Non-Sterile
- Lack of sterility assurance
- Transdermals

Torbeck does not see any surprises with the "focus area" recalls. OOS and dissolution failures account for a large number of recalls each year. "Of course," he explained, "non-sterile and lack of sterility are much more serious. Non-sterile being Class I by definition, lack of sterility being Class II by definition. So we are interested in those from the risk posture."

FDA's database on recalls is the primary source of data for the study. Additional information is being mined from 483s and Establishment Inspection Reports (EIR) as well as other sources like MedWatch. These are valuable, Torbeck said, because, for example, "it is not unusual for an investigator to talk to the company about previous recalls if they are out just for a routine investigation. So sometimes information shows up" in EIRs.

Because the information is text based, Torbeck is challenged to convert a qualitative analysis into a quantitative one. "Coupled with all that is trying to incorporate the knowledge that we collectively have on manufacturing quality, use of statistics and of course the regulations themselves," he stated.

Another hurdle is the difficulty of establishing a sound statistical study. "Recalls are not random events," explained Torbeck, "so the idea of the truly representative random sample from a normal distribution doesn't apply here. Also, the agency will target a topic from time to time, and of course then you find a number of recalls that they've targeted. Chinese herbals for example. The challenge that I mentioned earlier is trying to convert free-form text into fixed-form text. You wind up reading a lot. And so it is very interesting, particularly when you start reading the MedWatch, [the stories] can be heartbreaking."

Condensing terminology is another difficult task. "There are terms, multiple terms rather, for the same concept," stated Torbeck. "In other words, you are reading along and you keep seeing the same idea, but they are using different words and so you have to try to now condense that into the same concept with the same words." A source of variability in the study resides with the number of contributors to the data sources used. "There are at least 25 people…providing input for the recalls."

Drilling Down Data to find Root Causes

In analyzing the various reasons given for recalls—which range from "excuses, symptoms and root causes"—Torbeck is finding "one person's root cause is another person's symptom." In many cases, identifying a root cause amongst the multiple actions relating to a recall was also a challenge. To help with this, it was decided to draw the line at physical activities.

To demonstrate that decision, Torbeck offered an example of a recall action that could ultimately be traced back to financial decisions. "One batch was rejected because the temperature had been elevated. Why was the temperature elevated? Well because the pump failed. Why did the pump fail? Because there was no preventive maintenance. Why was there no preventive maintenance? ➤

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Well they cut the budget. Okay, where do you stop? So there were levels of root causes. Is it because of the pump failure or because there is no preventive maintenance? So the decision we made was to stop at a physical level where there was something physical taking place." Despite that criterion, "you still have multiple root causes and multiple levels of root causes. So you dig down, dig down, dig down [but] sometimes you just have to report that there is more than one possible root cause."

The example demonstrates how drilling down through the various data sources can help identify the final root cause. Doing so requires several "why" questions:

Why recalling?
Why did it occur?
Why is that?
Why?
Why?

Which elicits standard responses:

The obvious
Excuses
Symptoms
Reasons
Root Causes

This exercise will help firms identify what Torbeck described as the "ideal root cause," which he defined as possessing the following attributes:

- Clearly and specifically identified; there shouldn't be any ambiguity about the definition of it
- Substantial and non-trivial; "We need something we can [fix]"
- Supported by available facts and data
- Supported by knowledgeable experts
- Can be corrected and/or prevented by specific physical actions
- Management has resources and authority to correct the cause
- It can be corrected in a reasonable length of time
- The correction can be tracked over time
- Successful CAPA will lead to elimination of root causes
- Corrections lead to continuous learning

Torbeck reminded the audience that FDA's guidance on product recalls recommends firms inform the district recall coordinator of the root cause and the corrective actions developed.

Next, Torbeck honed in on the details of how he is going about the study. His "search and drill down" study involves the following five steps:

1. Select a focus area
2. Search main recall data base for recalls
3. Record key information

4. Drill down by searching other databases for additional related information
5. Summarize collected text information and analytical data

He offered a few examples of what he has found so far. In the first example, he examined recalls due to *B. cepacia* contamination, which was identified as the product flaw in 10 recalls since 2000 (six Class I, three Class II and one Class III). Looking at one of the specific recalls, the root cause reported by the firm was that either potable water or a residue of potable water came into contact with the process trains for the recalled batches. The major corrective action was twofold: use purified water, enhance the system to prevent potable water from contacting the process train.

The ultimate end result of the project is to help FDA hone the focus of inspections in areas causing variability, improve the inspection/compliance process, build feedback loops to reviewers, and inform industry to promote voluntary compliance.

Category of Recalls

Recalls are actions taken by a firm to remove a product from the market. Recalls may be conducted on a firm's own initiative, by FDA request, or by FDA order under statutory authority.

Class I recall: A situation in which there is a reasonable probability that the use of or exposure to a volatile product will cause serious adverse health consequences or death.

Class II recall: A situation in which use of or exposure to a volatile product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote.

Class III recall: A situation in which use of or exposure to a volatile product is not likely to cause adverse health consequences.

Recalls: Management's Role

Emily Hough, PDA

Ron Branning, VP, Gilead Sciences, shifted the focus of the session on recall root causes from Torbeck's project to management's perspective of product recalls.

Branning started off with an amusing discussion of how the well known superstition about things happening in threes applies to recalls and compliance. For one, he pointed out, there are three classes of recalls. Noncompliant firms risk the "big three" enforcement actions: injunction, seizure and prosecution. Getting to the big three usually involves the "slippery slope" of inspection, warning letter and recall. And finally, the origin of recalls typically is in the following three areas: ingredient quality, equipment/process failure and human-related issues.

Taking a closer look at ingredient quality, Branning said, "If you have a good idea of where your product is coming from, you have a pretty good idea of how quality is controlled." He warned of "bait-and-switches" that suppliers have pulled. "They put their name on things, but you have absolutely no idea where it came from. You don't know what that source of that material is, so even if you proof of suppliers, be sure you understand where their multiple source of supply can be."

In addressing equipment/process failure, Branning said, "Technology transfer is probably the biggest area for making mistakes….You get a firm or plant making product that is transferred to a supplier or contractor and the transfer of information is either incomplete or inadequate and you find that there are problems or mistakes at the transferee plant."

Multiple failures can factor into human-based recalls, according to Branning. Factors include the level of employee education, training and experience. Sometimes, he said, willful ignorance—when a worker doesn't know what exactly they are supposed to be doing and don't care to find out—and willful stupidity—making the same mistake over and over again—are in play, as well as general mischief and even sabotage.

The cost of recalls to the company, not to mention the patient, is immense. Recalls can cost companies millions of dollars. Reputations can be harmed. New product approvals can be delayed. All of these can impact the bottom line and depress the stock price.

Branning recommended that company management must play a role in preventing recalls by linking the quality system to business systems. "Obviously management cannot just sit there and be passive in terms of the reports," he said. "They have to support the initiation of the quality system. They have to be certain they are getting critical metrics and dashboard reports, and also that they have periodic quality reviews and that management insists on continuous or continual improvement."

Volunteer Spotlight

[PDA] has provided opportunities to meet people around the world, to develop my network in the industry and to increase my name recognition to a much higher level.

Miguel Montalvo

President, Expert Validation Consulting

Education: BS, Chemical Engineering, Rensselaer Polytechnic Institute
MBA, Unviersidad del Turabo

PDA Join Date: 1988

Areas of PDA Volunteerism:

Puerto Rico Chapter (president)
2008, 2009 Annual Meeting Planning Committee (member)
Process Validation Interest Group (member)
PDA-TRI (faculty)

Interesting Fact about Yourself:

I love sports, music, dancing and spending time with my family.

Why did you join PDA and start to volunteer?

I love that my work in this industry focuses on improving people's lives, and I feel PDA provides me with an opportunity to develop a network within the industry, share concerns/ideas and to develop my technical competence at the same time.

Of your PDA volunteer experiences, which stand out the most?

The Puerto Rico Chapter. Since I'm originally from the Island, nothing would please me more than to help the local industry to get stronger and technically proficient in preparation for the future.

How has volunteering through PDA benefited you professionally?

It has provided opportunities to meet people around the world, to develop my network in the industry and to increase my name recognition to a much higher level.

Which member benefit do you most look forward to?

Attending the conferences such as the PDA/FDA Joint Regulatory meeting where we have opportunities to contact regulatory agency representatives and see old friends.

Which PDA event/training course is your favorite?

PDA/FDA Joint Regulatory Conference

What would you say to somebody considering PDA membership?

PDA is an organization that provides the best opportunities to develop your professional career by improving your knowledge on the latest issues/technologies and also by providing opportunities to network with other industry representatives and share your concerns/ideas.

Volunteer Spotlight

Jacques Morénas

Associate Director, Inspection and Companies Department, Agence Française de Sécurité des Produits de Santé (AFSSAPS), and Chairman of the Pharmaceutical Inspection Cooperation Scheme (PIC/S)

Education: Pharmacist, University of Celermont-Ferrand

PDA Join Date: 2006

Areas of PDA Volunteerism:

Steering Committee for PDA/EMEA Conferences (member)
PDA Conference (presenter)

Professional Recognition:

1997 Chevalier de l'Ordre National du Mérite—awarded by French Minister of Health as recognition of good services as public servant

Interesting Fact about Yourself:

I am a member of the French Regulatory Authority, notably, in charge of inspections. I am always open to discussions for improving better understanding and cooperation between competent authorities and the industry, as we are both interested in having better medicinal products for the patients; we can improve our capacities by having an open, professional and confident relationship.

Why did you join PDA and start to volunteer?

I was invited to speak at PDA conferences a number of times, usually presenting on PIC/S or ICH activities. One reason PDA is attractive to me is because it is a membership association with participants from a variety of companies and segments of the market (e.g., suppliers, equipment manufacturers, etc.). I am always happy to participate in PDA meetings or to create events in collaboration with PDA in areas of mutual interest. We are doing this now with the Geneva workshop in November, cosponsored by PDA & ISPE with PIC/S, regarding revised Annex 1 and implementation of QRM principles.

How has volunteering through PDA benefited you professionally?

I think that I better understand industry concerns, positions and issues. This is crucial for me when I am discussing with my colleagues from other authorities about new regulations.

Which member benefit do you most look forward to?

I hope to maintain these very fruitful contacts in the future.

One reason PDA is attractive to me is because it is a membership association with participants from a variety of companies and segments of the market.

Please Welcome the Following Industry

Robert Adkins, Allergan

Dennis Agers, Allergan

Audrey Akland, Perrigo

Mika Alanko, Bayer Schering Pharma Oy

John Allen, DPT Laboratories

Katherine Arnold, Ikaria

Glenn Barbrey, Novartis

Markus Bauss, Schreiner Group

Mark-Thomas Beckmann, Bayer Schering Pharma

Michael Bender, MedImmune

C. Scott Bentham, YM BioSciences

Cathy Bernier, Allergan

Lisa Blankenheim, Organics

Tanja Bogicevic, Biotest Diagnostics

Zoya Borodanski, Daiichi Sankyo

Michael Brewer, Applied Biosystems

Jim Brown, Allergan

Bernardo Caceres, Diosynth Biotechnology

Andrea Canavero, Genentech

Kiva Carolan, Amgen

Kenneth Carroll, Talecris Biotherapeutics

Anne Casey, Allergan

Laura Castagno, PHF

Nicole Chesla, Medarex

Guang Choi, Inje University

Wee Ming Chua, Det Norske Veritas

Karen Clement, Lifecore Biomedical

Robert Corcoran, West Pharmaceutical Services

Stephanie Cowan, GlaxoSmithKline

Lynne Craig, Merck

Elizabeth Cross, Imclone Systems

Christina Davis, Baxter Healthcare

Joel Dean, Diosynth Biotechnology

Christophe Debacq, GlaxoSmithKline

Sean Deng, Amgen

Rosario Denoga, Amgen

Peter DeRobertis, Cardinal Health

Mariana Dimitrova, MedImmune

Mitchell Dupre, Alcon Laboratories

Tara Dzidowski, Emergent BioSolutions

Everis Engstrom, Daxor

John Erdner, IMA

Marilyn Eriksen, Federal Department of Canada

Alexandra Exenberger, Octapharma Wien

Frank Fabbro, Baxter

Marc Fages, Amgen

Steve Falcone, Amgen

Vincent Faustino, Schering-Plough

Amy Felty, Sagent Pharmaceuticals

Joseph Fire, Human Genome Sciences

David Furlano, Acadia Pharmaceuticals

Natalie Garrett, Abbott

Thomas Gaus, AstraZeneca

Jay Gerondale, Amgen

Moira Gilchrist, Philip Morris International

Laetitia Giovannacci, Baxter

Craig Gladden, SAIC

Geoffrey Glauser, Wyeth

Jacques Godelaine, GSK Biologicals

Beatriz Gonzalez, Amgen

Rory Graham, CSL

Carrie Groff, Teva Pharmaceuticals

Eric Grumbach, Waters

Keith Hansen, BioMérieux

Ryan Hart, Shire Pharmaceuticals

Norio Hasegawa, Yamatake

Keith Haynes, Alcon Laboratories

Eldon Henson, Covidien

Norman Herman, Halozyme Therapeutics, Inc

Elisabeth Hesser, Covidien

Maria Higgins, Thermo Fisher Scientific

Elizabeth Hodnicki, Sartorius-Stedim Biotech

Alexander Huber, Schott Forma Vitrum

Paul Huntly, Det Norske Veritas Pte

Jonathan Imhof, CSL Behring

Jian Irish, Amgen

Jeffrey Jackson, Bosch Packaging

Manfred Jantsch, Haupt Pharma Wolfratshausen

Kenneth Johnson, Abbott

Courtney Jones, King Pharmaceuticals

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Susan Kalk, Alexion Pharmaceuticals

Geetha Kassam, Novartis

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Jyoti Keswani, Mylan Pharmaceuticals

Brian Kim, Celltrion

Harry Kochat, BioNumerik Pharmaceuticals

Roxana Koutchekinia, Affymax

Eddy Kragten, Crucell

Mark Kropp, Self

Larry Lachowsky, Gerresheimer

Girard Laurence, Sanofi Pasteur

Richard Law, Amgen

Mark Leney, Univeristy of Massachusetts Medical School

Leaders to the PDA Community

Todd Lennon, Fort Dodge Animal

Lee Lin Lee, MedicalChain International

Michael Lopez, Sanofi Aventis

Barbara Lopiccolo, Sandoz

Steven Lum, Perrigo

Bob Lynch, Pfizer Biotechnology

Vivek Malhotra, Becton Dickinson

Rashmi Manda, Indiana University

Enid Marin, Amgen Manufacturing Limited

Michael Marini, Pfizer

Jennifer Marshall, Bristol Myers Squibb

Claude Martin, GlaxoSmithKline

Kellen Mazzarella, Genentech

Andrea McCauley, Astellas Pharma

Ailsa McDermid, CSL Bioplasma

George Miesegaes, FDA

Jay Miller, Sepracor

Timothy Miller, Kymanox

Timothy Mills, Biogen Idec

Seitaro Mizukami, Takeda Pharmaceutical

Emily Moore, TempTime Corp

Sheila Moran, Sagent Pharmaceuticals

David Mourra, Bayer Healthcare

Michael Muscarella, Baxter Healthcare

Donna Nelson, Genentech

Kingman Ng, Eli Lilly

Viet Nguyen, Genentech

Sandra O`Connor, Cubist Pharmaceuticals

Evelyn Obeng

Rick Ohi, SAFC Biosciences

Kevin Oliver, American Stelmi

Jeffrey Palmer, Schering-Plough

Linda Payne, Hill Dermaceuticals

Portia Peng, Baxter Healthcare

Bernardo Perez-Ramirez, Genzyme

Gabriele Peron, Stevanato group

Markus Piduhn, Gerresheimer

Elizabeth Pieszak, Amylin Pharmaceuticals

Esha Pillay, Pall

Cade Pippin, Alcon Research

Mary Plank, MedImmune

Neil Pothier, Chemic Laboratories

Andrea Pranti, Novartis

Joe Provo, Merck

Mike Puzak, Lifecore Biomedical

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Rosario Ramirez, Hill Dermaceuticals

Denise Rasmus, GlaxoSmithKline

Bill Reilly, Tunnell Consulting

Anne Renton, Eli Lilly

Stacy Rider, Covidien/Mallinkrodt

Michael Robertson, Hospira

Natalie Rosa, Stryker Biotech

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Irvin Santana, Amgen Manufacturing Limited

Hans Scholl, CuraGen

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Jesse Semf, Sanofi Pasteur

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Marisa Sepulveda, Centocor

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Vikki Smith, Bristol-Myers Squibb

Susan Smith, CSL Behring

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Andrew Stratton, Merck

Carmen Suarez Del Villar, Lannett

Lalitha Subramanian, Sandoz

Daniel Sweat, Eli Lilly

Christopher Taranto, Wyeth Pharmaceuticals

Michael Tarlov, NIST

Yuderki Tejada-Flotta, Cordis

Taylor Thompson, Millrock Technology

Lloyd Tillman, Isis Pharmaceuticals

Marcellus Ting, Merck Sharp and Dohme

Glen Tolman, Centocor

Raghu Vadlamudi, Donatelle

Jonathan Valtos, Sanofi Pasteur

Ranga Velagaleti, BASF

Carol Walker, GlobeImmune

Tom Walton, Eisai

Donna Welch, Alexion Pharmaceuticals

Silke Welsch-Kunze, Landesamt für soziale Dienste Schleswig-Holstein

Scott Whitlock, Wyeth Pharmaceutical

Jane Winkleman, Eisai

Andrew Wirths, Merck

Valerie Wolfe, Pfizer

Hideki Yano, Daiichi Sankyo

Sammy Yonan, APP Pharmaceuticals

Brant Zell, Cherokee Pharmaceuticals

John Zowtiak, Centocor

Willie Zuniga, Grifols Biologicals

2009 Global Challenges for Investigational Medicinal Products

28-29 January 2009, Rome, Italy

Call for Posters

Dear Colleagues:

PDA is organizing its third annual conference on Investigational Medicinal Products. This year's topic will be Good Practices from research through to commercial issues. In the light of the recently drafted ICH Q10 guidance, which clearly brings development within the framework of pharmaceutical quality systems, the conference will address the incremental application of GMPs and the design, implementation and maintenance of appropriate quality systems as well as their practical and operational implications at each stage of development. There will be a break-out poster session, and you are invited to submit abstracts for posters addressing any of the following points:

- QbD Case Study
- Tying-in Target Product Profile with CQAs
- Product Control Strategy
- Implementation of R&D Quality System
- Case Study: Manufacture of Pre-clincial Batches
- Case Study: Manufacture of Clinical Batches
- Analytical Methods Development
- Pharmaceutical Process Development
- Technology Transfer Challenges and Solutions
- Shipping/Transportation Issues for Clinical Trials Material
- Labelling Clinical Trials Material for Multi-National Trials
- Outsourcing Case Studies
- Case Study: Use of CAPA in R&D for Feedback/Feedforward
- Management Review as a Quality Tool in R&D
- Change Management and Deviation Reporting in R&D

All submitted abstracts will be reviewed by the Program Committee for acceptance. Upon review by the Program Committee, PDA will advise each submitter of your poster's status in writing by January 16th at the latest.

Case Studies are particularly desired. Commercial Posters featuring the promotion of products and/or services will not be considered. If you have any questions, please do not hesitate to contact us.

Please include the following information. Submissions received without full information will not be considered.

- > **Title**
- > **Presenter's biography**
- > **Additional authors**
- > **Full mailing address**
- > **Phone number**
- > **Fax number**
- > **Email address of the presenter**
- > **2 - 3 paragraph abstract, summarizing your poster**
- > **Key objectives of your topic and what new information you will present that has not been presented elsewhere**
- > **Explanation of specific take-home benefits your target audience can use immediately on the job**
- > **Target audience (by job title or department)**

Send a copy of the abstract and the presenter's biography (ca. 100 words in length) to Volker Eck at eck@pda.org.

Poster abstracts must be received by 9 January, 2009 to be considered.

Chapter Contacts

The following is a list of the PDA Chapters, organized by the regions of the world in which they are located. Included are the Chapter name, the area(s) served, the Chapter contact person and his or her email address. Where applicable, the Chapter's website is listed. More information on PDA Chapters is available at www.pda.org/chapters.

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PDA Israel Chapter Organizes Event about Impurities in Drugs and Investigational Drugs

Ilana Zigelman, MPH, Zigelman Consulting

Day One Topic: Impurities in Drugs

On July 15, the PDA Israel Chapter held an informative seminar for two hundred participants on the impurities found in drugs. Opening comments were delivered by **Raphy Bar,** PhD, President of the PDA Israel chapter. Raphy expressed his gratitude to the PDA Israel Chapter board members for their support as well to the speakers for their contributions. He also expressed his gratitude to **Georg Roessling**, PhD, for his support and encouragement in holding this special conference with the participation of a U.S. FDA official.

David Jacobson-Kram, PhD, started the day with an informative talk about the regulation of impurities in drug substances and products. He described the steps involved in performing a risk assessment to determine the consequences of an impurity. The fundamental question is whether the impurity has the inherent capacity to induce an adverse health effect at any dose; information to be analyzed includes hazard identification, dose response and exposure assessments and risk characterization. David reviewed the causes of impurities, qualification testing of impurities and the sensitivity of the tests used for qualification as well as the subject of residual solvents.

The next speaker was **Ori Lerman,** PhD; he spoke about the evaluation of impurities in API batches from the perspective of a regulator. He discussed the classification of impurities as organic, inorganic and residual solvents and their causes, as well as the justification for setting specifications, and submission requirements as seen and evaluated from the regulator's point of view.

Ran Rosen, PhD, presented an analytical aspect of impurity analysis under the title, "Detection of Impurities in Drugs by LC-MS and LC-MS/MS." Ran discussed Mass Spectrometry versus other Liquid Chromatography detectors, provided a technology overview with some examples and discussed the limitations and cost effectiveness of mass spectrometry. The talk was summarized by distinguishing between the analysis of known and unknown impurities; while impurity analysis of known impurities is a routine quantitative task, finding unknown impurities and their characterization is a complex task which requires mass spectrometry expertise and vast knowledge in chemistry.

Yoram Cohen introduced participants to detection and qualification of unknown impurities in stability samples.

After the coffee break, attendees returned to a take-home presentation on minimizing process related impurities in API synthesis by **Lior Zelikovich**, PhD. He discussed development methodologies for understanding the process mechanism and chemistry, design space, impurities in the API and their origins and prevention methods. He reviewed examples such as amorphous materials, crystallization parameterization, reaction surface, control of critical parameters and genotoxic impurities.

The next speaker, **Yoram Cohen,** introduced participants to detection and qualification of unknown impurities in stability samples. Yoram provided a comprehensive review of a particular anti-fungal case study involving an U.S. FDA deficiency letter request. Through use of LC/MS chromatogram and dissolving of the API in the same medium as the one used for the HPLC method, the molecular weight of the unknown impurity was determined. A pure sample of the unknown impurity was obtained using semi-preparative HPLC. The pure sample was then sent for a Nuclear magnetic resonance to determine the chemical structure. The company was then able to set an allowable threshold for the impurity in conjunction with FDA approval.

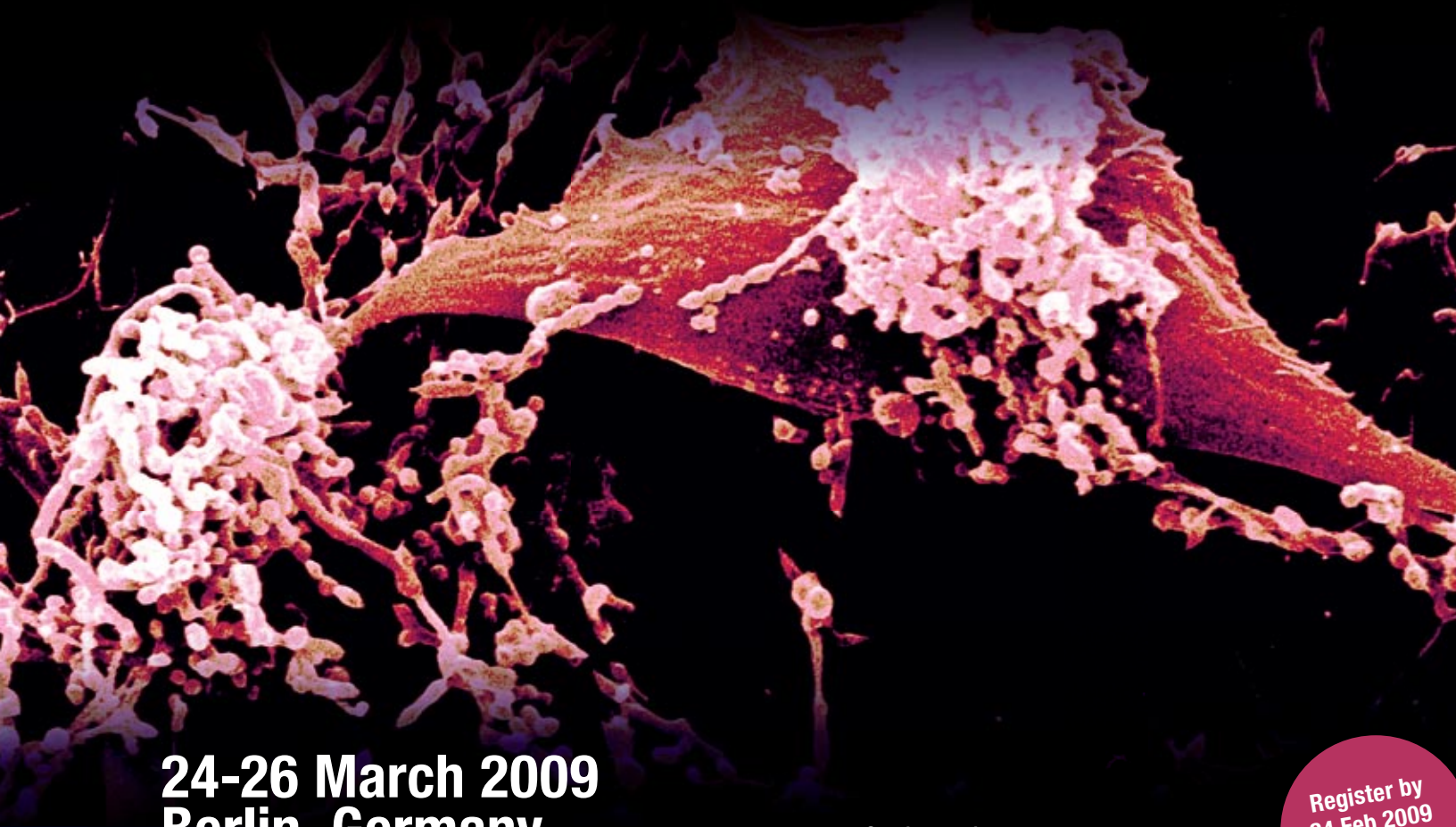
After lunch, Raphy introduced us to his presentation, entitled, "Leachables as Impurities: Analytical Methodologies." Raphy discussed the issues surrounding leachables and/or extractables from container closure systems and packaging materials, sources, safety thresholds, regulatory requirements and common difficulties. Raphy compared the Product Quality Research Institute Approach versus a general approach to Extractable and Leachable Studies. While the former approach is based on the Quality by Design methodology, the later emphasizes the investigation of product-related media which have the same propensity to extract as the drug product itself. Raphy stated that more and more regulatory agencies require information about leachables.

David finished day one with an interesting presentation on safety qualification of impurities in biopharmaceutical drugs. This presentation reviewed commonly used cell substrates (e.g., CHO, NSO, PER.C6 cells etc.,) and the biologic products produced from them (recombinant protein, monoclonal antibodies and Adenoviral vectors for gene therapy respectively). He addressed common examples of adventitious agents that would need to be tested for and/or excluded from these preparations and gave a list of guidances that should be considered. In particular, cell line changes on "end of production" cells can be a cause for ➤

PDA
Parenteral Drug Association
Connecting People, Science and Regulation®

2009 PDA

3rd Workshop on Mycoplasmas



24-26 March 2009
Berlin, Germany

Workshop: 24-26 March
Training Course: 23 March

See the complete program at:
www.pda.org/europe

Register by 24 Feb 2009 and SAVE!

The workshop will be an opportunity for scientists who are involved in mycoplasma issues in Academia, Biotechnology Industry, Agriculture and Regulatory fields to share data, information and new regulatory monographs on the detection of mycoplasma. Learn how to be proactive in detection methods not only for mycoplasma contamination of cell cultures by animal, plants or insect sources. In addition, a session on the biology of mycoplasma will showcase some of the leaders in the mycoplasma field including, Leonard Hayflick, Robert Davis and Shmuel Razin. A discussion on whether mycoplasma like bacteria are capable of forming biofilms will be lead by Hans-Curt Flemming.

concern, so these always need to be tested at the end of a bioreactor run. David provided a list of key questions to determine appropriate tests for both cell and virus banks including purity, identity and genetic stability. Characterization testing is based on the ICH points to consider document. The issue of mycoplasma testing and the 28 day CFR test was addressed and it was clarified that rapid PCR tests, while useful for in-process testing, are NOT currently accepted by the regulatory agencies. Morphological changes in cells should be checked for cytopathic effects in the next generation since true viral infection will result in failure of cells to recover and manifestation in the next generation. His presentation went into considerable detail regarding characterization of cell and virus banks in a systematic manner that also addressed the possibility of false positives for adventitious and endogenous contamination if samples are not prepared with sufficient care. Overall this presentation provided participants with a thorough overview of regulatory (FDA) expectations as they relate to safety qualification of biopharmaceutical products.

PDA's Who's Who?

Iris Alroy, PhD, Senior Vice President, Discovery Drug, Pharmos

Raphy Bar, PhD, Pharmaceutical Consultant, BR Consulting and PDA Israel Chapter President

Yoram Cohen, Head of Analytical R&D, Taro Research Institute

Karen Ginsbury, CEO, PCI Pharmaceutical Consulting

David Jacobson-Kram, PhD, Associate Director, Pharmacology and Toxicology, CDER, U.S. FDA

Ori Lerman, PhD, Deputy Director, Institute for Standardization and Control of Pharmaceuticals, Israeli Ministry of Health

Georg Roessling, PhD, Sr. VP., PDA

Ran Rosen, PhD, Manager, Applications and Technologies, Agentek

Lior Zelikovich, PhD, Director, Process Development, Chemagis

Day Two Topic: Investigational Drugs

On July 16, the PDA Israel Chapter held a seminar on investigational drugs.

Kicking the day off, **Iris Alroy**, PhD, started her presentation on the selection of clinical drug candidates. She talked about risk reduction in drug discovery, incorporation of pharmacokinetics, and Absorption and Distribution Metabolism and Excretion considerations during lead optimization for successful drug design and development. Iris discussed the Lipinski rule of five for oral drugs and early guidelines for lead-likeness, and reviewed the definition of a drug candidate in regards to purity, efficacy, pharmacokinetic parameters, safety, metabolism and selectivity.

David Jacobson-Kram, PhD, introduced us to the novel concept of exploratory investigational new drugs (IND); he described some of the challenges in improving efficiency of drug development which currently entails high risk and cost. The draft guidance on exploratory IND's was issued in 2005 to provide sponsors with the opportunity to evaluate up to five drugs or formulations simultaneously and study pharmacokinetic study and target interaction early in drug development. The sponsor is able to gain an understanding of the relationship between a specific mechanism of action and the treatment of a disease, allowing him to select the most promising lead product from a group of candidates designed to interact with a particular therapeutic target. David discussed microdose studies including the aim of identification of a minimally toxic dose and potential risk to subjects. The goal in some exploratory IND studies (but not microdose studies) is to achieve a pharmacological response but not the maximum tolerated dose.

To date, INDs have been only moderately utilized for various reasons including the fact that industry is typically slow to adopt change. The microdose studies may not be predictive of pharmacological dose studies because it is designed to kill drugs early that are likely to fail, which no development team wants to hear.

Karen Ginsbury gave a presentation on cGMP and investigation new drugs intended for use in clinical trials. Karen's prepared presentation was affected by a new final rule published just one day prior to the conference. The presentation addressed the anticipated effects of FDA's new rule which exempts manufacturers of drug products intended for phase I use, from the requirements of 21CFR part 211. This effectively puts into writing what has been common practice for many years in that INDs by their very nature cannot be manufactured in full compliance with cGMP's.

Karen reviewed some of the problems that have been encountered in recent years like the Baxter Heparin recall and the TeGenero case with the subsequent EMEA guideline entitled, *Requirements for First-in-Man Clinical Trials for Potential High-Risk Medicinal Products*. There has been intense regulatory activity on the subject of clinical trials and GMP/GLP/GCP interfaces including an EMEA think tank report, meetings with pharma and guidances published by the EMEA. Issues were raised at the EU Clinical Trials Conference 2007 where stakeholders expressed concern about the difficulties

in interpreting the definition of an investigational medicinal product (IMP) and recommendations for GMPs for IMPs were given. Additional concerns include the contents of the EU Batch Release Certificate and the Declaration of EU GMP compliance for the drug product. The EMEA Road Map for 2008–2009 will continue to address the issues raised.

David took the stage for the remainder of the afternoon. He started the afternoon with a presentation about the preclinical safety testing of drugs with insights into the realities of modern day drug development, reasons for the drop in new drugs, types of preclinical and non clinical tests, safety studies, and other preclinical issues including genetic toxicology and carcinogenicity testing. David discussed his vision of a future where everyone's DNA sequence will be on file in their computer, illnesses will be diagnosed in real time from a drop of blood and drugs will be custom designed based on individual characteristics (such as genetic polymorphisms, age, sex, weight and so forth).

David continued with a technical review of the regulation of genotoxic and carcinogenic impurities. He discussed cell mutations, mechanisms of activation/inactivation of cancer-associated genes, impurities in the drug substance and thresholds of toxicologic concern (TTC). David highlighted major points of the EMEA guideline entitled, *Question and Answers on the CHMP Guideline on the Limits of Genotoxic Impurities.*

He concluded with a presentation on calculating clinical start doses from toxicology studies, and estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. David discussed CDER's guidance entitled, *Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers,* on "start dose" consideration of no observable adverse effect levels, safety factors and history including a review of the TeGenero failure and regulatory repercussion and the "Minimal Anticipated Biological Effect" approach.


Israel Chapter President Raphy Bar, PhD

Membership Advisory Board Working to Enhance Member Experience

MAB Chair Sue Schniepp, Schniepp and Associates, and Hassana Howe, PDA

Have you ever asked yourself what happens after you pay membership dues to belong to an organization? Have you ever wondered where the money goes and what programs it supports? Have you ever thought you'd like to become more involved in an organization, but just didn't know who to contact or what to do to make it happen? Many people have asked these questions and PDA has an answer. The newly formed PDA Membership Advisory Board (MAB) is striving to make sure members are aware of all the benefits and opportunities available to them when they chose to join PDA.

The current members of the Membership Advisory Board are **Sue Schniepp** (Chair); **John Shabushnig,** PhD, Pfizer Inc; **Louis Zaczkiewicz,** Hyaluron Contract Manufacturing; **Ishwin Dembla,** Campbell University; **Saeed Tafreshi,** Intelitec Corp.; and **Matt Piasecki,** Middlesex Community College. This group of volunteers is supported by dedicated PDA staff.

Now that you know who is involved with the PDA Membership Advisory Board, it is time to understand what they doing that will benefit PDA members.

PDA New Member Breakfast

The PDA New Member Breakfast is featured at PDA's Annual Meeting, the PDA/FDA Joint Regulatory Conference and the PDA/EMEA Conference held in April, September and October respectively. The breakfast is intended to welcome new members to the PDA family and give them a brief overview of their member benefits. These members often get to meet and hear from the Board President, Senior PDA Staff, and a PDA member about how they became involved with PDA and how that involvement has enhanced their career opportunities. The atmosphere and tone of the breakfast is relaxed, friendly, inviting and informative.

PDA's New Member Breakfast is a great example of how members can network and learn about member benefits. Below are Jessica Chung and Andreas Nuhn, who came from New Jersey and Germany, respectively.

PDA Volunteer Luncheon

The PDA Volunteer Luncheon is held at PDA's Annual Meeting and PDA/FDA Joint Regulatory Conference. This luncheon is designed to explore and explain the many volunteer venues available to members. Some of PDA's functions explained at the luncheon, include: the activities of the Advisory Boards, Committees, Chapters, Task Forces, Interest Groups, as well as speaking, teaching and publishing opportunities.

Communication

The PDA Membership Advisory Board recognizes that communication is paramount in maintaining good relations with PDA members. The Board also realizes that not everyone likes to receive information in the same manner. To accommodate individual member preferences, the Board is looking into ways to allow PDA members to pick and chose the way in which they would like PDA to communicate with them. Allowing members to tailor PDA notifications to fit their preferences ensures that members will be informed of important announcements affecting their interests.

Membership Enhancement

Assist PDA in evaluating current PDA membership benefits and aid in the development of enhancing or adding new membership resources and benefits. This process may involve contacting current or expired PDA members to collect information and working with the MAB to evaluate responses and benefit offerings. In this process, MAB members are encouraged to think outside the box with the goal of improving membership acquisition and retention by improving the PDA membership experience.

The PDA Membership Advisory Board is diligently working to enhance and improve the experiences and opportunities for our members. Our mission is to make sure that each member is informed of the many member benefits and volunteer opportunities available to them. Start by getting involved now and tell us how you think we can better improve your membership experience or better yet let us know if you are interested in becoming involved with the PDA Membership Advisory Board.

If you are interested in joining or learning more about the Membership Advisory Board please visit www.pda.org/getinvolved or email Hassana Howe at howe@pda.org.

AstraZeneca and PDA UK Chapter Organize Risk-Based Inspections Meeting and Site Tour

Siegfried Schmitt, Parexel Consulting

On September 11, PDA's UK Chapter organized a meeting on the subject of risk-based inspections at Loughborough. The host company, AstraZeneca (R&D Charnwood) was represented by **Mark Gibson,** Associate Director, Product Development, who also helped organize the event.

Around 20 members and guests enjoyed an interesting afternoon. I got the proceedings underway with a few slides on the changing inspection regimes, the adoption of risk methodologies and how this may impact inspections in future. This led to a lively session of questions and answers and an open debate amongst the attendees.

Mark gave an interesting overview, explaining the various functions on this site, giving some background to the company's and the site's history. He also mentioned the substantial investments approved for enlarging the site's capacity and capabilities in R&D. The attendees could study the planned expansion in more detail on a series of layout diagrams and building plans that were displayed in the meeting area.

The delegates were then invited to a tour of the facilities. This is an impressive facility, which, as mentioned before, is undergoing extensive expansion, which created lots of interest. An excellent buffet provided sustenance. Many delegates stayed a bit longer to chat in small groups before it was time to bid farewell. There was consensus that the event, the format and the topics were well worth the effort, and we were strongly encouraged to continue with this type of concept.

In fact, it is bringing together peers and colleagues with similar ideas and concerns to find solutions that these meetings are all about.

In fact, it is bringing together peers and colleagues with similar ideas and concerns to find solutions that these meetings are all about. PDA plays an important role in enabling such meetings, especially for those who may not be able to attend some of the larger meetings organized by PDA Europe, headed by **Georg Roessling,** PhD, PDA.

Conference on Development and Regulation of Clinical Trial Supplies

Boston, Mass. • November 10–11 • www.pda.org/clinicaltrials

Program Chair Tatyana P. Touzova, Biolex

The word "harmonization" comes from the Greek word "harmonia," defined as the state of the rules when all the parts are fit together. Since the International Conference on Harmonization was initiated in 1989 between Europe, Japan and the United States, the world of pharmaceutical development has been changing rapidly. Industry professionals must be knowledgeable of global requirements and regulations in the development and clinical use of medicinal products.

The *PDA Conference on the Development and Regulation of Clinical Trial Supplies*, which will take place November 10–11 in Boston, Mass., is one of the leading events of the year. In the interactive case-driven discussion, the participants will learn about the challenges and solutions presented in a wide variety of technologies and at different phases of clinical development. Industry and regulatory professionals will share their experiences and will be available to answer questions.

Managing and tracking global submissions for new medicinal products is resource-intensive and expensive. Most importantly, it requires a strong knowledge of global regulations. The opening session of the conference will provide an overview of recent updates of regulatory guidances issued in the U.S. and Europe. U.S. FDA and EMEA speakers will address how the revisions and changes impact the regulatory filing process and discuss specific areas that have caused problems for those developing new medicinal products in a global regulatory environment.

New recombinant technologies emerged at the end of twentieth century providing many first therapies for otherwise untreated and devastating diseases. However, the path from the discovery to an approved drug is fraught with many challenges. With the emergence of highly sophisticated biologicals, such as monoclonal antibodies, autologus products, gene therapies and new vaccine technologies, the development program is not necessarily defined and new regulatory ground is being broken. How intensive and lengthy should be the pre-clinical toxicology package? What product should be used in the animal studies to most simulate human exposure and allow for a smooth transition to the first clinical trials? How is consistency maintained in the product process and quality between early toxicology studies through clinical development as scale up and process optimization is achieved? Insights to these and other important questions on the regulatory process applicable at earlier clinical stages will be provided at the plenary session on proof of concept to early phase development. Following the early stage of development, the discussion will transition to Phase 2 and 3 of clinical trials and concentrate on the integral implementation of GMP practices throughout product development. Topics include logistics of technology transfer and cycles of pharmaceutical development. We will also address regulatory hurdles and requirements during the lifecycle of the product.

As a product progresses, many changes are required in the manufacturing process and analytical testing of the API and the drug product. At each implementation of these changes, it is critical to demonstrate product comparability. Appropriate studies must be designed to demonstrate that any change does not have an adverse impact on the quality, safety and efficacy of the product. The extent of the comparability protocol depends upon the criticality and timing of the change. Changes made during early Phase 1, dose-ranging, pivotal clinical trials, prior to commercialization and post-approval may require different levels of comparability testing. During the session on chemistry, manufacturing and controls, practical approaches on how to manage process changes during these different phases will be discussed. Speakers will present real-life industry experiences with different classes of biologics and implementation of process change at different stages of development. Attendees will learn about the latest analytical and immunoassay technologies available for monitoring structural differences of the active ingredient and the potential impact of those differences on product safety.

The second day of the conference will begin with the plenary session on validation. Validation in biopharmaceutical production is critical for ensuring the manufacturing process is reproducible and that vital pieces of the process are controlled. Process and assay validation ensure the quality and safety of the final product. Validation practices can not be adequately applied without a thorough knowledge of the ruggedness of the manufacturing process and a complete understanding of differences between critical and non-critical process parameters. However, process development is continuing with clinical development and process validation/qualification must be re-evaluated with every change. The session about validation/qualification of clinical trial material manufacturing will provide an overview of QbD validation principles and will include a risk management approach to validation over the development continuum. The importance of the control of raw materials from the earliest stages of development will provide a clever link to the quality and safety of the product and regulatory implications.

An area often overlooked until too late is the clinical trial supply chain. With the need to conduct multi-national

clinical trials across the globe, the logistics of supplying clinical trial material is often overwhelming. Typically clinical trial timelines do not include the additional time needed for packaging/labeling in many countries or languages, import and export permits, import and export of clinical samples, shipping validation for temperature variations and distribution to many countries. These activities often create a bottleneck and can have a major impact to timelines without appropriate planning. Attendees of the session on clinical trial material supply and distribution will receive comprehensive information and advice on local, national and international requirements on this very important topic.

Another timely topic during the second day is the current GCP arena. Today more than ever, reliance is placed on clinical research organizations (CROs) to manage and conduct our clinical trials. This session will provide a better understanding of the ever-increasing and important role of the company's Quality Assurance unit in the oversight of CROs. Although the CRO is essentially doing the work, the sponsor is ultimately responsible for the conduct, integrity and validity of the data. QA's role no longer ends at the release of the clinical trial material. The sponsor's QA unit must be involved at all stages of protocol development and conduct. Detailed case studies of outsourcing multi-national clinical trials will provide real examples and trends in logistics, implementation and regulatory compliance.

The regulatory affairs-focused session will conclude the conference. The session will highlight global requirements for investigational medicinal product submissions in paper and electronic formats. It will address recent harmonization of IND and IMPD and will provide the regulatory strategy for simultaneous clinical investigations in the U.S. and Europe. Regulatory and industry experts will help you sort through the maze of regulations, strategy, and compliance. The participants will develop a more rounded and global perspective on clinical trial supply management and meet new partners for future networking.

The Program Planning Committee wishes to extend an invitation to all members and affiliates to attend the *PDA Conference on the Development and Regulation of Clinical Trial Supplies* on November 10–11, in Boston, Mass. You are guaranteed to expand your knowledge and awareness of clinical trial management and meet new friends and future advisors.

I look forward to seeing you in Boston.

Quality from the First to the Last Mile: Cold Chain Management

2009 Pharmaceutical Cold Chain Conference • Bethesda, Md. • March 23–24, 2009 • www.pda.org/coldchain2009

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

The pharmaceutical and biopharmaceutical community produces temperature-sensitive products on a daily basis. The proper handling, storing and distribution of frozen, refrigerated, and controlled room temperature products have received greater attention in recent years from all involved parties including manufacturers, service providers and regulators. The advent of risk-based compliance initiatives on a global basis has brought about fundamental changes in the evaluation of cold chain technologies and practice for the temperature-controlled products. Improved capabilities of the newer technologies and concepts have raised the awareness that risk to the patient can be reduced through these technical advances.

The *2009 Pharmaceutical Cold Chain Management Conference* will be held on March 23–24, 2009, in Bethesda, Md. A large attendance is expected this year with participation from pharmaceutical and biopharmaceutical manufacturers, cold chain service providers, academicians, regulatory authorities and pharmacopeial representatives. PDA's Pharmaceutical Cold Chain Management Conference has established itself as the premier technical conference covering the needs of the pharmaceutical and biopharmaceutical industry and its partners who work together to ensure that the quality, integrity, safety and efficacy of the temperature controlled products are not compromised in the handling, storage and distribution channels.

PDA's Pharmaceutical Cold Chain Management Conference has established itself as the premier technical conference.

The Program Planning Committee has selected, *From the First to the Last Mile – Management of the Distribution of Temperature Sensitive Pharmaceutical Products* as the theme for the Conference. The theme highlights the topics presented, discussed and examined with technical data and case studies.

Special sessions have been planned to explore the progress being made by:

- PDA's Pharmaceutical Cold Chain Interest Group (PCCIG) members
- Cold chain regulatory updates
- "Last mile – end users" – the patients
- The last mile for clinical trial materials
- International cold chain compliance
- Interaction with trade organization
- Partner solutions for the last mile—process
- Equipment
- Materials
- Updates from the PCCIG task teams

In addition, a poster session has been planned for the first time.

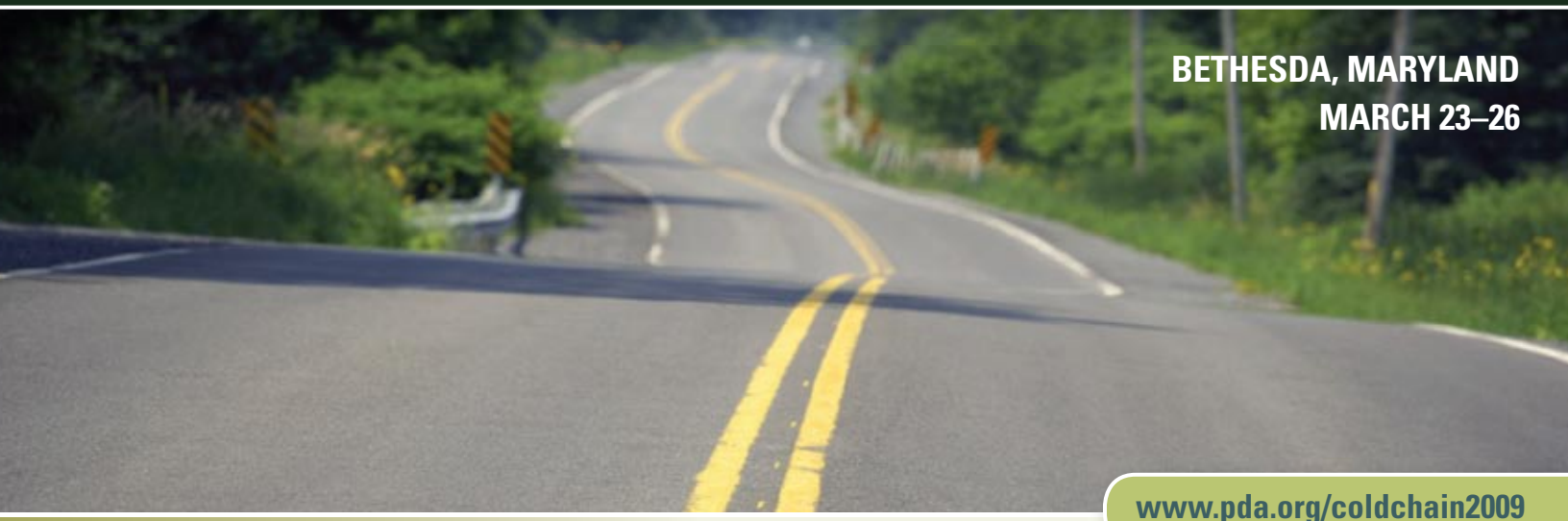
To compliment what has been learned at the conference, PDA TRI will host a post-conference course entitled, "Global Regulations and Standards: Influences on Cold chain Distribution, Packaging Testing and Transport Systems" on March 25–26, 2009.

We look forward to seeing you in March at the *2009 Pharmaceutical Cold Chain Management Conference*.

PDA
Parenteral Drug Association

2009 PDA Pharmaceutical Cold Chain Management Conference

*From the First to the **LAST MILE**—Management of the Distribution of Temperature-Sensitive Pharmaceutical Products*



BETHESDA, MARYLAND
MARCH 23–26

www.pda.org/coldchain2009

CONFERENCE ○ March 23–24
EXHIBITION ○ March 23–24
TRAINING COURSE ○ March 25–26

Learn directly from industry, regulatory representatives, compendial experts, academicians and solution partners regarding the handling and distribution of temperature-sensitive pharmaceutical products. Presentations will address the following topics and provide you with the information you need to maintain product integrity and ensure patient safety throughout the product life cycle:

- Global Regulatory Environment
- End-user Perspective: The Patient
- "Last mile" for Clinical Trial Materials (CTMs)
- Good Cold Chain Distribution
- PDA Pharmaceutical Cold Chain Interest Group (PCCIG) updates
- Partners' solutions for the "last mile:" processes, equipment and materials

A two-day exhibition during the conference will feature companies with commercially-available technology and services for the handling of temperature-sensitive pharmaceuticals. Immediately following the conference, PDA's Training and Research Institute (PDA TRI) will offer a two-day course, *Global Regulations and Standards: Influences on Cold Chain Distribution, Packaging Testing and Transport Systems*.

How Does Your Training Measure Up?

Anita Whiteford, PHR, Mallinckrodt Baker/Covidien

Training is an important element of compliance in a regulated manufacturing environment. The U.S. FDA recognizes training as a key function in the pharmaceutical industry for the simple, yet critical, fact that the drugs and medical equipment we rely on for are manufactured by human workers. Therefore, this leaves room for human error. This focal point of importance has driven the FDA to incorporate training into their regulations. While the importance of training is discussed in several regulations and guidelines, companies need to go further than the regulatory recommendations and evaluate the effectiveness of training as well as the time and money invested into training their workforce.

Regulatory References to Personnel Training

FDA requires personnel training in the cGMPs. The International Conference on Harmonization quality guidelines on *Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (Q7A)* and *Quality Risk Management (Q9)* also references personnel training as key to regulatory compliance.

Training Quality and Measurement

As a training professional, measuring training effectiveness is just as important as designing and implementing the training. There may be others outside of the training arena in the organization who question the purpose of measuring training effectiveness. They might wonder, "Why should I have to measure the effectiveness of the training event when I know by observation that my workforce has been trained?" Evaluation of training, however, serves many different purposes. Training evaluation proves the worth of the investment by the organization in the training, confirms the worth of the training department to the leaders of the organization, establishes that the needs assessment was correct in identifying training as a solution to close a gap, and verifies that the training was not only effective, but of good quality for the workforce.

There have been many views over the years from leading training and development professionals on the purpose of training measurement. One highly respected and noted expert in the training profession is **Donald Kirkpatrick**, PhD, who says training needs to be evaluated to:

- Determine the value of the training department
- Decide whether or not to continue or discontinue training programs based on whether or not outcomes are meeting compliance expectations
- Generate feedback from training participants on how to improve future training sessions[1]

Kirkpatrick is known for his famous four levels of evaluation, which are:

Level 1: Reaction (Participants reaction to training event)

Level 2: Learning (Knowledge/skills learned in training event)

Level 3: Behavior (Transfer of knowledge/skills back to the work area)

Level 4: Results (Impact of training event on the organization)

Measuring training effectiveness is crucial in the regulatory manufacturing environment. Without knowing the effectiveness of the training program, instances of noncompliant activities can spiral to the point where a company finds itself in the worse case scenario. The worse case scenario in a regulatory environment is that the manufacturing facility must be shut down due to results of an investigation being linked back to an ineffective training program that was the root cause of operator error.

FDA and Measurement

At this year's PDA Biennial Training Conference, **Rebeca Rodriguez**, National Expert Investigator, U.S. FDA, addressed the issue of training effectiveness. As Rodriguez pointed out, FDA regulations expect firms to evaluate the effectiveness of personnel training. She stated that it is no longer permissible to consistently use retraining as a corrective action. FDA now realizes that companies are probably not effectively training personnel when retraining is routinely offered as a corrective measure. As such, companies can lose credibility with FDA and other regulators for ineffective training approaches.

A key point of Rodriguez's presentation was that the quality system should be an instrument of the effectiveness of the company's training programs. She stated that the effectiveness of training in a company will ultimately be determined by the robustness of the company's quality system. What is meant by the robustness of the company's quality system?

Rodriguez mentioned key issues that should factor into a determination of the robustness of a quality system:

- Human errors captured, trended, investigated, and corrected (e.g., a CAPA system or internal/external audits)
- Quality system data such as complaints, failure investigations, audit results, batch record reviews, used, to assess training needs and effectiveness

In addition to the quality system, managers should work in conjunction with Human Resources and develop competencies and qualifications such as job descriptions for each position. Managers should then verify that the skills gained from training are implemented and training should be in alignment not only with the goals of the organization but also the individual's competencies. ➤

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Upcoming Web Seminars:

Silicone Oil Detection, Protein Aggregation and Flow Microscopy
October 30

This web seminar will describe the application of flow microscopy to the analysis of silicone oil emulsions in protein formulations for the purposes of characterizing and controlling the influence of silicone oil upon protein aggregation.

- Dave Thomas, Brightwell Technologies

Design of Pharmaceutical Quality Systems in the Current Global Environment consistent with ICH Q10 concepts
November 5

What issues should you consider when designing a robust modern and effective Pharmaceutical Quality System? This web seminar will focus on the expectation and considerations of a Pharmaceutical Quality throughout the product life cycle, as well as the elements that go into designing an effective Pharmaceutical Quality System.

- Zena Kaufman, Abbott Laboratories
- Neil Wilkinson BSc, David Begg Associates
- Barbara Allen, PhD, Eli Lilly and Company

How to Design Extractable / Leachable Studies for Pre-filled Syringe Applications
December 4

The purpose of this seminar is to provide more in depth information on the regulatory aspects of container/closure system testing, the mechanism of polymer migration, the design of Extractable and Leachable studies and how to avoid the typical pitfalls and mistakes in the E/L-study set-up. This comprehensive approach will be illustrated for a pre-filled syringe application.

- Piet Christiaens, PhD, Toxicon Europe

Securing Your Supply Chain
December 9

Participants will receive an overview into global guidelines pertaining to supply chain handling and quality assurance tips on managing manufacturers and brokers who supply your company with starting materials on the one hand, and managing the distribution chain at the other end.

- Karen Ginsbury, PCI Pharmaceutical Consulting Ltd

The Pen is Mightier than EDC – An Alternate Data Capture Approach
December 18

Participants will observe the most advanced paper-based CRF, the ExpeData CRF. ExpeData's CRF enables the automated extraction and routing of the handwritten information from the paper CRF pages, enabling the data to quickly and cost effectively populate the clinical database. Participants will witness the speed and efficiency of the data flow. Actual case studies and testimonials will be provided for this validated solution that has enabled clinical rials for over five years.

- David Nettleton, Computer System Validation
- Doug Patterson, ExpeData, LLC

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Several companies have been cited recently by the FDA for not having the appropriate training available for the workforce and for not considering the effectiveness of training. Below are excerpts from FDA warning letters citing companies for a lack of adequate training, implying that the effectiveness of the training was not measured:

- Failure to ensure employees are adequately trained to perform their assigned responsibilities, as required by 21 CFR 820.25(b). For example, your firm has not ensured employees responsible for handling complaints have been adequately trained as evident by employees misclassifying five calls as inquiries rather than complaints.[2]
- Failure to establish procedures for identifying training needs and for ensuring that all personnel are trained to adequately perform their assigned responsibilities, as required by 21 CFR 820.25(b). Your firm's training of operators was inadequate in that you have no document control of your operator training packet that consists of multiple, separate, non-sequentially numbered training documents; your operator training protocol is not linked to your written training procedures and has no document control to include management approval prior to implementation; and you do not have documentation of reviewing and approving an operator's training and testing records and results prior to the employee being released to receive medical alarm calls.[3]
- Failure to establish and maintain procedures for identifying training needs and to ensure that all personnel are trained adequately perform their assigned responsibilities and that their training is documented, as required by 21 CFR 820.25(b).[4]

Utilizing Measurement Methods in Regulatory Organizations

Each of the three warning letters cited directly mention the key words "failure to ensure personnel are adequately trained." This statement has a straightforward connection to training effectiveness. The questions, what is working, what is not working and how to fix the non-working parts, are derived from a deeper root of training adequacy. The most important avenues to training effectiveness are transfer of learning and training impact specifically the return on investment (ROI). If more companies measured transfer of learning in a consistent and conservative fashion, then many of the issues of retraining would be minimized. The companies would have a higher probability of finding out the problem areas of the training programs rather than repeating inadequate workforce training.

Transfer of learning is Kirkpatrick's level three in his evaluation model. Transfer of learning simply measures the knowledge learned in the training is transferred back to the work area. Measurement of transfer of learning can occur with several different data collection methods such as post tests thirty, sixty or ninety days after the training has been completed. This can occur from interviews, focus groups, surveys and observations with the participants that attended the training. The majority of training and human resource professionals conduct an evaluation study up to a level two which is measuring knowledge with a post-training test. It is very simple in the grand scheme of time and resources to conduct a reaction/satisfaction survey (level one) and a post test (level two) at the end of most training. Transfer of learning continues to be an area of training effectiveness that most companies do not devote a lot of time and effort. Measurement of transfer of learning is a crucial point, because if there is a lack of transfer occurring then the resources invested into the training event and the training event itself will have been unproductive and wasteful.

Impact of training involves the determination of how the training affected the company's bottom line worth. Proving the bottom line worth of the training to the company in conjunction to the adequateness of the training is just as important. Impact of training can be measured by simply using the measurements captured in production such as decrease in waste, production time, defects, rework, scrap and efficiency. Besides using company data records, impact can also be collected by using the same data collection methods mentioned previously for transfer of learning particularly follow-up surveys and interviews. ROI is a basic mathematical calculation that subtracts the benefits from the costs and then divides the number by the costs again multiplied by 100 to get a percentage. Many companies are fearful of conducting ROI studies because if the ROI is a high percentage then the results may not be believable by leadership. If the ROI is a negative percentage, then the leadership will question the existence of human resources and training. Another ROI calculation that would be highly beneficial to companies and is underutilized is forecasted ROI. Forecasted ROI is the same calculation as the basic ROI, however, forecasting is calculating the return on investment before the training event occurred in order to establish the value of the investment and the potential impact on the workforce.

Evaluation is not a process that should be feared or perceived as an intimidation to training professionals. As discussed earlier, the benefits of conducting evaluations are concrete proof of the value and worth. The disadvantages of not pursuing evaluation methods may be detrimental to organizations. The key to a successful evaluation process is to involve the

stakeholders from the beginning. Building partnerships with stakeholders will lead to bigger rewards than realized, such as ongoing support and credibility of the training function in the organization. Stakeholders can give insight into the evaluation study that will make the study all the more successful. Stakeholders should typically be upper management, middle management, and supervisors. The level of management will depend upon the leadership structure of the organization.

Conclusion

As a regulatory organization in today's competitive global economy it is imperative to take a step back and ask how training measures up. There is value alone in a well-rounded knowledgeable workforce that will produce effective consistent products in an efficient manner. The FDA has begun to recognize the untapped value of measuring training effectiveness. Gauging knowledge learned, transfer of learning back to the work environment, impact on the organization, and return on investment whether forecasted or actual are all areas of evaluation that should be focused on when measuring training effectiveness.

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About the Author

Anita Whiteford has been a Training Specialist with Mallinkrodt Baker/Covidien since 2005. As part of her duties, she develops and designs training content, methods, and materials for organizational needs. She is a PhD candidate in workforce education and development at the Pennsylvania State University, and is to defend her dissertation in February 2009. In her spare time, she has been an Adjunct Faculty member of the University of Scranton since July 2007.

Take a Look at New Sterilization Technologies

Sterilization Technologies in Pharmaceutical Development and Manufacturing • Milan, Italy • November 19–20

Wolfgang Schmidt, PhD, Bayer Schering Pharma

Being up to date with one of the major topics of parenteral drug manufacturing—sterilization processes—is key for doing successful business in the field of parenterals. Regardless of being a beginner or having a huge experience in dealing with sterilization, it is important to see what's new and to refresh knowledge to tackle future challenges. It is PDA's tradition to help its members staying abreast with the current best practices in this field. In continuation of the successful conference in Paris, France in 2006, PDA is organizing a conference called, *Sterilization Technologies in Pharmaceutical Development and Manufacturing* in Milan, Italy.

The main focus of the two-day conference is to give an understanding about conventional sterilization methods and also emphasize new and emerging sterilization technologies. Thus the conference is of interest not only for the drug manufacturer, but for the medical device manufacturer and the manufacturer of sterile disposables as well.

At the beginning of the conference a general overview of the relevant processes for sterilization and the typical application of those is outlined. This is followed by a presentation reflecting the impact of the updated EU GMP guide and its annexes upon sterile products. On the morning sessions of the first day, a number of presentations give relevant information about the underlying microbiologic issues in sterilization like bioburden and bioindicators. At the afternoon sessions on the first day, all the facets of moist heat sterilization, including risk based process validation will be shown. The first day will be closed by two sessions about process development of dry heat sterilization in conjunction with technical issues like qualification and design of such equipment.

The second day starts with two sessions about filtration for manufacturing sterile drug products and will highlight topics like filter selection, filter qualification and validation. After these two presentations the focus shifts to newer or more unconventional sterilization methods—from the view point of a pure drug manufacturer. Thus attention is moved to sterilization methods used more often in the field of medical devices and sterile disposables. Namely the morning session of the second day will deal with gas phase sterilization using hydrogen peroxide and ethylene oxide. In several talks it will be shown how to develop and achieve robust processes. To work out more clearly the relevant issues of gas phase sterilization, some case studies are presented as well. Day two of the conference will be completed in the afternoon by a couple of presentations on the use of electromagnetic sterilization methods. The day will close with lectures about notified bodies and their expectations and critical findings in the medical device industry.

The Milan conference of sterilization technologies offers a rare and excellent opportunity to get the whole picture of all the relevant sterilization issues and technologies in conjunction with a networking event in a relaxed atmosphere in the evening of the first day. Multiple question and answer sessions allow for clarifying special problems, and to share and network with colleagues from industry and regulatory agencies. This very intensive two-day conference is offered with the opportunity of participating at an optional course on regulatory requirements and compliance achievement for environmental monitoring in pharmaceutical manufacturing facilities. The course will be held in conjuction with the seminar and it will cover regulatory and compliance issues. There will also be a chance for optional site visits, at either an autoclave manufacturer or a contract manufacturer offering sterilization near the conference venue; they will give a comprehensive overview of sterilization processes in the pharmaceutical and medical device field.

The organizing committee is looking forward to seeing you in Milan.

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