Science • Technology • Quality • Regulatory • Community

PDA Letter

Volume XLIV • Issue #6

www.pda.org/pdaletter

June 2008

In This Issue…

Novel Delivery System Promises Electrifying Results

Walter Morris, PDA

It seems everything nowadays runs on electricity. If current clinical research pans out, there soon might be a host of drugs delivered to the human body with the help of electrical charges. Think Star Trek.*

The technique is electroporation and is not a new technology, but its application in the world of drug delivery is becoming evermore defined. In recent years, a number of human clinical studies have started to explore the possibility that electroporation can improve the effectiveness and safety of a whole category of drug products. If true, the technique just might serve as the catalyst for a generation of cures and immunizations for some of the worst human diseases.

The Promise of DNA Vaccines

For nearly two decades, researchers have been pursuing the use of DNA vaccines to prevent a number of diseases, including cancer, HIV/AIDS and hepatitis. While these vaccines have provided tantalizing results in animal studies for their ability to induce immunogenicity to the aforementioned illnesses, human results have been less than encouraging. A number of in-depth reports on DNA vaccines and their uses explain the problems found in clinical trials, particularly for the first generation of these product types.

For example, the authors of a well-researched 2003 review article entitled "Gene Vaccines" wrote: *The DNA vaccines have entered the clinic of initial safety and immunogenicity testing in humans. To date, the potency of the immune responses has been disappointing.*[1] Referring to Phase I clinical trials for an HIV-1 *env/rev* DNA construct, researchers found that subjects not infected with HIV demonstrated positive antigen-specific responses, *but these responses were weak and did not persist.* Subjects infected with HIV saw boosted env-specific antibodies, according to the article, *however, no consistent effect was observed in cellular responses.* The authors of the review article cited other examples of poor clinical results involving HIV and malaria.

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* Use of electroporation isn't quite like Dr. Bones' cure-all sensor probe which seemingly never had to touch the human body to work. Rather, the systems reviewed in this article make use of traditional needles in combination with an electrode needle array.

continued on page 19

PDA Parenteral Drug Association

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2008 PDA/FDA Joint Regulatory Conference

Harmonization, Implementation and Modernization: Achieving a Future Vision

September 8-12, 2008
Washington, D.C.

Conference	September 8-10
Exhibition	September 8-9
Courses	September 11-12

www.pda.org/pdafda2008

The US Food and Drug Administration (FDA) announced the Good Manufacturing Practices (GMPs) for the 21st Century initiative in 2002, giving the industry its first glimpse of the future of regulatory oversight for pharmaceutical production. The intent of the original initiative was to offer the industry the necessary tools to provide more post-approval flexibility, making continual improvement less of a regulatory burden, and to promote better self-regulation to improve regulatory compliance status.

In the five years that have passed since the announcement, regulatory health authorities and industry have partnered by harmonizing requirements and implementing new systems for assuring and maintaining pharmaceutical quality. The 2008 PDA/FDA Joint Regulatory Conference will provide examples of how these new approaches have been successfully implemented. In addition, the conference will examine what is working well and where the industry and regulatory health authorities still need to work to achieve modernized quality systems.

PDA is also offering an exhibition during the conference. The PDA Training and Research Institute (PDA TRI) will host courses immediately following the conference to complement what you learn at the meeting.

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Cover art:
The past and future in contrast: Electroporation intravenous delivery systems might salvage DNA vaccine development. Pictured in the foreground is Ichor's Trigrid system (image used with permission).
Photo collage by James Austin Spangle

Coming Next Issue:
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Editor's Message

Novel Delivery Systems Both Big and Small

It is always interesting to look at the novel delivery systems under development that might one day find their way onto the plant floor. In this issue, the PDA Letter identifies two such technologies, both of which hold the potential to revitalize an industry looking for the next generation of blockbuster therapies. The first delivery system is the combination syringe-electric pulse generator (see cover story), allowing for the delivery of DNA vaccines via electroporation. Preliminary results show that the effectiveness of such vaccines rises significantly with this delivery method, possibly salvaging the viability of this category of vaccines. The other technology we looked at involves the creation of machines and substances at nano scale. Of course, nanotechnology's impact is already evident in a variety of industries, but its use in drug delivery is just now being defined. The Technology Trend in the "Science & Technology Snapshot" (p. 12) focuses on preclinical research underway for nanocarriers, nanomachines and microphamacies. We hope you enjoy these glimpses into the industry's possible future.

Also in this issue, **Emily Hough** sorts out the latest developments in the ongoing U.S. FDA funding situation. The U.S. Congress appears set to increase the Agency's budget, and you can read all about it in "Proposed Legislation Provides FDA with Additional Resources" (p. 24).

In News & Notes, PDA honors a recently departed colleague, friend and exemplary member, **Steve Bellis,** who's passing is a true loss to not only his family, but to all those who's lives he touched (opposite page). The section also includes pictures of the winners from the 2007 PDA Honor Awards from the banquet at the 2008 Annual Meeting (p. 10). A six-page "Faces and Places" highlighting the sessions, the exhibitors and the networking at the Annual Meeting begins on page 40.

Finally, we are pleased to announce that **Hal Baseman** and **Sue Schniepp** have joined the *PDA Letter* Editorial Committee.

PDA Letter

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PDA Remembers Steve Bellis, Friend and Supporter for Over 20 Years

Long time PDA contributor Steve Bellis

PDA is saddened to report that long time friend and colleague Steve Bellis passed away on May 9, 2008. Steve was a PDA member for over 20 years and was a key contributor to the development of PDA's positions and a spokesperson for the Association on a number of topics, including the ICH Q7 Guidance and Annex 1 to the European GMP Guide. Among his contributions to PDA, Steve served on the Board of Directors in 2006, was a member of the Regulatory Affairs and Quality Committee and a member of the European Advisory Board. He co-chaired the Program Committee for the *2008 PDA/EMEA Joint Conference* and served on a number of other PDA Committees and Task Forces.

Steve was a Chief Quality Officer for CMC Biopharmaceuticals in Copenhagen, Denmark and a long service executive in several major pharmaceutical companies. Robert Myers, PDA President commented, "He was a friend to many of us at PDA and both he and his wife Julie Brett-Bellis were well known to me and to the PDA community. Although Steve was originally from the United States, his personality and outstanding knowledge of EU Regulations and pharmaceutical manufacturing controls made him a leader of our EU PDA organization. He was a valued colleague to many industry leaders both from the regulatory agencies and industry."

A memorial fund in his name will be established at the Oncology Department of the Righospitalet in Copenhagen. Donations can be made directly in his name or directed to Steve's wife or Tim Marten at the addresses provided. PDA will be making a donation to honor Steve for his long term contribution to the organization.

Donations to the Steve Bellis Memorial Fund can be made directly to:

Julie Brett-Bellis
Sunhope, Well Lane, Butley Town
Macclesfield, Cheshire SK10 4DZ, UK

Tim R. Marten, PhD
Vice President, Global Quality,
Operations, AstraZeneca
S 79 Alderley House
Macclesfield, Cheshire SK10 4TF, UK

New Format for Calendar

In this issue, we've made the decision to remove the "PDA Calendar of Events," and for good reason. Since 2005, the calendar has resided in the center of each issue. However, at the same time, we've increased the number of advertisements and articles for all of PDA's events and vastly improved the presentation of event information at www.pda.org. Earlier this year, the PDA marketing team led by **Dee Kaminsky** launched the "PDA Global Event Calendar" insert to be included in four issues per year. All these suggest to us that the two pages normally dedicated to the calendar can be used more effectively in the face of a burgeoning amount of content and advertising faced each issue.

Let us know how you feel about this decision; send your thoughts to morris@pda.org.

Visit www.pda.org/pdaletter

At the Letter's new website, you can read selected articles and link to the members-only archive *before* your hard copy arrives in the mail! Also, you can easily submit your comments and have them published as "Letters to the Editor."

Click on the "Authors Wanted" link to learn about upcoming topics and how to submit articles!

2009 PDA Annual Meeting

The Microchip: Impact on the Pharmaceutical/Biopharmaceutical Industry

Friends and Colleagues:

The PDA 2009 Annual Meeting will explore an area of immense importance to our industry - the current and future impact of computerization and automation. Few would disagree that the microchip has and will continue to revolutionize the pharmaceutical and biopharmaceutical industry. There is virtually no area of the industry that is not affected, from the discovery process to the management of clinical trials; from process development and design, plant control systems to automated batch records; from analytical technology to the management of Change Control and deviation handling - the list is endless.

Have you or someone you know in the bio/pharmaceutical community done something cutting edge or revolutionary in the past year that has involved the use of computerized systems, something that would be of particular interest to the global industry? Such as:

- Solved an unusually difficult technical problem
- Developed an efficiency or quality improvement idea
- Introduced a novel way of using computers and automation to improve process reliability or consistency
- Managed process development data with unique software applications
- Introduced new ways to automate Quality Assurance processes

PDA encourages you to submit a scientific abstract for presentation at the PDA 2009 Annual Meeting, which will be held on April 20-24, 2009, at The Red Rock Casino and Resort in Las Vegas, Nevada. Abstracts must be noncommercial in nature, describe new developments or work and significantly contribute to the body of knowledge relating to pharmaceutical manufacturing, quality management and technology. Industry case studies demonstrating advanced technologies, manufacturing efficiencies or solutions to regulatory compliance issues are preferable and will receive the highest consideration. All abstracts will be reviewed by the Program Planning Committee for consideration of inclusion in the meeting as a podium or poster presentation.

PDA is seeking presentations of 30 minutes in length, which present novel solutions and practical approaches. The following list is a guide of the suitable topics for papers. It is not exhaustive and any paper which fits the overall topic of the conference is welcome.

Development Science

- Advances in Aseptic Filling/Processing
- Advances in Dosage Form Delivery Systems
- Automated Sterilization Technologies
- Contamination Control/Facility Manufacturing Control
- Cell Culture/Line development
- Implication and application of ICH Q8 and the Q8 Annex to process design and development
- Implication and application of ICH Q9, Risk Management to process design and development
- Knowledge and Information Management
- Process Analytical Technologies (PAT)
- Process Modeling and Creation of a Design Space During Product Development

Manufacturing/ Process Science

- Aseptic Processing
- Automated Manufacturing Systems
- Barrier/Isolators/RABs
- Blow-Fill-Seal Automation
- Building Management and Control
- CIP/SIP and Multi-product Manufacturing
- Design/Management of Multi-product Facilities
- Electronic Documentation
- Innovative Manufacturing Approaches
- Knowledge and Information Management
- Online In-process Testing (e.g. Container Closure/Filter Integrity, etc.)
- Production Strategies for a Global Market
- Robotics
- Tracking and Tracing Technologies
- Visual Inspections
- Warehouse Control Systems

Quality Science

- Application of ICH, Q9, Risk Management to Quality Systems and GMP Compliance
- Compliance Monitoring and Trending
- Data Spreadsheet Qualification Case Studies
- Designing Pharmaceutical Quality Systems Across the Product Lifecycle, ICH Q10
- Environmental Monitoring
- Knowledge and Information Management
- LIMS and Lab Management Systems
- Microbiological Methods and Trends
- Quality Management Systems
- Supplier Quality Management Systems including Contract Manufacturing
- Tracking and Tracing Systems
- Training and Education Systems
- Validation of Pharmaceutical and Biopharmaceutical Processes

Photo courtesy of Bayer Healthcare

Call for Papers

April 20-24, 2009 | Las Vegas, Nevada

ABSTRACTS MUST BE RECEIVED BY JUNE 30, 2008 FOR CONSIDERATION

Visit www.pda.org/annual2009 to submit your abstract.

Upon the creation of your user profile, you will receive an email confirmation from Oxford Abstract Management System containing submission instructions. Submissions received without full information will not be considered.

Please include the following information with your abstracts:

- Title
- Full mailing address
- Email address
- Phone number
- 2-3 paragraph abstract, summarizing your topic and the appropriate forum (case study, discussion, traditional, panel, etc.)
- Take-home benefits
- Session objectives
- Rationale

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– FDA Guidance For Pharmaceutical cGMPs

Applied Biosystems

Rocky Mountain Banquet Honors High Achieving Members

At its 2008 Annual Meeting in Colorado Springs, Colo., PDA recognized last year's hard-working contributors that have shaped the Association into what it is today. PDA's 2007 Honor Award winners were recognized at the traditional banquet the night before the meeting commenced.

PDA congratulates each winner and thanks them for their service to the Association.

Frederick J. Carleton Award

Presented as a tribute to lifetime contributor, past President, past Executive Director and Honorary Member Frederick J. Carleton, this award is designated for a past or present board member whose services on the board are determined by his/her peers as worthy of such recognition. This year's Frederick J. Carleton Award recipients are:

Nikki Mehringer, Eli Lilly

Jennie Allewell, Wyeth

James P. Agalloco Award

The James P. Agalloco Award is presented annually to the PDA faculty member who exemplifies outstanding performance in education. The selection is based on student and faculty evaluations and is named for James P. Agalloco in honor of his work in developing the PDA education program. This year's James P. Agalloco Award recipient is:

Jeanne Moldenhauer, PhD, Excellent Pharma Consulting

Distinguished Service Award

This award is given in recognition of special acts, contributions or services that have contributed to the success and strength of PDA. This year's Distinguished Service Award recipients are (pictured, clockwise from top):

Sue Schniepp, Schniepp and Associates

Rafik Bishara,PhD, PDA

Vince Mathews, Eli Lilly

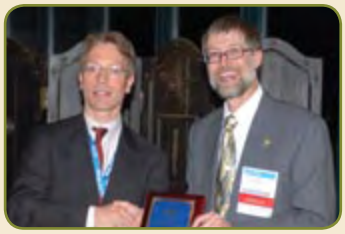
Yoshiaki Hara, Sartorius Stedium Biotech

Distinguished Editor/Author Award

This award is presented annually for the best editor/author of PDA-DHI co-published books as selected by PDA members. This year's Distinguished Editor/Author Award recipients are:

Scott Sutton, PhD, Vectech Pharmaceutical Consultants

Stephan Krause, PhD, Favrille



Gordon Personeus Award

Presented in memory of the late Gordon Personeus, past PDA President and long-time volunteer, this award is intended to honor a PDA member, for their long-term acts or contributions that are of noteworthy or special importance to PDA. This year's Gordon Personeus Award recipient is:

Richard Johnson, RMJ Consulting

Frederick D. Simon Award

The Frederick D. Simon Award is presented annually for the best paper published in the *PDA Journal of Pharmaceutical Science and Technology.* This award is named in honor of the late Frederick D. Simon, a previous PDA Director of Scientific Affairs. This year's Frederick D. Simon Award recipients are:

Yves Mayeresse, GSK Biologicals

Romain Veillon, GSK Biologicals

Philippe Sibille, Adixen Vacuum Technology

Cyrille Nomine, Adixen Vacuum Technology France

Korczynski Grant

This grant recognizes the contributions made toward the development of PDA's international activities by Michael S. Korczynski, PhD. This year's Korczynski Grant recipient is:

Hannelore Willkommen, PhD Pharmacy, RBS Consulting

President's Award

This award recognizes a PDA staff member, other than Senior Staff, whose exemplary performance has contributed to PDA's success during the previous year. This year's President's Award recipients are:

James Wamsley, PDA

Pateresa Day, PDA

Honorary Membership Award

This is PDA's most prestigious award, conferring lifetime membership benefits to the recipient. The award is given in recognition of very long and significant service to PDA. This year's recipients are:

Berit Reinmuller, PhD, Royal Institute of Technology

Bengt Ljungqvist, PhD, Royal Institute of Technology

The 2007 PDA Honor Award Winners

Science & Technology Snapshot

Technology *Trend*

A Look into the Future: Nanocarriers, Nanomachines and Micropharmacies

Walter Morris, PDA

Nanotechnology already is having an impact on drug delivery, but the industry is just on the cusp of maximizing the full potential of this technology.

Nanocrystal® Technology (an Elan Corporation product) is used in several U.S. FDA approved products. The technology allows manufacturers to reduce the particle size of ingredients under 400nm (billionths of a meter), thus improving drug dissolution via increased exposed drug surface area. The company is exploring the technology's ability to enable the development of poorly water-soluble compounds and to improve intravenous drug delivery.

While advancements like these indeed are remarkable, ongoing research at the University of Texas Health Science Center-Houston (UT-Houston), MIT and the University of California, Los Angeles (UCLA) offer a glimpse into truly radical ways of delivering medicines to the human body.

At UT-Houston, researchers led by **Mauro Ferrari,** PhD, have initiated preclinical trials on a new nanoscale delivery system aimed at increasing efficacy and reducing toxicity of injectable products.[1] These "nanocarriers" are engineered to search for and destroy diseased cells within the human body. A coating of targeted molecules allows the nanocarrier to function by recognizing and attaching onto cells lining the inner walls of disease-associated blood vessels. Degradation of the carrier allows nanoparticles to penetrate the blood vessels into the targeted cells, where therapeutic agents are then released.

UCLA is innovating the "nanoimpeller," a nano-scale killer designed to attack cancer cells.[2] This device collects and stores anticancer drugs inside cancer cells. The nanoimpeller is activated by light, thus allowing for the controlled-release of the anticancer agents.

At MIT, researchers are moving beyond brick and mortar pharmacies with the "micropharmacy." The delivery system is a thin-film coating, about 150nm, and can be implanted in specific parts of the body. The film is made from a negatively charged pigment (MIT uses Prussian Blue) and a positively charged drug molecule (or a neutral drug wrapped in a positively charged molecule)—these are arranged in alternating layers. Electric signals activate the system, allowing for controlled delivery of the drug inside.[3]

Each of these devices are in preclinical or earlier stages, but they demonstrate the magnitude of change nanotechnology can bring to the pharmaceutical industry. ***(references on bottom of opposite page)***

Technical Report *Watch*

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

- **TR-22 (Revised),** ***Process Simulation Testing for Aseptically Filled Products***
- ***Steam In Place***
- ***Moist Heat Sterilization Systems***
- **TR-15 (Revised),** ***Validation of Tangential Flow Filtration in a Biopharmaceutical Application***
- ***Microbial Data Deviations***
- ***Blow-Fill Seal***
- ***Biological Indicators for Sporicidal Gassing Processes: Specification, Manufacture, Control and Use***

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

- **TR-14 (Revised),** ***Validation of Column-Based Separation Processes (BioAB)***
- **TR-26 (Revised),** ***Sterilizing Filtration of Liquids (BoD)***
- **TR-41,** ***Virus Filtration (BioAB)***

Advisory Board *Update*

SABs Meeting in Colorado

The PDA Science Advisory Board (SAB) met at the 2008 Annual Meeting in Colorado Springs, Colo., for a status check on a number of current projects. The SAB is actively working on completing several projects, including technical reports related to product and equipment sterilization, filtration, lyophilization, investigational product manufacture, environmental monitoring, aseptic process simulations, biological indicators, and analytical testing.

In addition, the following initiatives have been proposed for 2008–2009:

- Track and Trace Requirements and techniques, e.g., RFID
- Investigational and Clinical Product manufacturing requirements
- Low bioburden intermediate manufacturing requirements
- Aseptic Process Validation
- Rapid Microbiological Techniques
- Spray drying and Lyophilization
- Facts and Fiction of QbD
- ICH Q8 Implementation Guide
- ICH Q9 Implementation Guide – additional "non-aseptic" models
- ICH Q10 implementation Guide

Attendees

Hal Baseman

Jens Eilertsen

Richard Johnson

Mike Long (via phone)

Lisa Hornback

Chris Smalley

Ken Muhvich

Kris Evans

Staff

Rich Levy

Bob Dana

Iris Rice

Guests

Véronique Davoust

Robert Chance

Technology Trend, continued from previous page

References

1. Compiled from information at http://nanomed.uth.tmc.edu/news and http://nanotechwire.com.
2. Nanomachine Releases Anticancer Drugs Inside Cells, www.washingtonpost.com, April 4, 2008.
3. Trafton, A. A Micropharmacy Inside; MIT TechTalk; vol. 52, no. 16, page 1.

In *Print*

Troubleshooting Microbiological Failures

From Radiation Sterilization: Validation and Routine Operations Handbook *by Anne Booth, Consultant*

Dose audit failures can be costly and result in delays in product distribution and sale. Any investigation to determine a probable cause depends on the data available and a thorough knowledge of both the manufacturing process and the test methods used. The following checklist can be used during an investigation to invalidate a failure and allow a reaudit.

Laboratory-related Issues

Personnel practices

- ✓ Were the operators properly trained, healthy or fatigued?
- ✓ Were appropriate aseptic handling procedures used?
- ✓ Was appropriate garb worn and donned in the proper sequence?

Housekeeping practices

- ✓ Were proper cleaning and decontamination methods used to prepare the test area?
- ✓ Were appropriate cleaning agents used for the proper exposure time?
- ✓ Was cleaning of all areas performed on schedule?

Environmental controls

- ✓ Were the temperature and humidity values within specification?
- ✓ Was the air pressure differential maintained continuously?
- ✓ Were the HEPA filters certified and working properly?
- ✓ Were the viable particulate monitoring results (for surface and air viables, personnel gloves and gown samples) within established limits?
- ✓ Was there any unusual activity in the room or has the room loading increased?

Sterility testing

- ✓ Did the test laboratory show a pattern of test positives?
- ✓ Were the growth media prepared and sterilized properly?
- ✓ Were the negative controls contaminated?
- ✓ Were test samples handled properly and disinfected before movement into sterility suite?
- ✓ Did any unusual events occur before or during the test?

continued on page 16

Recent Sci-Tech Discussions: Cleanroom Recovery Times

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

Are there any regulation or reference that defines the performance of recovery time in cleanrooms? So far I have checked EU Annex 1, but nothing is mentioned about this specific test. Any hint or comment will be welcomed. Best regards for all.

Respondent 1: The test method can be found in ISO standard 14644-3. It can be ordered from www.iso.org

Respondent 2: In the ISO 14644 you talk about recovery time in cleanrooms and others also in OMS GMP. This example of method test (in French):

Evaluer le temps de décontamination (temps nécessaire au système de traitement d'air pour permettre un retour des conditions initiales) de chaque salle.

- Sélectionner pour chaque local le point critique c'est à dire le point ou le produit est le plus exposé
- Identifier la classe de départ C0
- Mettre le compteur de particules en fonctionnement
- Polluer le local à l'aide d'un aérosol jusqu'à obtenir le taux d'empoussièrement de la classe supérieure C1 = C0+1
- Arrêter le générateur
- Sélectionner les tailles de particules 0.5mm et 5mm
- Effectuer une mesure pendant 20 minutes après avoir programmé l'appareil
- Conserver les tickets correspondants aux mesures du compteur de particules et les coller à la fiche de test sous le tableau correspondant
- Tracer le graphe des deux tailles de particules 0.5mm et 5mm: C = f (t) avec C la concentration particulaire et le temps en minutes
- Déterminer sur la courbe le temps nécessaire pour permettre un retour aux conditions initiales pour les salles classées ISO 7
- Déterminer sur la courbe le temps nécessaire pour atteindre 90% pour les salles classées ISO 8

Respondent 3: Look in ISO 14644. It's referenced in part 2 and the method is described in part 3. There may have other local country-specific references, however, these often quote the ISO standard.

Questioner: Merci pour le bon renseignement [Respondent 2], ça vien de la ISO? And thank you very much for the rest of the colleagues. We are already requesting the ISO 14644 parts I, II and III for consulting.

My question was also focused to see if this test is mandatory in specific situations, as we received remarks from some QA specialists for generalizing such a test. In my humble opinion it shall be determined from a risk analysis approach, for instance, intermediate airlocks between a cleanroom and a nonclassified area for product outlet or personnel access.

Respondent 4: Es tut mir leid ich nicht verstehe Franzosich.

Re: The clean up rate in clean rooms. This is something I have been doing and advising since pre-ISO 14 days, as it is a sensible parameter to understand. In revised Annex 1 it does actually state that rooms should be cleaned up after a short period, 15 to 20 minutes, and as the Annex now points to ISO 14 (test methods), one should follow those test methods to determine the actual values. I agree risk assessments should play a part in the monitoring of areas.

The revision of Annex 1 has at last turned up on the Eudralex website. This is due to be implemented in March 2009, with protection of partially stoppered containers for freeze drying to follow later in 2010.

Respondent 1: I interpret EU Annex 1 as making recovery time studies mandatory, in that they require "at rest" conditions to be achieved after 15–20 minutes. I believe this can be achieved by demonstrating during routine monitoring that your room recovers after filling operations cease. There may be other interpretations, however. I would be interested in hearing from persons who deal with European inspectors more often than we do.

Respondent 1: [Respondent 4 wrote]: *Re: The clean up rate in clean rooms. This is something I have been doing & advising since pre ISO 14....*

Yes. Thanks for pointing that out to everyone. We have been following the new Annex at [my firm] and are planning to implement corrective actions at our…facility. For those who haven't read the new annex yet, it requires lyophilized vials to remain under grade A conditions until capped, not just until fully stoppered. Capping operations should be in ISO class 5 conditions at rest, or should be supplied with class 5 air.

Respondent 5: The subject of Recovery Time was discussed in this forum last year. I reproduced below some of the comments that were made at that time….

Questioner: Without any intention of establishing a big controversy on this, I have a different interpretation on the matter. We are focusing on the following statement, which is the same in the old Annex 1 as a note (b) in section 3 and the recently revised one in section 14:

The particulate conditions given in the table for the "at rest" state should be achieved after a short "clean up" period of 15–20 minutes (guidance value) in an unmanned state after completion of operations.

From my point of view it is nothing new; it has been there all the time to give a guidance on how to reach the "at rest" conditions after a continuous usage period of the clean areas or maintenance operations. We have applied this for starting revalidation of our clean areas after a thorough cleaning, and sometimes we have given more than 20 minutes upon forbidding any access. I really do not see any other interpretation so far.

I surely have seen tests that I would say come from practice, for instance, to simulate critical situations like energy shutdowns in order to determine the time in which the clean areas recover their class status after the HVAC restarts or as I said in my former posting, intermediate airlocks between a cleanroom and a non-classified area with personnel or product outlet traffic. In all cases, I see these tests related to the air changes per hour for adjusting to demanded conditions, refine the HVAC balance and establish usage of these areas. Apart from these situations (and others that I can miss in particular) I do not see any rationale on generalizing recovery time tests to all clean areas, specially when air changes per hour; differential pressure balance and usage should be well established from design and verified upon particle counting to fullfill class specs during validation.

So I still do not see a explicit definition of Recovery Test in Annex 1, although as the revision makes full reference to EN ISO 14644 (1-3)… and after reading the set of postings recalled by Respondent 5, I recognize I have to look these ISO norms more deeply.

Anyway and far from being absolute, any correction to my points of view will be welcomed, and if there is a colleague in this forum who has participated directly in Annex 1 revision and can clarify all these interpretations. [That] will be even better.

Respondent 1: I don't think that what you are saying is controversial. ISO 14644-3 does give a method of establishing recovery time, but if you are monitoring your operations, and they come back to at-rest conditions within 15–20 minutes, you are fine. We do not perform any particulate challenges to establish recovery time. We just monitor for a few additional minutes after the end of operations. You are absolutely right that it is nothing new.

Respondent 3: Here are my thoughts following your last post. I guess it depends on what one wishes to achieve in performing the recovery test. What are you dealing with? Drug product or drug substance? Your approach for using a specific test such as recovery time might be different as a function of that. Whilst Annex 1 is for drug product, the way I have understood that the EMEA interprets EU GMP is that all sections are complementary and applied as appropriate. Thus, Annex 1 could apply, in addition to Part II, during an API manufacturing process for example, where an aseptic manufacturing step was required. You would need to demonstrate recovery time.

As an example, for me, the recovery test is relevant in many more cases than just those directly applicable in Annex 1, but as mentioned, based on a QRM approach. I use it as an indicator of how my HVAC system performs (amongst other indicators). In my case I use it almost everywhere since I operate a multipurpose facility for biologics, sometimes including virus manufacturing. Some may wish to argue non-necessity, but for me doing the recovery test provides a comfort factor compared to the additional cost, which is marginal.

For the record, ISO 14644 uses the 100 to 1 principle (recovery to 99%) and does not recommend using recovery time for ISO 8 and 9. Since everybody is becoming more international, there is a local reference in France, (as your French is ok !), NF S 90-351 (Juin 2003) Etablissements de santé. Salles propres et environnements maîtrisés apparentés – Exigences relatives pour la maîtrise de la contamination aéroportée. That deals with a 90% "cinetique de decontamination" for 0.5 µM and gives times for ISO 5, 7 and 8. You can get it from www.afnor.fr—my European perspective. I'd be happy to discuss further if you wish.

Respondent 6: [Respondent 3], You stated: *For the record, ISO 14644 uses the 100 to 1 principle (recovery to 99%) and does not recommend using recovery time for ISO 8 and 9.*

We are a contract API manufacturer with ISO 8 rooms and we have been cited by European clients for not performing this test. So, my question is, is this recommendation, not to perform this test for ISO 8 rooms, being ignored by European regulators?

Also, you stated, if I understood you correctly, that this requirement may not apply to APIs. Could you please clarify?

Respondent 4: [Respondent 1], My past experience of doing this was in the days of British Standard (BS5295 I think). More recently I used this to determine a clean up in a gowning room leading to a grade B area. We then set the procedure and interlocks such that the next operator couldn't enter until after the clean up period we determined had elapsed. This was inspected by an EU competent authority in 2004 and again in 2005. It was accepted as an approach on both occasions

Respondent 3: [Respondent 6], The ISO 14644 international standard describes specifications and methods that can generally be applied to clean room characterization used in a number of different industries, including the pharmaceutical industry.

continued on next page

Recent Sci-Tech Discussions: Cleanroom Recovery Times, continued from previous page

Nevertheless, it will be up to the user to interpret and apply the tests or verifications appropriate to their application or do what is currently accepted practice in that domain.

I don't think that the recommendation about recovery testing is being ignored. Whether or not you apply that test will depend on what your company does, the nature of your product and the risk associated to the product, personnel and environment. One could follow an "apply everything" strategy and consider that an overkill situation is ok.

That may be tenable for a small organization which possibly has to outsource the skills necessary for that work or for very large ones where you have a very high quality standard. But that's not in line with current thinking on quality and risk. There comes a time when, having taken into account regulatory requirements, one should be more analytical and, according to risk, decide on a scientific, technical and cost/benefit basis whether or not to implement certain tests. It may be, that for your application, you consider that a decontamination test in an ISO 8 clean area is necessary, regardless of what ISO 14644 says. If based on a sound scientific and technical argument, fine. If on the same basis you decide it's not necessary, then defend that position in the same manner (for various reasons it may sometimes still be easier to simply do the test...!).

I did not say that recovery testing does not apply to API's. In some cases it might. To summarize using my previous example. API manufacturing in EU is covered by Part II. It may be that if there are certain parts of your API process that are aseptic steps, then you may be expected to follow the relevant sections in Annex 1 to Part I for that part of your process. In that case, you might need to do recovery testing. Keep common sense and sound scientific and technical methodology in mind though.

In Print, continued from page 13

Product handling

- ✓ Were samples transferred to the lab in plastic bags?
- ✓ Was the packaging decontaminated prior to testing?
- ✓ Were all packages intact?

Organisms

- ✓ Identified to the genus and species level?
- ✓ Were the identified organism found in the product bioburden, or in the sterility suite?

Manufacturing-related Issues

Manufacturing

- ✓ Had the raw materials or components changed?
- ✓ Had there been a process change that could impact bioburden levels?
- ✓ Did equipment require maintenance?
- ✓ Had there been an increase in equipment numbers or number of personnel working in the room?

Product samples

- ✓ Were samples properly prepared and packaged?
- ✓ Was a SIP used and if so, how was it prepared?
- ✓ Was the bioburden distribution considered?

Irradiation

- ✓ Was the sterilization dose delivered properly?

Microbiological Considerations

Bioburden

- ✓ Were levels higher than historical values?
- ✓ Were spikes found in the quarterly audit samples?
- ✓ Did the bioburden trending indicate an upward trend?
- ✓ Were any positives in the sterility test identified as resistant organisms?

Radiation Sterilization: Validation and Routine Operations Handbook, by Anne Booth, offers practical procedures for the validation and routine monitoring of specific radiation sterilization processes. Although the scope of the standards refers to medical devices, the requirements and guidance may be applicable to other health care products.

PDA Interest Groups & Leaders

PDA Interest Groups are divided into five sections by subject matter. This aligns them for improved effectiveness, supports increased synergies and provides the opportunity for Interest Group members to play a more active role in Task Forces. The five sections are Quality Systems and Regulatory Affairs, Laboratory and Microbiological Sciences, Pharmaceutical Development, Biotechnological Sciences and Manufacturing Sciences. PDA's goal is for each group to have co-leaders from the three major regions in which the Association is active: Asia, Europe and North America. Any PDA member can join one or more Interest Group by updating their member profile (www.pda.org/volunteer). Please go to www.pda.org/interestgroups for more information.

SECTION TITLE

Biopharmaceutical Sciences	Laboratory and Microbiological Sciences	Manufacturing Sciences	Pharmaceutical Development	Quality Systems and Regulatory Affairs

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Novel Delivery System Promises Electrifying Results, continued from cover

The authors go on to profile the development of "second-generation" DNA vaccines. One technique involves the direct modification of the plasmids or coadministration of plasmid DNA encoding chemokines, cytokines and other molecules. In some cases, the modified plasmids have increased immunogenicity in human subjects.

Another review article,[2] "DNA Vaccines against Human Immunodeficiency Virus Type 1 in the Past Decade," highlights the various advantages of these promising vaccines, among which are:

- Simple design
- Improved safety over live virus vaccine
- Quick and easy manufacturing
- Better quality control
- Enhanced heat stability

The authors wrote: The *simplicity of design and development of DNA vaccines and the power they bring to the development of subunit vaccines that are expressed in cells have made them extremely popular over the last decade.*

The authors go on to review the method and route of administration that have been tried by researchers, and there are many. Most widely used have been intramuscular needle injections and intradermal inoculation using a gene gun. Noninvasive methods attempted include topical, oral, intranasally and intravaginally.

All these methods of delivery, however, have produced similar results, the authors reported. *The use of these different routes and methods of delivery of DNA vaccines in general has been more potent in smaller animals and not as effective in primates*. Only a few cases of successful immune responses in humans were known, the authors noted, and *the magnitude of these responses has not been substantial.*

Two companies are at the forefront of innovating such devices and have entered into partnerships with several major DNA vaccine manufacturers for clinical research in recent years.

Electroporation Jolts DNA Vaccine Research

Despite the poor results in primate and human subjects, researchers continued to explore methods to elicit immunogenicity in humans from DNA vaccines. Research over the last several years suggests that electroporation will be one such solution.

Over the last several years, a number of Investigational New Drug filings (INDs) have surfaced and actual clinical studies begun for the delivery of various DNA vaccines using electroporation.

Use of electroporation to deliver drugs typically involves the combination of a needle device with a pulse generator. Two companies are at the forefront of innovating such devices and have entered into partnerships with several major DNA vaccine manufacturers for clinical research in recent years.

California-based Ichor Medical Systems offers what it claims to be "the first integrated and fully automated system for electroporation-mediated DNA administration." Firms utilizing the TriGrid Delivery System as an enabling technology for their DNA drugs and vaccines are:

- Aaron Diamond AIDS Research Center
- Bayhill Therapeutics
- Genexine
- The International AIDS Vaccine Initiative
- The Johns Hopkins Bloomberg School of Public Health
- Memorial Sloan-Kettering Cancer Center
- The Pasteur Institute
- Pharmexa-Epimmune
- Rockefeller University
- The Scripps Research Institute
- The U.S. Army Medical Research Institute of Infectious Diseases
- The Naval Medical Research Center
- The Vaccine and Infectious Disease Organization

In May 2007, Ichor announced FDA approval of a Phase I clinical trial for a DNA melanoma vaccine. In a press release, Ichor stated that the TriGrid system can increase uptake of the melanoma vaccine by 10 times, 100 times or 1,000 times as compared with other methods of delivery. The New York-based Memorial Sloan-Kettering Cancer Center, home to the vaccine, stated, "DNA cancer vaccines offer a new approach to immunotherapy, but we need to improve the efficiency of vaccine delivery. We are hopeful that Ichor's TriGrid will help fulfill that potential."

What is it?

Electroporation: Method for temporarily permeabilising cell membranes so as to facilitate the entry of large or hydrophilic molecules as in transfection. A brief (ca 1msec) electric pulse is given with potential gradients of about 700V/cm.—The Dictionary of Cell and Molecular Biology, 3rd Ed., online.

DNA-based immunization: Refers to the induction of an immune response to a protein Ag expressed in vivo following the introduction of vector-carried DNA encoding the polypeptide sequence.

The other major player in the DNA vaccine-electroporation symbiosis is also based in California. Inovio Biomedical Corporation, like Ichor, boasts an impressive list of partnerships, many of which are with major pharmaceutical players:

- Merck
- Wyeth
- University of Southampton
- The Moffitt Cancer Center
- Vical
- Tripep
- The U.S. Army Medical Research Institute of Infectious Diseases
- VGX Pharmaceuticals
- The U.S. National Cancer Institute
- The International AIDS Vaccine Initiative

At the time this article went to press, Inovio and Maryland-based Advanced BioScience Laboratories announced a licensing agreement permitting ABL to use the Inovio's device in research. ABL's **Phil Markham,** PhD, Scientific Director, said, "We have used electroporation, like the results being produced using this technology, and feel it is an important tool in vaccine development. Clients have been requesting electroporation technology and we look forward to being able to provide this cutting edge tool and expertise as a service for customers."

Inovio offers the MedPulser DNA Delivery Systems for intratumoral and intramuscular vaccine delivery. It too operates with a pulse generator and needle combination. The electrode-needle array consists of two sets of opposite needle pairs, or a total of four needle-electrodes. The arrays are available in different sizes and can use different voltage pulses from the generators to create the optimal field strength.

Currently, five vaccines are in Phase I studies using Inovio's technology. Merck is using the device in its Phase I trials for DNA vaccines for breast, ovarian, colorectal and lung cancers. UK-based University of Southampton has entered Phase I/II for a DNA prostate cancer vaccine. Tripep is in Phase I/II for its DNA hepatitis C virus vaccine/Medpulser combination. In addition, two malignant immunotherapy Phase I/II trials are underway by Vical and the Moffitt Cancer Center. Vical also has an IND application for cytomegalovirus trial.

The interim data showed not only was electroporation safe and well tolerated among subjects, but the magnitude of the antibody response was significantly higher in the patients treated with the device.

Interim data from a Phase I/II study for a DNA prostate cancer vaccine presented publicly in 2007 was electrifying. At the 3rd International Conference on DNA Vaccines in Malaga, Spain, the University of Southampton presented results of a 24-patient study with recurrent prostate cancer.[3] The patients are receiving a PSMA27/pDOM Fusion Gene with or without the electroporation device.

The interim data showed not only was electroporation safe and well tolerated among subjects, but the magnitude of the antibody response was significantly higher in the patients treated with the device. The signs of efficacy came with patients showing significant antibody responses numbering 4 out of 10 in patients treated without electroporation and 9 out of 10 in the groups treated with electroporation.

While preliminary, **Christian Ottensmeier,** MD, PhD, senior clinical research fellow, stated during his presentation to the 3rd International Conference, "This data demonstrates for the first time in a clinical trial that the significant enhancement in potency of a gene-based vaccine delivered by electroporation in animals can also be seen in humans."

Boosting an Industry

It is too early to truly predict the ultimate impact electroporation will have on the future of DNA vaccines as viable options for preventing AIDS and a host of cancers. However, several companies and organizations are betting heavily in its favor.

In 2006, Wyeth's license for the MedPulser could be worth up to $64 million to Inovio. The firm also has received several milestone payments worth up to $2 million from Merck since 2005.

Ichor's agreement with the U.S. Army is worth $2.3 million, and the privately held company reports grant funding in excess of $10 million.

For a vaccine market that is counting heavily on the promise of DNA vaccines for hepatitis, cancers and AIDS, the use of novel delivery systems like electroporation offer just the kind of boost both patients and companies need.

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Quality & Regulatory Snapshot

Interest Group *Report*

The following are reports from two interest group meetings at the *2008 PDA Annual Meeting.*

Inspection Trends/Regulatory Affairs Interest Group

The U.S. FDA's **Susan Laska,** Acting Team Lead, International Compliance Team, Division of Manufacturing Product Quality, Office of Compliance, CDER gave a presentation which addressed a number of topics, including: FDA's GMP for the 21st Century initiative; recently issued and planned guidance documents; FDA's initiative to address marketed, but unapproved drugs; international inspections; and inspection trends.

With regard to the 21st Century initiative, she noted that the intent is to create the product quality regulatory system of the future. The three themes associated with this initiative are to encourage best practices in manufacturing, to encourage the use of risk-based approaches and to enhance coordination, consistency and predictability.

With regard to Guidance documents and activities, in addition to the revised guidance on INDs (*Approaches for Complying with CGMPs During Phase 1*) and the revised process validation guidance, she noted there are plans for a guidance on comparability protocols and provision of CMC information for protein drug and biological products. As noted in her slides, some of the expected features of the revised process validation guidance were described.

FDA's initiative for marketed unapproved drugs is intended to improve the safety and effectiveness of the nation's drug supply, encourage compliance with the drug approval process and minimize disruptions in the marketplace. Laska noted that drugs marketed illegally without approvals are subject to FDA enforcement actions at any time. Some examples of recent enforcement actions were provided.

On the topic of inspections, She said there were 1,100 GMP inspections and 200 PAIs conducted in the United States in 2007; internationally there were 200 inspections conducted. This number is expected to grow to 500.

Data on types of inspections and most frequent observations were presented. The leading observations in 2007 (and their rank in 2008) are:

- Quality unit responsibilities and procedures (1 in 2008 as well)
- Control procedures not established to monitor/validate processes which may be responsible for causing variability (5 in 2008)
- Laboratory controls do not include scientifically sound specifications, standards, sampling plans and/or procedures (4 in 2008)
- Written production and process control procedures not followed or documented (3 in 2008)
- Incomplete investigations

Quality Systems Interest Group

At the meeting, the Quality Systems IG discussed Quality Agreements. The following points were made by participants:

1. Some may call them Quality Agreements or Technical Agreements; some have separate Technical Agreements; but all agree that the Business Agreement is a separate document.
2. Template approach or "Key Elements" approach followed with line-by-line responsibilities. Some still prefer having a separate Technical Agreement.

3. Lawyer involvement/approval of anything is still an issue—holds up the agreement process. Maybe could establish a template, have legal approve it and then make it part of your Quality Agreements SOP/Form.
4. Keep all aspects of the business/financial requirements out of the Quality Agreement; don't include timelines, liabilities (monetary or otherwise).
5. Transport portion should be part of the Quality Agreement.
6. Quality Agreement and Business/Commercial agreement should cross reference each other.
7. Components of a Quality Agreement: Responsibilities (everyone liked the Table approach and have seen that typically used)
8. List point(s) of contact. Do you apply change control to the point of contact or changes in any other personnel? Some said they include key personnel as requiring change control approval; most said no.
9. Who reviews the batch records? Most said that they do; however, some said that after they feel comfortable with a contractor they then cut back on the amount of review of records. Typical was 3–5 batch production records full review; if okay, then cut back.
10. What deviations do you require review/approval on? Again, defined in the Quality Agreement. Some folks review and approve all of them; some list examples of what requires review/approval by the sponsor.
11. If deviations are indirectly associated with the production of their material all said it would depend; for review/approval. If, ultimately, a deviation affects their product/material, even if it is a system deviation, they would want to at least review it.
12. Having a complete, thorough investigation was the primary concern when it came to deviations, not necessarily root cause analysis. All want to be able to "chime in," but not necessarily review/approve.
13. One person said that they prefer trusting a CMO and letting them use their systems—after audit approval—rather than becoming involved with all deviations and investigations.
14. Proactive and routine audits were preferred rather than reactive audits. Increase the number of audits if needed.
15. All would like to see quarterly reviews or trending of all deviations at a CMO so that they could make a judgment on whether to audit again or not, increase review of deviations, etc.
16. In-house expertise in the area that the contractor was hired was also mentioned as key to becoming less involved in contractor investigations. Become educated in the area that the contractor is working for you.
17. Some folks review CAPAs from contractors when they affect the sponsor process; some don't review or approve CAPAs. Documentation of conclusions though was critical; want to make sure conclusions don't implicate the sponsor product if the deviation really doesn't.
18. Define the level of involvement of the sponsor in investigations/CAPA, etc., within the Quality Agreement itself. It's a tough area to define, but it should be part of the quality agreement.
19. Back to change control—must define what needs to be reviewed and approved and what doesn't. Level I versus II or Major versus Minor. Some folks said that since there is so much gray area, they want to at least review *all* changes that directly impact their product/material. Most stated that they don't want to review like-for-like change.
20. Is it healthy to hold the hand of your CMO? Ultimately you need to rely on the CMO's quality system.

Proposed Legislation Provides FDA with Additional Resources

Emily Hough, PDA

Over the course of 2008, the U.S. FDA's ability to protect the American public from unsafe and ineffective products because of inadequate resources has come under increased scrutiny. Already, the U.S. Congress has held several hearings on the situation prompted by adverse events from products entering the United States from overseas suppliers and the Agency's own report regarding internal scientific and manpower shortfalls **[Editor's Note:** See the *PDA Letter,* February 2008, p. 25.**]**

Steven Silverman, Assistant Director, Office of Compliance, CDER, FDA, said at the Food and Drug Law Institute's (FDLI) Annual Meeting in March that FDA has been limited in what it can and cannot do, because "the demands on the Agency have exploded in recent decades…." Silverman said that, "research factors into [the] ability to recruit and train new employees to attain [a] highly skilled and educated workforce and to send [the] workforce to the places of many of activities [where regulation] takes place. Now I make these points, not to cry poverty or to argue that we can't succeed as an Agency, but to the contrary…my point is that like many other federal agencies, private sector businesses for that matter, the scope of what we do is affected by our workforce and our resources."

In recent months however, some solutions have materialized to help the FDA receive more resources, both in terms of capital and its workforce.

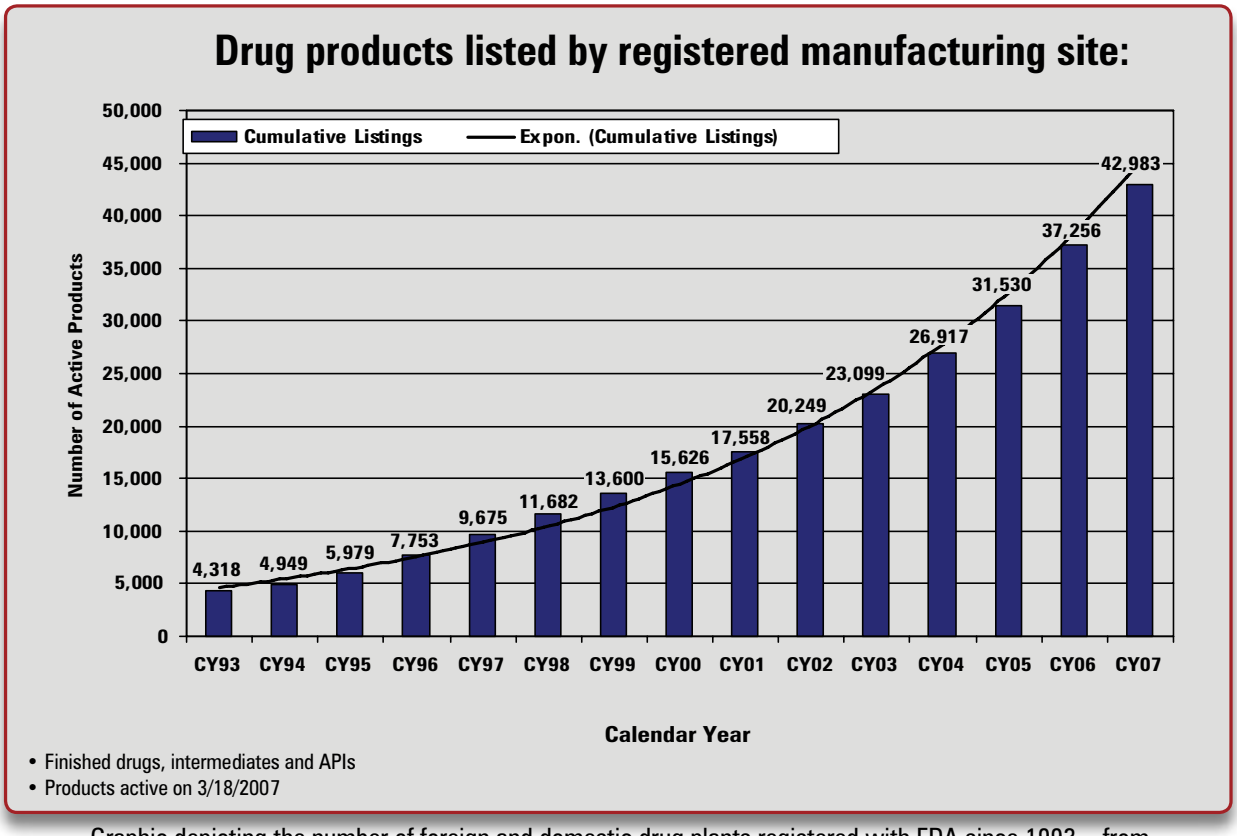
In May, the Senate Appropriations Subcommittee approved an additional $275 million for the U.S. FDA in an emergency supplemental appropriations bill.

"With serious concerns about the FDA lacking the resources to do its job, this much needed increase in funding means the Agency can hire more food inspectors, open offices overseas, expand data collection and take other necessary steps to prevent our food and drug safety being severely compromised," Senator Herb Kohl said who chairs the Senate Agriculture, Rural Development, and Related Agencies Appropriations Subcommittee.

The $275 million will allow the Agency to open its first two overseas offices; hire an additional 119 food safety inspectors; implement new drug safety initiatives, including pediatric drug and device safety, post-market study commitments, and improved drug surveillance and labeling, as required by the recent Food and Drug Administration Amendments Act; upgrade FDA's IT systems to improve drug safety, including more rapidly identifying adverse drug events; hire an additional 99 medical product safety inspectors; expand science training for FDA employees; and strengthen FDA's science programs to allow them to more effectively regulate new and complex products.

The funding level and specific activities included in the Senate versions of the supplemental appropriations bill were provided by the FDA and identified as the highest needs activities that they could immediately begin to implement. The funds were included in an emergency spending bill for the wars in Iraq and Afghanistan.

In mid-April, a discussion draft entitled, "FDA Globalization Act of 2008,"under the leadership of ➤



Graphic depicting the number of foreign and domestic drug plants registered with FDA since 1993—from Steven Silverman's presentation at FDLI

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Lonza

Proposed Legislation Provides FDA with Additional Resources, Funding, continued from page 24

Rep. **John Dingell** (D–Mich.), was presented for congressional consideration. The Legislation intends to strengthen the Agency's oversight capabilities overseas. It will also "provide adequate funding and authority for FDA to ensure the safety of the nation's drug, medical device, food and cosmetic supply in an increasingly globalized marketplace"—something that FDA Commissioner, **Andrew Von Eschenbach,** MD, has been concerned about. In March, he spoke at FDLI's Annual Meeting and said that FDA's problem is "further complicated by the radically and rapidly changing world that is now being immersed into a sea of change described by the words such as 'globalization,' 'just in time delivery,' 'fresh everyday,' not to mention words like 'bioterrorism' and 'pandemic.'"

In April, Von Eschenbach at a hearing on FDA's foreign drug inspection program said in front of the Energy and Commerce Committee's Subcommittee on Oversight and Investigations that "FDA needs a more continuous stream of information about the risks posed along the entire lifecycle of imported products, and the ways in which manufacturers, transporters, importers, and distributors are addressing those risks." Von Eschenbach said that that information would allow FDA to target its resources in the most efficient manner to best protect public health.

An overarching piece of legislation that seems to address many of FDA's problems is the Food and Drug Administration Act of 2007 (FDAAA). According to Von Eschenbach, the Act is an important component of "fixing" the FDA.

"In the past two years, we at FDA have been approached on how to manage and get out of this crisis….I will tell you that at the onset, the challenges are and will continue to be formidable and the current interventions are absolutely vital to be able to assure success in the future, and we must be and are acting to address these concerns," Von Eschenbach said. "The road to recovery will be longer rather than short and must absolutely be sustained over time. There will be no quick fix, no quick cure….The remedies are many, and I can not touch upon all of that. But I want to focus on one important component of this effort and that is our ability to fully implement the provisions of the Food and Drug Administration Act of 2007."

An overarching piece of legislation that seems to address many of FDA's problems is the Food and Drug Administration Act of 2007.

FDAAA was signed into law on Sept. 27, 2007, and adds new provisions to the Federal Food, Drug, and Cosmetic Act (FD&C). In the FD&C Act, certain existing laws were set to expire on Sept. 30, 2007; FDAAA has made it so changes to the previous laws were made and new amendments added.

Some of the provisions included in FDAAA that reauthorize existing laws are the Prescription Drug User Fee Act (PDUFA), which allows FDA to collect fees from drug companies to help fund reviews of new drugs. The act enables shorter review times and a more predictable review process, while still maintaining high-quality reviews; and the Medical Device User Fee and Modernization Act (MDUFMA) allows for user fees and will allow FDA to make significant improvements in the medical device review program. The reauthorization of the PDUFA and MDUFMA will provide for a tripling of funding from user fees for post-marketing safety surveillance.

Also, in accordance with the Act, FDA is also looking to fill over 600 new positions, as well as backfill over 700 existing spots. The 1,300 positions is nearly triple the number of people hired from 2005–2007. This comes as current top field investigators and managers are reaching retirement and have not been replaced by new investigators.

The law also provides for clinical trial registries, enhanced drug safety, and the creation of a foundation to modernize product development, accelerated innovation and enhanced product safety.

Also at FDLI, **Douglas Throckmorton**, MD, Deputy Director, CDER, FDA, focused on what FDA is currently doing to comply with the Act. "Obviously [the Act] is what the lawyers from the FDA are currently working on, and we are going to need to accomplish this as soon as we can. None of the work the FDAAA asks us to accomplish diminishes [from] the commitments that the Center has, that the Agency has, to make safe and effective drugs available to the public in a timely and efficient manner. I think everyone working within the Agency, like everyone in this room as well, is aware of the serious burden of unmet medical need in the U.S. and the need to have an efficient and timely medical product available. We are given additional resources, the promise of greater human resources most importantly, to support the things that FDA is being asked to do.

"FDAAA says a lot about pharmacoviligence and this is an area that there has been a lot of interest in. [The Act] promises us additional resources to address the dramatic increases against adverse events that we are receiving electronically, sort of day-to-day. We are approaching 500,000 adverse events reported per year now

and just managing the information flow is a challenge…. Second, FDAAA gives us a task that says that [we] need to expand our use of access to population databases, [we] need to form a link database to better understand efficiency, to better understand post marketing safety. It is an enormous task with enormous challenges and ambitious timelines. It's in the range of 100 million covered lives by 2025 or something thereabout. In order to accomplish that sort of a task, we are going to have to change the type of personnel that we are hiring out, and the kind of expertise that we have within CDER.

"There is obviously great expectation from the public that we are going to be communicating as much as we possibly can and health care providers are obviously interested in the information to the extent that we can give it. FDAAA sets up a new advisory committee with extensive roles and processes. It sets up in particular the committee around safety communications, and it tasks the FDA with interacting with that committee around several areas to better understand how best to communicate the safety information that we have uncovered….We understand we need to work better at communicating, we understand we need to work better to make best possible use of our resources.

"FDAAA will have a profound effect on drug regulation throughout drug lifecycle on events we don't yet see fully. We just started the process of implementing FDAAA. In addition to and consistent with the work on FDAAA, FDA and regulators have a critical role to support innovation, to reinvigorate efficient medical product development. All of us need to be able to question assumptions that have guided us up to this time and be ready to change when those assumptions can no longer be defended. It's not just a job for the FDA; it is a critical job for us to keep in mind."

Since it was signed, FDA has been working on implementing initiatives of the Act. In the next few months, FDA, in compliance with the Act, will be issuing a guidance on how certain requirements apply to pediatric post-market surveillance; develop an internet website that provides drug safety information to patients and providers; and establish the amount of a priority review user fee for priority review voucher program.

Visit the FDA website at: www.fda.gov/oc/initiatives/advance/fdaaa.html for more information about the Act.

For More, Turn to IPQ

The May/June 2008 issue of *International Pharmaceutical Quality* provides in-depth coverage of FDA's ongoing effort to better monitor overseas manufacturing facilities.

Keep track and make sense of the recent series of U.S. Congressional hearings on FDA and its capabilities in the wake of several well-publicized incidents of unsafe products entering the U.S. market. Read proposals in the so-called "FDA Globalization Act of 2008."

Balanced coverage includes the perspectives of big pharma, biologics, generics, distributors, and pharmacies. The "Voices from the Dialogue" include key players like: Congressman John Dingell (D-Mich.) on new congressional initiatives; Barr Labs CEO Christine Mundkur (representing the Generics Pharmaceutical Association) on foreign drug oversight; CDER's Janet Woodcock on the heparin investigation; and FDA's von Eschenbach on the Agency's global challenges.

Visit www.ipqpubs.com to learn more.

Summary: FDAAA

- Passed on a background of increasing public interest and expectation
  - Efficiency of development
  - Interest in safety of products
  - Communication about products throughout the life-cycle
- FDA will keep focus on FDA mission to protect and advance the public health
- FDA has just started the process of implementation for FDAAA. We will keep the public informed of our efforts as they unfold

Conclusion

- FDAAA will have a profound effect on drug regulation throughout the lifecycle, in ways we don't yet see fully. We've just started the process of implementation for FDAAA. We will keep the public informed of our efforts as they unfold.
- In addition to, and consistent with, the work on FDAAA, FDA has a critical role in supporting the innovation, to reinvigorate efficient medical product development. We all must:
  - Question assumptions
  - Be ready to change
  - **Not just a job for the FDA**

Douglas Throckmorton presented slides summarizing the FDAAA

Regulatory Briefs

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

North America

U.S. FDA to Fill over 1,300 Positions

The FDA is hiring individuals with science and medical backgrounds to help meet the Agency's responsibilities to assure the safety and/or efficacy of human and veterinary drugs, biological products, medical devices, food, cosmetics and products that emit radiation. Biologists, chemists, medical officers, mathematical statisticians and investigators are among the experts in demand, according to the FDA as it begins a multi-year hiring initiative.

"It takes a large pool of talented people for the FDA to protect and promote the public health," said John Dyer, FDA's Deputy Commissioner for Operations and Chief Operating Officer. "Each month there is a delay in bringing critical staff on board impairs the agency's ability to fulfill this mission."

In fiscal year 2008, the FDA is looking to fill more than 600 new positions and to backfill over 700 others to implement the FDA Amendments Act of 2007, the Food Protection Plan and the Import Safety Action Plan.

Parliament of Canada Amends Food and Drugs Act

The Food and Drugs Act was amended by the Parliament of Canada. The amendment seeks to modernize the regulatory system for therapeutic products and foods, to strengthen the oversight of the benefits and risks of therapeutic products throughout their life cycle, to support effective compliance and enforcement actions and to enable a greater transparency and openness of the regulatory system.

The purpose of the Act is to protect and promote the health and safety of the public and encourage accurate and consistent product representation by prohibiting and regulating certain activities in relation to therapeutic products, foods and cosmetics.

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Siddharth Advant, Tunnell Consulting

Reiko Akakura, Banyu Pharmaceutical

Kenjiro Akashi, Yamatake Corporation

Leanne Amitzi, Modigenetech

Sherry Appel, Merck

Thomas Arista, U.S. FDA

Nina Aschengreen (NADA), Novo Nordisk

Eiji Bando, Senju Pharmaceutical

Mario Barbini, Fedegari Autoclavi

Wesley Barnwell, Tessarae

Scott Bentley, Ben Venue Laboratories

Peter Bisp, Novo Nordisk

Meseret Bogale, Allergan

Allen Bolden, Human Genome Sciences

Larry Boos, Self Employed

Nathalie Brisebois, Draxis Specialty Product

Brian Brogie, Catalent Pharma Solutions

Lorraine Brophy, Centocor Biologics

Thomas Brush, Indiana University

Melissa Campo, Morphotek

Dennis Caron, Genentech

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Pierre Dubord, Wapiti Pharmaceutical Services

Sherita Eberhardt-Black, Ben Venue Laboratories

Itaru Endo, Daiichi Sankyo Propharma

Dave Ferrell, AcuTemp Thermal Systems

Adrianna Fidelibus, BioMarin

Leah Frautschy, Genentech

Kazuaki Furukawa, Asubio Pharma

Virginia Gagliardi, Penn State University

Gregory Gallegos, Genentech

Dawn Geesaman, Lonza Walkersville

Chad Gerbick, Ben Venue Laboratories

Elie Ghattas, B. Braun

Robert Giannini, IriSys

James Graves, Aptuit

Randi Hammond, Pacira Pharmaceuticals

Mary Haran, Shire Pharmaceutical

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Glen Harron, CIBA Vision Sterile Manufacturing

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Tsutomu Iwasaki, Corporate Research & Development Toyo Seikan Group

Mordechai Izhar, Ludan Engineering

Rachel Jelley, Bio Products Laboratory

Joseph Jerkins, Genentech

Kristina Joyce, U.S. FDA

Leaders to the PDA Community

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Wu Jun, Free-lancers

Chee Siong Kan, Aseptec Sdn Bhd

Seok Whan Kang, Celltrion

Yuko Kanou, Q.P. Corporation

Rachel Karpel, PCI

Deepak Kasbi, Lupin Limited

Royetsu Kato, Nihon Millipore

Shilpa Kaushik, Eli Lilly

Michael Kennedy

Tomohiro Kitagawa, Toyobo

Tatsuya Kobayashi, Daiichi Sankyo Propharma

Parag Kolhe, Pfizer

Naoko Koto, KNC Laboratories

Seizou Kurosaki, Nitto Medic

Yasushi Kuwabara, Denka-Seiken

Eric Lachance, GSK Biologicals

Diane Lane, Mountain West Quality Consultants

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Kevin Lin, Bayer Healthcare

Krista Liotta, Merck

Matthew Lorence, Tessarae

Lori Loy, Alcon Laboratories

Brian Lyons, Novartis

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Kinji Maemura, Yakult Honsha

Rostyk Mandzij, Protocol Link

Dean Marbury, Microbac Laboratory

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Randy Martin, BioMarin Pharmaceutical

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John McKenzie, General Econopak

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Yu Meng, Pfizer Pharmaceuticals

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Kathleen Mondazzi, EMD Serono

Saburo Murata, Astellas Pharma

Christine Murphy, CSL

Neritan Mustafa, Sensitech

Roman Mysak, Bristol Myers Squibb

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Masaki Naito, Ajinomoto

Kuniko Nakamura, Yell Pharmaceutical

Masaharu Nakanishi, Asubio Pharma

Manabu Nakatani, Nippon Boehringer Ingelheim

Yasutoshi Naraki, Zeria Pharmaceutical

Erikka Nelson, Bayer

Moshe Neuman, Bio Medical Research Design

Takahiro Nishikawa, Kirin Pharma

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Mami Okudaira, GE Healthcare Bio-Sciences

Claribel Oliveras, AstraZeneca

Yuuichi Oohashi, Nissin Pharmaceutical

Emilio Ortiz, Amgen Manufacturing

Yasumitsu Ouchi, Japan Poriomyelitis Research Institute

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Norimasa Ozaki, Nihon Pharmaceutical

Ralph Parchment, SAIC

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Rich Pascual, Pacira Pharmaceuticals

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Hung Peng, Wyeth

Gael Peron, Sartorius Stedim Biotech

Sharon Perry,

Martin Peterson, ThermoFisher

Steve Phan, Covidien

Nicolas Poulin, GlaxoSmithKline Biologicals

Vincent Pourbaix, GSK Bio

Joseph Provenzano, Genzyme

Miguel Quiles, Amgen Limited

We welcome more of this month's new PDA members on the next page ➤

Please Welcome the Following Industry Leaders to the PDA Community

continued from previous page

Roger Rajewski, Center for Drug Delivery

Abhishek Rajput, Indian Institute of Technology

Robert Ramos, PharmaBio Serv

Fraser Ramsay, Amgen

Chris Rea, Amgen

Jon Reich, Synertec

Joana Reymao, Hovione S.A.

Daniel Robins, Bioniche Pharma

Noemi Rojas, Wyeth

Udo Rossmann, MGlas AG

Cristen Rother, Genmab MN

Brad Rust, Novartis

Brian Sampson, MedInstill

Futoshi Sanematsu, Takeda Pharmaceutical

Brian Sanford, Genentech

Takeshi Sano, API

Takashi Sasaki, Rohto Pharmaceutical

Hideto Sasaki, Takeda Pharmaceutical

Norihisa Satoh, Nippon Kayaku

Shoji Satoh, Toa Eiyo

Jill Schurr, LABS

Martin Schwabe, CSL Behring

Emily Sechler, Three Rivers Pharmaceuticals

Robert Seiter, Ben Venue Laboratories

Taras Seniuch, Vertex Pharmaceuticals

Siti Khalijah Shabudin, B. Braun Medical Industries Sdn. Bhd.

Odelia Shachaf, Gamida Cell

Manish Sharma, Cephalon

Jeffery Sheffer, Merck

Mikako Shinada, Hauptpharma Toride

Susumu Shinagawa, Toray Industories

Satoru Shindoh, Seikagaku

Rebecca Silverstein, Talecris Biotherapeutics

Tania Simoncelli, Invensys

Jennifer Strom, Tolmar

Yoshihiro Sugioka, Otsuka Pharmaceutical Factory

Vivian Sui Man Chu, CIBAVision

Yoshinori Suzuki, Chugai Pharmaceutical

Hiroyuki Suzuki, Invitrogen

Shigenori Takahashi, Daiichi Sankyo Propharma

Hidekazu Takeuchi, Taiho Pharmaceuticol

Masatomi Tashiro, Daiichi Sankyo Propharma

Michel Tayzon, CIBAVision

Allison Thomas, Biotest Diagnostics

Inpone Thongthap, Bayer Healthcare

Wendy Tilton, Medical Imaging

Robert Toal, Moda Technology Partners

Hiroki Tomozawa, Astellas Pharmac

Derek Torre, Valsource

Kanako Uchiyama, Terumo

Junichiro Uda, Japan

Takeshi Udagawa, Terumo

Eiichiro Ueda, Asahi Kasel Engineering

Takuya Urushihara, Eisai

Ryan Verazin, Sanofi Pasteur

Masaaki Wada, Shionogi

Andy Wainwright, Expeditors International

Stephen Wallace, Covidien

Al Ward, Genentech

Takuji Watanabe, Ninon Generic

William Weiser, Liquidia Technologies

Melinda White, Medtronic

Lydia Wible, ImClone Systems

Ellen Williams, AMEC

Paul Wong, Bayer HealthCare Pharmaceuticals

Jeannine Wong, Amylin Pharmaceuticals

Tomoo Yamauchi, Toagosei

Vang Yang, Novo Nordisk Pharmaceutical Industries

Masamitsu Yano, Q.P.Corporation

Gen Yasuhara, GE Healthcare Bio-Sciences

Seijiro Yoshioka, Eisai

Jun Zhao, MGI PHARMA

Xuemei Zhu, Baxter BioScience

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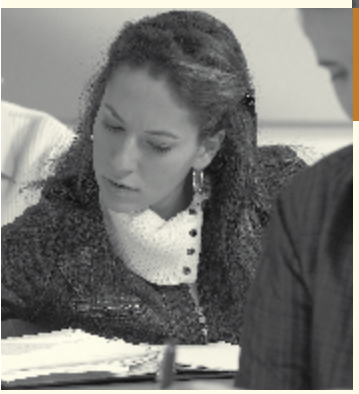

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Contact:
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www.pda.org/clinicaltrials

Chapter Contacts

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

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Volunteer Spotlight

I once owned a sub shop in South Florida with my brother-in-law …[who] could not make change correctly. They called him, "Two-Twenties-for-a-Ten Ben."

Hal Baseman

Company: ValSource LLC

Title: Principal and COO

Education:

BS, Biology, Ursinus College

MBA, Management, La Salle University

PDA Join Date: 1981

Areas of PDA Volunteerism:

Science Advisory Board (co-chair)
Board of Directors
Process Validation Interest Group (co-leader)
TRI Faculty
2008 Annual Meeting Planning Committee
2009 Annual Meeting Planning Committee (vice chair)
2010 Annual Meeting Planning Committee (chair)
Risk Management and Aseptic Processing Conference (co-chair)
Risk Management for Aseptic Processing Technical Report Task Force (co-chair)
TR-22 Revision Task Force (co-chair)

Professional Awards Won: PDA 2007 Distinguished Service Award

Interesting Fact about Yourself:

I once owned a sub shop in South Florida with my brother-in-law. We went out of business, because my partner could not make change correctly. They called him, "Two-Twenties-for-a-Ten Ben."

Why did you join PDA and start to volunteer?

At first I felt that it was a good way to learn more about the technical and regulatory aspects of our industry. Later, I learned that it was an effective way to network with the best people in the industry. Still later it became a way to help influence the industry. And finally it has become a way to give back to that industry.

More specifically, I started to present at PDA conferences in 1981 and then took over the "Protocol Development" course in 1991. In 2005, Don Elinski, Mylan, convinced me to attend an SAB meeting and lead the Process Validation Interest Group and I have been hooked ever since. For that I am very grateful.

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

Participating in and co-leading the Quality Risk Management for Aseptic Processing Technical Report Task Force. This was (and is) a unique and remarkable team. Working with them has truly been one of the most rewarding times of my career. Anyone seeking a rewarding professional experience or a way to get and stay involved should definitely consider joining a PDA task force.

How has volunteering through PDA benefited you professionally?

It has allowed me to better understand important scientific and regulatory aspects of our business and it has provided me the opportunity to meet and interact with the most influential people in our industry.

Which member benefit do you most look forward to?

I would have to say that re-connecting with friends and colleagues at PDA conferences and meetings.

Which PDA event/training course is your favorite?

The Aseptic Processing Training Program given at TRI by David Matsuhiro and his teaching staff, ably supported by James Wamsley and the TRI team,is the best educational event I have been involved with.

What would you say to somebody considering PDA membership?

What took you so long?

Volunteer Spotlight

Jens Henrik Eilertsen

Company: Novo Nordisk

Title: Sr. Principal Scientist, Global Quality Development

Education:

MSc, PhD, Chemical Engineering, Technical University of Denmark

PDA Join Date: 1996

Areas of PDA Volunteerism:

Science Advisory Board (co-chair)
2008 PDA Visual Inspection Forum Program Committee
2008 PDA Conference on Quality by Design: Practical Applications in Development and Manufacturing of Pharmaceuticals Program Committee
Task Force for *Technical Report No. 43, Identification and Classification of Nonconformities in Molded and Tubular Glass Containers for Pharmaceutical Manufacturing*

Interesting Fact about Yourself:

My wife, Birgit, and I have been married for more than 26 years. Birgit is a school teacher. We have two children, Peter, 22, and Julie, 20. We like spending our time off in the garden with family and friends, in our canoe on the lakes and streams north of Copenhagen, and on holidays across Europe.

Denmark is a flat country, so biking to and from work is also a tempting option, pending weather conditions.

Why did you join PDA and start to volunteer?

My then boss, Lars Peter Brunse [Ferring Pharmaceuticals] recommended me to join PDA as the place to establish my pharmaceutical industry network. My first PDA meeting was the 1998 conference in Basel.

At the 2001 PDA Visual Inspection meeting in Berlin, I had had a very fruitful talk with Georg Roessling, PhD, PDA about my potential involvement as a volunteer. Among others, Georg asked me if I wanted to participate in the founding of a Nordic/Scandinavian Chapter of PDA; after some reflection my answer was no, because to me the true value of PDA is its global perspective. At the 2001 PDA Annual Meeting in December in Washington D.C., when Jim Agalloco [Agalloco and Associates] presented the Science Advisory Board (SAB) Report it immediately caught my interest. It struck me that PDA was monitoring present and future trends in pharmaceutical science. After some discussions with PDA and my company, I was presented as a candidate for the SAB and approved. Then in 2007, I was persuaded to run for SAB co-chair.

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

For me as an SAB member, it is very rewarding every time a Technical Report is carried through to publication, because these reports are generally known and accepted as sources of state of the art scientifically sound information and guidance for industry and regulators.

How has volunteering through PDA benefited you professionally?

It has enabled me to establish and maintain a professional network across the industry and across countries that would otherwise be virtually impossible to establish.

Which member benefit do you most look forward to?

Really difficult to select just one networking opportunities

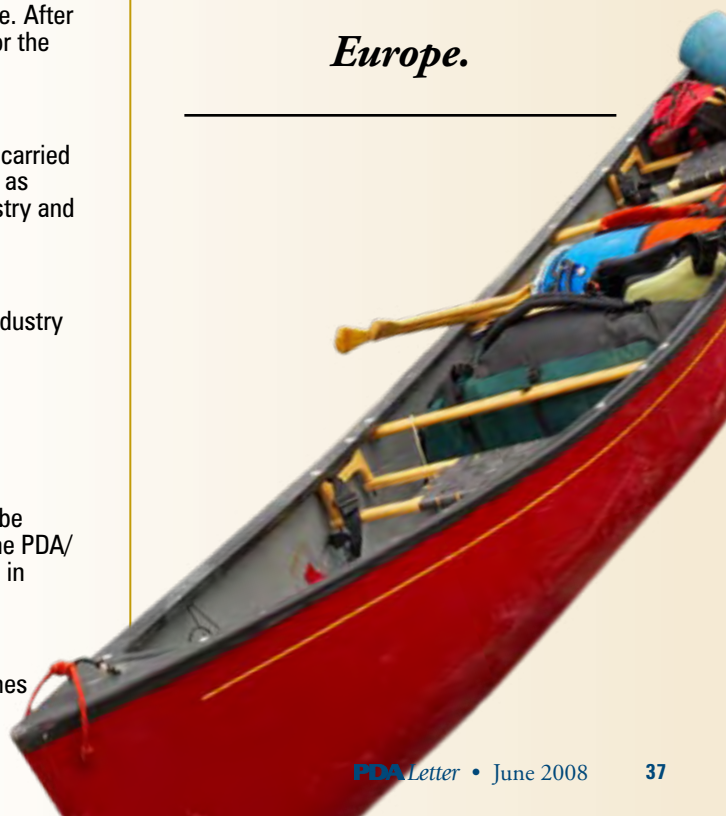
Which PDA event/training course is your favorite?

For almost a decade I have found the PDA/FDA Joint Regulatory Conferences to be very valuable. Now that the European EMEA has really established itself, I find the PDA/EMEA Joint Regulatory Conferences—of which we have now seen two, the first in London and the next in Budapest—equally beneficial.

What would you say to somebody considering PDA membership?

Getting the publications and access to the website is fine, but the real value comes from joining some of PDA's international meetings—maybe even as a speaker.

We like spending our time off in the garden with family and friends, in our canoe on the lakes and streams north of Copenhagen, and on holidays across Europe.



Sessions Satisfy Volunteers and New Members Hunger for Info

Emily Hough, PDA

PDA sponsored its first volunteer luncheon at the 2008 Annual Meeting in Colorado Springs. The PDA Membership Committee, led by PDA Chair **John Shabushnig**, PhD, decided to hold the luncheon to highlight the various ways members can impact the industry through PDA.

"I believe that many of our members would like to get more involved in the Association, but don't know where to begin," said Shabushnig. "We want to be able to take advantage of the extensive knowledge and practical experience of our members."

Martha Folmsbee, PhD, a first-time volunteer on the PDA Mycoplasma Task Force, attended the volunteer luncheon to learn about other opportunities. She started volunteering because her boss mentioned that it would be beneficial, and her current volunteer endeavors are closely related to what she does on a daily basis. Folmsbee said that volunteering is allowing her to get a better feel for what is going on in the Industry.

"It is a good way to learn more about the Industry since I am fresh out of an academia-government lab. [It's] a completely different world. It is a good way to network and see how others have solved similar problems. It is about the fastest way to really get to know the industry, and the most effective way, so far that I have found, to get a broad perspective and understand how the different aspects of microbiology fit together for industry."

PDA's Who's Who?

John Albright, Regulatory and Compliance Manager, Celsis

Keith Bader, Director of Technical and Quality Services, JM Hyde Consulting

Martha Folmsbee, PhD, Staff Scientist, Pall

Maria Funela, Quality Assurance Manager, Proteolix

Hassana Howe, Assistant Manager Membership Services & Chapters, PDA

Volunteer Luncheon Speakers:

Amy Davis, President, DHI

Frank S. Kohn, PhD, President, FSK Associates

Stephan Krause, PhD, Director, Favrille

Walt Morris, Director of Publishing, PDA

Susan Schniepp, Consultant, Schniepp & Associates

New Member Breakfast Speakers:

John Shabushnig, PhD, Sr. Manager/Team Leader, Pfizer

Susan Schniepp, Consultant, Schniepp & Associates

Louis Zaczkiewicz, Sr. Engineer, Hyaluron Contract Manufacturing

The day before, the tenth annual PDA New Member Breakfast entertained nearly 100 Association newbies. "The breakfast is a great way for members to understand what they can get out of their membership when they first join," according to **Hassana Howe.** She said that it also helps serve as an orientation into what benefits and career enhancement opportunities members have that they might not have known about.

Howe said the opportunity for new members to network with PDA staff, other new members, board members, and volunteers is also an invaluable service that the New Member Breakfast provides.

John Albright said the reasons he joined PDA were twofold: discounts on PDA materials, publications, conferences, etc, and the professional networking opportunities. Albright joined PDA so that he could participate in a task force and because membership would be beneficial to his roles and responsibilities to his company. Since joining in December 2007, his experience has been positive and he plans to become involved with his local chapter in the near future.

Overall Albright said, "PDA seems to foster a positive and collaborative attitude—something that I've found sometimes lacking in the pharma industry."

John Shabushnig, PhD

Maria Funela and **Keith Bader** said they enjoyed the breakfast and found that PDA was a great way to bring professionals together to develop the science-based industry.

Shabushnig said, "There are many opportunities to contribute; presenting and publishing technical work, developing comments on evolving regulatory guidance, serving on a PDA Task Force, serving on a program Committee, supporting a local chapter, leading an Interrest Group or teaching at TRI, just to name a few."

PDA would like to thank all the Volunteers and New Members for making PDA what it is today. PDA would also like to take this time and thank all the speakers who made both events possible.

Are You A New Member? Enjoy Breakfast with PDA in September!

Welcome new PDA members! If you joined PDA on or after April 1, 2008, you are invited to kick-start your PDA membership by attending this year's New Member Breakfast hosted on-site at the *2008 PDA/FDA Joint Regulatory Conference*. This is a wonderful opportunity to learn more about PDA and to meet other new PDA members, board members and staff.

Please RSVP before August 22 by emailing info@pda.org. For questions or to reserve call Hassana Howe at +1 (301) 656-5900 ext. 119.

Stephen Leung, Contec, on the New Member Breakfast:
"As a newcomer to the pharmaceutical industry, PDA has truly helped me develop my industry skills and background information, while also providing me with networking events to meet my professional colleagues. For me, attending the New Member Breakfast was both very interesting and helpful in getting me connected—the food was even top-notch! I'd recommend participating in this event if you've just joined PDA."

Refer a Colleague and Win!

Trevor Swan, PDA

PDA's Refer a Colleague Campaign is going strong, and has produced its first winner! **Stephen Westover,** Cook MyoSite, used PDA's new online service to recommend membership to his colleague, **Shannon Zelina**. When Shannon became PDA's newest member in February, Stephen was automatically entered to win a $50 American Express Gift Card. When the drawing was held in April, Stephen's name was selected. Congratulations Stephen!

Now, you have a chance to win a similar prize while sharing the valuable benefits of PDA membership with your colleagues. The second quarterly Refer a Colleague campaign has begun. Go to www.pda.org/refer and when you enter your colleague's contact information, an email from you will be automatically generated informing them of the PDA resources structured to support their work and advance their professional career.

Once your colleague has joined PDA, they will begin to receive valuable industry publications including the *PDA Journal of Pharmaceutical Science and Technology*, PDA Technical Reports, *International Pharmaceutical Quality* and the *PDA Letter*. They will also have immediate access to career enhancing tools such as participation on PDA Committees, Task Forces, Advisory Boards and chapters.

Members also receive discounts on conference and course registrations and purchases at the PDA Bookstore.

PDA members are an integral part of a distinguished community of industry leaders who hold the keys to first tier scientific and regulatory resources and unparalleled networking opportunities. Share the value of a PDA membership experience—refer a colleague!

To learn more about the refer a colleague program or to find out how to volunteer with PDA, please contact Hassana Howe at +1 (301) 656-5900 ext. 119 or at howe@pda.org.

2008 PDA Annual Meeting — Faces and Places: Sessions

Opening Plenary Session

(l-r) Keynote speaker Linda Armstrong Kelly, author and mother of cancer survivor, Lance Armstrong; John Shabushnig and Bob Myers pose with keynote speaker Shelley Morrison, actress and cancer survivor.

Visual Inspection of Parenterals Interest Group

(l-r) Andrew Dunham, Baxter; John Shabushnig, Pfizer; Juilius Knapp, Research & Development Association

Packaging Science Interest Group

Patty Kiang, Kiang Consultant;
Edward Smith, Packaging Science Resources

Pharmaceutical Water Systems Interest Group

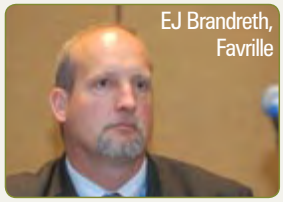
Theodore Meltzer,
Capitola Consulting

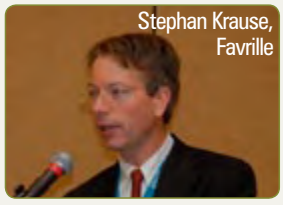
Process Validation Interest Group

Facilities and Engineering Interest Group

Christopher Smalley, Wyeth

Biotechnology Processes Session





Special Focus Session Mycoplasma—Part 3 and 4 Speakers

(l-r) Garry Takle, AppTec; Barbara Potts, Genentech; Sven Deutschmann, Roche Diagnostics; Radhakrishna Tirumalai, USP; David Asarnow, Bayer; Gurpreet Gill-Sangha, FDA; Thomas Haemmerle, Baxter

April 15 Microbiology Session

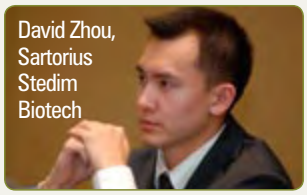

Ursula Busse, Novartis Pharma; Brandye Michaels, Wyeth

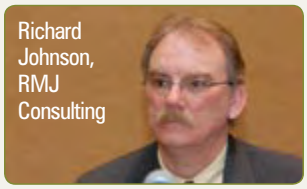
Technology Session


(l-r) Thomas Kosian, Robert Bosch; Amnon Eylath, Eli Lilly; Keith Richardson, Merck; Ian Elvins, Lonza

Disposables Session


Jerold Martin, Pall


David Zhou, Sartorius Stedim Biotech


Richard Johnson, RMJ Consulting

Combination Products Interest Group

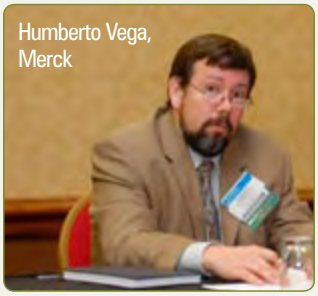

Matthew Young, Team Consulting and Michael Gross, Chimera Consulting

Dose Control and IMS Cleaning Method Validation Session


(l-r) Stacy Sherling, Eli Lilly; Michaela Simianu, Eli Lilly

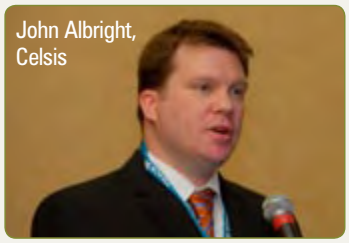
April 14 Microbiology Session


Sylvie Dufresne, TSO3 Inc


Humberto Vega, Merck


Graham Steele, Albert Browne

Environmental Monitoring Session


John Albright, Celsis

Microbiology Session


Michael Miller, Eli Lilly

Closing Plenary Session

Ian Elvins, Lonza, and Johnnie Godwin at the closing plenary session

Microbiology/Environmental Monitoring Interest Group

(l-r) Joseph Lasich, Alcon; Frank Kohn, FSK Associates; Dawn McIver, MicroWorks; Don Strauss, Rapid Micro Biosystems; Michael Miller, Eli Lilly; Arthur Vellutato, Veltek Associates; Jeanne Moldenhauer, Excellent Pharma Consulting; Gilberto Dalmasco, GSK

2008 PDA Annual Meeting Sessions

Facility Commissioning, Equipment Qualification and Cleaning Validation Session


Adam Mott, Lonza; Amnon Eylath, Eli Lilly

Downstream Processing Session



(l-r) Johan Hamminga, BAC BV; Harold Van Deinse, Baxter; Charles Lutsch, Sanofi Pasteur

Special Focus Session on Mycoplasma



Kurt Brorson, FDA; Ivar Kljavin, Genentech; Leonard Hayflick, University of California

Supply Chain Session

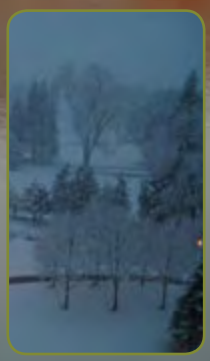


Leonard Smyth, Invensys Process Systems; Bob Dana, PDA; Rafik Bishara, PDA

Golf




The Fun Walk/Run Event



2008 PDA Annual Meeting Exhibitors


















Networking Bonanza!





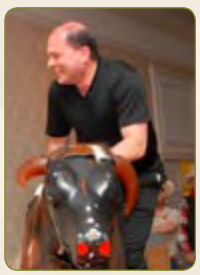






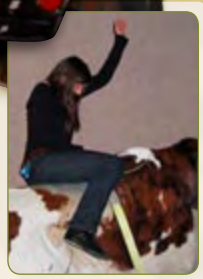

Yeehaw!

After rounding up information each day, attendees found various relaxing activities at the Broadmoor—though we are not sure riding the bull at the Gala Reception was one of them! Throughout the conference, a popular place to unwind was the Golden Bee. There, attendees sang along with the piano man and drank yards and half yards.












A Look Back at the Annual Meeting

Louis Zaczkiewicz, Hyaluron Contract Manufacturing

The global PDA organization has many conferences and programs throughout the year, four of which are labeled as their "signature" events: the Annual Meeting, the PDA/FDA Joint Regulatory Conference, the PDA/EMEA Joint Conference and the Asia-Pacific Conference. I attended the PDA Annual Meeting in April, held at the Broadmoor Resort in Colorado Springs, Colorado. I attended the meeting for many reasons:

- to represent the New England Chapter at the Chapter Council committee meeting
- to run the Chapter Council committee meeting in my capacity as its co-chair
- to address the new PDA members at the New Member Breakfast in my capacity as a member of the PDA Membership Committee
- to receive PDA Chair and President's appreciation award as President of the New England Chapter
- to network with old friends and to make some new ones
- to continue my education through attending the session presentations
- to attend a one-day training course on pre-filled syringe regulations put on by PDA's Training and Research Institute (TRI)

The conference began Sunday Night with the PDA Awards Banquet, held at the Cheyenne Lodge overlooking the city of Colorado Springs. Notable amongst the award recipients, **Susan Schniepp** (a NEPDA member and past chapter meeting presenter) received the 2007 Distinguished Service Award in recognition of the time and effort spent to further the reach and mission of the PDA by Board of Directors Chair **John Shabushnig,** PhD, Pfizer, and PDA President **Bob Myers**.

The theme of this year's meeting was to bring the patient's perspective into the picture to help us understand why we all work as hard as we do and to see the fruits of that labor. The four keynote speakers drove that message home to the attendees. On Monday, **Shelley Morrison**, star of the TV show Will and Grace, walked us through her 10-year journey battling Breast cancer. She thanked us and our industry for being there to provide the diagnostic tests and the drugs to battle the cancer. Next, **Linda Armstrong Kelly**, cyclist Lance Armstrong's mother, rode us through the course that Lance and she went through in his battle against Stage 3 testicular cancer. On Wednesday, the closing speaker **Johnnie Godwin** described the advances he personally received due to the new medications against Age-Related Macular Degeneration. Although the drugs did not come out in time to help his parents and grandparents, his disease is fully controlled by the medicine and his sight has been restored. Finally in a message that much work still needs to be done, the PDA presented **Randy Pausch**'s fight against the currently incurable disease Pancreatic Cancer by showing part of Pausch's "Last Lecture" (It is available for viewing on the web–search for Randy Pausch).

The meeting sessions were all well run. Twenty-seven educational sessions were held in virtually all aspects of parenteral drug development, manufacturing, testing, distribution and compliance. Additionally, 13 interest groups held meetings to discuss their progress and to solicit new members. Finally the Board of Directors and Scientific Advisory Boards held their business meetings.

From Wednesday afternoon through Friday, there was a Global PDA workshop on "Quality Requirements for Phase 0/1 Pharmaceutical Development Study" along with 11 educational programs put on by the TRI. This year they involved classes in environmental monitoring, regulations, risk management, cleaning validation and Mycoplasma to name a few. I was able to attend the course on the quality and regulatory aspects of prefilled syringes and combination products taught by **Michael Gross**, PhD, Chimera Consulting. Combination products are those that combine components regulated by more than one FDA office of compliance. For example, when a syringe is prefilled with a drug, the syringe is regulated by CDRH and the drug component is regulated by CDER (if the drug is a biologic then CBER would be involved instead). The approval process goes through the FDA's office for Combination Products, which assigns the agency that will handle the application based on its primary mode of action. Thus you only have to work with one compliance office instead of two (or three). Although the process can be cumbersome, in general this system has allowed many products to seamlessly pass the compliance journey onto approval.

As you can see this is a major event that touches all aspects of our work. It points out the fruit and failures and provides a venue for us to keep advancing the products and services that each of us provides. I encourage you to consider attending PDA global meetings as they will help you, your work and your company. The next PDA Annual Meeting will be held on April 20–24, 2009, in Las Vegas, Nev. and will focus on the microchip (computerization and automation). They are now accepting abstracts.

[Editor's Note: The preceding article was reprinted with permission from the NEPDA May 2008 Newsletter, Volume 3, Number 2. Louis Zaczkiewicz is a Sr. Engineer at HCM and serves as the current president of the PDA New England Chapter.**]**

Third Annual PDA Micro Conference Covers Big Picture Topics

Chicago, Ill. • October 20–22 • www.pda.org/microbiology2008

Program Co-chairs Michael J. Miller, PhD, Eli Lilly and Brenda Uratani, PhD, CDER/FDA

On behalf of the program planning committee, we are delighted to invite you to attend PDA's 3rd Annual Global Conference on Pharmaceutical Microbiology, Oct. 20–22, 2008, in Chicago, Illinois. This year's meeting will draw on the successes from the first two conferences by bringing together the world's leaders in pharmaceutical microbiology, contamination control and new technologies. This is by far the most comprehensive and informative pharmaceutical microbiology conference to date.

This year's conference theme is *The Role of Microbiology in Delivering Quality Products*. The opening plenary session will include a keynote address on the clinical microbiologist's view of objectionable microorganisms in non-sterile pharmaceutical drug products.

The first day of this year's conference will include dual-track options addressing current perspectives and case studies on the following topics:

- Microbial detection
- Aseptic processing and media fills
- Advances in microbial identification
- Microbial control issues and regulatory impact
- Environmental monitoring
- Cleaning and disinfection

The second day of the conference will provide targeted discussions on the impact that microbiology plays on the manufacture of quality products, sterilization and biological indicators, new technologies, such as rapid microbiological methods, and a comprehensive overview of PDA's technical reports on aseptic processing, parametric release, environmental monitoring and the validation of alternative methods.

The third day is dedicated to global compendial and regulatory perspectives, with speakers representing the United States and European Pharmacopeias, U.S. FDA, MHRA and other European regulatory authorities. There will be plenty of opportunities to listen to and directly interact with all of the speakers, in addition to lively Q&A sessions that promise to stimulate the discussions and encourage your participation.

We hope that you will join us for what we anticipate to be an interactive, informative and enjoyable conference.

EU and South African Regulators to Speak at *2008 PDA/FDA Joint Conference*

Washington, D.C. • September 8–12 • www.pda.org/pdafda2008

John Finkbohner, PhD, MedImmune, Inc

To be successful, our industry must strive to update our understanding of how new regulatory initiatives are implemented in the global environment. The successful implementation of harmonized regulatory requirements optimizes industry's ability to offer new treatments to a broad range of patients in an efficient and timely manner.

A primary focus of the *2008 PDA/FDA Joint Regulatory Conference* is to explore and understand the current state of harmonization activities as they apply to global regulatory requirements. The importance of streamlining and enhancing the ability of companies to submit the same regulatory filing to multiple jurisdictions must not be underestimated in the modern health care marketplace. The Program Planning Committee has built this year's conference around the theme, *Harmonization, Implementation and Modernization: Achieving a Future Vision*.

The opening plenary session will include a keynote presentation that will highlight the contributions being made by the United States Pharmacopoeia to the harmonization of monograph and general chapter requirements across pharmacopoeias. In addition, a representative of the U.S. FDA will focus on initiatives being taken to implement modernization programs in an effort to achieve global harmonization.

A number of concurrent sessions throughout the conference will focus in more depth on various aspects of global harmonization. These sessions, led by quality and regulatory experts, will update attendees on the current state of harmonization efforts that are impacting the development of global regulatory strategies. In addition, industry experts from some of today's leading pharmaceutical companies will present case studies on employing risk management and global strategies into daily processes.

Presentation topics will include updates on new guidance document development activities, new initiatives contributing to the ongoing rollout of regulatory modernization, and agency initiatives for modernizing regulatory oversight. The presenters will address activities occurring that foster globalization through examination of the current status of harmonization efforts that are in progress by various regulatory and consensus standard setting organizations.

Another emphasis of the conference is on the harmonization of GMP requirements and regulatory oversight systems (i.e., inspections). There are two sessions focusing on the Pharmaceutical Inspectorate and the Pharmaceutical Inspection Cooperation Scheme (PIC/S), respectively. These will provide insight into the current status of the efforts to streamline the regulatory oversight through cooperative inspection schemes and plans to drive the maintenance of the highest quality cadre of inspectors that can be established. On a related note, a representative of the South African regulatory health agency will present an update on how their agency utilizes risk assessment to prioritize inspection scheduling to target manufacturing operations with the potential highest risk to public health. The factors and assumptions being used in the risk ranking and filtering process could be of particular interest.

Proposed changes to EU regulations and their application to the manufacture of clinical trial materials (investigational medicinal products) will be covered in another session. Specifically, pending revisions to Annex 13 and their potential impact on the conduct of clinical trials on an international scale will be discussed. It is anticipated that an overview of updates to EU Annex 1 may also be available for discussion at the conference. The website for the conference, www.pda.org/pdafda2008, will be updated as more information about the EMEA presentations becomes available.

In response to the recent regulatory focus on the importance of monitoring product safety post-approval, the Planning Committee has included a session on product safety and pharmacovigilence intended to drive home the importance of monitoring the quality of outsourced API production in the global manufacturing arena.

Have you heard of or wanted to learn more about the current status of the Transatlantic Regulatory Initiative? The primary goals of the initiative are to promote and protect public health, reduce regulatory burden and costs to the consumer and industry, and bring innovative products to patients in a timely manner. In June 2007, significant progress was made on expanding transatlantic regulatory cooperation in the areas of pediatrics and orphan drugs, and in November 2007, a workshop was organized with all stakeholders identifying opportunities for administrative simplification in the field of quality and inspections, pharmacovigilence, scientific collaboration, and guidelines/format harmonization/electronic submission. In June 2008, a roadmap for the Transatlantic Regulatory Initiative will

be released by the two governments and will be the focus of a session at the PDA/FDA conference. The goal of the session is to demonstrate how the regulators in the United States and the European Unions are collaborating, sharing information (including important safety information) and helping industry understand regional regulatory systems.

A number of breakfast meeting and special interest group venues will provide additional opportunities for attendees to further explore specialized global harmonization topics. For instance, speakers representing Japanese industry and regulatory authorities will draw selected topics from a Japanese aseptic processing guidance published by the Pharmaceuticals and Medical Devices Evaluation Center. Participants will help tailor the case studies presented to facilitate further communication and information sharing.

The *2008 PDA/FDA Joint Regulatory Conference* promises to provide a rare opportunity for industry and regulatory health authority experts to explore how to successfully achieve the future vision of a science and risk-based approach to product quality by incorporating an integrated quality systems approach in pharmaceutical production. The opportunity for face-to-face dialogue on these issues provides pharmaceutical industry professionals an invaluable venue for direct information exchange with regulatory policy makers.

Please join us September 8–12, 2008 in Washington, D.C. and take advantage of this unique opportunity to gain insights into a number of global harmonization activities and the current status on progress being made to achieve the cross cutting goals of these initiatives, while interacting on current issues and hot topics with regulatory health authority representatives from five continents!

Attendance High for Rocky Mountain TRI Courses

Emily Hough, PDA

The snow-covered Rockies provided an ivory tower-like setting for the Training and Research Institute's 11 courses held in conjunction with the *2008 PDA Annual Meeting* in Colorado Springs. The courses covered a range of topics; attendance peaked at more than 100 students for the two days of learning.

Whereas conference participants were treated to two days of sun and summer-like conditions, course participants were treated to snow and wintery conditions; such is life in the fickle foothills of the Rocky Mountains. No matter the weather, the Broadmoor afforded students the chance to gain hands-on experience with golf clubs, tennis rackets and other instruments common to resort life.

The *PDA Letter* took advantage of the higher learning to elevate our knowledge of two towering topics by attending: "Quality and Regulatory Requirements and Development Strategy for Pre-filled Syringes, Pre-filled Drug Delivery Devices and Other Drug-Device Combination Products," by **Michael Gross,** PhD, and "Environmental Monitoring in Pharmaceutical Manufacturing," by **J. Kirby Farrington,** PhD.

Gross covered the different regulatory expectations for combination products in the United States and in Europe. In the United States, the U.S. FDA Office of Combination Products reviews and classifies the product by its primary mode of action. In Europe, however, a combination product can be classified by how the product is used. Although it does not appear that the differences between the two systems are as tall as Pike's Peak.

Farrington's course addressed what is included in an environmental monitoring program and specific ways in which to establish a monitoring plan. He said that excursions should be investigated and evaluated. "An excursion is not cause for panic or precipitous actions. If viables are involved, the incident happened in the past and there is nothing that can be done here and now to change or correct the situation that existed at that time."

The two courses were very interactive, with questions posed by the participants and the lecturers alike. Gross and Farrington both were skilled at adjusting their lectures based on the questions raised by their students.

If you are interested in either of these topics, Gross will teach the same course following the *2009 PDA/FDA Joint Regulatory Conference* on September 11 and Farrington will conduct his again in conjunction with the *PDA's Third Annual Global Conference on Pharmaceutical Microbiology* on October 23.

PDA wishes to thank the instructors who helped students scale to new heights of understanding:

Hal Baseman, ValSource

Anne Marie Dixon, Cleanroom Management Associates

J. Kirby Farrington, PhD, Eli Lilly

Wayne Garafola, Sartorius Stedim Biotech

Michael Gross, PhD, RAC, Chimera Consulting

Klaus Haberer, PhD, Compliance Advice and Services in Microbiology

Dustin LeBlanc, Cleaning Validation Technologies

Cynthia Romero-Arroyo, PhD, Prtho Biologics

Lynn Torbeck, Torbeck and Associates

Jeffrey Yuen, Jeff Yuen and Associates

The *PDA Letter* would like to thank the TRI staff and the lecturers for their generous hospitality and helpfulness.

PDA
Parenteral Drug Association

The Universe of Pre-filled Syringes and Injection Devices

Regulators and industry experts will share case studies and address issues such as supplier qualification, materials of construction and considerations, filling and manufacturing, regulatory and compliance, safety systems and alternative injection devices.

Don't miss your chance to attend this one-of-a-kind meeting. This forum won't be back in the United States until 2010!

www.pda.org/prefilled2008

October 6 – 7, 2008
San Diego, California

Conference | Exhibition

PDA
Parenteral Drug Association
Connecting People, Science and Regulation®

2008 PDA Conference on

Quality by Design

Practical Applications in Development and Manufacturing of Pharmaceutical Products

7-8 October 2008
Frankfurt, Germany

Conference and Exhibition: 7-8 October
Training Course: 6 October

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Register by 7 August 2008 and SAVE!

This conference will focus on sessions addressing the concepts of modern QbD approaches as well as novel technologies to gain fundamental process understanding from a practical point of view. To deliver practical information, case studies by acknowledged experts from industry and regulatory bodies will be presented.

PDA Conference to Dissect QbD

PDA Conference on QbD • Frankfurt, Germany • October 7–8

Mohammed Barkat and Volker Eck, PhD, PDA

A wide range of practical examples and illustrated problems and solutions will be presented at the upcoming PDA QbD conference. The genesis of the meeting was the PDA conference on process analytical technology in 2007. The committee's decision was to hold the meeting again in Europe, but with an emphasis on the larger QbD picture.

Quality by Design (QbD) is becoming a very often used but not so well understood term. Identification of the "design space" should be the goal of the QbD project. The design space can be understood as a multidimensional space encompassing combinations of product design and processing variables that provide assurance of suitable product performance. It is necessarily coupled to a control strategy to ensure the process will render the desired quality. The conference will demonstrate that this concept is not only applicable to the many well-publicized oral solid cases, but also to parenterals and other dosage forms.

To give an example of the application and validity of the approach, let us discuss a hypothetical design space definition in the context of developing, scaling up, and transferring freeze-dried products to a manufacturing setting as described in a recent publication by **Steven Nail** and **Jim Searles.** As the authors point out, smooth technology transfer in all stages starts with developing a robust and rugged formulation and an appropriate container and closure system.

For the benefit of understanding why there is value in a QbD exercise, the common arguments are:

1. Regulatory relief throughout the product life cycle, because post-approval changes within the design space are no change to the marketing authorization and hence don't require prior approval.
2. Potential reduction in the volume of data submitted because empirical data is replaced by optimized experimental designs that lead to knowledge-based submissions; the opposite to an iterative process.
3. Facilitation of continuous process improvement within the design space, because these process improvements again are already part of the marketing authorization and, hence don't require prior approval.
4. Replacement of the current model of process validation, as theoretically speaking, each successful performance of the process in itself reconfirms the validity of the design space established.

Coming back to the example, it is explained by the authors that the design space describing this can be visualized as a function of sublimation rate, shelf temperature and chamber pressure.

One boundary of the design space is established by failure of the formulation under aggressive cycle conditions. Other boundaries of the design space are determined by equipment performance, including refrigeration capacity, condenser capability, heating capacity, or limitations of the dynamics of water vapor flow within the system.

Once such a design space is defined, it represents a thorough understanding of both the product and the process, and it minimizes the probability of failure, not only in the technology transfer process but also in commercial manufacturing.

Next month, we highlight the role of PAT in QbD.

Reference

Nail, Steven and Jim A. Searles. Elements of Quality by Design in Development and Scale-Up of Freeze-Dried Parenterals. www.biopharminternational.com. January 2008.

PDA
Parenteral Drug Association
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Conference, Exhibition 14-15 October
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