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PDA Letter

Volume XLI • Issue #10

November/December 2005

In This Issue...

U.S. FDA Advances 21st Century Regulatory Program Across the Product Life Cycle

Walter Morris, PDA

The U.S. FDA made substantial progress throughout 2005 towards its goal of implementing the 21st Century initiative. This year's PDA/FDA Joint Regulatory Conference served as the perfect forum for the Agency to discuss its achievements and gather much-needed feedback as it pushes onward.

A milestone for the Agency and its regulatory partners in Europe and Japan was the publication of two International Conference on Harmonisation (ICH) quality guidelines, Q8, *Pharmaceutical Development*, and Q9, *Quality Risk Management*. The former introduced the new regulatory concept of "design space," opening a new spectrum of possible manufacturing changes requiring little regulatory oversight. The latter outlines risk management principles that can be applied to all aspects of pharmaceutical quality from development to postmarketing manufacturing (the product life cycle).

Q8 and Q9 are to work in concert with the proposed ICH quality topic, Quality Systems (Q10 if accepted), to fulfill ICH's vision: "A harmonized pharmaceutical quality system applicable throughout the life cycle of the product, emphasizing an integrated approach to risk management and science." This vision and the concepts encapsulated in these documents formed the foundation of the PDA/FDA conference, and FDA used the forum to help industry better understand the ongoing regulatory changes designed to help companies adopt modern manufacturing and control systems.

Once again, the Agency's support for the conference was strong, with 30 presentations covering a host of important topics, including ICH, cGMPs in early development, aseptic processing, cGMP inspection trends and process analytical technology.

Q10: Uncertain Origins

Unlike Q8 and Q9, which moved through the ICH process relatively quickly, Q10 has had an uncertain history. As of press time, it had not yet become a formal ICH quality topic, though its chances of being

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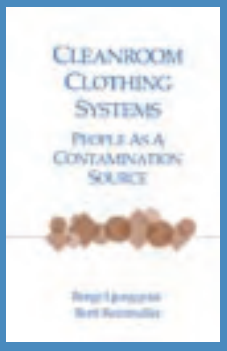

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President's Message

Bob Myers

Connecting the Industry and the Health Authorities

Last year the PDA/FDA Joint Regulatory Conference was described as "terrific," and it certainly was. The performance of this year's event required an improvement on that adjective, but I don't know which one best describes the 2005 PDA/FDA. Yes, I am proud to say this year's conference and TRI courses set a record for attendance for the second year in a row. PDA and its members already know our Joint Regulatory Conference with the U.S. FDA is one of the most important conferences around; the record attendance is proving the point! Numbers don't completely describe the quality of our program. We have been so consistent over the years that this has become an annual, "must-attend" event, and we are already receiving requests to register for the 2006 PDA/FDA conference. In all, over 1,200 people participated in the 2005 event, which also included a one-day workshop on mycoplasma (see page 11). I recommend that you turn to pages 34-41 of this issue to see photo highlights from this year's conference.

PDA, of course, could not sponsor an event as successful as the PDA/FDA Joint Regulatory Conference without strong support from the Agency. I want to thank our colleagues there for once again providing a number of great speakers and for attending sessions. We do our best at PDA to make the event mutually beneficial, and hope our FDA colleagues found the conference as rewarding as our membership did. Next year's meeting coincides with FDA's 100th anniversary, and we are planning to properly celebrate the milestone.

I also want to thank the members of the program planning committee, who volunteered countless hours forming a truly educational and beneficial program. Lastly, I want to thank PDA membership and industry for their continued support of this the event.

PDA is able to produce strong events like the PDA/FDA Joint Regulatory Conference because of our ability to provide neutral forums for the regulated and the regulators, and we strive to retain this neutral approach through our *Career-long Learning™* opportunities. Next year, we will offer a very unique service to the industry and to the regulators in Europe: the first annual PDA/EMEA Joint Regulatory Conference, which will be modeled after and, we expect, will be as successful as the PDA/FDA conference. The PDA/EMEA conference will be totally focused on European regulatory issues, and we hope it will serve as a forum for the EMEA and our membership to learn from each other.

Our membership may not be aware that our organization has provided training to various regulatory authority officials around the world. Building on the successful training PDA provided for the Italian inspectorate in 2002 and 2003 and for Taiwanese officials in 2005, PDA recently concluded a comprehensive GMP course for members of the Kazakhstan Ministry of Health and National Center for Assessment of Drugs. This effort is the largest single training project our organization has undertaken. We expect to provide training to approximately 200 members of the Kazakhstan government for development of their FDA. We are gratefully assisted by volunteer experts from our membership, the U.S. FDA and the U.S. Pharmacopeia.

To conclude, I'm proud to announce that 2006 will mark PDA's 60th anniversary. As we close this very successful year—which included the publication of four technical reports (at the time of press)—we can look forward to the celebration of another milestone year. We are planning many unique activities, including featuring comments from PDA's past leaders in the PDA Letter, launching an annual recognition program for members, offering service recognition awards and sponsoring other activities to celebrate PDA's many contributions to the pharmaceutical industry over the last 60 years.

Many of the events will take place at our Annual Meeting in Anaheim, California, in late April. I hope to see you there!

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PDA-Novatek-EMD Katrina Relief Fund to Benefit Bayouclinic, Inc.

Publicly-Supported Clinic Operating In Bayou La Batre, Alabama, To Receive $7,700 For Pharmaceuticals

In mid-October, the Katrina Relief Fund established by Novatek International and EMD Chemicals, with support from PDA and its Foundation for Pharmaceutical Education, Training and Research, was awarded to Bayouclinic, Inc., a not-for-profit clinic in Bayou La Batre, Alabama. The sparsely populated shrimping village was hit by a 25-foot storm surge which left 2,000 of the town's 2,300 residents homeless. Seafood processing plants, the lifeblood of the community, were permanently destroyed.

Bayouclinic has worked for 15 years in this poor community of hardworking, independent fishermen and factory workers. Prior to hurricane Katrina, the community suffered from a 50% unemployment rate and a 40% rate of residents without any medical insurance. Bayouclinic, along with other health care and social service providers, works to address those needs, servicing 4,200 patients from Bayou La Batre and the surrounding areas.

The clinic did not make it through the hurricane unscathed. Despite a foundation built on stilts, the clinic received five feet of water and everything inside was virtually destroyed. A local Red Cross Shelter and a U.S. Federal Emergency Management Administration (FEMA) trailer are serving as temporary homes for the clinic.

The Katrina Relief Funds will be used to provide patients at the clinic with prescription medicines.

PDA is pleased to have participated in raising money for and awarding the proceeds of the Novatek International-EMD Chemicals Katrina Relief fund. We thank all of the PDA members and staff who contributed funds.

PDA Virtual Career Fair Attracts Global Participation

Ryan McLimans, PDA

Over 700 industry professionals from all over the world logged-on and interacted live with representatives from Amgen, Bristol-Meyers Squibb, Genentech, Parnell Laboratories and Schering-Plough during PDA's first-ever Virtual Career Fair. Participants from Vice Presidents to Technicians learned about hundreds of available positions, exchanged résumés, and landed in-person interviews during the two-day online event.

Participants found the PDA Virtual Career fair to be well done and valuable:

"It was a few hours well spent!"

"This was my first experience with a virtual career fair," said Deborah Warner of Ontario, Canada. "I found the site well appointed, easy to navigate and user friendly. There was also a good selection of jobs in my field of Quality Assurance."

"I have since continued my contacts with two of the three companies I contacted and have had follow up interviews. It was a few hours well spent!" anonymous, recent participant.

"Confidentiality and convenience is what our participants found most appealing about the Virtual Career Fair," said Dorothea McGuire, PDA Sales Account Executive. "As working professionals located in many different countries, this was a great way for them to learn about new opportunities without having to travel or be restricted by time."

"I found the site well appointed, easy to navigate and user friendly. There was also a good selection of jobs in my field of Quality Assurance."

Approximately 20 percent of the Virtual Career Fair's participants were from countries outside the U.S. with one internationally-based employer, Parnell Laboratories, offering positions in Australia and New Zealand.

PDA plans to feature the Virtual Career Fair as an annual event and hopes to expand its size and interactive capabilities.

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Member Volunteer Opportunities

PDA Nanotechnology Interest Group: Call for U.S.-Based Volunteer

PDA is seeking a member volunteer from the United States to serve as a U.S. liaison to the European Branch of the PDA Nanotechnology Interest Group, which formed in 2004.

PDA needs a representative from its U.S. membership to participate in the IG's activities. If you are interested to serve as PDA's U.S. liaison and want more details about the opportunity, please contact **Iris Rice,** Coordinator, Regulatory Affairs and Science, at +1 (301) 656-5900, ext. 119 or rice@pda.org.

New *Career-Long Learning*™ Opportunity: Gain Financial Management Skills!

PDA's Board of Directors is seeking new members to serve on the Audit Committee to ensure that PDA maintains the highest level of integrity in its financial governance and provides proper oversight to ensure the security of its financial reserves. Though associations are not subject to the requirements of the Sarbanes-Oxley Act, PDA has chosen to pro-actively conform with good audit oversight practices in anticipation of future regulation affecting not-for-profit organizations.

This is an excellent opportunity to learn important financial skills such as reading and interpreting financial statements, investment portfolio management and understanding newly issued regulations affecting business management. Serving on the committee will help you build a financial foundation for business management, particularly if you are seeking to enter a management career path. If you are already on a management track, you will gain unique hands-on experience that will help accelerate your development and marketability.

For additional information or to express your interest in this volunteer opportunity, please contact **Lance K. Hoboy,** V.P., Finance & Strategic Planning at +1 (301) 656-5900, ext. 114 or hoboy@pda.org.

PDA Letter Editorial Committee (PLEC)

PDA is looking for member volunteers to serve on the new Editorial Committee for the *PDA Letter*. As PDA's primary publication on science, technology, quality, regulatory and our community, the *PDA Letter* requires member input to remain focused on and relevant to their evolving needs.

The PLEC will meet periodically each year via teleconference, and at the PDA Annual Meeting and the PDA/FDA Joint Regulatory Conference. The PLEC will work to develop a 10 issue editorial calendar of topics, comment on potential interview and feature story subjects and help PDA staff solicit articles from the membership.

If you would like to volunteer, please forward a brief summary of your professional experience and your contact information to PDA Senior Editor **Walter Morris** at +1 (301) 656-5900, ext. 148 or morris@pda.org.

Task Force: Revision of TR#15: *Industrial Perspective on Validation of Tangential Flow Filtration in Biopharmaceutical Applications*

PDA is organizing a Task Force to update TR#15. The Task Force's mission will be to describe current validation practices for TFF with a focus on Process Validation. We are seeking volunteers who are working at biopharmaceutical companies in the areas of Process Validation and Process Development as well as representatives from suppliers of TFF equipment and membranes. The Task Force will have regularly scheduled monthly teleconferences of 1-2 hours.

If you would like to volunteer for this Task Force, please contact **Iris Rice,** Coordinator, Regulatory Affairs and Science, at +1 (301) 656-5900, ext. 119 or rice@pda.org.

Task Force: Revision of TR#14: *Industry Perspective on the Validation of Column-Based Separation Processes for the Purification of Proteins*

Task Force members should have experience with production scale chromatography operations/validations. Most Task Force work will be done by e-mail and regular teleconferences. The expected duration of the Task Force is approximately one year. If you are interested in participating, please submit a short description of your job function and relevant experience to **Iris Rice,** Coordinator, Regulatory Affairs and Science, at +1 (301) 656-5900, ext. 119 or rice@pda.org.

Mycoplasma Contamination in Manufacturing Operations Originating From Plant-Derived Materials

John Geigert, Biopharmaceutical Quality Solutions

It all started with a question and answer on FDA's cGMP Web site (www.fda.gov/cder/guidance/cGMPs/default.htm) in August 2004:

"A firm has multiple media fill failures. They conducted their media fills using TSB (tryptic soy broth) prepared by filtration through a 0.2 micron sterilizing filter. Investigation did not show any obvious causes. What could be the source of contamination? The investigation was not successful in isolating or recovering the contaminating organism using conventional microbiological techniques, including the use of selective (e.g., blood agar) and nonselective (e.g., TSB and tryptic soy agar) media, and examination under a microscope. The contaminant was eventually identified to be *Acholeplasma laidlawii* by using 16S rRNA gene sequence. The firm subsequently conducted studies to confirm the presence of *Acholeplasma laidlawii* in the lot of TSB used. Therefore, it was not a contaminant from the process, but from the media source."

The result was a PDA workshop on "Mycoplasma Contamination by Plant Peptones," held in September 2005 immediately following the annual PDA/FDA Joint Regulatory Conference. Industry, regulators, vendors and academia all participated in trying to better understand this issue of mycoplasma in plant-derived materials.

Mycoplasma contamination is no stranger to the pharmaceutical industry. Reported cases of mycoplasma contaminations have affected upstream biological processes (e.g., cell culturing), especially with the use of animal-derived raw materials. Pranhitha Reddy, Senior Principle Scientist, Process Development, Amgen, presented several recent case studies that affected her company's biomanufacturing cell culture operations: (1) *Mycoplasma mycoides* subspecies Bovine Group 7, traced to a batch of Australian-sourced bovine serum, and (2) *Mycoplasma salivarium*, most likely introduced into the cell-culture vessels through human handling or error. The regulatory guidance on mycoplasma contamination for biological product manufacturing is clear:

(1) Contaminated cell substrates should not be used in production (ICH Q5D)

(2) Acceptance criteria should be established for in-process testing for mycoplasma at the end of cell culture (ICH Q6B)

What surprised the pharmaceutical industry was the FDA report of mycoplasma contamination in a downstream manufacturing operation without the presence of cells, specifically during a media fill study.

Recently, manufacturers have switched to nonanimal-derived raw materials, such as phytones or soy peptones, to avoid any possibility of inadvertent BSE introductions from animal-derived raw materials. According to **Barbara Potts,** PhD, Director, Genentech (Chairperson for the workshop), "We thought that our problems would all go away when we switched over to plant-derived materials. Much to our surprise, a different adventitious agent popped up as a major concern!"

Leonard Hayflick, PhD, Professor, University of California, San Francisco (keynote speaker and well-known authority on mycoplasmas) stated that mycoplasma can be found almost anywhere. Mycoplasmas are characterized by their small size (about 0.2 microns, compared to bacteria of about five microns or larger), their lack of a cell wall, and their difficulty to culture. Of the more than 100 mycoplasmas cultivated and identified today, all are parasites of humans, animals, plants or arthropods, inhabiting primarily the moist mucous surfaces of the respiratory and urogenital tracts and joints.

Tryptic Soy Broth (TSB), also known as Soybean-Casein Digest Medium, Trypticase Soy Broth, Tryptone Soya Broth and many other names, is suitable for the culture of both fungi and aerobic bacteria, and as such is used in process simulations to validate aseptic processing (i.e., media fills). It is with the use of TSB in an aseptic fill/finish manufacturing facility that the mycoplasma problem has surfaced.

Both FDA and industry shared their experiences with mycoplasma contamination in media-fill studies. **Patricia Hughes,** Consumer Safety Officer, Office of Compliance, Center for Drug Evaluation and Research, FDA, provided further information about the case study reported on the FDA Web site (see Table 1). ➤

Table 1. FDA Case Study of Mycoplasma Contamination in a Media Fill	
Discovery	A firm experienced media-fill failures on the aseptic fill line for a final drug product. Media fills were conducted using TSB, and cloudiness was observed in some containers. The TSB was prepared by enzymatic (animal-derived tryptic) digests of soybean proteins and was filtered through a 0.2 micron sterilizing filter.
Initial Investigation	No obvious cause could be assigned. No contaminating microorganisms were recovered or isolated using conventional microbiological techniques (e.g., plating on blood and tryptic soy agar in TSB media). No microorganisms were seen microscopically.
Further Investigation	The contaminant was eventually identified as mycoplasma (Acholeplasma laidlawii) by gene-sequence analysis. The source of the contamination was tracked back to the TSB raw material. A. laidlawii is capable of penetrating a 0.2 micron filter but is retained by an 0.1 mciron filter. A. laidlawi is known to be associated with animal-derived materials.
Corrective and Preventative Action	The firm currently filters TSB through a 0.1 micron filter. In the future, they intend to use sterile, irradiated TSB. The firm will continue monitoring for mycoplasma and has revalidated their cleaning procedures to verify its removal.

Ivar Kljavin, PhD, Senior Manager, ech, presented his company's experiences with mycoplasma contamination during media fills (see Tables 2 and 3).

Table 2. Genentech Case Study of Mycoplasma Contamination with Media Fill Media (2003)	
Discovery	In 2002, Genentech implemented the use of nonanimal TSB for media fills in order to eliminate the use of bovine-derived TSB. In 2003, during preparation of nonanimal TSB for a clinical media fill, cloudiness in some media bottles was observed following the 48-hour sterility check. Clinical TSB lots were sterile filtered (using 0.2 micron filters) into roller bottles, not autoclaved.
Initial Investigation	No other similar observations were seen prior to this event with TSB media. Cloudiness was never seen in any of the nonanimal, TSB validation samples. Validation samples were dispensed into glass containers and then autoclaved.
Further Investigation	Samples were sent to the vendor for testing: for cloudy media vs. noncloudy media from the same lot. Vendor analysis with a polymerase chain reaction (PCR) concluded that bacterial DNA was detected in the cloudy media, not in the noncloudy sample. But the vendor could not subculture, stain or identify the bacteria. PCR evaluation by the vendor ruled out mycoplasma. TSB media was prepared again and filled into sterile bottles, using, in one case, 0.2 micron filtration and in the other case autoclaving. Cloudiness was found only in the sterile-filtered media, not the autoclaved media. This time, the contaminant was identified as mycoplasma (Acholeplasma laidlawii).
Corrective and Preventative Action	Validate another source of TSB (nonAnimal, irradiated TSB).

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Table 3. Genentech Case Study of Mycoplasma Contamination in a Media Fill (2004)

Discovery	In 2004, Genentech experienced a media-fill failure on the aseptic fill line for a clinical drug product. Media fills were conducted using nonanimal-derived TSB. The media had been filtered through a 0.2 micron-sterilizing filter, not autoclaved. All media-fill vials exhibited turbidity at the seven-day inspection.
Initial Investigation	No contaminating microorganisms were recovered or isolated using conventional microbiological techniques. No microorganisms were seen microscopically. Turbid media, when subcultured into sterile TSB media, turned that media cloudy after three days. Media-fill vials were positive for mycoplasma in the FDA "Points to Consider" 28-day mycoplasma test. Preparation of another batch of filtered (0.22 micron) nonanimal-derived TSB, and filled into four sterile containers, showed three of the containers with turbidity after two days. The turbid media was positive for mycoplasma; the nonturbid media was negative. Water used to prepare the TSB media was negative for mycoplasma.
Further Investigation	Gene-sequencing analysis confirmed the contamination as mycoplasma (Acholeplasma laidlawii). A vendor audit provided no clear cause for the source of mycoplasma. TSB media was prepared again and filled into sterile bottles, using, in one case, 0.2 micron filtration and in the other case autoclaving. Cloudiness was found only in the sterile-filtered media, not the autoclaved media. This time, the contaminant was identified as mycoplasma (Acholeplasma laidlawii).
Corrective and Preventative Action	TSB vendor was changed. Used irradiated, nonanimal TSB. Cleaning procedures were evaluated and found to be sufficient.

Speakers at the workshop mentioned that they were aware of several other companies having the same problem with mycoplasma in media-fill studies.

What are the possible sources of mycoplasma in TSB and other plant-derived materials? The sources could be either animal based or plant based:

1. Animal-derived enzymes used in the hydrolysis of the plant material
2. Animal-derived contamination introduced during the growth or harvesting of the plant material (e.g., animal manure sprayed on plants)
3. Phytoplasmas (mycoplasma-like organisms) that cause diseases in plant species

The consensus of the workshop participants was that mitigation efforts should be considered for all raw materials used in manufacturing, not just the animal-derived ones. Mitigation efforts for plant-derived raw materials should include: (1) screening raw materials, (2) removal or inactivation of contaminants from raw materials derived from plants, and (3) implementation of the same cGMP practices used for animal-derived raw materials. Industry needs to partner with the raw material vendors, as these suppliers may not know of the intended use for their materials. Removal by filtration or inactivation by heat or irradiation of mycoplasma from raw materials has its challenges.

A number of filter vendors commented on the lack of a satisfactory definition of a "mycoplasma-removing filter." Jerold Martin, Senior Vice President, Scientific Affairs, Pall Life Sciences, pointed out that there is no industry or regulatory standard for an "0.1 micron" rating. Filtration of prepared solutions with an 0.1 micron filter (or with two or three filters in series) can result in a lower throughput than the standard 0.2 micron sterilizing filters, and it is theoretically possible for some mycoplasma to pass through. There is also no universally acceptable treatment of raw materials to inactivate mycoplasma contamination: gamma radiation, dry heat (45°C, 30 min.) or moist-heat ➤

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sterilization can destroy the nutritional value of the material.

Faster detection of mycoplasma contamination is also a great industry need. The current "gold standard" for mycoplasma detection is FDA's "points to consider" culture method, an assay that is well established and accepted by regulatory agencies, but an assay that requires 28 days of incubation to complete. Dr. Potts discussed Genentech's success with a PCR-based assay. The PCR assay measures mycoplasma DNA in a specific, sensitive (equal to the Points to Consider assay) and rapid approach (five hours). This PCR mycoplasma assay has been published in a format that a company can adopt and use in their own laboratory (Biologicals, 32, 2004, pages 183-193). **Audrey Chang,** PhD, Senior Director, Molecular Biology Services, BioReliance Invitrogen Bioservices, described a hybrid approach, the "HyMy" assay. It utilizes the culturing portions of FDA's point to consider assay, but uses PCR to detect mycoplasma as early as day two into the incubation.

Control of all raw materials used in a GMP operation is a key component of an overall quality-control strategy. Introduction of raw materials containing microbial contaminations (including mycoplasma) potentially compromise a manufacturing process. ICH Q9 (in draft) provides guidance in the area of assessing risk in manufacturing, and this guidance can be useful in the management of mycoplasma contamination.

The workshop participants also discussed ways that PDA could assist the biotech industry: (1) consider a task force to standardize testing of mycoplasma filters similar to that underway for virus filters, and (2) organize a mycoplasma interest subgroup to provide a platform for further discussion of these issues. PDA will publish the proceedings of the workshop shortly.

"We are safer using plant-derived cell culture raw materials rather than material derived from animal/bovine sources" has been the operating principle of the pharmaceutical industry. As emphasized by Dr. Kljavin, "Maybe we were too optimistic with this statement!" Concern should be equal but different when considering nonanimal vs. animal-derived raw materials.

U.S. FDA Advances 21st Century Regulatory Program Across the Product Lifecycle, continued from cover

accepted by the ICH Steering Committee had grown measurably. Immediately prior to the PDA/FDA conference, the Q10 expert working group had submitted a concept paper to the ICH Steering Committee outlining the scope of the project.

To help industry better understand the goals of the Q10 working group, three of its members presented updates during the third plenary session of the PDA/FDA conference: **Gerry Migliaccio,** VP of Global Quality, Pfizer; **Neil Wilkinson,** Director of Global Compliance, AstraZeneca; and **Christopher Joneckis,** PhD, Senior Advisor, CMC, Center for Biologics Evaluation and Research, FDA.

These three speakers provided the audience with a concise summary of Q10's uncertain history, the document's proposed scope and the intended benefits of the document. They agreed with the view that Q10 is the key ingredient of the recipe for regulatory relief and true life cycle process improvement. In a sense, it is "the holy grail" of the work begun by FDA's 21st century quality initiative over three years ago. Without Q10, the speakers stressed, the benefits promised by ICH Q8 and Q9 cannot be realized.

During his presentation, Astra's Wilkinson outlined Q10's "potted" history.

In spite of the importance placed on this guidance by industry experts, the ICH Steering Committee has yet to officially sanction the project due to divergent views of the project, particularly between the European Union and the United States.

During his presentation, AstraZeneca's Wilkinson outlined Q10's "potted" history. Preliminary discussions of the topic began in 2003, following the landmark Product Quality Research Institute conference in May of that year. A few months later, an ICH group developed the aforementioned "vision" for pharmaceutical manufacturing and regulation and identified three new quality topics; eight, nine and ten were born. Later that year, however, the ICH Steering Committee approved only the former two projects. Q10 was rejected.

The stalement over Q10 grew out of the belief held by European regulators that their regulatory system and GMPs did not represent barriers to continuous ➤

improvement. On the other hand, FDA had articulated the opposite conclusion regarding the U.S. regulatory system when it launched its 21st Century GMP initiative in 2002.

Despite this setback, the Q10 working group kept developing the quality systems concept. Internally, the European industry representatives on the expert working group were siding with the U.S. contingent (both regulators and industry).

Meeting at the end of 2003, the expert working group was presented an industry paper that outlined the concepts of quality by design in development and manufacturing, management responsibilities, risk- and science-based concepts and continuous improvement concepts. While the paper was received favorably by the Q10 proponents, the EU regulatory representatives were still doubtful, concerned primarily about the timing and scope of Q10.

Taking a new tact, the Q10 advocates agreed to an "incremental approach," explained Wilkinson. The idea of harmonizating the GMPs globally was taken off the table. Wilkinson stated the expert working group's rationale: "GMPs are written into legislation, so the view was at the time that this was too big a chunk to chew and we could not achieve that through the ICH process, at least not in this time scale."

Furthermore, the expert group adopted several new caveats, hoping to mollify the EU's concerns. These caveats required Q10 to:

- Have a defined business benefit
- Improve pharmaceutical manufacturing for all
- Eliminate "some" regulatory barriers
- Be accepted as worthwhile by the regulators

Wilkinson also noted that, the European Federation of Pharmaceutical Industries and Associations (EFPIA), which represents the EU industry on ICH, issued a statement around the same time calling Q10 an "essential enabler" for Q8 and Q9.

"Who is the Janet Woodcock in Europe?"

Nevertheless, the EU regulators remained unconvinced, Wilkinson said. Now, the EU was concerned with enlargement, its own new pharmaceutical directives/guidelines and the Q8 and Q9 projects.

While proponents continued to refine the scope of Q10 throughout 2004, the ICH Steering Committee failed to reach a consensus on the topic that year. The three industry groups and FDA were supportive of the proposal, and the Japanese authority was neutral, but the EU continued to hesitate. During the year, the EU stated its reluctance to initiate any further revisions to its postapproval changes regulations, which the EU continued to deem amenable to continuous improvement. The topic was not taken up at the ICH Yokohama meeting in November 2004. Another fruitless year closed.

By the end of the first quarter of 2005, both the Q8 and Q9 documents had reached ICH Step 2 for public comment. Q10 had not progressed at all.

Behind the scenes, however, EMEA's uncertainty over the Q10 concept was waning. In the beginning of 2005, EMEA invited EFPIA to discuss Q10 further. According to Wilkinson, the regulatory authority asked for a clear rationale for the document, a scope and possible benefits. Most importantly, the European Agency asked for examples illustrating the extent to which continuous improvement is impeded under the current regulatory system.

EFPIA went right to work, explained Wilkinson, and "pulled together numerous examples of where we believe we could and should be innovating our products, making improvements, and finding it impossible to do so, particularly on a global basis." The exercise provided "a greater understanding that there is a real issue" for EMEA.

A big problem throughout the process, Wilkinson observed, has been the lack of an advocate for Q10 within EMEA, equivalent to FDA's Center for Drug Evaluation and Research (CDER) Director **Janet Woodcock,** MD. "Who is the Janet Woodcock in Europe? We believe Janet's leadership in this has been tremendous, supported by a number of key people within the Agency. [In Europe] we don't have any equivalent, so maybe that was one of the root causes of the problem in terms of where do we go for leadership in this initiative."

Now, Wilkinson declared, "the EU regulators are on the same page as we [and they are even] willing to look at the variation [postapproval changes] regulations again. But this must be decoupled from Q10."

FDA's Quality System Guidance

In discussing FDA's opinion of the Q10 project so far, CBER's Joneckis likened the numerous preparatory meetings and the lack of progress to the American movie *Groundhog Day*, in which the main character relives the same day of his life over and over and over again. ➤

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With ICH negotiations stalled, the FDA developed its own quality systems guidance, a draft of which was published for public comment in September 2004. Titled, *Quality System Approach to Pharmaceutical cGMP Regulations* (QS guidance), the document's foundations included a "cross-comparison of various types of regulations across the world" and a review of "modern quality system standards," Dr. Joneckis explained.

Like the ICH Q10 group, FDA did not think it was feasible to attempt a rewrite of the GMPs. As such, noted Dr. Joneckis, the QS guidance serves a "bridge" between the 1978 regulations and 21st century quality systems. "For the most part, [the QS guidance and cGMPs] correlate very well. There are a few areas where the regulations are perhaps slightly deficient. Two of those would be management support and proactive quality control, as opposed to taking a more corrective approach."

Dr. Joneckis stressed that FDA wants "a meaningful guidance" and is not simply "reciting" existing International Organization for Standardization (ISO) guidelines. "That's not good for us. We really want to have something that is consistent and supportive of FDA goals and implementation of the cGMP initiative."

Moving forward, Dr. Joneckis predicted changes to the cGMPs to ensure constancy with the QS guidance. "These changes, when they are announced, will be very aggressive [but] not a revision of cGMPs."

FDA remains a proponent of the ICH Q10 initiative, yet is moving forward with its own guidance in the interim. Dr. Joneckis stated that FDA is "going to continue with the FDA guidance. We are revising it." In the future, FDA will consider modifying or replacing its QS ➤

Seen and Heard at the 2005 PDA/FDA Joint Regulatory Conference

PQRI Team Bio Working Group
PDA Biotech Interest Group

During the Biotech Interest Group meeting at the PDA/FDA conference, **Steven Mendivil** (Amgen) reported on a new PQRI Working Group to assess the Team Biologics Program. This newly formed team is developing and finalizing a survey to be issued to sites that have been inspected by Team Biologic over the past three years. The survey is part of FDA's effort to get feedback on the Team Biologic program that established a special cadre of investigators to conduct GMP inspections of plasma fractionation, biotech, vaccine, in vitro diagnostics and allergenic extract manufacturing sites beginning in 1996.

The PQRI Working Group members are **Victor Gangi** (Biogen Idec) Chairman, **Keith Webber, Mark Weinstein, Anne Johnson, Jacqueline Little, Calvin Koerner** and **Gilber Salud**—all from FDA. Industry team members are **Steven Buchholz** (Pfizer), **David Ostrow** (Hospira), **Josette Queminet** (GSK), **Carolyn Trott** (Genzyme) and **Steven Mendivil** (Amgen).

The challenge for the team is to develop a survey that provides meaningful feedback yet keeps the information anonymous. To mask firm-specific information, a third party is being utilized for data collection. Results of the survey will be shared with FDA and industry. The team's draft time line is to have the survey distributed later this year, with the results to be published in early spring of 2006. The intent of the survey is to identify strengths and weaknesses of the program and to assess the effectiveness and relative value with regard to industry compliance. The affected industry is strongly encouraged to participate in this survey, because the results could lead to a revision of inspectional procedures and/or program enhancements. A complete and accurate survey of the industry will enable FDA to assess resource effectiveness and program focus. It also allows industry to benchmark their inspectional experience against their peers and leads toward a better understanding of FDA expectations for the biologics industry.

Case Study: Applying PAT Principles to Manufacturing Legacy Products for the Biotech Industry
David Rubin, *Program Manager, Bioprocess Division, Millipore Corporation*

Faced with more stringent customer requirements, Millipore Corporation elected to upgrade the processes for manufacturing tangential flow filtration membranes and cassettes. The new processes apply many of the principles of process analytical technology by taking a risk-based approach to process and product development. Whereas quality is tested into current products, the next generation of products has quality built in by design through the use of:

- multivariate tools for design and analysis
- process analyzers
- process control tools

Critical process parameters are identified, monitored and controlled thus allowing operators to predict process outputs based on process set points.

continued on page 20

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guidance with Q10. "We are more than willing and looking forward to working on Q10. It will benefit industry and benefit us."

FDA remains a proponent of the ICH Q10 initiative, yet is moving forward with its own guidance in the interim. Dr. Joneckis stated that FDA is "going to continue with the FDA guidance. We are revising it." In the future, FDA will consider modifying or replacing its QS guidance with Q10. "We are more than willing and looking forward to working on Q10. It will benefit industry and benefit us."

The Case for Q10

One of the important accomplishments of the 2005 PDA/FDA meeting was the opportunity it afforded industry to hear from members of the Q10 group just days after it had submitted a concept paper to the ICH steering committee. Pfizer's Migliaccio, the Q10 Rapporteur, concluded the session by repeating the case made in that document for the harmonized guidance.

"Why do we need it?" he began, "we are a global industry. We are no longer regional industries. We make for multiple regions of the world at the same manufacturing facility, and yet we have to live with divergent approaches to quality systems....We have to deal with different expectations for making changes, quality improvements, efficiency improvements. We have to deal with different expectations—and we all know you might get an approval from one country in one or two months for a change, but you may be waiting for another one for two years. And so when do you implement that change? What that is impacting is our ability to make continuous improvement changes, it is potentially delaying new product launches, and it frequently may impact the availability of a product to a patient."

Migliaccio outlined a number of problems caused by divergent approaches to quality systems across regions:

- Suboptimal deployment of resources by both industry and regulators
- Potential impact on the availability of medicines
- Potential delays in the implementation of innovation and continuous improvement
- Potential delays in new product launches
- Inconsistent approaches to compliance inspections

Echoing Dr. Joneckis, Migliaccio emphasized that the group is "not advocating an ISO-style of certification, but we are going to take advantage of the ISO quality system guidance and we are going to take advantage, obviously, of the FDA quality system guidance draft. Those are both good places to start without reinventing the wheel." The document will likely have an ISO structure.

In explaining why industry and regulators "need" Q10, Migliaccio concluded, "Each of our facilities has to shift gears due to different approaches to compliance inspections. So, our hope is that by having a harmonized position on quality systems around the world, many of these issues will go way."

"We make for multiple regions of the world at the same manufacturing facility, and yet we have to live with divergent approaches to quality systems."

In addition, he said, "everyone believes that the Q10 guideline, if done properly, will help us realize the full benefits of ICH Q8 and Q9."

Eliminating unintended consequences is one of the key benefits. "What we should be able to realize is, if you have a robust quality system, you can demonstrate to any regulatory authority that when you make a change, you know what the impact of that change will be and you know that there will be no unintended impact of that change. The words

Applying PAT to Complex Biological Products
Pete Vandeberg, *PhD, Talecris Biotherapeutics Inc.*

Products derived from human plasma fractionation are generally classified as complex biological products. Developed over 50 years ago, Cohn Fractionation separates proteins from pooled human plasma into crude fractions using alcohol, pH, ionic strength and temperature to alter the solubility of various components. Plasma fractionators in the United States use essentially the same Cohn process for their early-stage manufacturing steps, with individual fractionators using modern purification methods downstream. Although the starting material and intermediates are quite complex, PAT methods such as temperature, conductivity, pH, A280, TOC and turbidity can be used to measure and control process parameters. Application of process measurements, along with extended characterization, statistical process control and multivariate data analysis can lead to a better understanding of processes and can be used to link critical process parameters to final product characteristics. Several examples were presented, demonstrating the use of PAT in plasma fractionation.

'self-management of change' start to creep in. We call it regulatory flexibility, we call it a number of other things, but in the end, it is the ability to self-manage change within a different regulatory framework—different from what we have now. So, we need to ensure that we can predict the impact of any change we make, and if we can do that, then we move into this new paradigm."

Migliaccio shared that the "most rewarding parts" of the Q10 activities have been "getting six parties—the three regulatory parties, the three industry parties—to actually agree on what the benefits of this would be."

Migliaccio anticipates that the work plan for Q10 would be established at the ICH meeting in Chicago, November 7, and a Step 2 draft would be available sometime in the second quarter of 2007.

Lockheed Martin's 6 Sigma Approach

The effectiveness of the concepts highlighted during the Q10 session were demonstrated during the closing plenary session of the 2005 PDA/FDA conference. Nearly all of the conference's participants stayed for the opportunity to hear a thought-provoking talk by Lockheed Martin Missiles and Fire Control Senior Process Improvement Specialist Arthur Trepanier on the company's "Lean Six Sigma" program. A "Lean Six Sigma Blackbelt," Trepanier outlined eight "lean" processes employed by the missiles and fire control division that operate at Six Sigma (see box). His instructive talk went into great detail and described how the system empowers individuals within the company to drive continuous improvement.

As a result of the program, Lockheed has seen five consecutive years of "sustained productivity improvements." Trepanier noted that the company is one of only seven in the Fortune 100 to achieve the Six Sigma capabilities.

In instructing the PDA/FDA participants that "Six Sigma works" and advising them to "just do it," Trepanier outlined a number of "lessons learned" at Lockheed. To be successful, companies need a strong commitment from senior executives. A structured Approach to implementing a Six Sigma program is required. Companies must ensure that a sufficient nucleus of expertise is available. Finally, the last two lessons speak to how successful a company ultimately can be with such a system: "Keep raising the bar" and "Challenge everything."

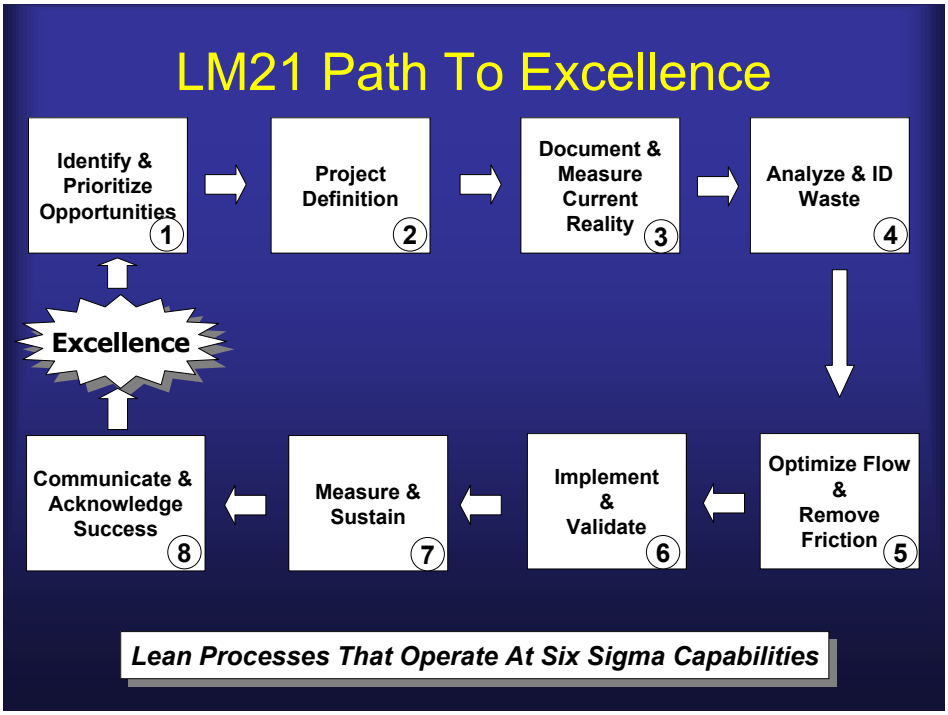
Overall, the 2005 PDA/FDA was once again the perfect forum for FDA to update and engage with industry. FDA speakers provided 30 individual presentations on a wide-variety of topics.

Following the main conference, PDA sponsored a workshop called, "Mycoplasma Contamination by Plant Peptones" *(see pages 11-16).* ➤

Q10 Potential Benefits

- Harmonize the concept of quality systems for the pharmaceutical industry between the three regions.
- Enable the potential benefits from ICH Q8, ICH Q6A and ICH Q9 to be fully realized.
- Encourage industry to improve manufacturing processes, thus reducing undesired variability and leading to a more consistent product quality, improved process robustness and more efficient processes.
- Demonstrate industry and regulatory commitment to robust quality systems and technical innovation and enhance assurance of consistent availability of medicines around the world.
- Facilitate innovation and continual improvement as defined in this guideline throughout the whole product life cycle.
- Provide the link between development and manufacturing to ensure systems are in place to ensure and to give confidence that the correct decisions are made by industry to manage changes, both within and outside the design space.
- Facilitate management commitment to quality.
- Encourage a science- and risk-based approach to quality decisions.
- Encourage a preventative action culture, which ensures actions are taken before a problem/issue arises.
- Improve quality monitoring and review (e.g., data evaluation, statistical process control and process capability measurements), which form the basis for continual improvement of processes.
- Provide greater assurance that there is no unintended consequence as a result of continual improvement activities.

NOTE: From Gerry Migliaccio's presentation "ICH Quality Systems (AKA Q10), 2005 PDA/FDA Joint Regulatory Conference



Lockheed Martin's Lean Six Sigma Process, presented by Arthur Trepanier at the 2005 PDA/FDA Conference

FDA's Quality Assessment System

FDA-industry dialogue on the concepts under development in the ICH Q8, Q9 and Q10 documents continued a few weeks following the PDA/FDA conference at an AAPS workshop on Pharmaceutical Quality Assessment – A Science and Risk-Based CMC Approach in the 21st Century, cosponsored with FDA and ISPE.

Conference participants gathered to help define several key concepts important to the Agency's pilot program on the Quality Assessment System (QAS). When fully developed, QAS will shift the review of chemistry, manufacturing and controls submissions to critical pharmaceutical quality attributes and critical process parameters. Announced earlier this year *(see the September* PDA Letter, *page 25)*, FDA is hoping to receive 12 new drug applications as part of the pilot program. Companies willing to participate have until March 2006 to indicate their interest, and the submission must be ready by March 2007.

The format of the Pharmaceutical Quality Assessment workshop facilitated dialogue among the industry and FDA representatives on a number of concepts critical to the QAS. The topics discussed were: pharmaceutical development, CMC regulatory process, CMC "regulatory agreement," communication, design space, quality overall summary, innovation and continuous improvement, post-marketing changes, integration of review and inspection, and pharmaceutical assessment practices.

The design space sessions were particularly relevant to PDA, which expressed concern about the lack of detail on design space in the Step 2 ICH Q8 guideline (see the June PDA Letter, page 17). The goals of the discussions were to flesh out: how to develop design space and present it in the pharmaceutical development (P2) section of the common technical document; how to update design space; what factors should be included in design space; and how regulators will differentiate between various degrees of knowledge about design space in applications and companies.

A number of "shared understanding and agreements" were identified during the sessions, as well a number of "remaining challenges," outlined in box 1 (page 26).

Conference participants also threshed out details on a potential new filing, the CMC "regulatory agreement." A definition of this agreement and summary points from the discussions are outlined in box 2 (page 27).

Following the conference, PDA had the opportunity to discuss the Pharmaceutical Quality Assessment workshop with two active PDA members; a transcript of portions of that discussion is included below.

Both the 2005 PDA/FDA Joint Regulatory Conference and the Pharmaceutical Quality Assessment workshop served as excellent forums for the Agency to outline the progress it has made in implementing its new quality initiatives and set the stage for even greater progress in 2006. The 2006 PDA/FDA Joint Regulatory Conference next September promises once again to be a key forum for industry and FDA to meet and share ideas.

Perspectives on the QAS Workshop

PDA's Richard Levy, Sr. VP Scientific and Regulatory Affairs, and Walter Morris, Senior Editor, spoke with PDA Board member Tim Marten, DPhil (AstraZeneca) and PDA/FDA conference program planning committee member Susan

continued on page 26

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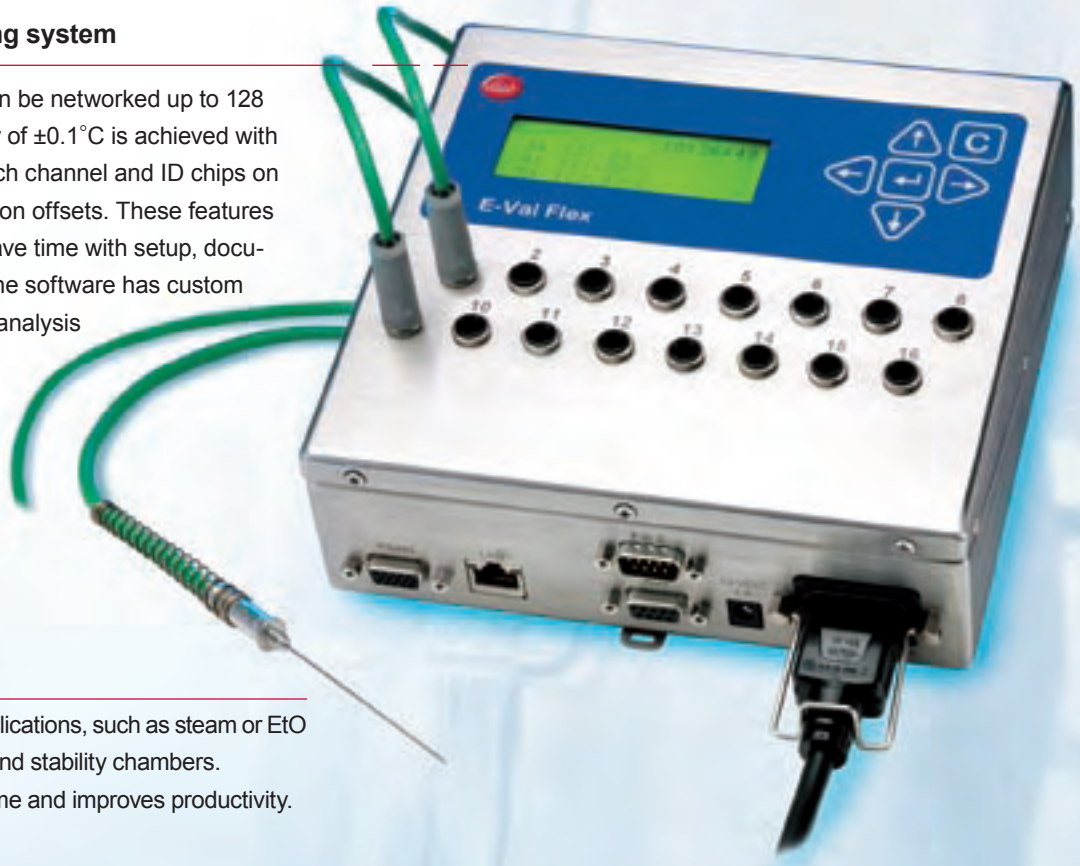

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Conferences

April 24-26, 2006
2006 PDA Annual Meeting
Anaheim, California

May 8-10, 2006
2006 Biennal Training Conference
Philadelphia, Pennsylvania

September 11-13, 2006
PDA/FDA Joint Regulatory Conference
Washington, D.C.

March 2-3, 2006
Pharmaceutical Counterfeiting:Applications of Security Technologies
Bethesda, Maryland

Training

Lab and Lecture calendar events are held at PDA-TRI Baltimore, MD unless otherwise indicated.

Laboratory Courses

November 7-9, 2005
Cleaning Validation

December 1-2, 2005
Environmental Mycology Identification Workshop

December 8-9, 2005
Developing and Validating Cleaning and Disinfection Programs for Controlled Environments

January 30-February 3, 2006
Aseptic Processing Training Program (session 1, week 1)

February 16-17, 2006
Environmental Mycology Identification Workshop

February 27-March 03, 2006
Aseptic Processing Training Program (session 1, week 2)

March 8-10, 2006
Cleaning Validation

March 15-16, 2006
Validating a Steam Sterilizer

Lecture Courses

May 15-17, 2006
Biotechnology: Overview of Principles, Tools, Processes and Products

September 20-21, 2006
Computer Products Supplier Auditing Model:Auditor Training
Research Triangle Park, North Carolina

Course Series

November 29-December 1, 2005
Bio/Pharmaceutical Training Course Series
San Antonio, Texas (relocated from New Orleans)

February 6-8, 2006
Lake Tahoe Course Series
Incline Village, Nevada

March 13-15, 2006
Research Triangle Park Course Series
Research Triangle Park, North Carolina

April 27-28, 2006
PDA Annual Meeting Course Series
Anaheim, California

May 11-12, 2006
PDA Biennial Training Conference Course Series
Philadelphia, Pennsylvania

Chapters

November 15, 2005
PDA Southeast Chapter
USP Course - Basic Statistics and their Practical Applications to the USP-NF
Raleigh, North Carolina

November 17, 2005
PDA Midwest Chapter
Dinner Meeting
Northbrook, Illinois

November 17, 2005
PDA Mountain States Chapter
Speaker Dinner Vendor Night

November 17, 2005
PDA New England Chapter
Dinner Meeting

November 17, 2005
PDA West Coast Chapter
Dinner Meeting

November 17, 2005
PDA Delaware Valley Chapter
Vendor Show
Malvern, Pennsylvania

December1, 2005
PDA Metro Chapter
Dinner Meeting
Cleaning Validation
Clark, New Jersey

Europe/Asia Pacific/Middle East

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EUROPE

November 10, 2005
PDA and PDA Europe
PDA Nanotechnology Conference 2005
London, England

November 24, 2005
PDA and the PDA Central Europe Chapter
PDA EuroForum
Pharmaceutical Product Labeling
Vienna, Austria

December 1, 2005
Viral Safety: Evaluation of Biotech Products used in Clinical Trials
Langen, Germany

December 7, 2005
PDA and the PDA France Chapter
Biosimilars/Extractables & Leachables
Paris, France

March 21-23, 2006
Practical Aspects of Aseptic Processing
Basel, Switzerland

October 10-13, 2006
PDA/EMEA Joint Regulatory Conference
London, England

ASIA/PACIFIC

November 8-9 2005
PDA Japan Chapter
Annual Meeting
Tokyo, Japan

November 13-15, 2006
2006 PDA Asia-Pacific Congress
Tokyo, Japan

November 24, 2005
PDA Australia Chapter
Annual Meeting and Holiday Dinner

MIDDLE EAST

December 27, 2005
PDA Israel Chapter
Annual Meeting

May 17-18, 2006
PDA and the PDA Israel Chapter
Quality Tools for the 21st Century
Eilat, Red Sea, Israel

U.S. FDA Advances 21st Century Regulatory Program Across the Product Lifecycle, continued from page 22

Schniepp (Hospira) about their impressions of some of the key issues discussed at the October AAPS Pharmaceutical Quality Assessment workshop. Below are selected portions of that dialogue.

Walt Morris: PDA expressed concern with the concept of design space in its written comments on ICH Q8. The main concern was that the concept was vague. I feel the sessions at the AAPS meeting were trying to get to more specificity on the topic. Do you think those at the workshop leave with a better idea what this concept is?

Tim Marten: I think we got a better idea. I don't think it is universally well-understood yet. It is not simple and it will vary from process and product. Each process and product will have its own boundaries for what you might define as design space. But I think it really comes down to knowing your process well and understanding where the critical process parameters and critical quality attributes fit into defining your product and process better. That is the key to it. It can become very mathematical and statistical or it can be relatively simple. And it will vary on the parameter and the product. To be fair, I think it wasn't really intended that this should be a conference to delve deeply into what design space is.

Sue Schniepp: I would agree with that. I think one session that they had, it was the case studies. That really helped to tantalize people to go forward on trying to define what design space is. I agree with Tim, I don't think [the meeting] actually solved it, but it started people thinking in the correct direction.

Rich Levy: Do you think after hearing what was discussed at the meeting companies are really doing anything differently? Regarding the quality assessment system pilot program, I think everyone wants to know, are these submissions really different? Same with design space, are companies really doing anything differently?

Tim: I think so. I think people are trying to really look at and test, not necessarily the extremes—I mean I think they use to be called proven and acceptable ranges—they were ad hoc, not necessarily supported with a huge amount of data. I think the new paradigm means

"Design Space" Sessions Summary from the Pharmaceutical Quality Assessment Workshop

Shared Understanding and Agreements

- New paradigm obviates need for traditional process validation
- For small molecules, drug substance specifications, including relevant physico-chemical parameters, could define the design space (less likely for biotech products)
- For drug products, specifications, accompanied by sufficient knowledge and process understanding, could define the design space
- The criticality of raw material characteristics and variability should be factored into risk assessment and potential prospective studies
- Firms are generally in agreement with the concept of differential treatment by regulators resulting from the use of a design space (expectation is that time to approval is not impacted)
- Specifications should be related to clinical relevance rather than only process capability
- Regulatory interactions during development regarding design space are valuable and encouraged
- Firms should have the flexibility to decide on the degree of "pre-investment" in when they define design space (pre-investment leverages R&D expertise) (deferral requires manufacturing scale experience)

Remaining Challenges

- Extent and means for updating design space (does it need prior approval?)
- There is a broad spectrum of expectations among industry regarding regulatory relief
- Conservatism within industry remains a challenge with respect to leveraging benefits of Quality by Design
- Do we use a single design space and, if not, how do we combine multiple ones for the same product?
- How do we define specifications that are clinically relevant and not limited to a reflection of process capability
- Global implications of post-approval changes
- Complex algorithms and models will be challenging to incorporate into design space descriptions in an application
- Must resolve divergent opinions on the extent to which quality attributes (vs. process parameters) define the design space
- Degree of allowable change of the design space, without prior approval, is linked to the capabilities of the firm's quality systems

the acquisition of what Gerry Migliaccio would call knowledge about your product, not just data. Understanding better what the impact of making a change is…understanding it a bit better than we have done traditionally.

Walt: A lot of people said that design space would change after marketing authorization. Can you really have a well-defined and approved, so to speak, design space at marketing approval?

Tim: It is quite possible you won't have defined it well enough. And I think this is still an area that needs to be developed both with industry and the agency.

Sue: I agree with Tim. I thought one of the stumbling blocks going through this though seems to be—and this is kind of nebulous—but company culture. There were a lot of comments about acceptance by senior management or just company culture being conservative versus more entrepreneurial…. A lot of the discussions focused on how to change the culture.

Walt: One of my thoughts about the culture is pharmaceuticals are businesses and you are already putting a lot of resources into drug development and a lot of the products may not make it to market. I think this concept is proposing that companies do more development work. Are the cost savings on the other side going to be that great to pay off this additional development work, considering it is a risk to do all this work before approval?

Tim: There is a huge benefit in being able to make changes without a huge amount of regulatory scrutiny after the NDA. But that's got to occur worldwide. Just getting that more easily achieved in the United States is not enough. We need to have that worldwide, which is why all of the ICH topics have been raised, so that we can get a harmonious approach to making continuous improvement and post-approval changes, then there is a huge benefit.

At the moment, every company makes a change and then waits up to two years waiting to get those changes approved in different countries. Very complicated for managing the supply chain, because you've got the old product going into one country, the new product going into a half dozen countries, you are not sure if is ever going to get approved in the next 15 countries and so on. So FDA is leading the way in trying to help the industry achieve that. I think they generally believe this is the right thing to do. But ➤

"CMC Regulatory Agreement" Sessions Summary from the Pharmaceutical Quality Assessment Workshop

Definition

An agreement between FDA and applicant at the time of approval that:

- Lists critical quality attributes and critical process parameters and their acceptance criteria and ranges
- Define boundaries of design space
- Describe manufacturing control strategy
- Allow freedom to make changes within the design space by relying on manufacturer's quality system and GMP controls
- Can be updated and/or modified after approval
- CMC Regulatory Agreement CMC Regulatory Agreement

General Understanding and Agreements

- Concept was endorsed
- Brief document
- Value to industry and regulators:
  - Focus on what is important (sponsor, review and inspection)
  - Elimination of unnecessary supplements
  - Continuous improvement
  - Clear understanding of postapproval filing requirements
  - Science-based GMP inspection
- Elements:
  - Only critical quality/process parameters
  - Specifications
  - Boundaries of design space
  - Stability and other postapproval commitments
  - Inclusive of API, dosage form and container closure system

Next Steps

- CMC pilot program to evaluate the concept and to address implementation challenges
- FDA to assess implementation under existing regulation
- If successful, develop a white paper (FDA/Industry) to define elements, utility and implementation strategy
- Training for industry and Agency

Regulatory Briefs

United States

Ajaz Hussain Leaves FDA OPS; Joins Sandoz

Ajaz Hussain, PhD, announced that he will leave the Center for Drug Evaluation and Research (CDER) Office of Pharmaceutical Science as its Deputy Director to join Sandoz as Vice President and Global Head for Biopharmaceutical Development. Dr. Hussain's last day at FDA was October 28, 2005.

Throughout his tenure with FDA, Dr. Hussain has been a proponent of pharmaceutical product quality and a leader of numerous FDA initiatives, such as the "*Pharmaceutical cGMPs for the 21st Century — A Risk-Based Approach*." He is also the architect of the CDER's Process Analytical Technologies efforts to establish a regulatory framework that will encourage the voluntary development and implementation of innovative approaches in pharmaceutical development, manufacturing and quality assurance.

Before joinng OPS as deputy, Ajaz was the driving force for several Center initiatives including SUPAC (Scale-up and Postapproval Changes) and BCS (Biopharmaceutics Classification System). He also conducted major research projects which have served as the foundation for regulatory reform.

NCI Director Andrew Von Eschenbach Asked to Serve as Acting FDA Commissioner

In the wake of Lester Crawford's sudden resignation as FDA's chief, the Bush Administration asked National Cancer Institute Director **Andrew Von Eschenbach** to serve as the Acting Commissioner for the Agency. Crawford informed staff via e-mail in September that his age, 67, was the reason for his resignation. Crawford's time as Acting Commissioner and his two months as Commissioner were somewhat controversial. Despite these controversies, FDA launched its cGMPs for the 21st Century and Critical Path initiatives.

Dr. Dal Pan Appointed Director of Drug Safety

In mid-October, FDA announced the selection of **Gerald J. Dal Pan,** MD, MHS, as Director, Office of Drug Safety, CDER. As the Director of the Office of Drug Safety, Dal Pan will be at the center of critical issues facing the nation on the safe and appropriate use of medications. He will work closely with stakeholders, including patient and consumer groups, the health care community, and Congress; develop and maintain international and national contacts with regulators; implement policies and initiatives related to adverse drug events (such as the Drug Safety Oversight Board and the Medwatch program), and represent FDA and CDER in scientific and regulatory matters related to drug safety and risk management.

Dal Pan previously served as the Director, Division of Surveillance, Research and Communication Support, Office of Drug Safety in CDER, a position he has held since 2003.

New Goals for CDER Announced

In a mid-October statement, CDER Director **Steven Galson,** MD, announced new goals for the Center as part of his annual State of CDER address to employees. He outlined a proposed Center reorganization to better align staff

U.S. FDA Advances 21st Century Regulatory Program Across the Product Lifecycle, continued from page 27

we have to get it done globally and then there will be a huge benefit all around.

Sue: Exactly.

Walt: A new concept of the CMC Regulatory Agreement was discussed at the meeting, but there was no real agreement at the meeting as to where and when to file it. It seemed people weren't sure if it was worth having another agreement, etc.

Sue: It can be a bit confusing as a topic.

Tim: I think it is a bit like these days you would call it a Phase 4 agreement.

Walt: The way I understand it, the agreement would be an additional submission under the CTD, along with the quality overall summary and the pharmaceutical development report. I think companies are going to have to take a look at this.

Tim: I think you are right. I don't think anybody is quite sure what it is going to look like yet.

[Editor's Note: PDA thanks Richard Levy, Tim Martin and Susan Schniepp for contributing to this article.]

functions with CDER's goals and FDA's public health mission. The goals of the proposed reorganization include:

1. Positioning CDER to fully participate in the Critical Path Initiative and improve regulatory and drug development science—the Agency's top scientific policy initiative for the next five years.
2. Increasing the visibility of the sustained, multi-disciplinary, cross-Center approach to drug safety that engages more than 50 percent of CDER's resources.
3. Centralizing risk communication efforts to ensure efficiency and consistency of CDER's important public health messages.

Dr. Galson stated his confidence that such changes "will lead to greater improvements in regulatory and drug development science," as well as in how Center officials "evaluate and ensure the safety and efficacy of the products" they regulate, resulting in "greater protections for patients and consumers who depend" on CDER.

Specific organizational changes will be announced by early November and will be implemented over the following six months.

FDA Publishes PET cGMPs and Guidance for Comment

The U.S. FDA is issuing proposed regulations on cGMPs for positron emission tomography (PET) drug products. The regulations are intended to ensure that PET drug products meet the requirements of the Federal Food, Drug, and Cosmetic Act regarding safety, identity, strength, quality and purity. The rule will apply to approved PET drug products. For investigational and research PET drugs, the proposed rule states that the requirement to follow cGMP may be met by producing PET drugs in accordance with the U.S. Pharmacopeia general chapter on compounding PET radiopharmaceuticals. FDA also published a companion draft guidance to the rule, entitled, "*PET Drug Products—Current Good Manufacturing Practice (CGMP).*" The public comment period for both the proposed rule and the draft guidance closes on December 19, 2005. For a link to the document, go to www.pda.org/regulatory/RegNewsArchive.html.

FDA Publishes Final Regulatory E-Submission Guidance

In mid-October, FDA published a final version of its Guidance for Industry on Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Product Applications and Related Submissions Using the Electronic Common Technical Document Specifications. The document is one in a series of guidances on providing regulatory submissions to FDA in electronic format, and discusses issues related to the electronic submission of new drug applications, abbreviated new drug applications, biologics license applications, investigational new drug applications, master files, advertising material, and promotional labeling using the electronic common technical document specifications. The submission of these documents in electronic format should improve the agency's efficiency in processing, archiving and reviewing them. For a link to the document, go to www.pda.org/regulatory/RegNewsArchive.html.

Europe

EMEA Publishes Concept Paper on Allergen Products

Needing to revise its 1996 guideline on allergen products, the EMEA published a concept paper to generate public input. Since the approval and publication of the guideline in 1996, the scientific knowledge on the structures, cross-reactivity and stability of allergens has increased drastically, and many allergens have been produced as recombinant proteins.

This scientific progress has several implications for regulation and standardization of allergen products. Special emphasis has to be granted to recombinant allergen products. Therefore, the revised guideline should: redefine the statements on batch-to-batch consistency, characterization and the use of in-house reference preparations and control tests, as well as the statements on safety and efficacy testing. Moreover, it should be aimed at covering aspects specific for recombinant allergens that are not covered or specifically addressed by other guidelines on biotechnology-derived proteins.

EMEA is proposing that the scope of the revised guideline will encompass: production and quality issues concerning natural and biotechnology-derived allergen products including derivatives with reduced IgE binding capacity and/or enhanced immunogenicity, fusion constructs containing polypeptides derived from allergens, and nonallergenic functional polypeptides. The Agency anticipates that the draft revision of the guideline will be released for consultation by the second quarter of 2006. The comment period for the concept paper closes December 31, 2005. For a link to the document, go to www.pda.org/regulatory/RegNewsArchive.html.

There and Back Again: A Chapter Manager's Tale

Kelly Coates, PDA

In the June issue of the *PDA Letter,* I began chronicling my travels around the world to visit with the membership and Chapter leaders. Since then, I have touched base with even more members by journeying across the United States and back again.

PDA Metro Chapter Dinner & Lecture

On June 13, I dined with the members of the PDA Metro Chapter in Clark, New Jersey. The evening started with a cocktail hour and vendor displays. After dinner, there was an intriguing presentation entitled, "Risk Analysis and Aseptic Processing Alternatives - Are Isolators Still the Best Answer?" by **James Akers,** PhD, Akers, Kennedy & Associates. This timely presentation perfectly complemented a delicious buffet dinner and dessert!

Nate Manco, ECO Animal Health

James Akers, Akers, Kennedy & Associates

Naomi Baer, Millipore, meets potential clients

Anne Shandy, Genentech

Ken Schirado, Chiron

Attendees register for the West Coast Chapter event

PDA West Coast Chapter Dinner & Panel Discussion

The next month I flew across the country for a dinner meeting with the PDA West Coast Chapter in Millbrae, California. On July 21st they hosted a panel discussion on "Inspection Trends in the Bay Area." Moderator **Elizabeth Leininger,** PhD, BAS Medical, led the discussion with panelists **Dennis Haggerty,** PhD, Bayer, **Ken Schirado,** Chiron, and **Anne Shandy,** Genentech. The panel discussion format was very well received, as evidenced by the active audience participation. ➤

Up to $40,000 in available funding!

STUDENT PROGRAMS

PDA and the *PDA Journal of Pharmaceutical Science and Technology* have established three Student Scientific Programs to promote applied research in areas of study relevant to the scientific foundations of pharmaceutical and biopharmaceutical product development, drug manufacturing and quality assurance technologies.

1 Annual Graduate Research Symposium

Graduate Students are invited to submit papers for presentation at the PDA Annual Graduate Research Symposium, to be held in conjunction with the PDA Annual Meeting, April 24-26, 2006 in Anaheim, California. Authors of papers selected for presentation will be awarded travel grants.

Travel grants!

2 Pre-Doctoral Fellowship Program

Doctoral Candidates are invited to submit dissertation research proposals for consideration. Up to four fellowship stipends will be awarded to assist selected applicants in their efforts to conduct the dissertation research projects.

Funding for your research!

3 Student Poster Sessions

Students are invited to submit papers of relevant work for presentation at the PDA Annual Meeting, April 24-26, 2006 in Anaheim, California. Authors of selected papers will prepare and present a poster exhibit and possibly an oral presentation.

Great networking opportunity!

Advance your studies!

www.pda.org/ssp

Advance your career!

Application Procedure
Visit **www.pda.org/ssp** to download an application

Or contact:
Iris Rice, Coordinator, Scientific and Regulatory Affairs
PDA Global Headquarters
3 Bethesda Metro Center, Suite 1500
Bethesda, MD 20814 USA
Tel: +1 (301) 656-5900, ext. 129
E-mail: rice@pda.org

Submission deadline: January 15, 2006

PDA℠
Parenteral Drug Association

About PDA

The Parenteral Drug Association (PDA) is a nonprofit international organization and a leading global provider of science, technology, and regulatory information and education for the pharmaceutical and biopharmaceutical community. PDA is committed to developing scientifically sound, practical technical information and resources to advance science and regulation through the expertise of its more than 10,000 members worldwide. More information about PDA is available at www.pda.org.

Connecting People, Science and Regulation℠

Michael Hayes, ALSCO, tees off

Tony Bafranciukas, ALSCO, lining up a shot

PDA Midwest Chapter Golf & Luncheon

I ended the summer by attending my first golf outing with the PDA Midwest Chapter on August 26. The golf outing and luncheon was hosted at the Antioch Golf Course in Antioch, Illinois. I had never held a golf club in my life but managed to have a wonderful time due to the support and patience of my team (thank goodness we were playing best ball!). After 18 holes, attendees were rewarded with cocktails and prizes for best team score, longest putt, longest drive and closest-to-pin. As their first golf event, it was certainly a success, and we all hope they make this an annual event.

PDA Joint Regulatory Conference

In September, I joined nearly a thousand PDA members in Washington, D.C., for the industry's premier regulatory event, the PDA/FDA Joint Regulatory Conference. This year's meeting was bigger and better than ever. I had the pleasure of meeting many of our members at the PDA booth during the conference, and I attended both the Japan Chapter meeting and the Chapter Council meeting. Nearly 25 members of the Japan Chapter were on hand for the event. Kudos also go to the Taiwan Chapter and the India Chapter for sending a member each from the remotest location to attend the Chapter Council meeting.

Midwest Chapter members enjoying a good time in the clubhouse

Exhibits at the Soutwest Chapter event were popular places to network

PDA Southeast Chapter Fall Meeting & Vendor Show

My latest trip was to the PDA Southeast Chapter Fall Meeting & Vendor Show in Durham, North Carolina on September 28. This was a full-day event, including a Chapter business meeting, vendor show and two speakers. The morning presentation by **Jim Veale,** PhD, Lighthouse Instruments, LLC, was on "Laser-Based Measurement Technology for Container Closure Integrity Testing." After lunch, the second speaker, **Ernesto Renzi,** BOC Edwards Pharmaceutical Systems, presented on "Advances in NonContact Check Weighers: New Technology." Throughout the day, attendees spent their breaks visiting with 35 vendors. It was a full day of networking, education and information exchange.

I want to thank all of the Chapters that hosted me over the last few months. It has been a pleasure to spend time with people so dedicated to the industry and to their profession. I look forward to meeting more of you as I continue my travels.

Capital Area Chapter Awards Second Annual Joint Scholarship

Barry A. Friedman, PhD, Cambrex Bio Science Baltimore

The PDA Capital Area Chapter recently announced the awardee for the second year of its joint scholarship program with the University of Maryland, Baltimore County (UMBC). This scholarship program represents the only joint program offered by one of PDA's 24 worldwide chapters. The scholarship was designed to assist individuals considering a career in biotechnology or pharmaceuticals. This joint program with UMBC is the first of several that the Capital Area Chapter hopes to initiate with area universities.

Applicants for this award were initially screened by UMBC, and the executive board of the Capital Area Chapter made the final selection. The awardee for the 2005-06 academic year is **Leonard Salter,** who is currently a senior majoring in biochemistry and molecular biology. He is an honors student within the UMBC Honors College and has spent the past three summers working in Pfizer's Global Research and Development Immunology Department in Connecticut. Following graduation, Leonard plans to attend graduate school. He was the Capital Area Chapter's guest at our dinner meeting on Wednesday, September 28th at the Holiday Inn in Gaithersburg, Maryland and received his quarterly award at that time.

Salter issued the following statement upon learning of his award: "I am delighted and honored to be the recipient of such an award and will most definitely remember the support of the PDA Capital Area Chapter as I prepare to enter my professional career. The benefits of belonging to such an organization are clear and I can only hope that I will eventually have something substantial to contribute in the future. Many thanks to **Dr. Barry Friedman, Dr. Peter Alexander, Dr. Peter Smith, Mr. Matthew Clark** and **Mr. Chris Bartlett** for all of their warmth and support; I look forward to meeting everyone again soon."

Monies for these scholarships are derived from vendors that support each of our dinner meetings. These vendors participate with tabletop exhibits during our "Meet 'n Greet" hour that precedes dinner. The Capital Area Chapter would like to recognize the following vendors as contributors to these scholarships: Accugenix, BD, BioLog, Chemunex, Doe & Ingalls, Lancaster Labs, Millipore, PML Microbiologicals, Pall, Perfex and Veltek.

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 e-mail address. Where applicable, the Chapter's Web site is listed. More information on PDA Chapters is available at www.pda.org/chapters/index.html.

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2006 PDA/EMEA Joint Regulatory Conference: A Landmark Event

Tim Marten, AstraZeneca and Anders Vinther, CMC Biopharmaceuticals, Co-chairs of the PDA/EMEA Joint Conference 2006

Join PDA in London Next October and Meet Representatives from EMEA, the European Commission and the 25 EU National Health Authorities

We are proud to announce that the first-ever PDA/EMEA Joint Regulatory Conference will be held in London, October 12-13, 2006. For quite some time, there has been a keen interest among PDA's members worldwide for a forum hosted jointly between PDA and European regulators in order to learn more about the European pharmaceutical regulations and to discuss and interpret current trends in science, technology and GMPs.

What was once only a wish is now a reality: EMEA has accepted PDA's suggestion for a joint conference and is actively assisting to put together an excellent program for next year's event. The EMEA Inspectorate, headed by **Emer Cooke,** hopes that by having this conference, the European GMPs will be better understood in Europe, the United States and the rest of the world.

At the conference we expect to have speakers from the EMEA, the European Commission and from several of the 25 European national medicines agencies.

The program committee had an exciting and stimulating kick-off meeting in early September in London, where we decided the general outline of the program. Topics under consideration include:

- Understanding the regulatory framework in Europe
- Consistent implementation of EU GMPs in the national member states
- EU inspections: past, present and future
- Emerging markets
- Investigational medicinal products, including biotechnology issues
- Active pharmaceutical ingredients and excipients (Annex 18)
- Science and compliance topics
- New technologies in the pharmaceutical industry
- Veterinary GMP topics

The program format will stimulate discussion among regulators, inspectors and industry. We will be developing the program further over the next months. Stay informed about this exciting event-of-the-year conference at www.pda.org and in the *PDA Letter*.

Program Planning Committee:

Tim Marten (Co-chair), *AstraZeneca, United Kingdom*

Anders Vinther (Co-chair), *CMC Biopharmaceuticals, Denmark*

Emer Cooke, *EMEA, United Kingdom*

David Cockburn, *EMEA, United Kingdom*

Enzo Baselli, *Pall Italy*

Steve Bellis, *Ivax, United Kingdom*

Veronique Davoust, *Pfizer, France*

Gabriella Detari, *National Institute of Pharmacy, Hungary*

Tor Graberg, *Medical Products Agency, Sweden*

Kathleen Greene, *Novartis, United States*

Frank Hallinan, *Wyeth, Ireland*

Gerald Heddell, *Medicines and Healthcare Products Regulatory Agency, United Kingdom*

Jiri Holy, *USKVBL, Czech Republic*

Hiltrud Horn, *Consultant, Germany*

Susanne Keitel, *Federal Institute for Drugs and Medical Devices, Germany*

James Lyda, *PDA, Switzerland*

John Lynch, *Irish Medicines Board, Ireland*

Carlo Pini, *ISS, Italy*

Stephan Roenninger, *Roche, Switzerland*

Georg Roessling, *Schering, Germany*

Frank Talbot, *Consultant, United Kingdom*

Anne Marie Vangsted, *DMA, Denmark*

PDA/FDA Joint Regulatory Conference Photo Highlights

The 2005 PDA/FDA Joint Regulatory Conference was one of PDA's best attended events. The following eight pages contain photo highlights of the event, starting with photos of various speakers. Next are two pages dedicated to the exhibitors, followed by photos of the various PDA-related groups. The last page contains "miscellaneous" photos that help capture the essence of the conference. We hope you enjoy them.

Over 1,200 industry, academia and health authority professionals attended the 2005 PDA/FDA Joint Regulatory Conference, Mycoplasma Workshop and TRI Courses

PDA Directors Tim Marten, AstraZeneca and Anders Vinther, CMC Biopharmaceuticals A/S

Development History Report and Technical Transfer (l/r): Julie Garren, Abbott; Paul Allen, Clarkston Consulting; Jon Clark, PhD, FDA

FDA Inspections and Quality Trends (l/r): John Eltermann, FDA; Kathleen Greene, Novartis; Joseph Famulare, FDA

Risk Assessment and Management (l/r): Maria Guazzaroni, PhD, Pfizer; Jeffrey Priem, Cubist Pharmaceuticals; Luann Pendy, PhD, Hospira; Steven Anderson, PhD, FDA

ICH Q10 (l/r): Neil Wilkinson, AstraZeneca; Sue Schniepp, Hospira; Christopher Joneckis, PhD, FDA; Gerry Migliaccio, Pfizer

Management Specifications (l/r): Karen Walker, Abgenix; Elizabeth Leininger, PhD, BAS Medical; Jon Clark, PhD, FDA

Post-Marketing Surveillance for Drugs (l/r): Victoria Dedrick, PDA Consultant; Jon Clark, PhD, FDA; Liz Coulson, Pfizer

Barry Friedman (Cambrex), PDA Capital Area Chapter President, opens the 2005 PDA/FDA Joint Regulatory Conference

Kathleen Greene, Novartis, introduces the Keynote Speaker

Keynote Speaker Meredith Manning, JD, Hogan and Hartson, LLP, discussing the "buzz" surrounding generic biologics

Opening Plenary Session Speakers (top l/r): Barry Friedman, Cambrex; Bob Myers, PDA; Louise Johnson, Vertex; Nikki Mehringer (Eli Lilly) PDA Chair; (bottom l/r): Kathleen Greene, Novartis; Meredith Manning, JD, Hogan and Hartson, LLP; Kathryn Carbone, MD, FDA

Closing Plenary Session Speakers (l/r): Cindy Rockel, Millipore; Arthur Trepanier, Lockheed Martin Missles and Fire Control; Joseph Famulare, FDA

Validation (l/r): Sabra Seyer, Pfizer; Jim Lyda, PDA; Grace McNally, FDA; Christopher Joneckis, PhD, FDA

Applied GMPs for the 21st Century (podium l/r): Robert Sausville, FDA; Sue Schniepp, Hospira; Zena Kaufman, Pfizer

VTS Consultants Inc.

Perfex Corporation

Eisai Machinery USA, Inc.

PSI Pharmaceutical Systems Inc.

Dallas Semiconductor/Maxim & Pall Life Sciences

Cryovac – Sealed Air Corporation

STERIS Corporation

Sparta Systems (left) and Eisai Machinery USA, Inc.

PAREXEL Consulting

Clarkston Consulting

PDA

Working Words, Inc.

Novatek International

PDA's PAT Working Group's first meeting: (top left l/r) John Shabushnig, Pfizer and Lynn Torbeck, consultant; (center l/r) Suresh Vunnum, Wyeth and Michael Lennick, GBSC; (bottom left l/r) Walt Morris, PDA; Michael Miller, Eli Lilly; Lynn Torbeck

PDA Science Advisory Board

PDA Biotechnology Interest Group

PDA Microbiology Interest Group

The PDA Letter Editorial Committee's first face-to-face meeting (l/r): Walt Morris, PDA; Elizabeth Martinez, Terra Farma; Vinod Gupta, PhD, Organon

PDA Technical Book Advisory Board meeting: l top to bottom) Janny Chua, PDA; Amy Davis, Davis Healthcare International Publishing; (r top to bottom) Berit Reinmuller, PhD,Swedish Royal Institute of Technology; Bengt Ljungqvist, PhD, Swedish Royal Institute of Technology; Nahid Kiani, PDA

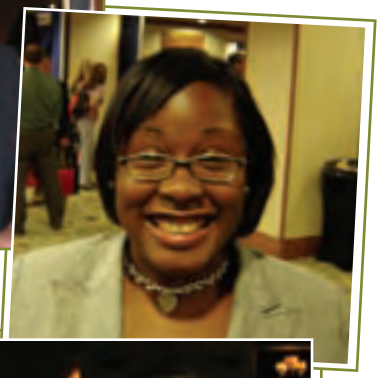
2006 PDA/FDA Program Planning Committee

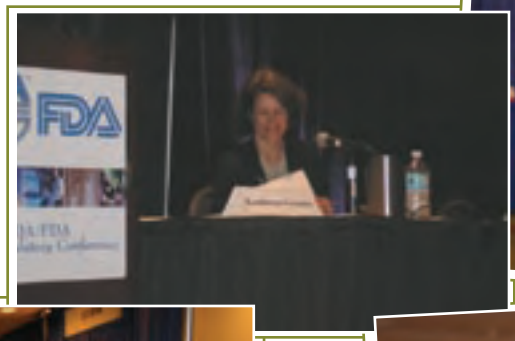
PDA Biotechnology Advisory Board

(Top) The Katrina Relief Fund raised thousands of dollars at the 2005 PDA/FDA Conference. (middle l/r): Relief fund partners Mike O'Grady, EMD Chemicals Inc.; Bob Myers, President, PDA; Parsa Famili, President, Novatek International. (bottom): FSK President Frank Kohn hands a check to Nahid Kiani with Novatek's Famili watching

The Mycoplasma Contamination by Plant Peptones workshop Planning Committee

Over 1,200 attendees drank over 1,000 gallons of coffee...





...and provided thousands of smiles!

Vice President's Message

Gail Sherman

Surprise! Advancing PDA's Health Authority Training Program

I am pleased to announce that TRI teamed up with Purdue University and Eli Lilly to train members of the Kazakhstan Ministry of Health and National Center for Assessment of Drugs (KMOH/NCAD). In addition to several well-attended laboratory courses, a phenomenal turnout at PDA/FDA training courses and a new training catalog mailed to our members, the PDA TRI's participation in the Health Authority Training program for the KMOH/NCAD made for a very exciting and successful end to 2005.

Developing the Health Authority Training Program for the Khazaki officials involved a number of surprises. It began in the summer when Eli Lilly contacted TRI to propose we join with them and Purdue University to conduct regulatory affairs and compliance training for KMOH/NCAD staff members. Since PDA has trained the inspectorates in Italy and Taiwan, we felt we were more than capable and qualified to participate.

PDA agreed that this would be a great opportunity to provide training to a global audience. We planned on developing a cadre of qualified instructors who would conduct the training in Kazakhstan. We sorted through the proposed topics, refined them into seven areas, assigning each to Purdue, Lilly or PDA, and began to move forward. Later, we were surprised to learn the training was to take place in the United States, but we were adaptable and continued to move forward with our joint proposal.

Initially, KMOH/NCAD wanted 20-25 officials trained in pharmaceutical cGMPs across the product life cycle, from development through postapproval manufacturing. Eventually, we were informed the number of officials to be trained was closer to 44, and this 44 might actually grow to 200 over three years—Surprise! We were relieved that we would have several months to work out the details of this now massive training endeavor, which we were later informed, needed to be translated and delivered in Russian—Surprise!

The surprises kept coming: Next we were informed that KMOH/NCAD needed the first 44 participants trained in by the end of 2005. So much for "several months" for planning—Surprise! Now, in panic mode, we anxiously sought instructors who were available on these new and very limited dates that KMOH/NCAD and our partners had agreed upon for the training. We also had to accelerate our assessments of training locations, translators and other logistics. Lastly, KMOH/NCAD wanted the first group trained in four weeks—two weeks in Baltimore and two weeks in Indianapolis—Surprise!

Despite all the surprises, the contract was signed officially on October 19, and training started on October 31—nothing like cutting things close to the wire. The format of training was a lecture with simultaneous translation. PDA also made sure the trainees had some fun with a Saturday tour of Washington, D.C., highlighting its monuments and museums. All in all, this was an exciting and rewarding program, and we look forward to training the next group starting in early 2006.

Before I close for the year, I really want to thank all of the people who took time out of their busy schedules to participate in this training; the PDA staff who jumped in to assist and my colleagues at FDA who provided lectures on some very critical topics.

Furthermore, I wish you all a very healthy, happy New Year, and hope to see you in 2006, either as a student, a lecturer or just a friend of TRI! Happy holidays.

PDA Parenteral Drug Association

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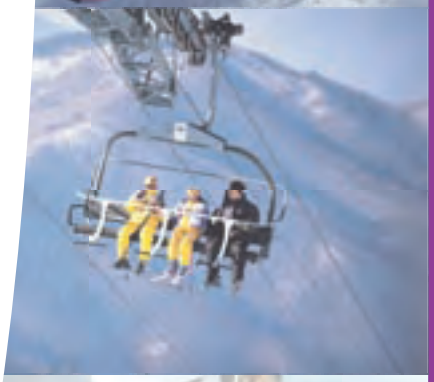

For course related inquiries contact:

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For additional information and to register visit:

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That Thankful Time of Year

James Wamsley, PDA

With the arrival of November and December comes the holiday season in the United States and many other countries around the world. Giving gifts, lighting the menorah or Christmas tree, playing in the snow, congregating with family and possibly even enjoying a day or two away from work are the ingredients that make the holidays the most memorable time of the year for many.

The holiday season also provides many with time to express their gratitude to those around them—to colleagues for a year's worth of hard work and friends and family for their loyalty and support. So, it seems only fitting that we at PDA's Training and Research Institute (TRI) show how much we truly appreciate all the support we received throughout the past year from the three most important ingredients in our successful recipe: vendors, instructors and, of course, the students.

TRI relies on a number of vendors who donate nearly all of our equipment and supplies as well as critical services, including equipment calibration and preventative maintenance services, agar plates, microbes, equipment and laboratory instrumentation, cleaning supplies, cleanroom gowns and software. Anyone that is involved in the purchasing of supplies, equipment, software and services for their companies understands how quickly the cost of these supplies can add up. Because of our benefactors, we are able to offer lab and lecture courses at prices that are still affordable for most companies. Not only do vendors supply commodities and equipment, but a few donate their employees' valuable time to provide training as instructors.

TRI's instructors, the second key ingredient, are experts in their fields. All of our instructors spend numerous hours developing course materials, traveling and delivering the training outside of their normal jobs, often at the expense of their sparse free time. This kind of dedication from these terrific men and women has helped solidify PDA's reputation as a worldwide leader in training and education for pharmaceutical/biopharmaceutical professionals.

Although my space here is too limited to list all the vendors and instructors that support TRI, you can find their names at www.pdatraining.org. Also, if you feel that you would like to join this group of dedicated sponsors and instructors, please contact us at tri@pda.org.

This brings us to the final ingredient in our recipe, the glue that binds us, if you will: the students. Without people to attend our courses, TRI would not exist. And, to all the students from this and prior years, my colleagues and I want to say, thank you. We are here to help you and educate you. We appreciate the time you take away from your careers and your families to come to our training.

Like mom's (or dad's) special holiday recipes, TRI's recipe for delivering the best pharmaceutical/biopharmaceutical professional education is tried and true, and the ingredients are better than ever!

From Educating Children to Providing Education for Adults – Change Couldn't Have Come at a Better Time

Jessica Petree, PDA

My change in career from middle school teacher to a manager of lecture education at TRI was a nerve-racking step, but one that couldn't have come at a better time personally and for the Institute. I was fortunate to join the Institute in the midst of a successful string of courses, and the PDA/FDA Joint Regulatory Conference courses were just six weeks away.

When I walked into the whole experience, I was wide eyed and excited, yet nervous. Not knowing what to expect, I was surprised about how similar this conference was to the education conferences I attended as a school teacher. The difference, however, was that now I was on the other side. First, I was involved with helping during the conference—monitoring sessions and assisting and directing attendees to the appropriate session locations. Then finally the course series began, and I had my first opportunity to participate in a major educational opportunity for PDA members. What an experience!

Though a bit overwhelmed, I was excited to take on the challenges a course series presents. There were some glitches along the way, but with the help of many around me, the series was a success. Our numbers were staggering; the 160 registrants were more students than TRI had ever enrolled for a single series before! Topics offered included *API Qualification and Validation, FDA Pre-Approval Inspections, Auditing Foreign API Manufacturers, OOS Regulations, Change Control, Biopharmaceutical QA/QC Strategy, Auditing Techniques for cGMP Compliance and Sterile Drug Submissions to the FDA*. These courses proved to be valuable to our students, as many evaluations had glowing comments about both our courses and our instructors. Many students even requested additional time on the topics. Even more were grateful for the resources provided them during the duration of the course series.

My first months as the manager of lecture education have proved rewarding. With the success of courses at TRI in Baltimore and the success of the PDA/FDA Joint Regulatory Conference Course Series, we have had plenty to smile about. Where I was once apprehensive about a change in career, I am now looking forward to the challenges that lie ahead.

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