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PDA Letter

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June 2010

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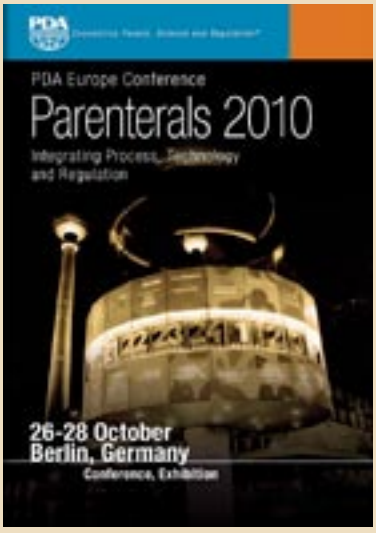

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Frederick Carleton Passed Away, May 20

James Agalloco, Agalloco & Associates

Frederick J. Carleton, PDA Honorary Member, past Officer, Director, and Executive Director, passed away on May 20 in Boynton Beach, Florida. Fred's name was virtually synonymous with PDA during the 1970s and 1980s, a period when PDA experienced perhaps its greatest growth in membership and influence. Fred seemed, at times, to be virtually everywhere and his energy and enthusiasm for PDA were unlimited. He served as a Board Member from the 1970's through 1988, a period in which he also chaired numerous committees and task forces.

A review of PDA records would show that Fred also served on many other committees as an active contributor. In 1980, Fred was appointed as PDA's first official delegate to the United States Pharmacopeial Convention. Fred served as President (Chairman) during the years 1978 and 1979, and the more significant events of his tenure was the establishment of the PDA Foundation for Pharmaceutical Sciences; the first international meetings in Mexico; and the publication of PDA's first Technical Monograph on the validation of steam sterilization processes (now called *Technical Report No. 1*, revised in 2007).

In the early 1980s, he provided the impetus for the start of PDA's professional educational activities, which have evolved to the present-day Training and Research Institute. Fred became Executive Director (President) of the Association in 1988, and he helped support the emergence of local PDA chapters domestically and internationally. Under Fred's leadership, program and educational offerings expanded in both number and location. Fred retired from PDA in 1991 and continued to volunteer his services at PDA meetings. Later that year, Fred was made an Honorary Member of the Association. In 1992, the Association further acknowledged his many contributions by establishing the Frederick J. Carleton Award to recognize "those past Board of Director Members whose service best exemplifies Fred Carleton's dedication and leadership."

Fred gave so many years of service to PDA in so many varied capacities, but his single greatest contribution to PDA was as a recruiter and mentor. An entire generation of PDA leadership became active in PDA as a result of Fred's persistence. Among the many PDA leaders and contributors who can trace their PDA participation largely to Fred's efforts are: James Agalloco, James Akers, Joyce Aydlett, Michael Anisfeld, John Bontempo, Doris Conrad, Daniel Gold, Robert Kieffer, Michael Korczynski, Henry Kwan, Carole Lampe, Solomon Motola and Richard Wood.

Fred's legacy to the Association is beyond measure; his participation serves as a shining example of selfless, altruistic volunteerism.

[Editor's Note: Turn to page 7 for more on Fred and on sending condolences.**]**

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1 United States Pharmacopeia Convention, Inc. 2009. The United States Pharmacopeia 32/The National Formulary 27. 2009. The United States Pharmacopeial Convention, Rockville, MD.
2 European Pharmacopeia, 6th Edition. European Directorate for the Quality of Medicine, Council of Europe. 226 Avenue de Colmar BP907, F-67029 Strasburg Cedex 1, France.
3 Japanese Pharmacopeia, Fifteenth Edition.
4 Clinical and Laboratory Standards Institute. 2004. Quality control for commercially prepared microbiological culture media. Approved Standard – Third Edition, M22-A3. Clinical and Laboratory Standards Institute, Wayne, PA.

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Coming Next Issue:
Sterile Drug Manufacturing and Aseptic Processing

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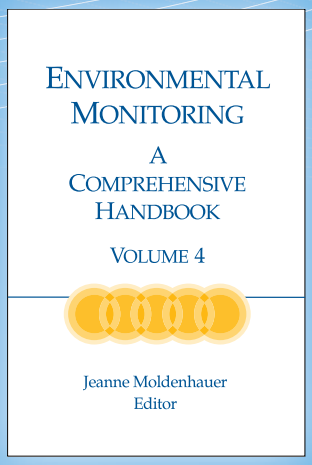
New Release at the PDA Bookstore



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By Jeanne Moldenhauer

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- Overview of Recent Warning Letters for Environmental Monitoring
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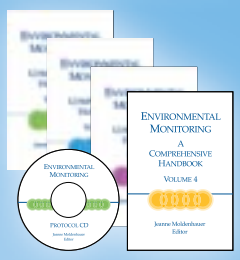

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Editor's Message

What PDA Really Stands For

In this issue, we remember **Frederick Carleton**, whose contributions to PDA over the years are recounted on a cover story and in an article in "News & Notes" that we decided to reprint from a 2006 issue. I worked on that article and got to know Fred for the first time. **James Agalloco** offered the cover article and **James Akers** is quoted in the other article, and from my brief time knowing Fred, I can say that their descriptions of Fred's commitment and love of PDA are not overstatements. In fact, they just might be understatements. Fred truly loved and was dedicated to PDA, so much so that he spent the last 20 years of his career ensuring the Association progressed and prospered. Fred wanted to give back to the people and the organization that helped him as he advanced his career.

In my role as editor of the Letter, I have the opportunity to get to know many of PDA's key players intimately, and in these interactions, a common theme always is evident: PDA's volunteers love PDA and their desire to give back to the Association and their profession is a driving force behind what they do.

This issue also includes an interview of new SAB member **Joyce Bloomfield**. In reading her words about PDA and the SAB, I can hear a little of Fred coming out. Joyce joined the SAB because of a desire to give back. She, like Fred, takes responsibility for becoming not just a customer of PDA's materials, but steward of the Association's future. The same is true of all the people who are involved with PDA, from the members of our Board to the Chapter leaders.

So, as you think about Fred Carleton, whether you knew him or not, also think about honoring his memory and accomplishments by offering a little of yourself to the greater community of PDA that brings us all together. Volunteerism, contribution, community… these are things that PDA really stands for.

PDA Letter

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Past Leader Spotlight: Fred Carleton, President 1977-1979, Executive Director 1988-1991

Reprinted from the September 2006 *PDA Letter*

For 30 years, one PDA member played a central role in every major meeting, training event and recruiting effort at PDA: Fred Carleton.

Fred joined PDA in 1960 while working for Pfizer Inc. His career with Pfizer would extend for 29 years, ending in 1988, as the Manager, Scientific Affairs for the company's domestic facilities (seven in total). Fred joined Pfizer as a radiological biochemist, with degrees from City College, Purdue University and the Oak Ridge Institute of Nuclear Studies. He was one of the first experts in the industry trained to work with radioactive compounds. Fred also was an adjunct professor at the Fairleigh Dickinson University (1960-1970) where he taught biochemistry and radiochemistry.

Fred's first experience with PDA was at the National Meeting (now called the Annual Meeting). After attending for the first few years, the educator in Fred came out. He approached the PDA Board of Directors in the mid-1960's and proposed a number of changes to enhance the conference. Impressed with his ideas, PDA named Fred to the planning committee for the national meeting. In 1971, Fred became a member of PDA's Program Committee, on which he served until 1991. In those two decades, he participated in planning every event PDA sponsored!

Fred by no means wants to take all the credit for PDA's phenomenal success in that period of time. He acknowledges the hard work and dedication of those who served with him. "I was a member of a team," he says. "I'm a team player."

In the late 1970's, Fred and other PDA leaders of the time, started looking to develop better educational offerings. Fred helped recruit experts to teach courses for PDA at no fee. Dr. **Irving Pflug** was one of the early educators brought on board to lead PDA courses. Fred personally invited two members of the Pfizer staff to teach courses on computer programming, PDA's first foray into the world of IT!

Two important events happened to bolster PDA's education mission during Fred's tenure as President. First, the Association received accreditation from the American Council on Pharmaceutical Education, the strongest possible endorsement of PDA's educational qualifications at the time. Second, the Association created the PDA Foundation for Pharmaceutical Sciences, Inc., to support research and education in parenteral sciences and technology. Fred joined with other PDA volunteers, including **Nina Demuth, Jack Cole, Nathan Kirsch** and **Leon Lachman** to launch the venture.

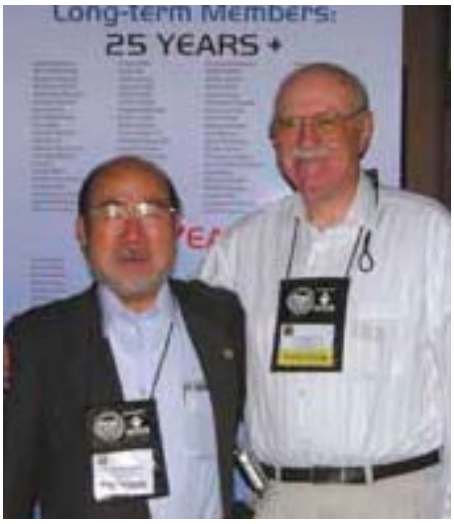
Perhaps none of Fred's contributions can outweigh his role as top cheerleader and recruiter. His honest dedication to PDA helped him recruit many of its foremost leaders during his 30 years of active involvement.

Upon Fred's retirement as PDA Executive Director in 1991, PDA President **Michael Korczynski** provided perhaps the best summary of Fred's role ever written (*PDA Letter* vol. 27, no. 7):

Fred's contributions and activities during his 30-year association with PDA are almost too numerous to count. He has either chaired or been a principal member of every major committee or activity within the Association. Fred has been instrumental in identifying and encouraging talented individuals in the pharmaceutical industry to participate in PDA… Fred exemplifies PDA.

Former PDA Chair **James Akers** describes Fred's devotion to PDA as infectious:

"He had an enormous love of PDA which manifested in an untiring effort to recruit talented volunteers. Fred was directly responsible for recruiting half of the people who served on the Board of Directors in the late 1980's and 1990's. Without Fred's persistence, I probably would not have gotten as involved with PDA, for which I am very grateful to have done!"



Honorary Members: Fred Carleton (r) poses with Kunio Kawamura at the 2006 PDA Annual Meeting. Kunio joined Fred as a PDA Honorary Member this year.

The Frederick J. Carleton Award was created in recognition of his hard work and dedication. It is awarded to past or present Board members whose services on the Board are determined by his/her peers as worthy of recognition.

When asked why he gave so much to PDA, Fred replies simply, "The thing I loved was PDA. I mean it. It has been a love affair for me."

PDA is fortunate to have had a leader like Fred involved for so many years!

If you would like to send condolences to Fred's wife, Helen, please mail them to PDA at the following address:

PDA, Inc.
Attn: Brianne Dornbush, In Memory of Fred Carleton
4350 East West Highway, Suite 150
Bethesda, MD 20814

Science & Technology *Snapshot*

Advisory Board *Watch*

Joyce Bloomfield Talks About Her First Year on the SAB

Joyce Bloomfield is one of the newest members of the PDA Scientific Advisory Board (SAB), which helps set PDA's scientific and technical agenda by sanctioning Task Forces to draft technical reports and the Interest Groups. The SAB also votes on whether or not a technical report drafted by one of its task forces should be advanced.

Joyce is Executive Director, Global GMP Systems Compliance at Merck, where she has worked since 2008 following a 17 year career in pharmaceutical manufacturing, consulting, and the U. S. FDA. Joyce noted that she was encouraged to join PDA while at FDA, and after years of benefiting from the scientific products produced by the membership, she is enjoying her opportunity to give back as a member of the SAB, which she joined in 2009. The *PDA Letter* talked to Joyce about her experience so far on the SAB.

PDA Letter: What motivated you to join the SAB?

Joyce: I wanted to personally and professionally commit and contribute to SAB's mission, and that is to establish the strategic direction for PDA's scientific and technical activities through the development of guidelines, technical reports and technical bulletins. And on a personal level, I feel I'm giving some of myself back to each of the really dedicated professionals who have helped guide me to where I am today professionally. My first introduction to PDA was through my early years as an FDA investigator, and I literally cut my teeth on the technical reports (TR), journal articles and technical bulletins. After I joined the PDA, I really looked forward to the monthly Letter, and I would very intently pore over every word in the articles, and I still do.

I really see that the TRs are far reaching and they serve as a virtual teacher to a remote academic audience of industry professionals. I wanted to be a part of that, and I'm proud to be associated with their implementation.

PDA Letter: How have you benefited professionally and personally from your activity on SAB?

Joyce: Personally, I am finally content to know that I can channel my experience and enthusiasm for science and pharmaceutical manufacturing to the PDA SAB's mission. Professionally, I enjoy the networking, the technical discussions with great thought leaders and dedicated professionals in my field. And I cannot think of a better way to benefit both personally and professionally.

PDA Letter: There are a lot of important issues that SAB has been dealing with over the last year. For instance, prioritization of PDA's various projects and the launch of the Paradigm Change in Manufacturing Operations (PCMO) initiative. Are you seeing progress and results so far?

Joyce: I have just in my short time. The fact that we are publishing technical reports and moving them forward to get published more quickly that had been in development for a while. For example, we recently published *Technical Report No. 48*. Again, on a personal level, I get great satisfaction knowing I was part of that.

PDA Letter: In your opinion, what was the hardest task that the SAB has had to complete or is working to complete?

Joyce: I think the hardest task is getting the TRs to completion sooner. I know the SAB is proactively working to prioritize and complete a number of TRs that have been under development for some time. I think reenergizing that and the prioritization is really important to get the information out to industry as soon as possible. I believe that, again, as a virtual teacher, we owe that information to the industry as soon as we can get it to them.

PDA Letter: Finally, what would you say to other PDA members to encourage them to join SAB?

Joyce: Follow your passion! If you are really interested in joining, pursue your path to the SAB. If you have a regulatory background or experiences that you feel would truly contribute to development and implementation of the TRs and moving PDA forward then pursue that passion.

I personally reached out to PDA members and asked about the other advisory boards at PDA, like the Regulatory Affairs and Quality Committee, and explored what all of those groups do, and decided that I was very interested in the SAB and contributing to strategy, since that has been a part of my experience. I encourage anyone to strive to get engaged in the areas in which they are most interested.

Journal *Preview*

ICH Turns 20

The May/June Journal includes an editorial by Associate Editor **Antonio Moreira** on ICH's 20 year anniversary. In the Research section, there are nine articles that cover a myriad of topics from an investigation into the potential of electroporation facilitated topical delivery of Cyclosporin A to a case study on the identification of an extraneous black particle in a glass syringe. The latter article by a team at Amgen's Department of Formulation and Analytical Resources demonstrates how the firm used various methods to determine the source, identity and leachables of a black particle unexpectedly found adhering to the interior shoulder of a prefilled glass syringe containing a biological product. This and all the articles can be found at journal.pda.org.

Editorial

Antonio Moreira, "Happy Birthday, ICH!"

Research

San-ming Li, Hong-zhuo Liu, Yong-jun Wang, Lu Xu, "Investigation into the Potential of Electroporation Facilitated Topical Delivery of Cyclosporin A"

Dennis Jenke, "Extraction of Stearate Salts from Plastic Materials Used in Pharmaceutical Applications"

Luis Jimenez, Narendra Rana, Kasey Travers, Verce Tolomanoska, Kimberly Walker, "Evaluation of the Endosafe® Portable Testing System™ for the Rapid Analysis of Biopharmaceutical Samples"

Ajit S. Kulkarni, Jayashree B. Gaja, "Formulation and Evaluation of Liquisolid Compacts of Diclofenac Sodium"

Veerabrahma Kishan, Isnepally Venkateshwarlu, Kandadi Prabhakar, Mubarak Ali, "Development and In Vitro Cytotoxic Evaluation of Parenteral Docetaxel Lipid Nanoemulsions for Application in Cancer Treatment"

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Jennifer Claire Gray, Alexandra Staerk, Manfred Berchtold, Werner Hecker, Gunther Neuhaus, Andreas Wirth, "Growth-promoting Properties of Different Solid Nutrient Media Evaluated with Stressed and Unstressed Microorganisms: Prestudy for the Validation of a Rapid Sterility Test"

Yamasani Madhusudan Rao, Mittapalli Pavan Kumar, G. Y. Srawan Kumar, Shashank Apte, "A Review of Solubilization Techniques for a Poorly Water-Soluble Drug: Carbamazepine"

Sanjay K. Jain, Yashwant Gupta, Lathaeswari Ramalingam, Anekant Jain, Aviral Jain, Piush Khare, Divya Bhargava, "Lactose-Conjugated PLGA Nanoparticles for Enhanced Delivery of Rifampicin to the Lung for Effective Treatment of Pulmonary Tuberculosis"

Technology *Trend*

Baxter's Case Study on Utility Monitoring and Predictive Utility Management

Emily Hough, PDA

Rising costs often are an impetus for facilities to employ "green" systems, as environmentally-sound practices are efficient and frequently lead to a greater return on investment.

Robert Perks' firm, Baxter, encountered such a situation and developed an approach to optimize the energy and utility savings within its manufacturing facilities two years ago when oil prices were rising. According to the Engineering Specialist, "As utility costs have both increased and become more volatile, the need for greater control over utility and energy usage has become more important." He outlined the approach in a case study entitled "Utility Monitoring and Predictive Utility Management System," which he presented at the *2010 PDA Annual Meeting* during the Facilities and Engineering Interest Group session.

Under the umbrella of its new "Energy Management System," Baxter has decreased its utility usage and has been able to effectively and efficiently compliment its "Lean Energy Initiative" by optimizing the performance of processes that are run.

How It Works

Baxter is able to better control its manufacturing process by using the predictive scheduling functions of its Manufacturing Tracking & Control System (BMTCS). BMTCS, is a rules-based system that both tracks and controls product flow based on specific quality and product manufacturing parameters. The system "communicates" with process control equipment to provide set-up information and to collect data. It controls the manufacturing process by inhibiting further product processing when the process exceeds product parameters, e.g., mix to sterilize time, sterilization cycle aberrations, etc. As it is currently installed, BMTCS tracks production and product from mixing through packing for moist heat terminally sterilized products.

Product is tracked through the manufacturing process using bar codes mounted on the product trucks. An order is associated with a truck and all the parameters pertinent to that product are then assessed in real time as the product moves through the manufacturing process.

The feature that Baxter is utilizing to optimize the energy and utilities usage are BMTCS' scheduling functions. The system knows the product, when the sterilizers will be required and can determine utility requirements ahead of time. Using this knowledge and applying some basic algorithms to the utility requirements, the EMS controls the utility generation based on the manufacturing requirements. This not only optimizes the

continued on page 11

Recent Sci-Tech Discussions: Sampling by Production Personnel

The following unedited remarks are taken from PDA's Pharmaceutical Sci-Tech Discussion Group, an online forum for exchanging practical, and sometimes theoretical, ideas within the context of some of the most challenging issues confronting the pharmaceutical industry. The responses in the Sci-Tech Discussions do not represent the official views of PDA, PDA's Board of Directors or PDA members. Join at www.pharmweb.net/pwmirror/pwq/pharmwebq2.html.

Sampling by Production Personnel

Questioner: Can you share your view/ industry practice on the idea that environmental sampling i.e., plate exposure and sampling of WFI for routine analysis, can be carried out by the production staff? The purpose is to reduce the number of people entering in the clean area for these activities. Suitable training to the manufacturing staff for the above procedure would of course be given.

Respondent 1: A couple of 483's are been issued for process guys doing EMP. We can justify if the persons in production report to QC .

Respondent 2: It is acceptable if you have QA overseeing this operation (observing and giving instructions from the corridor), if feasible.

Respondent 3: Any sampling by production person is not seen in a good light by inspectors. Doubts are raised as they are known to keep a master sample ready to give to QC every time!

Respondent 4: [Respondent 3], Sorry, but I have to disagree with you. In-process sampling by production folks is fine as long as:

- They are trained to take samples according to the SOP, and the training is documented
- There is routine monitoring of their sampling technique by QC or QA, and retraining is provided if necessary

If these are in place, I have never had a regulatory inspector ever make an adverse comment.

Respondent 5: This is a violation of the cGMP since quality control and production must be kept separate. In-process controls performed by production personnel at the time of operation is to insure that machinery is producing output within prestablished control limits.

Respondent 6: I agree with [Respondent 4]. Providing that the training is good and QA monitor the system, production can and do take samples and carry out environmental monitoring tasks. This was routine for many years when I managed an aseptic production department. It was accepted by inspectors on both sides of the Atlantic.

In Europe, it is possible for the Qualified Person (QP) to be the head of production. The QP signs the register for every batch, to state that it has been manufactured and tested in accordance with GMP and its license conditions. For professionals within the industry, there is not a conflict of interest; we all want the best possible product for the patient. To suggest that production would provide "special" samples is returning to the 1950s, early '60s, when there was a "them and us" attitude. Them—production—were aways bad, Us—QC—were always correct. I started life as an "Us" and became "Them!" My experience is that QC/QA can and do make as many mistakes as production. Most failing inspections are due to poor Quality Systems.

Finally, before I put my feet up for good, how many of you have production carry out internal audits of QA? Try it and see where the problems are.

Respondent 7: Not a violation of GMP... exactly as [Respondent 4] says... trained, appropriate SOP's, are monitored on regular basis. In fact, I am at a loss to understand why anyone should have a problem with it. You rely on production people to follow the production rules, you rely on QC to act as honest staff and you monitor and train. So why do you not trust trained and monitored production staff to take samples? Quality control and production kept separate? "The heads of production and quality control generally have some shared, or jointly exercised, responsibilities relating to quality."

It is true that "the independence of quality control from production is considered fundamental to the satisfactory operation of quality control," but that is the difference between decisions which are independent and responsibilities which may be shared.

Respondent 8: I agree with [Respondent 4's] position. Personnel monitoring is an in-process control and new technologies offer the promise of real time monitoring. Remember, we train the operators to make the product and trust their competency and integrity so with the appropriate controls we should be able to designate the environmental and personnel monitoring to them.

Respondent 3: We rely on production people to do "production jobs," rely on QC people to do "QC jobs" which is sampling. Do not rely on each other for cross departmental jobs! Sampling is not production job and do not rely on them for that. If you do, be prepared for some suspicious or nasty inspectors to give you 483s.

Respondent 4: [Respondent 6], Did I read you correctly—the QP can also be the head of production? Please can you provide some background to your logic on this.

Respondent 9: I guess the general rule is to do what you need to do to stay out of trouble with the authorities, whoever they are and wherever you happen to be operating. I believe that in the United

States such sampling by production personnel is not unusual. However, I'm sure we have all seen situations in which samples can be 'biased' and the prudent company will make sure the sampling is done by a disinterested party.

Respondent 10: I fully agree with the comments made by [Respondent 4]. We also decided to remove IPQA from the production in-process checks. We trust all the trained and qualified people who will be involved in the manufacturing, packaging and storage of the drug products.

In addition to this "done by production and checked by IPQA" will dilute the responsibility, and also the point of perfection at work which could leads to a chance of more mistakes. However, let me understand, is there any regulatory obligations if we remove IPQA from the routine checks like in-process, line clearance sampling etc? Let me keep IPQA as an auditor in the Production Block, What is your opinion on this?

Regards.

Respondent 11: At the end of the day it really shouldn't matter who takes the samples. If the concern is that production would bias the result in the collection of a sample in some manner, then the problem is far deeper than just what an inspector might say about that practice. There are so many things the production personnel do that can violate CGMPs that would be impossible to detect in any manner. Quality begins in production, not in QA or QC. To suggest that production can't be trusted to sample the environment is merely the tip of the iceberg. Everyone in the firm has to perform within the structure of the regulations at all times. Anything else is just wrong. If you're relying on QA, because you don't trust in the honesty and integrity of the production workforce, then shut the place down.

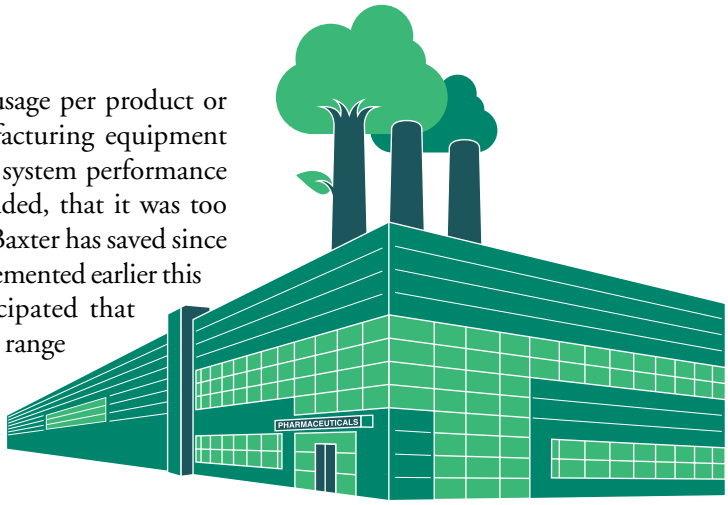
We are all in this together, and everyone has to be honest and ethical in all that they do.

Technology Trend, continued from page 9

energy and utility usage but also prevents delays in the manufacturing process due to a lack of utilities.

What was Learned

By developing the energy management system in a modular fashion, the system has the ability to be implemented at any facility within Baxter and can be configured based on the specific requirements of the facility without having to re-engineer the system. According to Perks, it allows the manufacturing and engineering staff to monitor utility usage per product or per piece of manufacturing equipment to provide valuable system performance information. He added, that it was too early to share what Baxter has saved since the system was implemented earlier this year, but it is anticipated that savings will be in the range of 3-4%.



Technical Report *Watch*

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 to 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.

- *Points to Consider for Biotechnology Cleaning Validation* **(BioAB)**
- *Technical Report No. 22: Process Simulation Testing for Aseptically Filled Products* **(BoD)**
- *Recommendations for the Production, Control and Use of Biological Indicators for Sporicidial Gassing of Surfaces with Technical Exposures* **(BoD)**
- *Technical Report No. 3: Validation of Dry Heat Processes Used for Sterilization and Depyrogenation* **(BoD)**

In Publication: TR is published and available for a free download at store.pda.org/bookstore until June 11.

- *Technical Report 48: Moist Heat Sterilizer Systems*

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Supply Chain Best Practices ID'ed at PDA Workshop

Quality, procurement and operations experts representing global pharmaceutical manufacturers, working side-by-side with the U.S. Food and Drug Administration, articulated tangible solutions for securing components and finished products during high-level breakout discussions at the *2010 PDA/FDA Pharmaceutical Supply Chain Workshop*.

Concerned over the growing problem of cargo theft and a myriad of other security and quality vulnerabilities in the pharmaceutical supply and distribution chain, and the threat to public health that these pose, FDA championed the workshop in an effort to get drug manufacturers to share and implement best practices. **Janet Woodcock**, MD, Director, CDER, U.S. FDA, gave the keynote address at the workshop.

Over 200 industry experts answered the call to action. Attendees broke into five different brainstorming sessions to share ideas and identify best practices that can be implemented immediately at their respective firms. These were summarized and presented during the meetings final day.

Priority solutions identified include proactive mapping of the ingredient supply chain for each product, the use of risk models to identify which ingredients pose the highest threat to patients, the implementation of standardized global auditing practices, and the development of an industry-wide alerting process to help identify unethical and criminal suppliers.

PDA will continue to support the industry and FDA's efforts to protect the public health from insecure pharmaceutical supplies. **Deborah Autor**, JD, Director, Office of Compliance, CDER, U.S. FDA, said that industry needs better systems in place for safeguarding its products and must start thinking about where the gaps are and what is missing in its supply chain controls "The biggest risk is the risk we haven't thought of," she said.

"The public and the industry should appreciate FDA's role in helping to find and pushing for common solutions to the serious challenges and risks inherent to the global pharmaceutical supply chain and marketplace," PDA President **Richard Johnson** said following the workshop.

PDA sent preliminary reports from the workshop to all attendees following the workshop. In the coming months, PDA will work with conference planners and discussion facilitators to develop and publish detailed reports on the best practices identified.

The Industry Fights Back

Pharma Companies Fight Multi-Front War Against Criminals and Unethical Suppliers

Walter Morris, PDA

Facing threats to the integrity of ingredients and components through economically motivated adulteration and attacks on finished products, like the recent theft of product from an Eli Lilly warehouse, the pharmaceutical industry is advancing and sharing strategies to safeguard medicines across the supply chain.

The time for identifying problems is over; the public, lawmakers, and the regulatory agencies globally are demanding solutions. Already, many companies are meeting the call and advancing sound, protective strategies.

You have to consider the hidden costs to the company

To help these solutions come to light, the U.S. FDA and PDA cosponsored a workshop in April designed to facilitate dialogue and to identify tangible practices companies can implement immediately to safeguard the supply chain.

Janet Woodcock, MD, Director, CDER, opened the meeting with several salient points that set the tone for dialogue. For one, she noted the fact that so many participants—over 200—showed up for the conference despite travel disruptions do to volcanic activity in the North Atlantic and tough economic times. This was an indication, she said, "that there is wide appreciation of the vulnerability in the current system, and the need to prevent patient exposure to the risk posed by today's industrial supply chains.

"So I think we are all here at this workshop for the same reason," said Woodcock. "Recent events make it clear that the industry and FDA, in particular, must take more action to better protect the drug supply chain."

Without action, she maintained, "Weaknesses in drug supply chains can threaten to undermine the quality and authenticity of the global drug supply and ultimately would further undermine consumer confidence in both the industry and the Agency's ability to protect them."

Attendees "are here over the next few days to help drive the implementation of real solutions to these problems and to bring them back to you critical daily work of producing and distributing safe drug components and drug products, every batch, every day, to those patients who need them."

Woodcock offered a spot-on explanation right out of an Economics 101 class as to why companies must bear the greatest burden in safeguarding patients. "We have what economists would call a market failure in a sense that patients, or even physicians, usually cannot tell if there is a quality problem with a drug, unless it is overtly visible. People inject insulin, but they cannot tell why their blood sugar is [still] going out of control, for example, because it happens for so many reasons; there is so much variability there…. Patients cannot readily attribute an adverse event or lack of therapeutic effect to a quality problem, and certainly [neither] they nor their physicians would be able to trace it to an unscrupulous member of the drug supply chain."

Woodcock said firms need to understand the full cost of doing business with overseas suppliers.

"We all recognize the reason for this outsourcing is cost minimization—people would like to get the cheapest, most efficient source of their ingredients…. So the accounting departments would be very happy about going to the least expensive source for any given operation or component. However, you have to consider the hidden costs to the company." Corporate management, she said, needs to understand the costs beyond those for goods and services, "because there are higher costs of due diligence if you are outsourcing somewhere that is not known to be reliable, doesn't have a long track record, doesn't have, for example, a strong regulatory system in that region or country, has known criminal elements, for example, involved in counterfeiting, and so forth. These all need to factor into how you determine the actual cost of sourcing from any given supplier."

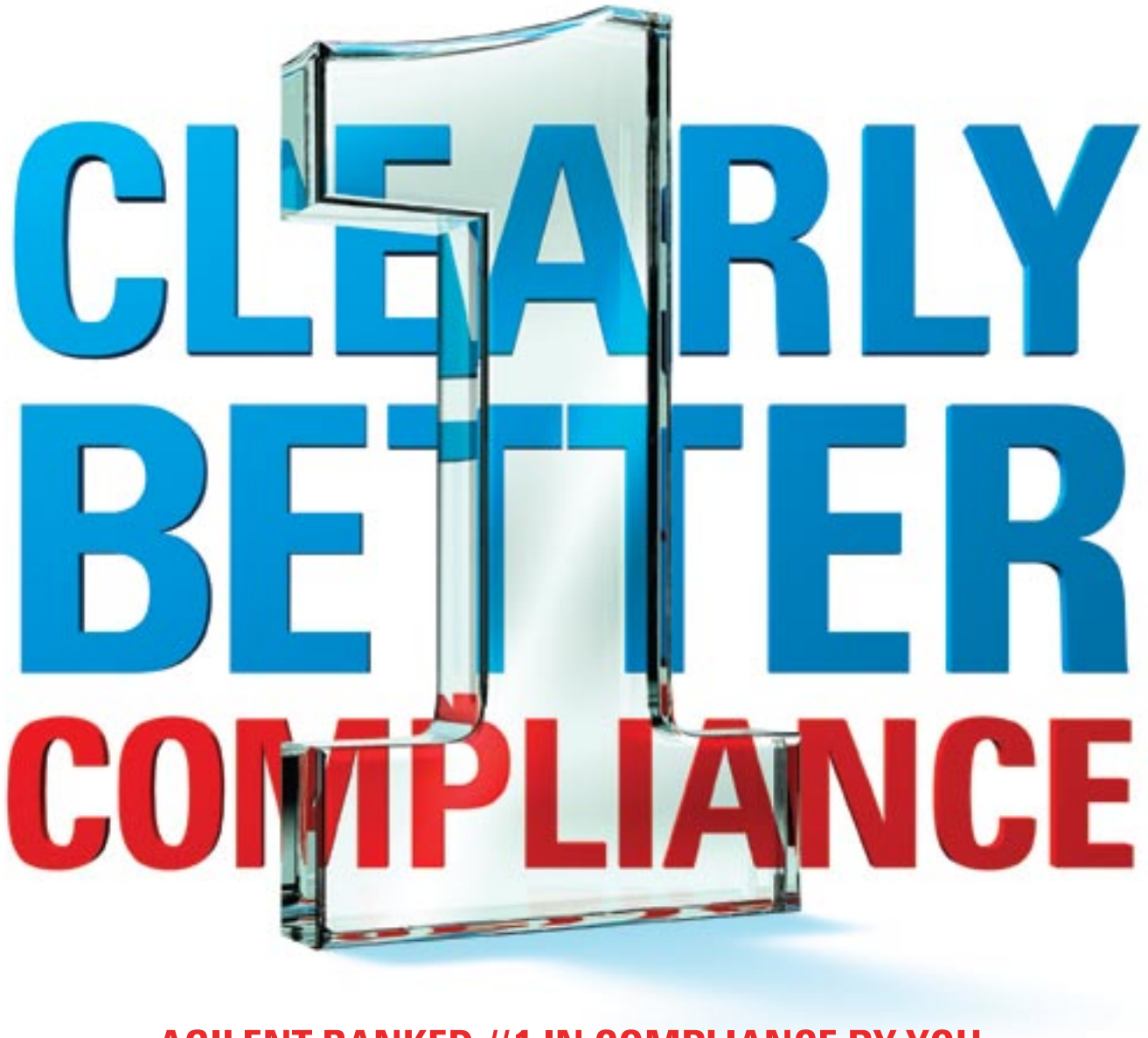
Next, Woodcock outlined a number of solutions to help induce further discussion during the next two days of brainstorming sessions.

Serialization, track and trace and other technologies rated high on her list. "Technology should be considered a part of everyone's toolkit to monitor product security and authenticate incoming materials," she said. Recognizing the cost of these technologies, however, she said, "The real question in is how to apply them in this setting, what is appropriate, what will provide tangible benefit as far as mitigating risk?"

The Quality System also "plays a core role" in securing product suppliers, she said. A good Quality System would account for all the actors throughout the supply chain, and even keep track of changing economic conditions that could impact quality and integrity of supplies. "The question would be, how sophisticated can we be on that? How meaningful can that be? Obviously for a biological material, I think we can do a very good job. For certain other chemicals, the question might be, is there some other competing use that is siphoning them off?"

Good quality agreements with suppliers augment the Quality System by establishing strong change control procedures. Other key weapons, according to Woodcock, include quality risk management and managerial involvement.

Finally, Woodcock posed the idea of an information sharing network for companies regarding potential hazards in the supply chain. This idea ignited significant deliberation in some of the brainstorming ➤



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sessions that followed the plenary sessions. In particular, to what degree can companies share information?

Woodcock seemed to think public health should trump antitrust issues. "We cannot view a company's learning of a hazard as commercially valuable information. We have to view it as public health information that we would get around to everybody as rapidly as possible."

Further thought on the matter could flip the idea of illegal collaboration between companies on its head. According to Woodcock, "Sharing information with regulators and with other companies is a key component of assuring synergy… This is really pro-competitive information. It is public health information. It is information that will help everyone function better. It isn't commercially valuable information. You don't want to see the industry's reputation diminished, you don't want to see patients be harmed because information wasn't shared that could have prevented that."

The reluctance to share information between companies is strong. Even in the clinical trials world, companies are remiss to alert others about unethical investigators out of fear of antitrust litigation. "We've seen this in the clinical trial area, where companies would drop an investigator they found to be falsifying data, and that person would go on to falsify data in perhaps dozen of other trials, thus damaging hundreds of other people in development programs," explained Woodcock. "So people's first instinct is just to drop the supplier and not talk about it."

She acknowledged that the regulators also need to be better at sharing information vital to public safety. "We recognize that when this comes up any place in the world, the regulators need to share it as well. If we learn about it, we need to share it with industry. So that obligation goes both ways."

Drug Security Expert Opens Eyes

Prior to the brainstorming sessions, the audience heard tips on protecting product in storage and transit from **Charles Forsaith**, Corporate Director – Supply Chain Security, Purdue Pharma Technologies. Forsaith also heads the Pharmaceutical Security Coalition.

Purdue markets a product specifically targeted by criminals—OxyContin—providing the company impetus to be extra vigilant in its efforts to protect shipments. Forsaith appeared at the conference to share common-sense strategies employed by the firm. These tips were unrelated to securing ingredients used to manufacture drugs. Rather, they focused on post-manufacturing distribution.

First off, companies must employ multi-functional strategies, according to Forsaith. Groups that must participate in securing distribution channels include the regulatory affairs, corporate security, manufacturing, sales and marketing, logistics, risk management, and the company's insurer.

Companies also need to conduct background investigations on everyone involved with handling product, including drivers and others involved in downstream transport and warehousing. Forsaith noted that criminal and motor vehicle records should be scrutinized, as well as employment histories.

Security training is another element, alongside threat assessments of facilities, warehouses and other places where product will be held. Companies need to check who has access to these facilities, if there is gated access, and whether or not there is electronic surveillance and security guards. The routes in which products are shipped also need to be well-understood.

Although the meeting was focused on solutions, Forsaith's presentation included some eye-opening revelations about the rising incidents of crime in the pharmaceutical distribution chain. His list of "Notable Pharma Truck/Warehouse Thefts" in 2009 and 2010 raised eyebrows.

By analyzing these cases, Forsaith picked up on commonalities that helped him develop strategies to prevent theft. He presented 11 practices that increase the chances product will be stolen (see box below).

He noted that the Pharmaceutical Cargo Security Coalition, which includes several large pharma companies, the FDA and the U.S. Drug Enforcement Agency, has had success in recovering stolen cargo. In 2008 and 2009, the group helped recover over $90 mil. in stolen cargo.

Conference Generated Take-Home Ideas

In the end, the PDA/FDA Supply Chain Workshop produced a number of sound recommendations for companies to implement immediately (see related article, p. 13).

Eleven Practices Raising Risk to Shipments – From Charles Forsaith's Presentation

1. Using single drivers as opposed to a driver team
2. Hauling product in a refrigerated trailer (whether refrigeration is required or not)
3. Utilizing a carrier who has solid "white" color trailers with limited or no unique name or markings
4. Not being aware that, in certain instances you shipment may be subcontracted to another carrier
5. Shipping late in the week (Thursday/Friday), over a weekend, or during a holiday period
6. Packing a mixed trailer load with the highest value commodities closest to the trailer door, as opposed to the more protective nose of the trailer
7. Not exchanging information with the driver(s) so that two way communication is possible during an emergency
8. Not having the driver, or driver team, aware of your specific security requirements
9. Being dependent on your carrier's GPS tracking capabilities (surface mount)
10. Stopping in high-risk areas (Olive Branch, Memphis, Louisville, Indianapolis)
11. Not utilizing a "layered" approach to truck/trailer security

The Status of Current Good Distribution Practice (GDP) Regulations in Israel

Rachel Karpel, PhD, PCI Pharmaceutical Consulting Israel

Current Israeli legislation in the area of storage and distribution of medicinal products has typically been legislated in a somewhat piece-meal manner. Over the years, Good Distribution Practice regulations have been addressed both directly and indirectly in various contexts. Moving forward, however, big changes are anticipated with the completion of the formal GDP legislation in Israel at the end of 2010. The changes to the legislation are very much in line with current thinking in the EU and US regarding securing the supply chain. While GMPs were legislated many years back and are under constant revision, GDP has been something of a poor relation and there seems to be a consensus that updating is needed.

This article will first review the legislation and regulations in Israel, proposed changes in conformance with the World Health Organization GDP requirements, and current practices of wholesalers.

In the Pharmacist Ordinance of 1981 there is a requirement for wholesalers to have a "responsible pharmacist" on-site—an advanced requirement even when compared to the current European legislation. Missing from the Ordinance, however, is the description of the duties and expectations of the responsible pharmacist, with respect to Good Distribution Practices. It was assumed that the responsible pharmacist, based on professional knowledge, responsibility, and ethical and legal obligations, would ensure the maintenance of appropriate conditions of shipping and storage, in accordance with the professional standards current at that period.

The first mention of Good Distribution practice in Israeli law appears in the 1999 legislation for parallel import of medicinal products. The law specifies that a medicinal product imported via the parallel import route must be shipped and stored in appropriate conditions. As with earlier legislation, however,this law fails to specify what constitutes "appropriate conditions," other than the requirement for imported product to be stored and shipped by licensed wholesalers "from recognized countries." ("Recognized countries" are those countries that are unilaterally recognized by Israel as having appropriate pharmaceutical regulations and enforcement standards including the United States, all EU member states, Canada, Switzerland, Norway, Iceland, Australia, New Zealand and Japan.)

In 2008, the "Pharmacist Regulations" (Good Manufacturing Practice for Medicinal Products) were revised in order to achieve harmonization with the European legislation in anticipation of, and as a prerequisite to, signing a trade accord (ACCA–see below) with the European Union. The revised regulations adopted the European GMP (Eudralex volume 4) as the regulatory standard in Israel, including the requirement for a qualified person (QP) for batch release and direct licensing of medicinal product manufacturers and importers by the Ministry of Health.

The GMP regulations originally included a clause requiring wholesalers to comply with the GDP rules as set out in the European Directive 2001/83/EC, as well as a requirement for direct licensing by the Ministry of Health based on periodical inspections. The regulations primarily designed to address GMP were somewhat vague regarding GDP. The Ministry of Health therefore decided to enact separate and specific regulations in the area of GDP. Following this decision, in the amendments introduced to the 2008 Pharmacist Regulations–(Good Manufacturing Practices for Medicinal Products), all mention of Good Distribution Practice was omitted.

The 2008 legislation requires the release of each imported batch of drug product by the importer's qualified person. This is a significant change in the law, since to date, the responsible pharmacist releases imported batches after a sample has been submitted to and released by the Ministry of Health. Provi-

Good Distribution Practice

The purpose of the Good Distribution Practice guidelines are to ensure the proper distribution of medicinal products in all stages of the distribution/supply chain. Since October 2005 when the World Health Organization's (WHO) was adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations, the guidelines have been sent for comments and revised a number of times by the Expert Committee.

In the European Union, the principles and guidelines for GMP are stated in directive 92/25/EEC. It says that wholesalers must comply with the principles and guidelines of Good Distribution Practice. Compliance of these guidelines is mandatory within the European Economic Area.

In the United States, the U.S. FDA specifically covers good distribution practices under its Good Manufacturing Practices in sections 21 CFR 211.142 and 21 CFR 211. 150

sions for grandfathering in responsible pharmacists (at both manufacturers and importers) to the QP role are in place, although a prescribed course of study and individual application and approval by the Ministry of Health will be required. This provision is scheduled for implementation on April 1, 2011.

In 2009, an Agreement on Conformity Assessment and Acceptance of Industrial Products (ACCA) was initialed between Israel and the European Union. Once finalized, the accord will result in mutual recognition of GMP inspections and pharmaceutical products will be able to move freely into Israel from the EU and vice versa with no additional laboratory testing. As mentioned earlier, Israeli legislation in the area of GMP was amended to be equivalent to that of the EU. Legislation in the area of GDP is currently under preparation and expected to be finalized by the end of 2010.

In August 2009, the Israel Ministry of Health circulated a draft of the GDP regulations to stakeholders (manufacturers, wholesalers, distributors, importers, agents and brokers) requesting comments. The draft adopts both the existing EU GDP guide and the World Health Organization (WHO) GDP guideline. The guidance is a work in progress and, as yet, it is still not clear if the final version will include both the EU and the WHO guidelines, adopted as the Israeli regulatory standards. Ultimately this may be a moot point, since the EU has already issued a concept paper for revision of their GDP guidance and has indicated they plan to adopt the WHO guidance in place of their regulations. Both guidances require that pharmaceutical distributors have a quality system in place that ensures the safety and efficacy of the distributed products through to delivery to the pharmacy or other point of use. In the light of the global counterfeiting problems, the WHO GDPs have been revised to address safeguards that should be incorporated into the quality system to minimize the opportunities for introduction of fake medicines into the legitimate supply chain.

Wholesalers in Israel have been supervised for many years by the Ministry of Health. However, while GMP oversight at drug product manufacturers is centrally managed by a GMP Inspectorate and based on detailed standards, the supervision of wholesalers is conducted by District Pharmacists (Israel is divided into six districts) with no centralized standards. The new legislation will allow better standardization in this area. In parallel to circulating the draft regulations, a pilot program was initiated for mutual inspections by GMP inspectors and district pharmacists. This pilot programmed to identify gaps between the current level of GDP compliance and the level required by the draft regulations.

The current picture regarding GDP compliance standards in Israel indicates substantial differences in practices between different stakeholders. At present, there is a considerable amount of uncertainty, since the legislation has not been finalized. In the meantime, following the increase in awareness of pharmaceutical manufacturers all over the world regarding the criticality of the supply chain and the pressing need to inspect and qualify their

wholesalers, customer-driven changes are occurring in practice among wholesalers in Israel. In the last five years or so, Israeli wholesalers distributing products imported from the United States and Europe are exposed to increasingly intensive audits by multinational manufacturers and are being required to sign quality agreements/technical contracts addressing the minutiae of product handling, shipping, storage and distribution.

The standards imposed by the foreign manufacturers are often far more stringent than those specified by the current EU or WHO guides. Consequently, those Israeli wholesalers who distribute imported medicinal products are generally already in compliance with high standards of GDP. Apart from the role of the responsible pharmacist, which is required by Israeli law, these wholesalers employ quality assurance professionals and have well-established quality systems. Warehouses and vehicles are equipped with climate control systems and online monitoring, tracking and alarm systems. Premises and equipment including computerized systems are commonly validated. Several large wholesalers are currently in the process of constructing state of the art logistic centers that will further raise standards. In the meantime and in the absence of the enforcement threat presented by formal legislation, the playing field is not yet level and there are still some operators who started their upgrading process more recently in response to the legislative initiatives in the GDP area, and have some way to go to close the gap.

In conclusion, while existing GDP legislation in Israel is somewhat unclear regarding the role of the responsible pharmacist and the exact requirements, most stakeholders either already have quite advanced quality systems in place or are working actively to implement such systems in time for the finalization of the new regulations. If the GDP legislation is finalized on schedule, at the end of 2010, it looks as if Israel will be ahead of the EU in adopting the WHO guidelines and putting in place the necessary safeguards for the country's pharmaceutical supply chain.

About the Author

Dr. Rachel Karpel is a Senior Associate at PCI Pharmaceutical Consulting Israel and has worked with wholesalers, distributors and importers in auditing, designing and upgrading GDP compliant quality systems. Prior to joining PCI as a consultant, she headed the Israeli Ministry of Health's Institute for Standardization and Control of Pharmaceutical Products in which role she was responsible for managing the GMP Inspectorate, for review of the quality section (previously CMC) of CTD submissions for local and imported products and for the official Israeli Medicinal Products Control Laboratories.

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North America

Genzyme Signs Consent Decree and Limits Production of Hormone, Receives Marking Approval for Unrelated Drug Product

On May 24, the U.S. FDA announced that Genzyme signed a consent decree to correct manufacturing quality violations at its Allston, Mass., manufacturing facility and has agreed to pay to the U.S. government a $175 mil. disgorgement penalty equaling the profits from the sale of products that were made at the plant. Under the consent decree of permanent injunction, the plant agreed to adhere to a strict timetable to bring it in line with the regulatory requirements of the Agency.

The regulatory and legal case began with a late 2009 FDA inspection that uncovered a number of serious GMP problems.

In the decree, Genzyme agreed to submit to a remediation plan based on recommendations by an independent expert. FDA has the right to refuse the plan if deemed inadequate. In addition, the consent decree provides a deadline for Genzyme to transfer its operations for filling drug vials from its Allston facility to other manufacturing sites or else it will have to give up profits from the sales of drugs filled at Allston after that specific date.

FDA is working with Genzyme during the company's remediation to ensure availability of the company's medically necessary drugs since it is the sole supplier of several enzyme replacement drugs for injection that are used to treat rare genetic disorders.

In a corporate release, Genzyme announced a day after entering the consent decree that the Agency has granted it U.S. marketing approval for Lumizyme, which is used to treat patients with late-onset Pompe.

FDA Issues Advisory On Cargo and Warehouse Thefts

On April 28, the US FDA released a letter to companies and a wide range of key stakeholders regarding the serious and growing problem of cargo and warehouse thefts of FDA-regulated products. The FDA also held a stakeholder teleconference to explain the letter in more detail.

Three Q4B Agency Guidances Available

The U.S. FDA has announced the availability of three Q4B guidances: Annex 7, Dissolution Test General Chapter; Annex 9; Tablet Friability General Chapter; and Annex 10, Polyacrylamide Gel Electrophoresis General Chapter.

The guidances are intended to recognize the interchangeably between the local regional pharmacopoeias, so redundant testing can be avoided in favor of a common testing strategy in each regulatory region.

Europe

Second Public Consultation on EU GMP Annex 2, Covering Biological Medicinal Substances and Products

Annex 2 of the GMP Guide entitled, *Manufacture of Biological Medicinal Substances and Products* has recently been published by the European Commission for a second public consultation. The original consultation closed in March of 2008 after an 6 month period which included a public meeting on the Annex, organized by PDA in Budapest, Hungary.

The Annex has been revised as a consequence of the restructuring of the GMP guide; the increased breadth of biological products now includes several new product types such as transgenic derived products and advanced therapy medicinal products (ATMPs). There will also be a public Stakeholders Meeting at the EMA offices in London on May 18, 2010, which will primarily focus on the ATMP (e.g., gene therapy, cell therapy, tissue engineering, etc) aspects of the revised Annex.

Please send comments to entr-gmp@ec.europa.eu. The deadline for comments is July 15.

Key Regulatory Dates

Comments Due:

July 15
The European Commission is requesting comments on the Manufacture of Biological Medicinal Substances and Products Annex.

August 31
The commenting period is due for the European Medicines Agency draft guideline on Real Time Release (RTR) Testing.

European Medicines Agency Draft Guideline on Real Time Release Testing Available for Comments

The European Medicines Agency's note for guidance on Parametric Release, now revised as a draft guideline on Real Time Release (RTR) Testing, has been published for public consultation.

The draft guidance is intended to outline the requirements for applications that propose RTR testing for active substances, intermediates and finished products. The guideline highlights the different requirements that have to be fulfilled in the application and the role of related inspections (pre-authorization and routine GMP inspections).

The guideline was renamed because it elaborates on the application of RTR testing to a number of areas of pharmaceutical development and manufacture, in addition to traditional sterilization processes associated with parametric release.

The deadline for comments is August 31. and completed comments should be sent to QWP@ema.europa.eu.

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Focus on Possibilities Not Problems During Difficult Times

Pat Heydlauff

Today's unstable economy requires you to have a "we're going to succeed" attitude. When there is so much chaos, change always follows and leaves room for great opportunities. So how can you limit the damage caused by all the recent turmoil and negativity? You need to not only manage the change, but also focus on the opportunities and take action to turn them into new jobs and bottom line profits.

It takes more than managing efficiently and effectively to turn chaos and change into calm, so you can focus on finding the opportunities. It also takes more than commitment to the "we're going to succeed" mantra to maintain market share and create future growth.

To manage the chaos of the current economic crisis and its potential damage to your business and employees, you need to be aware of what the chaos is doing. Are sales plummeting? Are your employees buying into the doom and gloom of the news cycle? Are you losing market share and dipping into financial reserves?

1 First and foremost, develop a plan for dealing with the chaos. By now everyone has or is developing a plan to financially deal with a long-term economic crisis but many have not yet developed a plan for dealing with the emotional crisis of watching their world around them crumble. The chaos created by moving from balance and stability to precariousness and uncertainty can be debilitating for all levels of a business enterprise.

Balance in the workplace must be re-established. This movement throughout a business can begin at any level–from a department head in the warehouse to the CEO of the organization. Begin to bring balance back into your business by re-visiting your company vision first, and then your company mission statement. Involve everyone in the company in this process from the top down, the bottom up and the inside out. Discover if these documents are still relevant during such an economic downturn.

By evaluating these documents as a whole company, instead of just by a limited few, you will help bring balance and a bit of stability back into the workplace. Make sure your mission statement is short–six words or less–so it can easily be memorized. This process will also help you expose problems that can be corrected and open doors to new possibilities. Survival during difficult economic times is the mother of new ideas, products and techniques.

2 Communicate, communicate, communicate. Employees at all levels need a cheerleader; and they need to know someone is in their corner looking out for them and encouraging them. Communication is key–from all levels of management and leadership to all levels of employees. Communication is the glue that holds a thriving company together and helps manage a company struggling through difficult times.

Depending on the size of your business, use all of the electronic equipment you have to communicate: e-mails, CDs, videos, texting, social media sites, etc. Don't just send bad news such as chopping the budget for the fifth time in two months, or more people need to be laid off. Rather, focus on the good news or encouraging messages. The old adage, "no news is good news," no longer works.

Create an employee briefing sheet and add a motivational quote or a joke at the end to lift up their spirits. The more informed your employees are, the less precarious and uncertain they feel, thus the more efficient and productive they will be. Communication also builds better employee-employer relationships, which are important for long-term survival and growth.

3 Create a business vision board and place one in every department, lunch room and water cooler area. Unless you have electronic flat screens in those locations, the best way to create a vision board is with a bulletin board and push pins. The vision board should proudly display your company vision and mission statement. It should also feature your mantra such as "We're going to succeed!" To communicate more effectively, don't just use words on vision boards–add visuals such as pictures, graphs and charts.

Encourage everyone to submit ideas for inclusion on the board. One of those ideas just might be the key to showing you where to look for the next

opportunity. By reading and seeing the company's future on your vision board, management and employees alike are encouraged and hopeful that a brighter more stable future lies ahead.

4 Begin with the end in mind with everything you do. Bringing balance and stability back into your business means staying focused on the positive, not the negative. When in doubt, ask the simple question "Will this move me (the company) closer to or further from accomplishing the mission?" A simple rule like this can be understood by everyone at every level of the business, whether your organization consists of two or two thousand.

Begin with the end in mind when you prioritize tasks, production or sales. Begin with the end in mind when you evaluate and prioritize your time. Even begin with the end in mind when on personal time whether with your family, doing recreational activities or watching the television. In fact, in order to maintain balance watch as little negative news as possible, find things to do in the evenings that are creative and help regenerate the right side of your brain so you can better cope with hectic daytime schedules.

When you control the amount of havoc chaos creates in the workplace, you are better able to manage all of the changes bombarding you daily. By encouraging and involving employees in the company vision, the balance and stability you create will lead to maintaining your market share, and you won't have to dip into financial reserves. All of this adds up to finding the better opportunities that lie ahead–which means keeping people employed and improving bottom line profits.

About the Author

Pat Heydlauff is president of Energy Design, a company that uses proven Feng Shui design principles to improve the bottom line. As a consultant and speaker, Pat helps organizations and businesses of all sizes remove stress and clutter, while increasing creativity, employee retention and productivity. Her book, *Feng Shui: So Easy a Child Can Do It* outlines the small changes that can lead to a big improvement in one's personal and professional success. For information, visit: www.Energy-by-Design.com or call: 561-799-3443.

Metro Chapter Symposium Aims to Reduce Errors

Emily Hough, PDA

When I am out of compliance at work, the consequence can be that my articles get held out of an issue, or, even worse, the *PDA Letter* is delayed, but when a pharmaceutical company is out of compliance, much greater consequences come in to play—patient safety is compromised, 483s and recalls are issued.

As I learned at the *5th Annual PDA Metro Chapter Day Symposium*, it is critical for PDA members to keep abreast of regulatory changes. That is why it was the goal of the the PDA Metro Chapter to educate members about how to stay in compliance in the new decade of U.S. FDA enforcement. The all-day symposium, held in Somerset, N.J., featured six prominent members of the pharma to discuss various compliance issues.

Joel Schwartzman, the first speaker, outlined the different scenarios in which companies receive 483s. For example, a company might receive a warning letter because of a QC failure to "extend investigations to other batches of drug product that may have been associated with the specific failure or discrepancy and failure to include conclusions and follow up in written records of the investigations." Failure to follow written procedures, particularly those applicable to the quality control unit, and failure to have adequate procedures in writing also will likely draw a warning letter. Schwartzman said that failing to follow procedures happens when people work at a plant for a while and find shortcuts to procedures.

He mentioned that companies with few or no 483s have incorporated similar strategies that facilitate compliance, such as quarterly management review meetings with a formal agenda, where complaints, CAPAs and internal audits are analyzed; detailed documented quality procedures that are sent through a review process; strong CAPA programs; and a complete training program based on the procedures.

Ellen Moskowitz spoke next on the U.S. FDA process validation guidance, which was issued because of ongoing sterility problems in industry and the finding of products on the market that were nonsterile. Many of the problems with sterility assurance begin with the marketing approval, said Moskowitz. Companies get approval from the Agency to manufacture products that still require major process changes in order to move forward. "This proves that there is still a need for improvement in this field and is the basis of this new guidance document. It really goes to the heart of this problem–how did we get to process validation batches and still have major failures?"

She said that as a consultant she has seen a lot of documentation but very little science used with process validation. But that will change. In the guidance, FDA has altered the definition of process validation so that the word "documented" will be replaced with the term "scientific." The guidance also strongly recommends statistical methods of evaluation and change control.

Moving to the scientific basis of process validation, Moskowitz said, "Our fundamental problem in the industry is that we don't test enough samples in any one batch to statistically have any confidence that the rest of the batch is good." She said that while testing more than three batches would give a more reliable prediction of future results, errors could still occur and that when sampling, sampling bias needs to be taken into account. Process validation should predict future success, as the guidance says "*Before* any batch from the process is commercially distributed for use by consumers, a manufacturer should have gained a high degree of assurance in the performance of the manufacturing process such that it will consistently produce APIs and drug products meeting those attributes relating to identity, strength, quality, purity and potency."

The symposium changed direction when U.S. FDA Consumer Safety Officer **Kelli Dobilas** gave an overview of preapproval inspections (PAI). She stressed that the preapproval inspection was very critical as it is one of the last items of the drug manufacturing process. She said the objective of the preapproval compliance program is to ensure that establishments involved in the manufacturing, testing or other manipulation of new drug dosage forms and new drug substances are audited for compliance to cGMP and commitments that are made in the application.

The role of the firm during this time is to make development reports, batch records, laboratory records and SOPs available to conduct the pre-approval inspection. It is important for the facility to list the manufacturing and all associated firms on the application, and these should be ready for inspection once an application is submitted to the Center for Drugs Evaluation and Research (CDER).

Dobilas next detailed the roles of PAI managers and FDA investigators. She said that the PAI manager, once they receive an assignment from either CDER/CVM to review a firm's GMP history, contacts the firm for clarification on operations related to the application and on NDAs, ANDAs, NADAs and INDs are inspected which are manufactured, tested or packaged at either domestic or international facilities. The FDA investigator works in conjunction with the PAI manager and conducts the preapproval inspection by evaluating the firms overall cGMP compliance; specific product and process; R&D information; and looking at the product development report. Next, they notify the PAI manager of their (approval or withhold) recommendation.

She presented the following list of common reasons for "withhold" recommendations:

- Ill defined API quality-particle size, potency failure, quality attributes
- No processing equipment qualification
- Inadequate manufacturing environment
- Ill defined processing procedures
- Laboratory data and results reporting
- Inadequate change control procedures
- Deviation from DMF/NDA/ANDA
- Contamination

Following the PAI, the facility receives a post inspection letter from the inspecting district informing them of recommendations made to CDER and receives a copy of the establishment inspection report.

Complementing Dobilas's talk, **Robert Seltzer** gave a presentation on conducting a preliminary audit to a preapproval inspection. He said that companies should focus their attention on the integrity of their submission by looking at the raw data in lab notebooks, lab data sheets or electronic raw data, with a sampling of results from several development studies.

"Whole process of raw data is a critical link and if you get that wrong, you are not going to have a viable submission and have the ability to submit to the FDA and be bullet proof for a preapproval inspection and you won't be patent protected. The data has to be rock solid and peer reviewed to have the benefit of the fact that the data represents the work of discovery."

The next step is to ensure that development and validation studies have been conducted properly (GMP appropriate) and the correct information has been written down. The last stage is that all investigation on batches furnishing submission data follow internal procedure, prove logical, answer the correct question and be data/fact-based. A week link in the chain of submission-support data, studies and investigations can unravel the best laid plans.

Xiaoming Wang started her presentation on the best microbiology laboratory practices by cautioning the audience that the U.S. Pharmacopeia is merely a guideline to follow and that it is intentionally vague and general. When it came to her question and answer session, she was asked if there was a requirement that if an isolator placed in the iso classified area. She responded with, "USP says that an isolator has to be at the same condition that you manufacture or better, you can put it in the parking lot if you like. It all depends on how you understand USP. As long as you are politically correct in telling the auditors… this is very general you can understand it in many ways."

She reminded audience members to not be intimidated by auditors. "The auditing system is just to help you to help you go through your quality system and check if your quality system is in compliance."

Ending the packed day, **Jim Agalloco** gave a presentation on USP activities impacting sterilization and sterility assurance, namely on <1211> and newly created <1229>.

He said that chapter <1211> *Sterilization & Sterility Assurance of Compendial Articles* has now been revised so that sterilization content has been separated from sterility assurance content. USP <71> is the only chapter with relevant sterility information.

PDA has recently released a technical report on moist heat sterilizer systems. Visit www.pda.org/bookstore to learn more

In addressing USP <1229>, which covers the concepts of sterilization via dry heat depyrogenation, sterilization by steam, liquid, dry heat, gas, chemical, vapor, radiation and filtration... Agalloco said, "[It is] generally accepted that sterilized articles or devices purporting to be sterile attain a 10-6 microbial survivor probability, i.e., assurance of less than 1 chance in 1 million that viable bioburden microorganisms are present n the sterilized article or dosage form."

This event was a huge success with over 80 attendees and two exhibitors. Audience members walked away with a greater understanding of how to comply with FDA and USP expectations.

After the conference, I thought about how firms provide training and instructions to personnel in order to deliver a quality product that is compliant with relevant regulations, yet mistakes still occur even though care and supervision have taken place. It reminded me of the *PDA Letter*: Checklists are followed and it is reviewed by multiple eyes but up until the magazine is printed, errors are found. It struck me that no industry is without error, but some mistakes carry greater consequences than others. Since PDA members operate in a patient-based industry, they do not have the same margin of error that others have.

PDA Who's Who

Jim Agalloco, President, Agalloco & Associates

Kelli Dobilas, CSO, DHHS, FDA, ORA, U.S. FDA

Ellen Moskowitz, GMP Consultant, Moskowitz Consulting Services

Joel Schwartzman, QA Specialist, QA, Enzon

Robert Seltzer, Regulatory Compliance Manager, Regulatory Compliance, GlaxoSmithKline and Secretary, PDA Metro Chapter

Xiaoming Wang, QC Manager, Imclone Systems

Volunteer Spotlights

Scott Bozzone, PhD, Senior Manager in Global Quality Operations-Validation, Pfizer Global Manufacturing, Pfizer

PDA Join Date: 1983

Areas of PDA Volunteerism: PDA Task Force on the FDA Process Validation Guide Co-leader (2008- 2009); Process Validation Interest Group Co-leader (2008-present); PCMO Process Validation Initiative Co-leader(2009- present); PDA TRI Lecturer (2009-present)

Interesting Fact about Yourself: My family and I lived in Ireland for over four years on a global assignment, which we enjoyed immensely.

Why did you join PDA and start to volunteer? I joined PDA originally as a scientist in a parenteral formulation and process development role. I started to volunteer in 2008 due to new initiatives in process validation, as the PDA had plans for active contributions in this area.

Of your PDA volunteer experiences, which stand out the most? Workshops in 2009 with FDA on Process Validation and the PCMO Process Validation Task Force standout.

How has volunteering through PDA benefited you professionally? My professional and technical knowledge in the field has been broadened. I also met several new fellow industry and regulatory colleagues and have seen some past friends as well.

Which PDA event/training course is your favorite? The "signature" events: The annual meeting in March and PDA/FDA meeting in September, as well as occasional local chapter meetings.

What would you say to somebody considering PDA membership? Give it a try and see if you like the information, people, events and training courses. Take the time to attend an event or two.

Recipients of the 2009 Honor Awards

www.pda.org/2009honorawards

The honor awards have been presented to esteemed PDA members since the first award was given in 1958. It is our intention to highlight each of the 2009 Honor Award Winners in each upcoming issue of the Letter until the 2011 Annual Meeting. This month, we have chosen to spotlight the individuals who were awarded the Honorary Membership and Distinguished Service Awards.

Honorary Membership

Honorary Membership: This is PDA's most prestigious award. It confers lifetime membership benefits to the recipient. The award is given in recognition of very long service, of a very significant nature, to PDA. This year's recipient is Edmund Fry.

Edmund Fry

Edmund is best known as the past President of PDA with service from 1991 to 2002. During his tenure, PDA moved from Philadelphia to Bethesda, Md., launched the PDA Training and Research Institute and experienced a period of international growth in membership and chapters. Edmund is the author of numerous papers on compliance and regulatory matters published in the *PDA Journal of Science and Technology* and elsewhere.

Distinguished Service Award

Distinguished Service Award: This award is given in recognition of special acts, contributions or service that has contributed to the success and strength of PDA. This years recipients for the award were Stephan Rönninger, PhD; Peter Rauenbuehler, PhD; Jean-Louis Saubion, PhD; and Amy Scott-Billman.

Stephan Rönninger, PhD

Within PDA, Stephan acts as co-chair and the European Regional Leader within the Regulatory Affairs and Quality Committee (RAQC). He is one of the founders and steering committee members of PDA's project on Paradigm Change in Manufacturing Operations, commonly know as PCMO.

Peter Rauenbuehler, PhD

For the last 18 years Peter has been an active member of the West Coast Chapter, serving in positions of Treasurer, President and Chapter Board member. For the past several years, he has co-chaired the PDA Chapter Council with Louis Zaczkiewicz from the New England Chapter.

Jean-Louis Saubion, PhD

Jean-Louis is the past president of the PDA French chapter which he launched 10 years ago. He is still active within the chapter organizing meetings in France and Europe.

Amy Scott-Billman

Amy is a long time member of PDA and has made numerous contributions to PDA, including chairing the PDA/FDA Conference Committee; co-leading the PDA Vaccines Conference Committee and chairing the RAQC. She has also been a member of BioAB, TRIAC and has been on PDA's Board of Directors for two terms.

EM Discussed at PDA Midwest Chapter Meeting

PDA Midwest Chapter Member-at-Large Jeff Stockman, RCM Technologies

The PDA Midwest Chapter recently hosted a dinner seminar in Northbrook, Ill. on March 25. **Dawn McIver,** President, MicroWorks, presented valuable environmental monitoring (EM) oversight, introduced the latest technologies in capturing EM information and proposed a number of tools and techniques in trending EM data. Present were over 50 industry representatives and PDA members from the surrounding Chicago area from companies including APP, Baxter, GE Healthcare and Hospira.

Dawn's presentation was very informative and interactive. She guided the audience to formulate its own working definitions of common EM terminology and built upon that platform to lead a healthy debate and discussion regarding industry best practices and future considerations. Dawn discussed the latest in real-time paperless EM solutions such as MODA-EM™ and the Novatek EM system. She facilitated a healthy debate with the audience on real-world experiences, problems and benefits of each solution. This information-sharing forum provided answers to users of each system and was a valuable benefit for those in attendance.

The discussion continued to address EM trending techniques in order to capture the correct state of control of a company's facilities. Dawn provided novel and representative ways in which quality assurance teams can pinpoint and trend EM excursions as it relates to type of microflora, facility location or by personnel data. Dawn used various charts, graphs and facility maps to help streamline root cause analysis and visualize a facility's state of control.

The presentation concluded with a snapshot of the benefits of a properly executed EM program. Regulators are looking for a controlled manufacturing environment and a state of control. Tools and techniques used in any EM program are beneficial to document evidence and provide a knowledge base of historical trending. Ultimately this collection of information allows management to determine root cause analysis to improve and maintain the state of control for its facilities.

Dawn McIver speaks to an audience member after her presentation

Attendees relax during PDA's Midwest Chapter event

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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Deval Patel, Astral Pharmaceutical Industries
Rick Persichitte, Environmental Resource Associates
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Stefan Popescu, Sensitech
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Rick Rackley, CSAFE
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Sunao Takeda, Chugai Pharmaceutical
Koji Tanaka, Hisamitsu Pharmaceutical
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Ryoichi Tsuchida, BSD Medical
Hiroshi Tsumuraya, Ajinomoto Pharmaceuticals
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If your information appears inaccurate in this list, please visit www.pda.org to update your profile or email changes to info@pda.org.

2010 PDA/FDA Joint Regulatory Conference is Coming Soon

Washington, D.C. • September 13–16 • www.pda.org/pdafda2010

Bob Dana, PDA

Washington, D.C. in September–*why should you be there?* Well, the Washington Nationals baseball team might be still in contention for the National League Championship–they're playing reasonably well early in April, as I write this article. The Washington Redskins National Football League will be opening their 2010 season with a new head coach and a new quarterback. But the best reason for being in Washington, D.C. in September will be to attend the *2010 PDA/FDA Joint Regulatory Conference* and training courses. This represents the 19th such conference, and this year will build on the successes of the previous eighteen.

Built around the theme, *The New Paradigm: Quality and Compliance in Merging and Emerging Culture*, the conference will take place September 13–15 at Washington, D.C.'s Renaissance Hotel. This year, the Program Planning Committee, consisting of representatives of the U.S. FDA, the regulated industry and PDA have put together an extremely impressive program designed to help you get the most out of this conference.

Monday morning, FDA Commissioner **Margaret Hamburg**, MD, has been invited to give the opening keynote address. As of this writing (April 2010), Dr. Hamburg's participation has not been confirmed. However, in thinking about her contribution, should she be able to take part, and we remain hopeful that she will, someone on the Program Committee said "If you don't know why you should come hear Dr. Hamburg speak, you are in the wrong industry." And that is so true. Who would want to miss the opportunity to hear directly from the Commissioner about FDA's priorities, initiatives and hot topics?

A second plenary session will follow the opening; this one featuring senior executives from our industry addressing the challenges and opportunities involved in corporations achieving an appropriate balance of their responsibilities to the patients they serve and the regulators who provide oversight in the rapidly changing world where the pharmaceutical and biopharmaceutical industry operates. The session will conclude with a return appearance by **Barbara Ryan**, Managing Director and Research Analyst, Deutsche Bank Securities Inc. Anyone who heard Ryan speak at this conference last year will want to hear her assessment of what's changed in the business outlook for our industry over the past year.

On Tuesday morning, a third plenary session will address the topic of cross-cultural dynamics and quality compliance in times of change. The pharmaceutical/biopharmaceutical industry has seen a number of major mergers and acquisitions in the past twelve months, as well as some less publicized ones. This session will examine the impact of such realignments from the perspective of both the regulated industry and the regulators. The session will conclude with an introduction about working more effectively with the cross-cultural dynamics which are increasingly evident in our global manufacturing environment.

A series of concurrent sessions is scheduled for both Monday and Tuesday as well. These sessions, organized into three tracks focusing on **Foundations, Quality Today** and **Merging and Emerging Environments** will provide ample opportunity for attendees to listen and enter into question and answer dialogues with a variety of presenters from both the industry and the regulatory authorities. Each concurrent session typically includes a speaker from the industry and one from FDA, allowing for presentations of divergent experiences and viewpoints. The Q and A following promises to be lively and informative, as always.

Some of the topics to be addressed during these concurrent sessions include CAPA, supply chain, responsibilities of the quality unit, regulatory communication, recall root causes, knowledge management, managing inspections and process validation. The difficult task will be to choose which of the myriad of concurrent sessions you want to attend. All will give participants an opportunity to hear the latest updates and thinking on these very important topics.

But wait–there's more! Start the day on Tuesday and Wednesday at one of the eight interactive breakfast sessions. These will begin each morning at 7:30 a.m., but topics such as *Ask the FDA About Regulated Products and Standards; Cooperative Manufacturing Arrangements; PCMO Risk Management in Manufacturing;* and *Change Control* will make getting up early well worth your time. These and the other breakfast sessions will feature a mix of company and FDA speakers who will be sure to engage you with their presentations and provide you the opportunity to ask them questions.

Having started the day early, conclude the day on Monday and Tuesday with attendance at one of the twelve PDA Interest Group meetings which will take place. These meetings provide, in a more intimate setting than a large lecture room, the opportunity to engage in discussions and question and answer session with your fellow attendees who have the same interests as yours. They are a great place to get your questions answered from your peers who have experienced the same challenges you are experiencing.

Some of the Interest Groups meeting include: Clinical Trial Materials, Supply Chain Management, Process Validation, Inspection Trends, Quality Risk Management and the brand new Regulatory Affairs Interest Group. If you work in or are involved with Regulatory Affairs, you'll want to join Interest Group Leader **Amy Giertych** from Baxter Healthcare for the kickoff meeting of this Group. It will be a great opportunity to get in on the ground floor.

The conference will conclude on Wednesday morning with two plenary sessions that always are immensely popular. First, hear from each of the Directors of the Compliance Offices in CBER, CDER, CDRH, CVM, as well as within ORA's Office of Enforcement. You will hear first hand from these key executives about what compliance issues they have seen, what they are and will be focusing on and what their expectations are of the industry.

Following the Compliance Office Directors, the Center Directors will take center stage if you'll excuse the pun. The Directors of CBER, CDER, CDRH, CVM and ORA will conclude the conference with presentations on their view of the state of the industry and their plans for future initiatives in each of their areas of responsibility. Both of these plenary sessions are structured to allow ample time for questions for the presenters.

More than forty FDA staff have been invited to speak at this conference. Their participation and support have always been generous and appreciated and this year is likely to be another example of this support.

And, if that isn't enough, immediately following the conference, on Thursday, PDA's Training and Research Institute will be offering six courses designed to expand and build on what you have learned at the conference. Courses being offered include:

- "Quality by Design for Biopharmaceuticals"
- "A Former FDA Investigator's Perspective on Conducting Effective Deviation Investigations"
- "Root Cause Investigations and Corrective and Preventive Actions"
- "The Quality System: Design, Implementation, Evaluation and Management of Processes"
- "Making the Grade with the FDA, Essentials of US and EU GMPs for the Manufacture of Active Pharmaceutical"
- "Ingredients Establishing and Operating an Effective GMP Auditing Program"

Extend your stay in Washington, D.C. and take advantage of the educational opportunities offered by participating in one of these courses.

And finally, there will also be a post-conference *Leachables and Extractables* Workshop on Wednesday afternoon and Thursday. This workshop will focus on the impact and quality of packaging, processing materials and delivery systems.

And, did I mention, that lest you think this is all work, attendees at the conference will be able to take part in the PDA gala reception on Tuesday evening? This relaxed get together provides the perfect opportunity to network with old friends and make new ones and provides a great social evening of fun, food and festivities.

So, as you can see, even if you aren't a baseball or football fan, Washington, D.C. is the place to be September 13–16 for the *2010 PDA/FDA Joint Regulatory Conference*. I look forward to seeing you all there.

Extractables Workshop to Follow PDA/FDA Conference

Desmond G. Hunt, MS, PhD, U.S. Pharmacopeia

The selection and control of container-closure systems for pharmaceutical products, along with those used in the manufacturing process, are important parameters in drug development and throughout a drug product's life cycle. Selecting the appropriate container-closure component and material depends upon sound extractable data in order to facilitate leachable assessments to avoid any negative impact on drug product quality and patient safety.

The *2010 PDA Extractables and Leachables Workshop*, immediately following the conclusion of the *2010 PDA/FDA Joint Regulatory Conference*, will bring together pharmaceutical scientists, suppliers, manufacturers and regulatory officials to discuss current industry issues and challenges with extractables and leachables. This year's conference theme is *Impact on the Quality of Packaging, Processing Materials and Delivery Systems*. The meeting will open with a presentation from the FDA on extractable and leachables in drug product contact material with subsequent talks addressing current industry issues and challenges.

The two-day workshop will include sessions covering current perspectives and case studies on the following topics:

- Case studies on product/container compatibility and the strategies used to minimize risk in the selection of a container-closure system
- Process/product understanding related to drug product contact materials and considerations for leachables throughout the drug product life cycle
- Industry practices regarding change and knowledge management for materials in contact with a drug product
- Safety concerns related to leachable substances and risk assessment considerations for human safety evaluation
- Case studies illustrating how extractables and leachables guidances applies to different types of devices/combination products
- Supplier section and qualification, along with dealing with component changes due to changes in raw materials or in the manufacturing process

On behalf of the Program Committee and PDA, we invite you to the *2010 PDA Extractables and Leachables Workshop*, September 15 -16, 2010 in Washington, D.C. Please do not miss the opportunity to learn about the latest developments, as well as to network with colleagues and experts.

For more information on this workshop, visit www.pda.org/eandlworkshop.

Microbes in Space Topic of Micro Meeting Keynote

Washington, D.C. • October 25-28 • www.pda.org/microbiology2010

Program Co-Chairs Ed Balkovic, PhD, Genzyme and Lynne Ensor, PhD, U.S. FDA

On behalf of the program planning committee, we would like to invite you to attend the *5th Annual Global Conference on Pharmaceutical Microbiology*, October 25–28 in Washington, D.C. This year's meeting theme is *Advances in Microbial Control and Product Quality*. This conference offers a tremendous opportunity to network with fellow microbiologists, global regulatory representatives, key product vendors and other global leaders in pharmaceutical microbiology.

Two keynote addresses will be featured at the conference. Invited speaker **Duane Pierson**, PhD, Senior Microbiologist, NASA, has been asked to present "Microbes in the Controlled Environment of Spacecraft." The discussion of controlled environments and potential for microbial contamination in spacecrafts should provide a unique perspective to be pondered for potential applications in pharmaceutical microbiology. **Thomas Arista**, Investigator, National Expert, Pharmaceutical/Biotechnology, Division of Field Investigations, U.S. Food and Drug Administration, will give a presentation entitled, "Practical Regulatory Guidance on Risk Assessment of Microbial Issues." He is expected to present a regulatory compliance perspective on applying risk-based approached to microbial controlled strategies in pharmaceutical/biopharmaceutical manufacturing and related areas.

Expert regulatory, industry and consultant speakers have been invited to discuss the following topics:

- Objectionable microorganisms
- Investigations of microbial data deviations
- Manufacturing and product attributes impacting sterility assurance
- Bioburden contamination control
- Quality of biopharmceutical products
- New technologies

Additionally, urban myths and expert panel discussion sessions are planned. Posters presentations selected from submitted abstracts and vendor exhibitors will be highlighted in the conference's exhibition hall.

New to the conference this year is a full third day featuring a partnership with the U. S. Pharmacopeia. These sessions will focus on topics related to rapid microbial methods. Various global regulators have been invited to discuss their perspectives related to this topic.

For meeting and abstract information, to submit an abstract and to register, visit www.pda.org/microbiology2010.

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Diagnostic, Therapeutic Sides Bridged at Workshop

San Diego, Calif. • November 17-18 • www.pda.org/freezedry2010

Program Chair Edward Trappler, Lyophilization Technology

The application of lyophilization to preserve health care products continues to expand, with new and innovative products being introduced at a growing pace. Novel formulations and delivery systems for administration and use present new challenges. And these challenges are to those in development, manufacturing, technical services and quality.

With a more global perspective in the application of science and technology, this meeting is also intended to bring together and engage both diagnostic, as well as therapeutic sectors of the health care product industry. Driven by specific needs for product function, preservation, processing, quality assessment, product delivery and use that may be different, there are common challenges in both sectors of the industry. For therapeutics, purity and potency are crucial for a safe and efficacious effect; for diagnostics, suitable function and sensitivity are more the critical attribute. There are some formulation components that are suitable for each type of product, with more options available to construct reagent formulations for diagnostic products. Even with such differences, the objectives for an adequately stable solution for preparation and dispensing, suitable dried product characteristics and ease of reconstitution are identical.

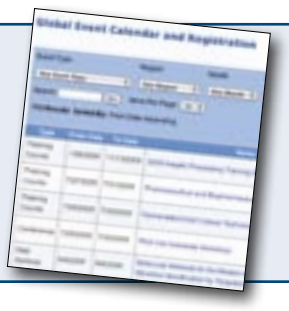
Packaging for parenteral products are classically glass vials. Though vials are used for some diagnostic products, advances in sophistication and miniaturization has driven product packaging that includes the use of specialized devices, cassettes, microtitre plates and even chips to insert directly into a diagnostic instrument. And, as formulation and packaging affect processing requirements, the basic techniques and need for a robust and reproducible process are the same. With the end use of these types of products being different and diverse, so to is the way in which we test finished product and the quality attributes that are defined as being critical.

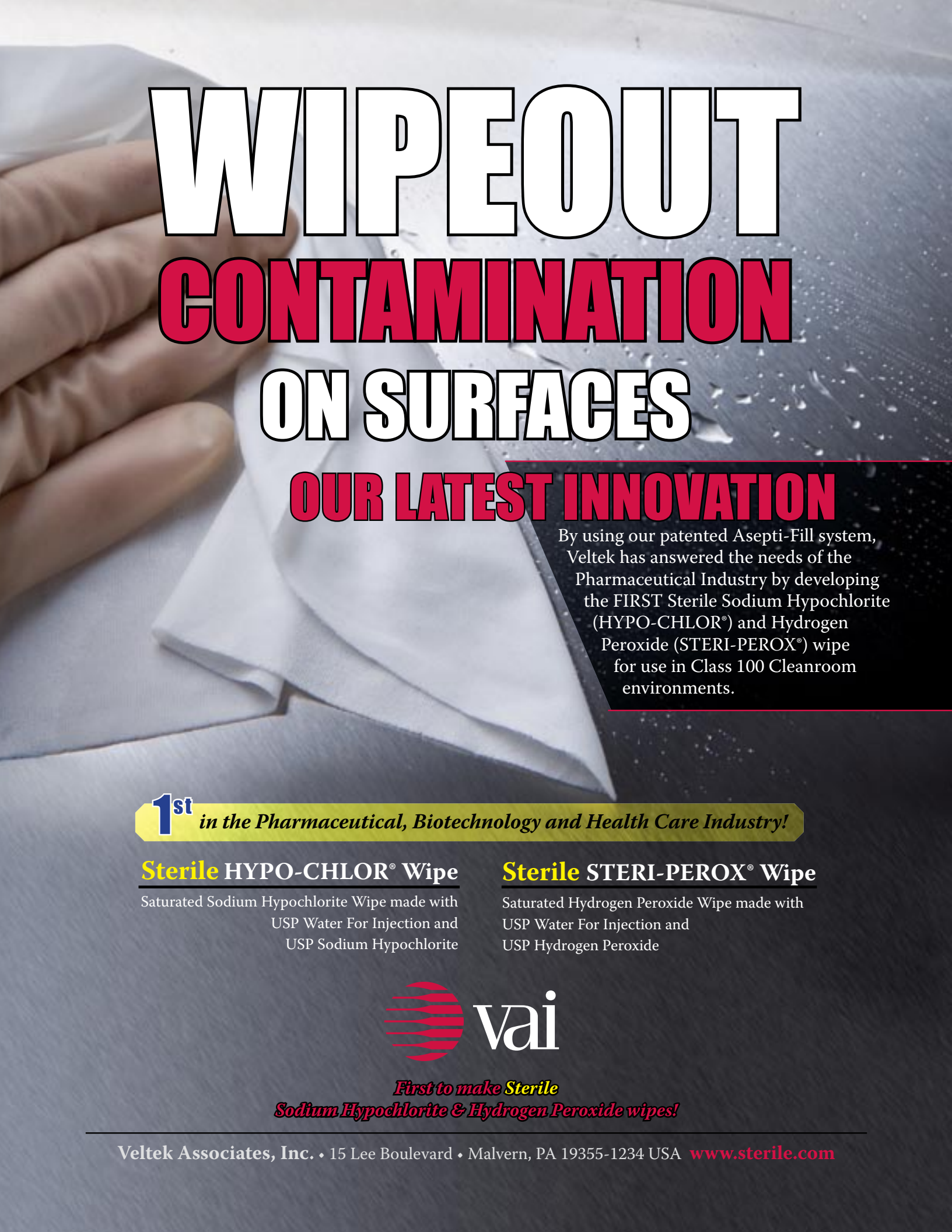
The theme of this workshop is *Current Science and Technology of Lyophilization: Diagnostics and Therapeutics*. With differences in the product types, use and function, there are many common elements in the design, manufacturing and testing of lyophilized products. This workshop offers the opportunity to join colleagues applying the same principles using different practices in developing and producing lyophilized products. Attendees can learn the aspects of formulation and product design for the different types of products, perhaps sparking innovative approaches to their own product development, manufacturing and testing challenges. Discussions will also provide insight into the considerations of different approaches to process development and establishing a robust process. Participants will benefit from shared experiences that will address the challenges of scale-up, technology transfer and large scale routine manufacturing. There will also be an opportunity to hear about ways of achieving batch uniformity and product consistency, as well as the current regulatory expectations. Round table discussions are also planned at the end of the workshop to review the highlights and share different perspectives on the topics presented.

Presentations delivered by experts in their field, a poster session covering the latest developments, exhibits by prominent industry vendors with the latest innovations and the workshop networking opportunities create an environment that stimulates discussion to provide a wealth of information.

We look forward to seeing you in November at this unique industry event that bridges the diagnostic and therapeutic sectors of the industry using lyophilization in providing critical, unique and diverse products to the health care industry.

To learn more about upcoming meetings, conferences, workshops and training events, go to www.pda.org/calendar.





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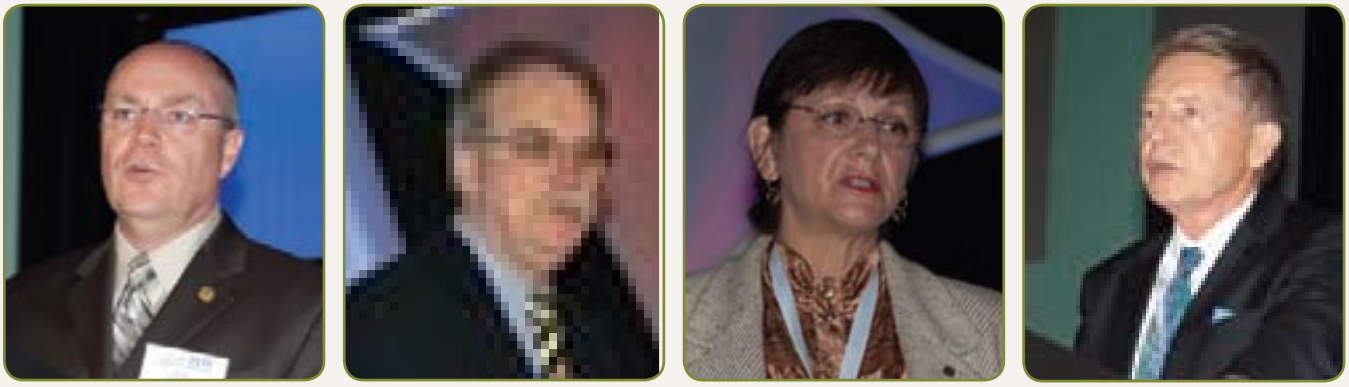
2010 PDA ANNUAL MEETING

Faces and Places: Sessions

Opening Plenary Session

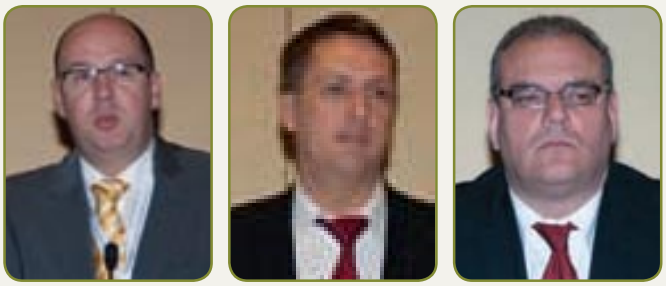


(l-r) Maik Jornitz, Sartorius Stedim; Richard Johnson, PDA; Janice Meck, NASA; Per Carlson, KTH Royal Institute of Technology

Effective Technology Transfer by Applying QbD Principles

(l-r) Barbara Berglund, Hollister–Stier Laboratories; Miguel Montalvo, Expert Validation Consulting; Edward Narke, Design Space InPharmatics; Michael Koivula, Hollister–Stier Laboratories

Manufacturing Excellence for Sterile Products and Blow-Fill-Seal Technology



(l-r) Thomas Schwarz, Novartis; Stefan Sundström, Royal Institute of Technology; Stefan Köhler, AstraZeneca

Excellence in Quality Control and Quality Management Resulting from the Application of Lean Tools and Computerized Systems

(l-r) Jon Voss, Genzyme; Geary MacQuiddy, Genzyme; Ciaran Crosbie, Pfizer

Optimizing Quality Systems

(l-r) Jeffery Hartry, Cangene; Matthew Pearson, Genentech; Kurt Brorson, FDA; Theresa Friend, Genentech

Design, Control and Operation of Manufacturing Facilities



(l-r) Niels Andersen, NNE Pharmaplan; Christian Lamont, Merck; Phil DeSantis, Merck

Implementation of Rapid Micro Methods


(l-r) Michael Miller, Microbiology Consultants; Marsha Hardiman, BSI Product Service (now with Avrio Biopharma)

Applications of Applied Science, Statistics and Risk Assessment in a Life Cycle Approach to Process Validation



(l-r) Anthony Pavell, MKCS; Michael Sadowski, Baxter; Scott Bozzone, Pfizer

Evaluating Risk and Variability in Product Manufacturing

(l-r) Karen Ginsbury, PCI Pharmaceutical Consulting; Felicia Ford-Rice, Parexel; David Wolozyn, Talecris

Disposable Technologies for Biopharmaceuticals



(l-r) Ursula Busse, Novartis; Carolyn Williamson, Bristol Myers Squibb; Maik Jornitz, Sartorius Stedim

Optimizing Upstream and Downstream Processes in Biotech Manufacturing


(l-r) Kurt Brorson, U.S. FDA; Jonathan Romero, Biogen Idec

Best Practices in Project, Program and Document Management

(l-r) Babara Berglund, Hollister–Stier Laboratories; Christopher Smalley, Pfizer; William Allen, Hollister–Stier Laboratories; Jessica Hunt, Merck; Veronica Onumah, Merck

2010 PDA Annual Meeting

Faces and Places: Sessions

Using ICH Quality Guidance and Quality by Design for Price Competitive Products

(l-r) Sandy Weinberg, Clayton State University; Felicia Ford-Rice, Parexel; Eric Minguely, Debiopharm Group

Prospectively and Retrospectively Addressing Design Space

(l-r) Karen Bossert, Lyophilization Technology; Arpan Nayak, Human Genome Sciences

PAT Case Studies and Data Testing

(l-r) Thirunellai Venkateshwaran, Pfizer; Daniel Allende, Pfizer; Gerhard Schramm, Wilco; Luc Pisarik, Merial

Recent Developments in Mycoplasma Clearance

(l-r) Barbara Potts, Biologics Consulting Group; Rich Levy, PDA; Dmitriy Volokhov, FDA

Closing Plenary Session

(l-r) David Jaworski, FDA; Martin Lafleur, Aéro Montréal

Maximizing Utilitization of Chromatography

(l-r) Peter Watler, Hyde Engineering and Consulting; Christopher Smalley, Pfizer; Ernst Braendli, Sanofi Pasteur; Raf Lemmens, GE Healthcare

Improving the Efficiency of Rapid Micro Methods

(l-r) Jeanne Moldenhauer, Excellent Pharma Consulting; Berit Reinmueller, KTH Royal Institute of Technology

Golf

The Fun Walk/Run Event

2010 PDA ANNUAL MEETING

Exhibitors

Fun and Networking

Harness the Power of Knowledge at the 2011 Annual Meeting

2011 PDA Annual Meeting • San Antonio, Texas • April 11-15, 2011 • www.pda.org/annual2011

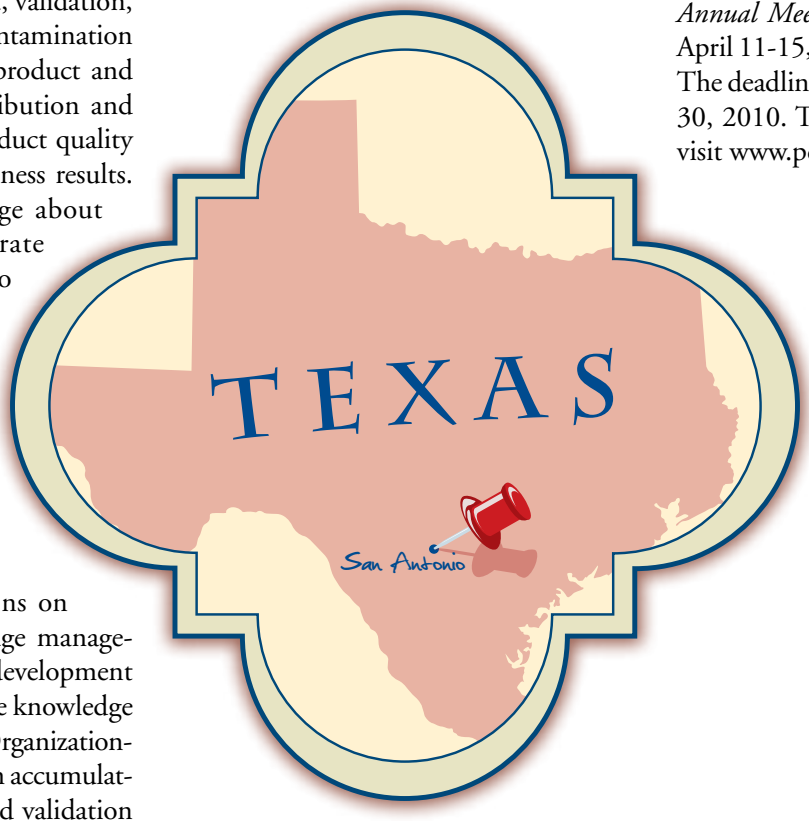
Christopher Smalley, PhD, Pfizer; Marsha Hardiman, Avrio Biopharma; and Hal Baseman, ValSource

Manufacturers and distributors of pharmaceutical, biologic and medical device products face the challenge of optimal performance and improvement in an unprecedented economic environment. PDA recognizes that this challenge reflects a global need and that is why the Program Planning Committee has chosen to emphasize *Knowledge Management* as the theme of the *2011 PDA Annual Meeting*.

The *2011 PDA Annual Meeting* will explore an area of immense importance to our industry – *Harnessing the Power of Knowledge to Drive World Class Science and Technology*. The manufacturing of quality products is a keystone of our industry. Properly planned and performed process design, development, validation, sourcing, process control, contamination control, testing, handling, product and supply chain security, distribution and manufacturing all drive product quality and essentially positive business results. Information and knowledge about these processes are corporate assets and companies need to develop strategies, tools and policies for managing these assets. Implementation of knowledge management may include use of technology-driven methods for accessing and delivering this information.

We are seeking presentations on subjects related to knowledge management. All of us, from the development scientist to the operator, have knowledge of the product and process. Organizationally, we need to do better than accumulating data in batch records and validation reports. With use of automation, as well as PAT and Rapid Micro Methods in our manufacturing processes, the information we generate is increasingly complex. Managing this information is an opportunity for achieving significant improvements in human performance, product quality and cost savings.

In today's economy, many companies in our industry are outsourcing manufacturing both domestically and internationally. There is a need to manage and share the information generated from the contractor. Ensuring that quality and compliance are upheld are a direct result of how companies manage the information from their suppliers. Properly captured, organized and made accessible, knowledge can improve yields, reduce process failures, reduce costs and processing time, conserve energy and contribute in a myriad of ways to process excellence. Have you or a colleague in the pharmaceutical, biological, medical device or related industry been involved in or solved an issue related to harnessing the power of knowledge to drive world class science and technology? If so, please consider submit an abstract for presentation at the meeting; this is the opportunity to promote understanding and learning from collective experiences.



At the *2011 PDA Annual Meeting*, PDA will also be adding a new track to the meeting to focus on basics and fundamentals of industry practices. This track will principally take place on one day (Tuesday) and is intended for those who are new to the industry or who have a new focus in their career. Presentations are being solicited for this track as well.

PDA encourages you to submit an abstract for presentation at the *2011 PDA Annual Meeting*, which will be held on April 11-15, 2011 in San Antonio, Texas. The deadline to submit an abstract is July 30, 2010. To submit an abstract, please visit www.pda.org/annual2011cfp.

PDA Parenteral Drug Association

Connecting People, Science and Regulation®

2010 PDA Europe Workshop

Lean Manufacturing

Gaining a Competitive Advantage

21-22 September 2010, Dublin/Ireland

Workshop, Exhibition

For more information see:
www.pda.org/LeanMan2010

Register by 27 Aug 2010 and SAVE!

Today Lean manufacturing is a key to competitiveness in industry. The Lean manufacturing approach has emerged from the paradigm of Japanese car manufacturing. It aims to increase value for the end customer and to reduce waste by continuous process improvements. Such processes are facilitated by approaches and tools like Lean Thinking and Six Sigma. Also for pharmaceutical and biotech companies Lean manufacturing is a competitive advantage. That is why Lean processes have to be implemented. Nevertheless in such a strongly regulated environment drug safety, quality and regulatory requirements have to be met while changing to and applying lean processes. The program of this two-day workshop will comprise a comprehensive introduction to lean approaches, tools and its application to pharmaceutical and biotech production. The value of Lean to pharmaceutical production will be explained by Experts from industry. They will present successful examples, point-out challenges and identify pitfalls in changing to Lean manufacturing. Regulatory support, requirements and inspection issues of lean processes will be outlined by experts from regulatory authorities, focusing on ICH guidelines Q8, Q9, Q10 and EU variations. The current best practice of Lean drug manufacturing will be illustrated by a biotech case study and a pharmaceutical case study from Ireland. Poster session, networking activities and pauses will provide additional time to deepen your knowledge, discuss with experts and network. Join our workshop and learn from the experts how Lean can be implemented into your production environment and how it will be a competitive advantage for your company.

Upcoming PDA Training and Research Institute Courses

Developing a Moist Heat Sterilization Program within FDA Requirements
June 2 – 4, 2010
Bethesda, Md.

Elements of Risk Management
June 3 – 4, 2010
Bethesda, Md.

PDA Training Course: Development of Biotech Products and Advanced Therapy Medicinal Products
June 14, 2010
Berlin, Germany

Fermentation/Cell Culture Technologies Training Workshop
June 23 – 25, 2010
Bethesda, Md.

Downstream Processing: Separations, Purifications and Virus Removal
July 20 – 23, 2010
Bethesda, Md.

Basic Microbiology for Aseptic Processes
July 26 – 30, 2010
Bethesda, Md.

Rapid Microbiological Methods
August 2 – 6, 2010
Bethesda, Md.

Writing Standard Operating Procedures
August 10, 2010
Bethesda, Md.

Six Sigma in Process Validation
August 11, 2010
Bethesda, Md.

2010 Aseptic Processing Training Program – Session 4
August 16 – September 24, 2010
Bethesda, Md.

Developing an Environmental Monitoring Program
August 24 – 26, 2010
Bethesda, Md.

Application of Disposables in Biopharmaceutics
August 26 – 27, 2010
Bethesda, Md.

Pharmaceutical Water System Microbiology
August 30 – September 1, 2010
Bethesda, Md.

2010 PDA/FDA Joint Regulatory Conference Course Series
September 16, 2010
Washington, D.C.

Establishing and Operating an Effective GMP Auditing Program
September 16, 2010
Washington, D.C.

Essentials of US and EU GMPs for Manufacturers of Active Pharmaceutical Ingredients
September 16, 2010
Washington, D.C.

Making the Grade with the FDA
September 16, 2010
Washington, D.C.

A Former FDA Investigator's Perspective on Conducting Effective Deviation Investigations, Root Cause Investigations, Corrective and Preventive Actions (CAPA)
September 16, 2010
Washington, D.C.

Quality by Design for Biopharmaceuticals: Concepts and Implementation
September 16, 2010
Washington, D.C.

The Quality System: Design, Implementation, Evaluation and Management of Processes
September 16, 2010
Washington, D.C.

Developing the Regulatory Rationale for the Reduction of Environmental and Utility Testing within an Environmental Monitoring Program
September 28 – 29, 2010
Bethesda, Md.

Denver Course Series
September 30 – October 1, 2010
Denver, Colo.

Computer Product Supplier Auditing Process Model: Auditor Training
September 30 – October 1, 2010
Bethesda, Md.

Risk Management for Aseptic Processing
September 30 – October 1, 2010
Denver, Colo.

Integration of Risk Management into Quality Systems
September 30 – October 1, 2010
Denver, Colo.

What Every Biotech Startup Needs to Know about CMC Compliance
October 1, 2010
Denver, Colo.

PDA Training Course: Good Cold-Chain Management
October 5 – 6, 2010
Berlin, Germany

PDA Training Course: An Introduction to Visual Inspection
October 5 – 6, 2010
Berlin, Germany

2010 PDA Biennial Training Conference Course Series
October 14 – 15, 2010
Bethesda, Md.

Designing and Presenting Effective GXP Training Programs to Meet New FDA Training Requirements
October 14, 2010
Bethesda, Md.

Introduction to Competency-Based Training
October 14 – 15, 2010
Bethesda, Md.

Developing and Using Virtual Learning Opportunities – New Course
October 14, 2010
Baltimore, Md.

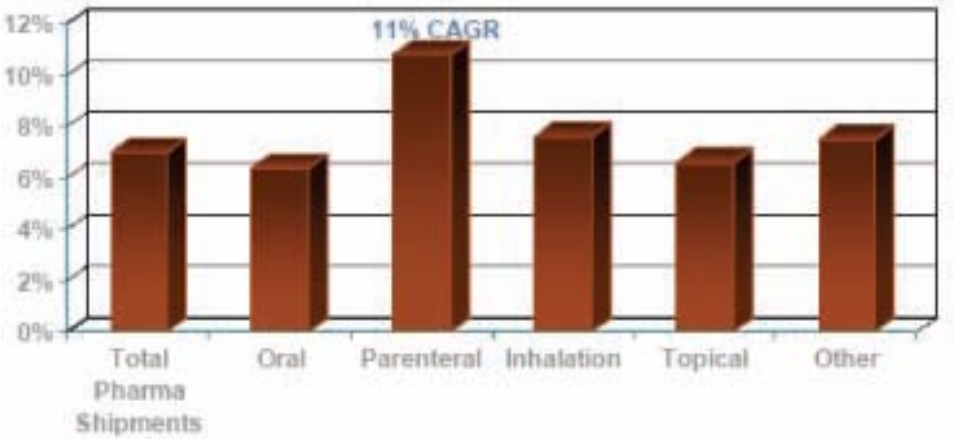
Trends and Challenges Addressed at Parenteral Conference

Berlin • October 26-28 • www.pda.org/europe

Georg Roessling, PhD; PDA, Volker Eck, PhD, PDA; and James Lyda, PDA

It is predicted that in coming years parenteral products will outpace all other dosage forms. A projection of cumulative annual growth rate (CAGR) foresees the shipment of parenterals will increase by 11% in the period of 2007 to 2013 (See **Figure 1**).

Figure 1 CAGR of Pharmaceutical Shipments by Dosage Form (2007-2013)



Presented by Michelle Fromholzer at the Informex 2009

In the period from 2002 to 2011, for example, outsourcing of cytotoxic parenterals will exhibit a CAGR of 10% and the outsourced API contract manufacturing alone will have a market value of approximately 25 Billion USD (See **Figure 2**).

However, there remain significant hurdles to overcome. Some of them are based on the regulatory situation the pharmaceutical industry is in. Deficiency data presented by **Di Morris** has conveyed that based on 359 relevant inspections from March 2008 to April 2009 there have been 33 critical observations. For example, three of the six most frequent observation topics in production are concerning microbial contamination, sterility assurance and environmental monitoring. This underpins the criticality of sterile dosage forms.

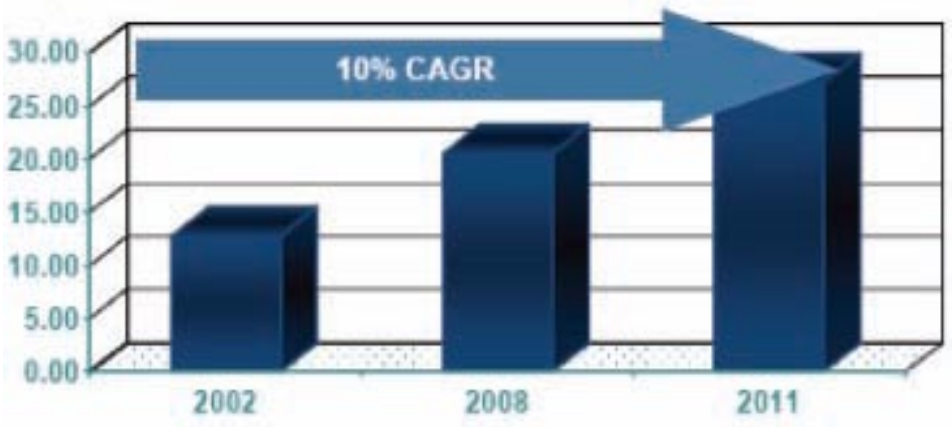
PDA's *Parenterals 2010* conference will, therefore, specifically address issues, trends and challenges to comply with regulatory requirements in sterile manufacturing. But this will not be the only aspect in focus. Correct interpretation and opportunities offered by advanced technologies to maintain and enhance compliance are within the scope of this meeting. Regulations will impact and direct the continuous development of GMPs. To prepare for this and other important manufacturing aspects the conference will cover:

- Production environments and their control
- Components and costs of quality including packaging, serialization, tolerance for defects, glass breakage, ready-to-use and ready-to-sterilize
- Manufacturing including total process control, high speed automation, in-line testing, knowledge management, continual improvement, single-use systems
- Innovative manufacturing facilities including production planning (push/pull, flexibility), dedicated, single and multipurpose facilities
- Isolators and RABS, and current industry trends
- Impact of recent regulatory guidances, especially ICH Q8, Q9 & Q10, variations, FDA guidances; PIC/S Annex 1 interpretation; dedicated facilities; Inspection trends; EU GMP Annex 1
- Cost reduction and efficient management
- Other topics relating to parenterals

Abstracts for the poster sessions can be submitted at any time until September 30 to **Ailyn Kandora** at kandora@pda.org. The subject line of your email should read "Poster Session Parenterals 2010" and follow the same content guidelines as full abstracts. Visit www.pda.org/europe for additional information.

The organizing committee comprises well known experts and is chaired by **Friedrich Haefele**. Other members are **Karin Leth**, **Hal Baseman**, **Tor Gråberg**, **Johannes Rauschnabel**, **Rainer Schmidt**, **Sébastien Ribault** and

Figure 2 Cumulative Annual Growth Rate of Global API CMO Market in Billion USD



Presented by Michelle Fromholzer at the Informex 2009

John Shabushnig.

For more information about the *Parenteral 2010* Conference, contact **Volker Eck** at eck@pda.org.

PDA's Who's Who

Hal Baseman, COO, Valsource

Tor Gråberg, Chief Inspector, Medical Products Agency, Sweden, and First Deputy Chair, PIC/S

Friedrich Haefele, Vice President, Biopharma Operations, Boehringer Ingelheim

Karin Leth, Specialist, CMC Supply, Novo Nordisle

Di Morris, GMP Inspector, MHRA, UK

Johannes Rauschnabel, PhD, Director, Process Engineering, Robert Bosch

Sébastien Ribault, PhD, Appl. Biology R&D Manager, R&D, Millipore

Rainer Schmidt, Head of Sterile Drug Manufacturing, Sterile Drug Manufacturing, F. Hoffman–La Roche

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Minimize Glass Breakage With the Pre-filled Syringe IG

Pre-filled syringe Interest Group Workshop • Berlin • December 2010

Georg Roessling, PhD, PDA

On April 15 about 50 people from the pharmaceutical industry, glass container suppliers and other suppliers met to discuss issues pertaining to glass breakage of pharmaceutical containers.

The meeting was organized by the Pre-filled Syringes Interest Group. The chair of the Interest Group, **Brigitte Reutter-Haerle** welcomed the participants. Presentations were given by **Georg Roessling**, PhD, PDA and **Andreas Rothmund**, PhD, on zero glass breakage and container quality. Additional presentations were given by representatives from the glass container manufacturers Nuova Ompi, BD Medical, Schott forma vitrum and Gerresheimer. The talks educated audience members about the efforts these companies have gone through to produce containers with a low defect rate.

The presentations were followed by an intensive discussion about types of defects in containers which can lead to glass breakage

The main message of the discussion was that the whole process from glass tube forming to glass container manufacturing fill finish operation, including labeling and packaging to the distribution and handling by the patient, can have an impact on glass breakage.

Questions about sources of defects, the measurement and control of defects, as well as what types of stress can lead to glass breakage were topics which were discussed. The current level of glass breakage is in the ppm-range. Further reduction seems realistic, but it doesn't seem possible to avoid glass breakage completely.

The meeting ended with a presentation by **Nik Seidenader** who delved into how certain glass defects can be detected and analyzed.

The following morning, a group of ten people met to discuss, in detail, which next steps should be taken to address some of the topics like:

- Glass syringe specification
- Defect evaluation quantification
- Impact of processing of glass breakage like fill finish, labeling and use of auto-injectors

There are more topics to be discussed and communication between all partners of the product supply chain including regulators is needed.

Within PDA, a number of Interest Groups and Task Forces are working on the different aspects of glass quality and the processing and handling of glass containers. They all are working towards having a better understanding of the handling of glass containers to minimize glass breakage; It was decided to have a follow–up workshop by the Pre-filled syringe Interest Group in December 2010 in Berlin.

Look for more updates on this workshop in future issues of the Letter.

At the October Visual Inspection Forum in Berlin one session will be dedicated to glass defects analysis.

PDA's Who's Who

Brigitte Reutter-Haerle, Director Corporate Marketing, Corporate marketing, Vetter Pharma International

Georg Roessling, PhD, Vice President, PDA Europe, PDA

Andreas Rothmund, PhD, Qualified Person, Quality Control, Vetter Pharma Fertigung

Nik Seidenader, Managing Director/President, Sales, Seidenader Maschinenbau