Science • Technology • Quality • Regulatory • Community

PDA Letter

Volume XLI • Issue #6

June 2005

In This Issue...

PAT: Tool to Explore/Expand Design Space

Process Knowledge & Control of CQA's Allow Design Space Flexibility

Process Analytical Technology (PAT) is the key tool for pharmaceutical and biopharmaceutical companies to explore and expand their manufacturing "design space," creating regulatory flexibility hitherto scientifically unjustifiable.

Other quality control tools that allow firms to build quality into the product/process and to share information with the regulatory authorities are also critical to gaining regulatory flexibility. They include: design of experiments, multivariate data analysis (chemometrics), the pharmaceutical development report, quality systems and risk management/mitigation.

Development of the manufacturing design space bestows tangible benefits on the manufacturer, the regulator and the public. Firms enhance the scientific foundations of their process controls and end-product specifications, ideally resulting in the reduction of deviations, regulatory infractions, manufacturing waste and time lost to investigations and corrective actions. The regulator gains increased confidence in a company's ability to internally monitor critical quality attributes (CQA's) of the product and process, allowing for less regulatory oversight—both of the facility through risk-based inspection and of changes to manufacturing processes through reduced application supplements. The public receives drugs of a quality even higher than that already achieved through the current regulatory framework.

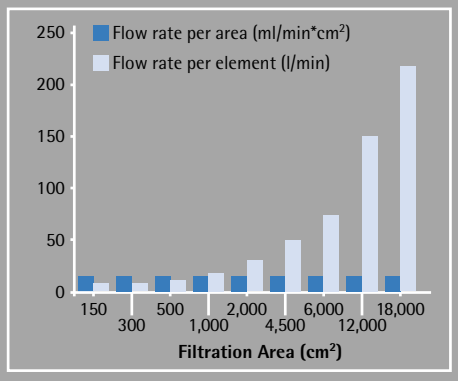
In discussing the future of specification setting at the 2005 PDA Extractables and Leachables Forum in Bethesda, Md., May 23-25, the U.S. FDA's **Moheb Nasr,** PhD, identified the benefits companies can derive from establishing design space. The Director of the Office of New Drug Chemistry in the Center for Drug Evaluation and Research (CDER) appeared at the conference to discuss CDER's new Pharmaceutical Quality Assessment program.

Dr. Nasr explained that, under the current system for chemistry, manufacturing and control (CMC) submission and review, sponsors often argue they do not have enough information to establish tight

continued on page 14

sartorius

Sartorius Biotechnology! Scale up your innovations.



First come visions – then innovations. When you want to see the realization of your innovations becoming products within the shortest time to market, you need to have an experienced partner on your side.

Whether you need laboratory or process scale filter units, we've got just what you need for manufacturing sterile products in the pharmaceutical and biotechnology industries.

Offering a wide choice of 150 cm² to 18,000 cm² of filtration area, we supply filter units in all required sizes. Yet we use the same geometry, construction and pleated filter materials in all unit sizes to enable ideal scale-up.

We focus on your entire process not just our products. We do the entire range to meet your needs, from consultation to training, certification and validation, all the way to provide excellent service.

For example, FACTS® – our complete Sartorius service program. Whatever you ask for...

Yes, we can.

Sartorius North America Inc.
131 Heartland Blvd.
Edgewood, New York 11717
Phone +1.800.368.7178
Fax +1.631.254.4253

Sartorius AG
Weender Landstrasse 94–108
37075 Goettingen, Germany
Phone +49.551.308.0
Fax +49.551.308.3289

scaleup@sartorius.com
www.sartorius.com

June's Top 10 Bestsellers

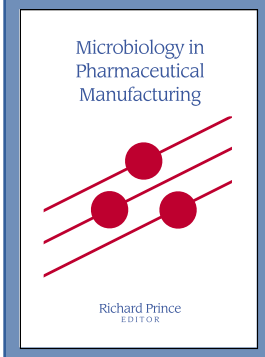
From the PDA Publications Store

Sterilizing Filtration of Gases, Technical Report No. 40

This technical report is designed to assist the reader in the selection, qualification, and validation of an appropriate filtration process and is a complement to PDA Technical Report No. 26, Sterilizing Filtration of Liquids

Item No. 01040

Featured Titles



Microbiology in Pharmaceutical Manufacturing
Item No. 17185

Virus Filtration, Technical Report No. 41
Item No. 01041

PDA Archive on CD-ROM – 2004 Update
Item No. 01002

Check out these titles and more from the PDA Publications Store.

1. **Sterilizing Filtration of Gases, Technical Report No. 40.** Item No. 01040
   PDA Member $75; Nonmember $270
2. **Technology Transfer: An International Good Practice Guide for Pharmaceuticals and Allied Industries,** by Mark Gibson. Item No. 17218
   PDA Member $200; Nonmember $249
3. **Pharmaceutical Quality,** edited by Richard Prince. Item No. 17207
   PDA Member $240; Nonmember $299
4. **Sterilizing Filtration of Liquids, Technical Report No. 26.** Item No. 01026
   PDA Member $75; Nonmember $270
5. **Filtration Handbook: Liquids,** by Maik W. Jornitz and Theodore H. Meltzer. Item No. 17208
   PDA Member $185; Nonmember $229
6. **Laboratory Validation: A Practitioner's Guide,** edited by Jeanne Moldenhauer. Item No. 17201
   PDA Member $250; Nonmember $309
7. **Steam Sterilization: A Practitioner's Guide,** edited by Jeanne Moldenhauer. Item No. 17183
   PDA Member $215; Nonmember $269
8. **Fundamentals of an Environmental Monitoring Program, Technical Report No. 13.** Item No. 01013
   PDA Member $75; Nonmember $270
9. **Good Practice and Compliance for Electronic Records and Signatures – Part 3: Models for Systems Implementation and Evolution.** Item No. 13003
   PDA Member $95; Nonmember $190
10. **Quality Control Systems for the Microbiology Laboratory: The Key to Successful Inspections,** by Lucia Clontz. Item No. 17176
    PDA Member $170; Nonmember $209

www.pda.org/estore

PDA Books and *Career-long Learning*™ Resources
Empowering pharmaceutical and biopharmaceutical professionals to make a difference in the world

Tel: +1 (301) 656-5900
Fax: +1 (301) 986-1093

Table of Contents

Coming Next Month...
Sterile Products & Aseptic Processing

SimpleMix RTU

DISINFECTANTS & SPORICIDES

- All chemical agents and the WFI Quality Water are filtered at 0.2 microns and manufactured in a Class 100 filling operation
- Eliminates regulatory concerns for mixing and sterility of the solution
- Lot sterility tested per current USP compendium
- The contents of the double bag package are sterilized through a validated gamma radiation cycle.
- The system assures the appropriate dilution is made each time in a closed, sterile system
- Concentrate solutions are never handled
- Available in 16 ounce and gallon containers

US and Foreign Patents Pending

Made for Veltek's DECON-PHENE®, DECON-PHASE®, DECON-CYCLE®, DECON-QUAT100®, DECON-Clean® and DECON-SPORE 200 Plus®

vai
Veltek Associates, Inc.
(610)-644-8335
www.sterile.com

INNOVATIVE CLEAN ROOM PRODUCTS

President's Message

Robert Myers, Acting President

Members Are PDA's Strength

PDA's volunteer members are the strength of the Association and the reason why PDA's programs and educational offerings remain current and are always of the highest quality.

In fact, four voluntary advisory boards sanctioned by the PDA Board of Directors began meeting this year: the Biotechnology Advisory Board, the Training and Research Institute Advisory Board, the Programs Advisory Board and the Europe Advisory Board (*see related story, next page*). In addition, the *PDA Letter* Editorial Committee met for the first time in May. These groups are comprised of experienced, dedicated and talented volunteer PDA members who are working to ensure that all of our offerings meet the needs of our PDA community.

Our ability to come together as an association to advance pharmaceutical science and technology and to help impact regulatory requirements has been punctuated by the success of our events during the first half of 2005. We sponsored four major meetings since January, the International Congress in Rome, the Annual Meeting in Chicago, the Viral & TSE Safety Conference and the Extractables/Leachables Forum. Nearly 1000 members of our community attended the four events combined.

The community also greatly benefited from our continued training on the U.S. FDA aseptic processing cGMP guidance. Three workshops were held this year in San Francisco, Philadelphia and London, and more than 400 of our colleagues took advantage of this unique training.

Likewise, our Training and Research Institute has offered very successful courses this year, serving over 500 professionals, including staff from FDA's Center for Drug Evaluation and Research.

Another of our successful activities is the Audio Conference program. We have held eight conferences to date that have brought needed scientific and regulatory information to thousands of our members and their colleagues. We plan over 20 more that should be of interest to many of you.

PDA's global Chapters—one of the core strengths of our association—are doing their part as well. A number of Chapters have sponsored very successful events so far this year (*see related story, p. 26*).

We have also enjoyed a renaissance in our publishing activities. The first two issues of the *PDA Journal of Pharmaceutical Science and Technology* included supplemental Technical Reports: no.'s 40 (*Sterilizing Filtration of Gases*) and 41 (*Virus Filtration*). Several more TR's will be published this year. In addition, through our collaboration with Davis Healthcare International Publishing, we already have published four technical books this year and expect to publish six more by year's end.

The common thread among all of these activities is the energy of our member volunteers working behind the scenes. It is the strength and quality of PDA's membership that makes our association so valuable to the pharmaceutical and biopharmaceutical community.

While I serve PDA as its Acting President, my goal is to focus on the short term activities to assure the volunteer groups continue to be well supported from our home office in Bethesda. However we have not lost sight of our future as we plan for the various programs and educational sessions of late 2005 and 2006. The professional staff will do its job to support our dedicated, motivated and skilled membership to ensure that we keep providing the products and services which have made PDA the respected association it is today.

PDA Launches Four New Advisory Boards

Nikki Mehringer, Eli Lilly and Company and PDA Chair

PDA is capable of offering quality scientific and educational activities because of the strong base of active member volunteers who help us identify the key issues impacting the pharmaceutical and biopharmaceutical communities. The quality of our various conferences, courses, laboratory training and publications reflects PDA's ability to bring together a broad spectrum of expertise from the private sector, global health authorities and academia.

Each initiative undertaken by PDA is vetted before a high-level group of dedicated and experienced member volunteers. These advisory groups provide the highest level of oversight to PDA's activities after the Board of Directors. The Board of Directors appoints the members and chairpersons for each.

Traditionally, the Science Advisory Board (SAB) and the Regulatory Affairs/Quality Committee (RAQC) served the most important PDA groups. The PDA Board expanded this volunteer governance structure through the creation of four new advisory boards.

Based on information gained through the PDA Strategic Planning process and with input from some of our most experienced members, we saw the opportunity to expand our volunteer committee and board structure to provide for more focused activities and more opportunities for member participation, influence and leadership. Many of these new groups have met only a few times, but we can already see the energy and ideas generated from bringing PDA members together to guide and contribute to the activities and work of the association, just as we have seen in the past from the SAB and the RAQC.

These new advisory boards address all facets of PDA's activities. Due to the growing importance of biological products and the complexity of the science involved with manufacturing them, PDA created the Biotechnology Advisory Board (BioAB). In addition, to provide greater focus on the most critical regulatory and scientific issues and to help better hone our educational offerings, the Training and Research Institute Advisory Board (TRIAB) and the Program Advisory Board (PAB) were created. The fourth group, the European Advisory Board (EAB), was formed to better coordinate our activities in Europe.

The formation of these new advisory boards allows for more member participation in the activities of PDA. They were populated with established volunteer leaders and members who responded to the "Call for Volunteers," which was given at the 2004 PDA/FDA Joint Regulatory Conference last September, posted on the PDA Web site and published in the *PDA Letter*.

The SAB establishes the strategic perspective and provides oversight for PDA's scientific and technical activities through the development of technical reports and bulletins for publication with the *PDA Journal of Pharmaceutical Science and Technology* and interaction with regulatory authorities. The SAB is composed of individuals who have a demonstrated history of scientific and technical excellence within the scope of PDA's activities.

To develop technical reports and bulletins, the SAB appoints an expert task force and names the task force chair. Once their work is completed, the task forces submit the technical reports/bulletins to the SAB for approval, and, if approved, the reports go to the PDA Board for final consideration. Technical reports are published as supplements to the PDA Journal. TR#40, *Sterilizing Filtration of Gases,* and TR#41, *Virus Filtration,* were published this year with the January/February and March/April editions of the Journal, respectively.

The RAQC is a critical source for identifying global regulatory issues of interest to PDA members. Once a regulatory issue is identified, the RAQC forms a task force to study and prepare written comments. The list of recommendations they prepare—PDA Regulatory Comments—is sent to the PDA Board. Once approved, they are submitted back to the originating agency/organization (e.g., FDA, EMEA, WHO, etc.) for review and inclusion into the public record. Regulatory agencies take great care to consider public comments when revising draft guidances and/or regulations. PDA Regulatory Comments are also posted to the PDA Web site for public viewing and are highlighted in the *PDA Letter*.

The newly created BioAB is PDA's new source for identifying biotechnology issues of interest to our members globally. The BioAB is intended to be proactive in the identification of scientific/techni-

cal/regulatory issues affecting biotech products for which PDA can provide a forum for discussion. The BioAB also serves to support the activities of the SAB and the RAQC by, for example, providing insight into regulatory documents and technical reports related to biopharmaceuticals. The group already has initiated an expert review of TR#42 on protein validation, which had previously been approved by the SAB. TR#42 is now heading for a vote by the PDA Board, and will likely publish later this year.

The TRIAB was formed to help focus the TRI curriculum to best serve industry, academia and health authority audiences with practical training courses. The TRIAB will establish instructional design criteria, oversee course development and guide the implementation of comprehensive training curricula and certificate programs as they relate to the needs of the PDA membership and the pharmaceutical and biopharmaceutical communities.

The PAB provides oversight and support for all of PDA's conferences and workshops. Its members select the chair of individual program planning committees. They advise on the themes, topics and tracks, as well as the timing and locations of meetings. Most importantly, with membership representing the SAB, RAQC and PDA Interest Groups, the PAB serves as a critical link between those member volunteers who help devise PDA's programs and those involved with our critical scientific and regulatory initiatives.

The EAB is comprised of the PDA Chapter leaders in Europe and those Board members based there. It collaborates with PDA staff in Europe and in Bethesda, Maryland.

These groups offer many opportunities for volunteers. Please contact the staff liaison (named below) at any time to inquire about volunteer opportunities, and/or look for announcements in the *PDA Letter*, the Journal and on the PDA Web site.

PDA's New Advisory Boards

BioAB

Co-Chairs
Gail Sofer
GE Healthcare

John Geigert, PhD
BioPharmaceutical Quality Solutions

SAB Liaison
James Fernandez
Fernandez and Associates

RAQC Liaison
Rebecca A. Devine, PhD
Regulatory Consultant

Robert J. Seely, PhD
RMC Pharmaceutical Solutions

Christopher M. Bussineau, PhD
Chiron Corporation

Peter F. Levy
Altus Pharmaceuticals

Michael E. Wiebe, PhD
Biogen Idec

Norbert Hentschel
Boehringer Ingelheim Pharma

Kurt A. Brorson, PhD
CDER, U.S. FDA

Anders Vinther, PhD
CMC Biopharmaceuticals A/S

Dr. Ron Taticek, PhD
Genentech

Amy Scott-Billman
GlaxoSmithKline

PDA Staff Contact:
VP, Science and Technology

PAB

Chair
Glenn Wright
Eli Lilly and Company

Sue Schniepp
Hospira, Inc.

Deborah Neckorcuk
Boston Analytical, Inc.

Lother Hartman
F. Hoffman -LaRoche

Cindy Rockel
Millipore

Robert Dana
Elkhorn Associates, Inc.

Kathleen Green
Novartis Pharm.

Louise Henry
Vertex Pharmaceuticals

Jerold Martin
Pall Corporation

Micheal Eakins
Eakins & Associates

Joyce Winters
Wyeth

Maik Jornitz
Sartorius Corporation

Carmela Luangdilok, PhD
American Pharmaceutical Partners, Inc.

Michael Miller, PhD
Eli Lilly and Company

PDA Staff Contact:
Director, Programs and Meetings

TRIAB

Chair
Robert Myers
Beacon Pointe Group

Eddie Ballance
Eisai

Suraj B. Baloda, Ph.D.
Millipore Corporation

Amy R. Barker, Ph.D.
Eli Lilly and Company

Lina Divitt
Chiron Corporation

Gina Graf
Eli Lilly and Company

George J. Grigonis, Jr.
QA Edge, Inc.

Barbara van der Schalie
MedImmune, Inc.

Gregory Meyer
Compliance Media

Raymond R. Roy, Jr., PhD
Chemist USGS

Eric Rudolph
Millipore Corporation

Gregg Sherman
Biogen Idec

John K. Sicurella
Avecia Biotechnology, Inc.

Mark Trotter
Sartorius North America, Inc.

PDA Staff Contact:
VP, PDA TRI

Member Volunteer Opportunities

PDA Viral Filtration Task Force

The PDA Viral Filtration Task Force is seeking new members to assist in their work to establish a nomenclature system for small virus removal filters. The Task Force will produce an addendum to Technical Report 41, specifically addressing the removal of small viruses by filtration. The Task Force meets approximately four to six times per year and requires active participation and contribution.

If you would like to participate in the Viral Filtration Task Force, please provide a brief summary of your professional experience and your contact information to Iris Rice, PDA Coordinator, Quality, Regulatory Affairs and Science, at +1 (301) 656-5900 ext. 119 or rice@pda.org.

Product Quality Research Institute (PQRI) Technical Committees

PDA is looking for 2 very special volunteers to represent PDA in the Drug Substance Technical Committee (DSTC) and the Drug Products Technical Committee (DPTC) within PQRI. Committee members meet monthly by teleconference and quarterly in person. The normal commitment timeframe is two years.

If you are interested in participating in a PQRI Technical Committee representing PDA please contact Iris Rice, PDA Coordinator, Quality,Regulatory Affairs and Science, at +1 (301) 656-5900 ext. 119 or rice@pda.org.

PDA Letter Editorial Committee (PLEC)

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

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

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

PDA Training and Research Institute Advisory Board (TRIAB)

The TRIAB is now looking for volunteers for its newly formed subcommittees on E-learning strategies; Standards and Certification; and Content Needs Assessment. If you would like to volunteer to participate on one of these subcommittees, please provide a brief summary of your professional experience and your contact information to PDA Vice President of Education, Gail Sherman at +1 (410) 455-5981 or sherman@pda.org.

PDA Conference Planning Committees

PDA is looking for volunteers to serve on the planning committees for upcoming PDA events. We are currently forming committees for the PDA Annual Meeting, PDA/FDA Joint Regulatory Conference, PDA International Congress and PDA Asia/Pacific Congress through 2008.

If you are interested in participating on a PDA Program Planning Committee, please contact:

- PDA Annual Meeting, PDA/FDA Joint Regulatory Conference, PDA Asia/Pacific Congress: *Wanda Neal, Director, Programs and Meetings, at +1 (301) 656-5900, ext. 111 or neal@pda.org*
- PDA International Congress: *Nancy Barkan, Manager, Programs and Meetings, at +41 41 766 05 82 or barkan@pda.org*

Member Participation Program

The Member Participation Program provides an opportunity for PDA members to volunteer at PDA events and receive a discount on their event registration. Participants are asked to commit at least six hours per conference and in return they receive a 50% discount on their registration. If you are interested in volunteering for the PDA Member Participation Program, please click here to download the application form. Complete this form and submit it at least five months prior to the event. This program is available for the PDA International Congress, PDA Annual Meeting, and PDA/FDA Joint Regulatory Conference. For more information contact Kelly Coates at +1 (301) 656-5900, ext. 149 or coates@pda.org.

PDA
An International Association For Pharmaceutical Science And Technology

2005 PDA Journal of Science and Technology

Pre-Doctoral Fellowship Program Winners

The PDA Journal of Science and Technology Pre-Doctoral Fellowship Program promotes applied research in pharmaceutical and biopharmaceutical product development, drug manufacturing and quality assurance technologies by encouraging outstanding pre-doctoral students to continue their studies and earn the PhD in pharmaceutical science or a related field. Each winner was presented with a $10,000 stipend.

We are proud to present the 2005 winners:

Stuart Cantor
University of Maryland, Baltimore
Project Title: *Design and Characterization of a Unique Compacted Multiparticulate System for Modified Release*

William T. Riordan
University of Wisconsin, Madison
Project Title: *Virus-Ligand Interactions in Adsorptive Membrane Separation Processes*

Michael Allen Hanson
University of Maryland, Baltimore
Project Title: *Gene Arrays, Cell Culture Process Changes and Comparability*

Madhushree Gokhale
University of Iowa
Project Title: *Studies of the Kinetics and Mechanism of the Reaction of Kynurenine with D-glucose in Aqueous Solutions*

Now Accepting Submissions

PDA Journal of Science and Technology. 2006
Pre-Doctoral Fellowship Program

www.pda.org/ssp

Chemometrics in PAT and Pharmaceutical Production

Svante Wold, PhD, Research Group for Chemometrics, Umeå University, Sweden, and Umetrics AB

Chemometrics was started around 35 years ago to cope with the analysis of the rapidly increasing volumes of data produced in chemical laboratories. The methods of chemometrics mainly concern the analysis of multivariate data—giving an overview of complex data, multivariate classification and discriminant analysis, and multivariate calibration and similar quantitative relationships—as well as making the data representative and contain reliable information, i.e., design of experiments (DOE).

Chemometrics pioneered the analysis and understanding of data where the number of measurements (K) exceeds the number of observations (N).

Graphical presentation of the analytical results, as well as graphically oriented academic and commercial software running on small and large computers, helped the acceptance of the chemometrics approaches in both academia and industry.

Early chemometrics applications in analytical chemistry, environmental chemistry and medicinal and bioorganic chemistry were expanded into all fields of chemistry and increasingly also biology and engineering.

Today, major application areas of chemometrics include:

(1) Multivariate calibration

(2) Structure—(re)activity modelling

(3) Pattern recognition classification, and discriminant analysis

(4) Multivariate process modelling and monitoring

The combination of the last and first above application areas has recently been given the name PAT when done in pharmaceutical and biotech manufacturing. The demands on manufacturing processes are rising rapidly, with higher target levels of quality, throughput and yield, at the same time as lower cost, less waste and less pollution are desired. Meeting these demands necessitates better knowledge about the processes and the process operations, as well as better control of process conditions, such as temperatures, flows, pressures and concentrations. This, in turn, demands better and more frequent measurements in all parts of the processes, and here process analytical chemistry provides valuable tools with online spectrometers, chromatographs and other devices.

The results of frequent process measurements with multiple instruments and sensor arrays are, however, a rapidly increasing volume of process data. Chemometrical projection methods, such as principal components analysis (PCA), projection to latent structures (PLS) and their generalizations work very well for the modelling and analysis of these large and complex data sets. These methods deal with multitudes of collinear, noisy and incomplete data and give easily interpretable and statistically reliable results, such as scores, deviations from the model and variable contributions.

The gains of PAT are related to the elimination of waiting for the return from the lab of analytical results after each process step. In addition, the richer multivariate process analytical data—properly visualized—potentially provide more information about the quality of the intermediates and final product than do the traditional lab analyses.

Other areas where chemometrics techniques show very promising results include the analysis of gene array data, metabonomics and metabolomics, and fault detection in semiconductor manufacturing processes.

About the Author

Svante Wold, PhD, studied chemistry at Uppsala University, Sweden. At this time he got greatly interested in computers when having a summer job at Uppsala's first computer, an Alwac IIIE. He then signed up as a graduate student in physical organic chemistry in Uppsala. In 1965, he moved to the new university of Umeå in northern Sweden. After his dissertation in 1971 (physical organic chemistry) he coined the term "Chemometrics", and was then invited to University of Wisconsin in Madison as the "Statistician in Residence" for the academic year 1973-74. In the United States, Svante helped found the International Chemometrics Society. In 1987, he started the company Umetrics in Umeå together with colleagues from the organic chemistry department, where he has spent most of his time since 1990. Today, he is active in expanding Umetrics' U.S. operations.

PDA Interest Groups & Leaders

The following is a list of PDA Interest Groups (IGs). The list below includes the IG's name and contact information for each IG's leader, including the leader's affiliation and his or her e-mail address. More detailed information on PDA's Interest Groups and contact information is available on the PDA Web site at: www.pda.org/science/IGs.html.

Aseptic Processing

Richard Johnson
Abbott Laboratories
E-mail: richard.m.johnson@abbott.com

Biotechnology

Frank Matarrese
GxP Consulting
E-mail: Frank_matarrese@alamedanet.net
- **European Branch**

Roland Günther
Novartis
E-mail:
roland.guenther@pharma.novartis.com

Computer Systems

Barbara L. Meserve
Acculogix, Inc.
E-mail: bmeserve@acculogix-usa.com

Drug–Device Delivery Systems

Raymond A. Pritchard
Consultant
E-mail: raypri@comcast.net
- **European Branch**

Alexander Schlicker, PhD
Hoffmann La Roche Ltd
E-mail: Alexandra.schlicker@roche.com

Georgios Imanidis, PhD
Pharmaceutical Technology
E-mail: georgios.imanidis@unibas.ch

Filtration

Jack Cole
Jack Cole Associates
E-mail: jvcole@aol.com
- **European Branch**

Roger Seiler
Sartorius
E-mail: roger.seiler@sartorius.ch

Inspection Trends/ Regulatory Affairs

Robert L. Dana
Elkhorn Associates Inc.
E-mail: elkhornassoc1@aol.com

Isolation Technology

TBD

Lyophilization

Edward H. Trappler
Lyophilization Techology
E-mail: etrappler@lyo-t.com

Microbiology/Environmental Monitoring

Jeanne E. Moldenhauer, PhD
Vectech Pharma. Consulting
E-mail:
jeannemoldenhauer@yahoo.com

Nanotechnology

D. F. Chowdhury
Aphton Corporation
E-mail: fazc@aol.com

Ophthalmics

Chris Danford
Alcon Laboratories Inc.
E-mail: chris.danford@alconlabs.com

Packaging Science

Edward J. Smith, PhD
Wyeth Pharmaceuticals
E-mail: smithej@wyeth.com

Pharmaceutical Water

Theodore H. Meltzer, PhD
Capitola Consulting Co.
E-mail: theodorehmeltzer@hotmail.com

Production and Engineering

Frank Bing
Consultant
E-mail: frankbingjr@aol.com
- **European Branch**

Philippe Gomez
Sartorius SA
E-mail: philippe.gomez@sartorius.com

Quality Assurance/ Quality Control

Don E. Elinski
Eli Lilly & Company
E-mail: elinski@aol.com

Stability

Rafik H. Bishara, PhD
Eli Lilly & Company
E-mail: rhb@lilly.com

Technology Transfer

Volker Eck, PhD
Nerviano Medical Science S.r.l.
E-mail: volker.eck@nervianoms.com

Zdenka Mrvova
Zentiva
E-mail: mrvova@leciva.cz

Training

Thomas W. Wilkin, EdD
University of New York
E-mail: twilkin@citytech.cuny.edu

Vaccines

Frank S. Kohn, PhD
FSK Associates Inc.
E-mail: fsk@lowatelecom.net

Validation

Harold Baseman
ValSource, LLP
E-mail: halbaseman@adelphia.net

Visual Inspection of Parenterals

John G. Shabushnig, PhD
Pfizer Inc.
E-mail: john.g.shabushnig@pfizer.com
- **European Branch**

Markus Lankers, PhD
APSYS GmbH
E-mail: markus.lankers@apsys.de

The reasons to use our flexible packaging are

PERFECTLY CLEAR

☎ : 1-800-845-3456 | : www.cryovacmedical.com | : cryovac.mkt@sealedair.com

Sealed Air
CRYOVAC®
Medical Products

PAT: Tool to Explore/Expand Design Space, continued from cover

acceptance criteria; yet they use the same limited data to pursue lengthy expiration dates for the product. This situation is "not really scientific," he asserted.

FDA would like to solve this dilemma by creating conditions that entice companies to share the appropriate scientific product and process development data. "I want people to come and say, 'Here is the science I have in my development report, here is the manufacturing scheme that I developed and here is how they link together,'" said Dr. Nasr.

The linkage between product development and manufacturing design is the **design space,** explained Dr. Nasr. "Once we establish that space, if you make changes within that space, you would not have to come to us."

The PAT-Design Space Link

The PAT initiative and design space are intricately linked. FDA's final PAT guidance, published in September 2004, takes a nibble at the design space concept by contrasting it with the current state of manufacturing.

In Section III, Background, FDA states that today's manufacturing procedures "are treated as being frozen, and many process changes are managed through regulatory submissions." Later in the section, FDA outlines the "desired state of pharmaceutical manufacturing and regulation." One of the characteristics identified is continuous *real time* assurance of quality. The PAT guidance, continues FDA, "is intended to facilitate progress to this desired state."

In Section IV, PAT Framework, the agency emphasizes that "*quality cannot be tested into product; it should be by design.*" It is the PAT tools described in the guidance, FDA contends, that "should be used for gaining process understanding and can also be used to meet the regulatory requirements for validating and controlling the manufacturing process."

In Section IV.A, Process Understanding, FDA refers specifically to design space in describing the factors that contribute to a "well-understood" process: "(1) all critical sources of variability are identified and explained; (2) variability is managed by the process; and, (3) product quality attributes can be accurately and reliably predicted over the **design space** established for materials used, process parameters, manufacturing, environmental, and other conditions."

...product quality attributes can be accurately and reliably predicted over the design space established for materials used, process parameters, manufacturing, environmental, and other conditions...

This predictive capability, by reason, allows for a diminished "burden for validating systems by providing more options for justifying and qualifying systems intended to monitor and control biological, physical, and/or chemical attributes of materials and processes."

Indeed, FDA's Office of Regulatory Affairs published revised Compliance Policy Guide 7132c.08 on process validation last year to acknowledge this new thinking. The revision includes the following caveat regarding the manufacture of "conformance lots" prior to marketing authorization: Use of advanced pharmaceutical science and engineering principles and control technologies "can provide a high assurance of quality by continuously monitoring, evaluating, and adjusting every batch using validated in-process measurements, tests, controls, and process endpoints. For manufacturing processes developed and controlled in such a manner, it may not be necessary for a firm to manufacture multiple conformance batches prior to initial distribution."

FDA offers a cautionary note in the PAT guidance, however, to firms aspiring to implement PAT controls to their processes without the prerequisite scientific understanding. "In the absence of process knowledge, when proposing a new process analyzer, the test-to-test comparison between the online process analyzer and the conventional test method on collected samples may be the only available validation option." For many firms, the agency notes, "this approach may be too burdensome," thus discouraging the use of new technologies. In addition, just the mere "transfer of laboratory methods to on-, in-, or at-line methods" does not necessarily represent the attainment of PAT.

PAT Guidance Spin-Offs

Further elaboration of the relationship between design space and PAT occurs in the International Conference on Harmonisation (ICH) guideline, Q8, *Pharmaceutical Development,* which is itself a product of the PAT initiative.

As the PAT framework unfolded, FDA acknowledged a number of barriers to the implementation of new process control technologies, the largest being a regulatory system that emphasized empirical quality standards versus science-based standards.

Quality. Consistency. Support.

For Peace of Mind, Specify Texwipe®

At ITW Texwipe we believe cleanroom wipers are unique contamination control products that are pivotal in the maintenance of critical environments. ITW Texwipe takes the guesswork out of specifying cleanroom consumables. We ensure consistent quality and put our reputation on the line with every product we make. With ITW Texwipe you can be assured you are receiving the highest quality, most technically advanced products available. Specify ITW Texwipe and secure peace of mind.

Dry Wipers • Pre-Wetted Wipers • Swabs • Sterile Products • Stationery • Mops

ITW Texwipe®

Quality. Consistency. Support.

	North America	Europe	Asia
Tel	201 684 1800	+45 87 400 220	+65 6468 9433
Fax	201 684 1801	+45 87 400 222	+65 6468 6772
E-mail	info@texwipe.com	europe@texwipe.com	asia@texwipe.com

www.texwipe.com

For firms to feel comfortable pursuing PAT, they require assurances that they will not be punished for sharing the full spectrum of data generated to implement the technologies. More basically, there is a need for an adequate procedure for sharing such information and regulatory bodies capable of properly interpreting it. Finally, an industry well-experienced in the "current state" of design and specification setting needs better guidance on risk management and quality systems.

To address these needs, FDA called on its ICH partners to provide international guidance in each area. The Pharmaceutical Development guideline, released as a "Step 2" draft for comment in November 2004, outlines the expectations for filing a Pharmaceutical Development Section (3.2.P.2) of the Common Technical Document format (ICH M4). ICH Q9, *Quality Risk Management,* defines various risk management tools and how they can be applied. Finally, ICH is moving forward with Q10 to address quality systems.

For companies to feel comfortable pursuing PAT, they require assurances that they will not be punished for sharing the full spectrum of data generated...

According to ICH Q8, the pharmaceutical development section of a drug marketing application is the appropriate place for companies to "present the knowledge gained through the application of scientific approaches, and risk management, to the development of a product and its manufacturing process" (Section 1, Introduction). This data "can be updated to support new knowledge gained over the lifecycle of a product."

More flexible regulatory approaches will be available to firms that provide "a more comprehensive understanding of the product and manufacturing process for reviewers and inspectors."

Section 2 of the Q8 document states how a firm establishes design space through product/process design. By making changes to formulations and manufacturing processes during development, companies are generating the scientific knowledge that supports "establishment of the design space." The document implies both positive results and negative results are important to understanding design space.

At a minimum, the development report should provide information to support the formulation and manufacturing processes proposed. To meet this goal, the report should identify properties of the active ingredient(s), excipient(s) and manufacturing process "that are critical and that present significant risk to product quality, and therefore should be monitored or otherwise controlled."

However, applicants "can choose" to perform additional pharmaceutical development studies that can enhance "knowledge of product performance over a wider range of material attributes, processing options and process parameters." Sharing such information with the regulatory bodies in the development report section of the marketing application "provides an opportunity to demonstrate a higher degree of understanding of manufacturing processes and process controls," which effectively "establishes the design space."

PDA and PAT

PDA is helping its members understand the FDA PAT initiative with a variety of *Career-long Learning*™ offerings. The following are courses and events (past and future) offered by PDA in 2005 that relate to the PAT initiative.

Audio Conferences

ICH Q8 Pharmaceutical Development *June 2005*

ISO 14971: A Worldwide Risk Management Standard (date TBD)

Programs and Meetings

International Congress, Rome:
- Session on ICH Q8 Update
- Presentation on PAT at AstraZeneca

Annual Meeting, Chicago:
- Sessions on Applications in Process Analytical Technology; System Applications Risk-based Management as Part of the Quality System Approach; Rapid Microbiological Methods; and the FDA PAT initiative
- Breakfast tutorial on PAT Statistical Concepts

PDA/FDA Joint Regulatory Conference *(Upcoming! September 12-16)*:
- 2 Sessions on PAT Principles
- Sessions on Development History; Risk Assessment; ICH Q8; and Identification of Critical Control Points
- Lunch sessions on USP and PAT
- Closing Plenary session on Continuous Product and Process Improvement

The PDA Training and Research Institute

DoE Basics for P.A.T. Applications

Rapid Microbiological Methods Laboratory Course *(Upcoming! October 31 – November 4)*

To register for upcoming events or to learn more, go to www.pda.org/calendar.

By sharing scientific knowledge of the design space with the health authorities, companies open the door to:

- Risk-based review and inspection
- Manufacturing process improvements within the approved design space without further regulatory oversight
- Real-time quality control leading to a reduction of end-product release testing

Critical to obtaining these benefits is the demonstration of "an enhanced knowledge of product performance over a range of material attributes…processing options and process parameters." Material attributes can include particle size distribution, moisture content and flow properties. PAT and experimental designs can facilitate the acquisition of such knowledge.

ICH Q8 offers the first regulatory definition of design space: "The design space is the established range of process parameters that has been demonstrated to provide assurance of quality. In some cases design space can also be applicable to formulation attributes. Working within the design space is not generally considered as a change of the approved ranges for process parameters and formulation attributes. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process."

PDA's written comments on ICH Q8 (*see page 26*) addressed design space. Overall, PDA would like to see the concept better defined.

The comments state: "Understanding 'design space' as a concept is crucial to a complete understanding of this guideline and the benefits contained within. It would be preferable to include the definition within the body of the text where the term is first used in addition to the definition in the glossary."

Moreover, "the concept of design space would also benefit from a more detailed definition and description. It is not clear if the design space refers to product specifications or to processing parameters. Also, the intended inter-relationship between the design space, the critical processing parameters and product release specifications is not clear. PDA supports the recent discussions at the PQRI Workshop on Specifications. At that meeting, the concept of separation of release specifications based on clinical relevance (critical quality attributes) from critical processing parameters internally controlled during manufacturing was advanced."

...the concept of design space would also benefit from a more detailed definition and description...

Finally, PDA asks for clarification of "the mechanism by which a design space becomes an approved design space by different regulatory authorities. There should be assurance across the three regions concerning consistent interpretation of the design space."

Expanding Design Space

All is not lost if the pharmaceutical development report does not support a large design space and regulatory flexibility.

At the PDA Extractables/Leachables Forum, Dr. Nasr addressed this issue. No matter how well-defined in the original application, design space can be expanded post-approval with new scientific data gained over the product lifecycle. "When you have more science, more design of experiments, more manufacturing information, more manufacturing batches…you can come to us…and say I want to expand that space and here is the information that is needed to establish the new boundaries of the design space and will get you the flexibility within that design space."

At the 2005 PDA International Congress in Rome, March 1-3, the Center for Biologics Evaluation and Research's **Christopher Joneckis,** PhD, Sr. Advisor, CMC, spoke about the flexibility built into the Q8 draft for development reports of various levels. "The guideline was in fact intentionally constructed so that not all of the information that one provides is mandatory," Dr. Joneckis said. The document does establish that the regulatory authorities have "clear baseline expectations" for the submission. For instance, "you have to clearly describe the knowledge for both the type of dosage form and the proposed formulation and show they are satisfactory…for your intended purpose."

FDA is assuring industry that the use of the development report is not meant to force firms to generate and submit additional data. Instead, explained Dr. Joneckis in Rome, "The opportunity here now is…to move away from just reams and reams of data, but to communicate knowledge…and to communicate risk and the risk mitigations metrics." Dr. Nasr echoed this thought: "We are not asking for more information.

continued on page 20

PDA Calendar of Events for North America

Please visit www.pda.org for the most up-to-date event information, lodging and registration.

Conferences

September 11-14, 2005
PDA/FDA Joint Regulatory Conference, Courses and Exhibition
Washington, DC

October 20-21, 2005
2005 PDA Visual Inspection Forum
Bethesda, Maryland

November 3-4, 2005
Aseptic Processing Guidance
Las Vegas, Nevada

April 2006
PDA Annual Meeting

May 8-10, 2006
2006 Training Conference
New Orleans, Louisiana

Training

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

Laboratory Courses

July 26-29, 2005
Pharmaceutical and Biopharmaceutical Microbiology 101

August 10-12, 2005
Developing a Moist Heat Sterilization Program Within FDA Requirements

August 22-26, 2005
Aseptic Processing Training Program (Week 1)

September 7-9, 2005
Advanced Environmental Mycology

September 19-23, 2005
Aseptic Processing Training Program (Week 2)

October 6-7, 2005
Fundamentals of D, F and z Value Analysis

Lecture Courses

August 8, 2005
Maximizing SOPs–An Untapped Resource of Training Solutions

August 9–11, 2005
***Career-long Learning*™**
Biotechnology: Overview of Principles, Tools, Processes and Products

September 7-9, 2005
Fundamentals of Pharmaceutical Filtrations and Filters

Lecture Courses

August 8, 2005
Maximizing SOPs - An Untapped Resource of Training Solutions

August 9-11, 2005
Biotechnology: Overview of Principles, Tools, Processes and Processes and Products

September 7-9, 2005
Fundamentals of Pharmaceutical Filtrations and Filters

September 26-27, 2005
Computer Products Supplier Auditing Process Model: Auditor Qualification

September 26-28, 2005
Basic Skills for the Training Professional

Course Series

October 24-26, 2005
Medical Device Course Series
Denver, Colorado

November 29-December 1, 2005
***Career-long Learning*™**
New Orleans, Louisiana

Chapters

June 13, 2005
PDA Metro Chapter
Isolator Technology
Clark, New Jersey

June 14, 2005
PDA Midwest Chapter
USP Course
Analytical Method Validation
Rosemont, Illinois

June 15, 2005
PDA Delaware Valley Chapter
Current USP Prospective on Alternative Microbiological Methods
Malvern, Pennsylvania

October 2005
PDA Midwest Chapter
Dinner Meeting
Northbrook, Illinois

November 10, 2005
PDA Mountain States Chapter
Speaker Dinner

PDA Calendar of Events for Europe/India/Asia Pacific

Please visit www.pda.org for the most up-to-date event information, lodging and registration.

EUROPE

June 13, 2005
PDA and the PDA UK/Ireland Chapter
PDA EuroForum
Risk Assessment and Risk Management in Pharmaceutical Manufacturing
London, England

September 20, 2005
PDA and the PDA Italy Chapter
Rapid Micro TM 33
Milan Italy

September 21-22, 2005
PDA Training & Research Institute
***Career-long Learning*™**
Basel, Switzerland

October 24-25, 2005
PDA Conference on the Universe of Pre-filled Syringes
Munich, Germany

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

November 15, 2005
PDA and the PDA Prague Chapter
PDA EuroForum
PAT - Industry, Regulator and Academic
Budapest, Hungary

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

November 30-December 2, 2005
PDA Training & Research Institute Laboratory Course
Practical Aspects of Aseptic Processing
Basel, Switzerland

INDIA

September 16-17
PDA IndiaForum
PDA and the PDA India Chapter present
Certificate of Suitability CEP
TBD

September 16-17, 2005
PDA and the PDA India Chapter present
PDA IndiaForum
Certificate of Suitability CEP
TBD

November 22-23, 2005
PDA and the PDA India Chapter present
PDA IndiaForum
In-Licensing
TBD

ASIA/PACIFIC

June 8, 2005
PDA Taiwan Chapter
Annual Meeting
Taipei, Taiwan

June 16, 2005
PDA Australia Chapter
Dinner Meeting
Supplier Software Audits
Mt. Waverly, Australia

June 2005
PDA Japan Chapter
Training Course: Aseptic Processing
Tokyo, Japan

November 2005
PDA Japan Chapter
Annual Meeting
Tokyo, Japan

December 2005
PDA Korea Chapter
TBD

PAT: Tool to Explore/Expand Design Space, continued from page 17

We are asking for the right information, and that means we will get more in the area of development and process understanding." One of the strategies for generating more scientific information about the product and process during manufacturing is the implementation of PAT—a strategy favored by the agency. Over the past few years, CDER officials have stressed the importance of better in-process manufacturing controls and quality systems to forestall product failures, deviations, recalls and regulatory actions.

The need for more robust in-process controls and quality systems is even greater in light of the more complex and innovative products in development. Dr. Nasr addressed this: "There has to be more reliance on process control and in-process testing and less dependence on end-product testing," he asserted. With an over-reliance on end-product testing, companies go through cycles of product failure, investigation, enforcement and delays. "You could not afford to do that in the past," and will be less able to in the future as "the drug substances are becoming more expensive and drug devices and combination which we are dealing with now…are very expensive," he maintained.

With more reliance on process control and in-process testing, there is opportunity to place less emphasis on end-product testing and eliminate certain release tests that are redundant to the control of critical quality parameters. Dr. Nasr identified the control of impurities, stereoisomers and particle size as such attributes that can be controlled in-process. "You don't have to test for some of these attributes at the end if you can tell us that you are controlling them while you are doing the manufacturing," he said.

Dr. Nasr stated that current specification-setting practices represent a "vicious cycle" (*see Figure 1 below*). In the future, he said, specification setting needs to be risk based, distinguishing between:

- critical quality attributes with specifications that assure desired quality and clinical performance
- other quality attributes to assure the consistency and robustness of the product

Companies need to move away from using specifications to control the manufacturing process, which has prevented innovation and continuous improvement.

At FDA's Science Forum in April in Washington, D.C., CDER Office of Pharmaceutical Science Deputy Director **Ajaz Hussain,** PhD, commented on the use of the product/process design to improve quality control. Quality by design, he said, is the marriage of the science of product design with manufacturing science. Without designing quality into the product/process, companies merely "test to document quality."

It is "too late" for companies to begin thinking about quality by design after clinical trials, asserted Dr. Hussain. "Quality by design starts before an established clinical trial material." Companies failing to make a clear connection between final product quality and clinical performance face greater uncertainty, variability and risk throughout the product lifecycle.

Dr. Hussain cited the material properties of excipients as an area where uncertainty, variability and risk are high. The properties of excipients are the "worst understood" in the manufacturing chain, he declared. Variability of these materials results "essentially [from] USP-NF-type of [certificate of analysis] which does not tell you anything about the 'processability' of the material."

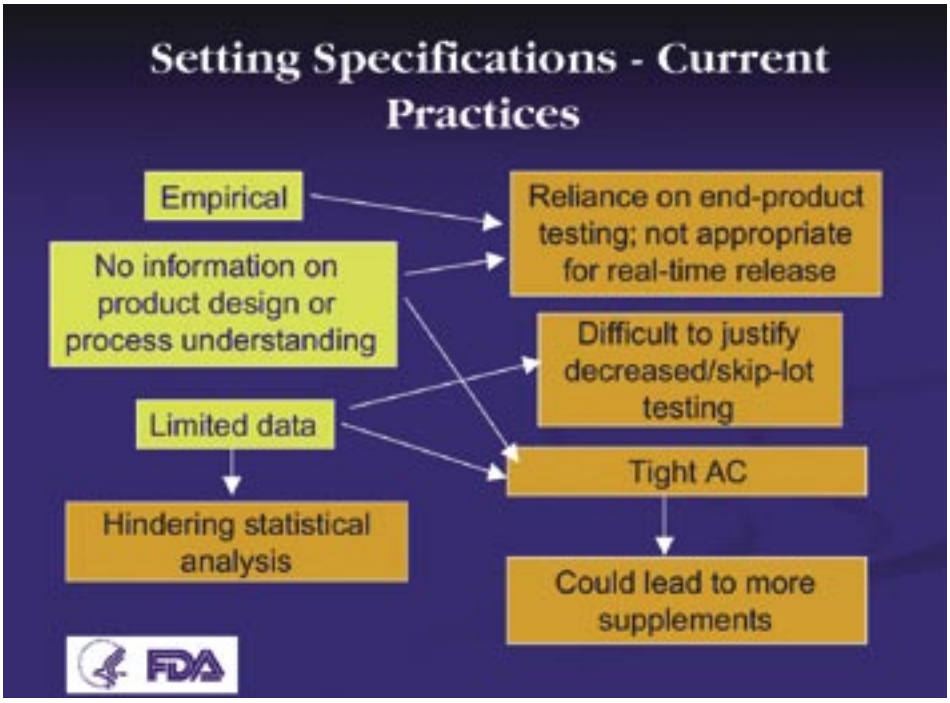


Figure 1: The Spec Setting "Viscious Cycle"—CDER's Moheb Nasr

Avoid the Fright

Just twist for a safe, secure lock

DON'T LET A NIGHTMARE BECOME REALITY WHEN YOUR PLATES DROP.

Now there's a simple way to ensure the integrity of your plates, media and samples. PML's new locking lids provide a secure seal for 60mm contact plates, without compromising performance. Just twist for a safe, secure lock. The triple-bag packaging guarantees sterility and freshness. Extended shelf life allows for longer lot usage and reduced QC testing. So why take risks with what's lurking out there? Avoid the fright, lock it down tight.

To lock up a free sample, email PML at orders@pmlmicro.com today.

PML microbiologicals

PO Box 570, Wilsonville, OR 97070
Phone 800.628.7014
www.pmlmicro.com

Dissolution testing, he noted as an example, introduces variability into the process because it hinges on the calibration of analytical equipment using "an unstable calibrator tablet made under non-GMP conditions." This variability is acceptable today.

The problem, as Dr. Hussain describes it, is that companies relying on such test methodologies cannot distinguish between "special cause" variability and "common cause" variability. The former requires investigation and corrective actions, whereas the latter is acceptable but should be controlled and reduced.

Referring again to dissolution, Dr. Hussain argued that companies do not have the capability to determine whether deviations are the result of the product, the process or the measurement system, because calibration relies on "an unstable calibrator tablet."

When such failures occur, he doubted that firms truly "know whether the process is stable, under control or capable."

Addressing process validation, Dr. Hussain insisted that the current paradigm creates an "artificial system," iin which three-batch validation is "perfect" only because companies bring in their "best R&D folks to do it, use the same lot of raw materials and [keep] their fingertips crossed."

The lack of true process knowledge gained under the current approach creates many unknowns, according to Dr. Hussain. Regarding lots that are rejected and lots that are released, he asked rhetorically, "How much difference in quality is there between the two lots?—big question." In addition, "How many failures do you need before you say this is no longer validated?—unknown answer." The solution, according to FDA and its ICH partners, is quality by design. Early in the process, companies need to "define acceptable variability and not worry about it, and then get on the path to continuous improvement," said Dr. Hussain.

At-Line: Measurement where the sample is removed, isolated from, and analyzed in close proximity to the process stream.

On-Line: Measurement where the sample is diverted from the manufacturing process, and may be returned to the process stream.

In-Line: Measurement where the sample is not removed from the process stream and can be invasive or noninvasive

PAT Tools

PAT is viewed by the regulatory authorities in the United States, Europe and Japan, as well as by a growing number of companies, as the ideal tool for building robust in-process control systems for most drug products, and as such, for establishing broad design spaces.

Dr. Hussain describes PAT and the PAT guidance as "opening the door to realize the benefits of connecting Fisher, Shewart and Deming."

FDA established a definition of PAT that has been broadly accepted by the industry and its regulatory partners. In the PAT guidance, FDA defines PAT as: "a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality." This definition appears in the glossary of the draft ICH Q8 guideline.

The types of technologies that can be applied at-, in- and on-line to measure, monitor and control products and processes are becoming well known and include: near-infrared spectroscopy, Raman spectroscopy, GC/LC and acoustics. These analytical devices enable companies to fulfill the goal of performing "timely measurements of critical quality and performance attributes."

While determining what attributes to measure and which analytical tools to employ is a significant challenge, learning how to use and interpret large quantities of data necessary to successfully apply the analyzers can be even more daunting.

Such development data (whether generated preapproval for the original application or post-approval to expand the design space) provides the "knowledge base to support and justify flexible regulatory paths for innovation in manufacturing and post-approval changes." Companies will be best served when this knowledge base "consists of scientific understanding of the relevant multi-factorial relationships…as well as a means to evaluate the applicability of this knowledge in different scenarios." Relationships to be fleshed out through design studies can include those between the formulation, the process and the quality attributes.

FDA stresses that multivariate mathematical approaches and "knowledge management systems" are key in realizing the benefits of building a scientific knowledge base. Statistical design of experiments, response surface methodologies, process simulation and pattern recognition tools are examples of multivariate approach-

es named in the guidance. *(See related story on chemometrics, p. 11.)*

The agency states that "one-factor-at-a-time experiments do not address the interactions among product and process variables." Rather, "methodological experiments based on statistical principles of orthogonality, reference distribution, and randomization provide effective means for identifying and studying the effect and interaction of product and process variables."

According to the guidance, once in manufacturing, companies are faced with the challenge of handling "large volumes of data," changing the nature of batch records. "In a PAT environment," FDA states, "batch records should include scientific and procedural information indicative of high process quality and product conformance. For example, batch records could include a series of charts depicting acceptance ranges, confidence intervals, and distribution plots (inter- and intrabatch) showing measurement results." Data should be secure, yet easily accessible "for real-time manufacturing control and quality assurance." Selecting the information technology systems to "accommodate such functions" is the challenge.

Another difference between traditional batch records and those generated in a PAT environment is the type of data collected. Whereas the goal of traditional pharmaceutical manufacturing is to prevent variability, a PAT-controlled process allows for the management of variability. The guidance explains: "A flexible process may be designed to manage variability of the materials being processed. Such an approach can

PAT Guidance: "Connecting Fisher, Shewhart and Deming"— FDA's Ajaz Hussain

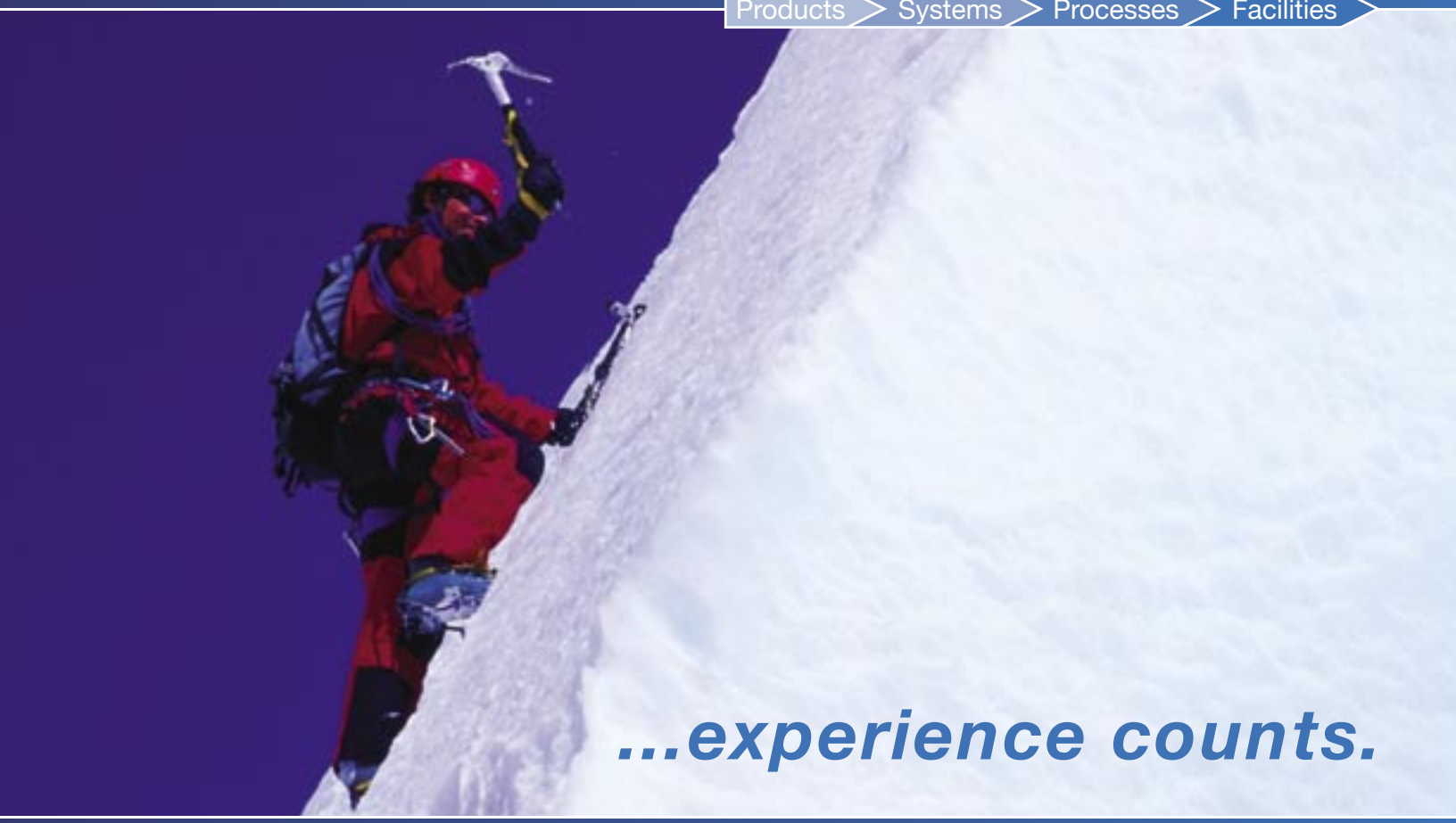
Sir Ronald A. Fisher (1890–1962) was an English statistician and geneticist, educated at Cambridge University. From 1919 to 1933 he worked at the Rothamsted Experimental Station. He was professor of genetics at University College, London (1933–43) and at Cambridge (1943–57) and conducted research at the Commonwealth Scientific and Industrial Research Organization, Adelaide, Australia from 1957 until his death. He revolutionized inferential statistics, developing the concepts of analysis of variants and factorial experimentation. He wrote the classic *Statistical Methods for Research Workers* (1925) and *Design of Experiments and Statistical Methods* (1934). He also made extraordinary contributions to the field of genetics and statistically reconciled the principals of Mendelian inheritance with Darwin's notion of natural selection. He wrote the seminal work *The Genetical Theory of Natural Selection* (1930). (ref.: The Columbia Electronic Encyclopedia, 6th ed. Copyright © 2005, Columbia University Press. All rights reserved)

Walter A. Shewhart (1891-1967) received a doctorate from the University of California, Berkeley in 1917. For most of his career, he worked for the Bell Telephone Company, where he advocated the use of statistical control to improve the reliability of transmission systems. His work with Bell was summarized in his book, *Economic Control of Quality of Manufactured Product* (1931). Shewhart's charts were adopted by the American Society for Testing and Materials (ASTM) in 1933. In the late 1930's, Shewhart began studying statistical inference, and he published a second book, *Method from the Viewpoint of Quality Control* (1939). In 1938 his work came to the attention of physicists W. Edwards Deming, and the two began a long collaboration that involved work on productivity during World War II. Later, Deming championed Shewhart's ideas in Japan. Deming developed some of Shewhart's methodological proposals around scientific inference and named his synthesis the Shewhart cycle. During the 1990s, Shewhart's work was rediscovered by a third generation of industrial managers as the Six Sigma approach. (ref.: Wickpedia, *The Free Encyclopedia*)

William E. Deming (1900–1993) received a doctorate from Yale University in 1928. He used statistics to examine industrial production processes for flaws and believed that improving product quality depended on increased management-labor cooperation as well as improved design and production processes. He greatly influenced Japanese industry as it rebuilt in the years after World War II. Deming's beliefs formed a pillar of the Total Quality Management movement in the United States. He encapsulated his beliefs in his 1986 book *Out of the Crisis.* (ref.: T*he Columbia Electronic Encyclopedia*, 6th ed. Copyright © 2005, Columbia University Press. All rights reserved.)

When you're leading the way...

Products > Systems > Processes > Facilities



...experience counts.

Stedim is celebrating 25 years as the world's leading designer and manufacturer of single-use, sterile bag systems for medical and pharmaceutical products. As the pioneer of single-use technology for bioprocessing, Stedim has developed the broadest range of biotechnology bag systems and ground breaking products. Stedim is joining its experience and commitment to excellence with a growing confederation of strategic partners to break through barriers in bioprocessing and lead the way to the future of single-use biomanufacturing.

1979 - 2004

25

YEARS OF QUALITY, INNOVATION, SERVICE

STEDIM

Please visit our new website at www.stedim.com

STEDIM

Leading the Way to the Future of Single-Use Bioprocessing.

be established and justified when differences in quality attributes and other process information are used to control (e.g., feed-forward and/or feed-back) the process."

Once again, use of multivariate mathematical tools "are often necessary to extract critical process knowledge for real-time control and quality assurance." In addition, statistical and risk analyses of the process should be conducted to assure the soundness of predictive mathematical relationships.

Finally, it is critical that companies possess strong quality systems and risk-management capabilities in order to derive the full benefit—manufacturing and regulatory—of a PAT system.

FDA Approves PAT CP

FDA's efforts to help industry adopt PAT systems is bearing fruit. At the 2005 PDA Annual Meeting in Chicago, Ill., April 4-6, CDER Office of Compliance official **Albinus D'Sa,** PhD, reviewed the steps FDA has taken since 2001 to advance the PAT initiative.

At the outset of the initiative, Dr. D'Sa explained, "many and systemic" obstacles to PAT implementation existed at CDER. "We had a culture mindset that was not integrated. We had organizational barriers. Interdisciplinary communication and collaboration was nonexistent. There was inadequate support of fundamental pharmaceutical science and technology." Problems at the agency were "probably" mirrored in industry.

FDA overcame its PAT obstacles with the creation of its multi-center PAT Team, which includes a steering committee, a policy development team, training coordinators and the PAT Review - Inspection Team (PATRIOT). The latter group received certification in September 2004 following intensive training. A second round of training is in the works, as are plans to assemble additional teams.

Three months after certification, PATRIOT approved its first PAT comparability protocol (CP). The team as a whole assessed the submission, with the goal of: understanding the scientific rationale for the approaches taken; evaluating how robust the company's process understanding was pertaining to prediction, monitoring, control strategies and continuous improvement; and understanding the risk-management approaches and the concept of real-time release. The team also evaluated the CP for its adherence to the PAT guidance.

At the IFPAC 2005 conference in Arlington, Va., in January, **David Radspinner,** Aventis Pharmaceutical, discussed how his firm received approval for a PAT CP.

The company needed to develop a "new way" of approaching the agency in order to be successful, explained Radspinner. In order to build trust with the agency, the company "had to establish that it knew what it was doing." Discussions with the agency were focused on science and technology, and covered the company's failures.

The comparability protocol covered a 15 step process from API through drug product production. A key aspect of Aventis' PAT project was developing "predictive dissolution," which might allow the firm to move away from end-product dissolution testing.

Overall, the company achieved approval of the CP in a short time frame. In 2003, initial discussions with FDA began in January and PATRIOT visited the facility in May. Drafts of the CP were shared with FDA beginning in November 2003. The CP was finally approved in December 2004.

Radspinner advised that companies "think outside the box," "drive PAT from the factory floor," "don't have assumptions" and "be relentless."

Walter Morris, PDA

June 10, 2005

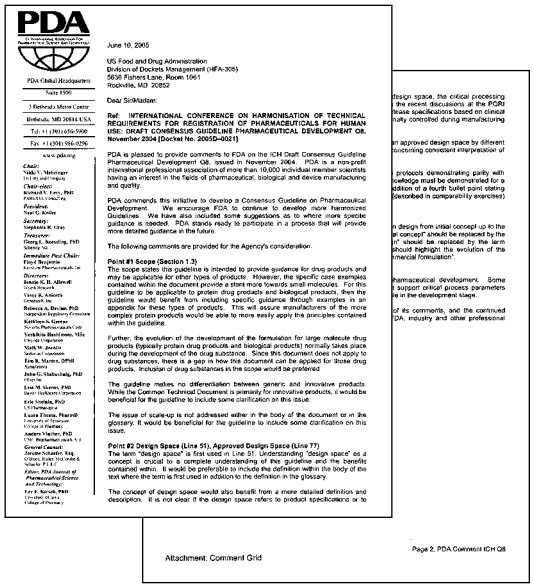
US Food and Drug Administration
Division of Dockets Management (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Dear Sir/Madam:

Ref: INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE: DRAFT CONSENSUS GUIDELINE PHARMACEUTICAL DEVELOPMENT Q8, November 2004 [Docket No. 2005D–0021]

PDA is pleased to provide comments to FDA on the ICH Draft Consensus Guideline Pharmaceutical Development Q8, issued in November 2004. PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological and device manufacturing and quality.

PDA commends this initiative to develop a Consensus Guideline on Pharmaceutical Development. We encourage FDA to continue to develop more harmonized Guidelines. We have also included some suggestions as to where more specific guidance is needed. PDA stands ready to participate in a process that will provide more detailed guidance in the future.


PDA

June 10, 2005

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

Dear Sir/Madam:

Ref: INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE: DRAFT CONSENSUS GUIDELINE PHARMACEUTICAL DEVELOPMENT Q8, November 2004 [Docket No. 2005D–0021]

PDA is pleased to provide comments to FDA on the ICH Draft Consensus Guideline Pharmaceutical Development Q8, issued in November 2004. PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological and device manufacturing and quality.

PDA commends this initiative to develop a Consensus Guideline on Pharmaceutical Development. We encourage FDA to continue to develop more harmonized Guidelines. We have also included some suggestions as to where more specific guidance is needed. PDA stands ready to participate in a process that will provide more detailed guidance in the future.

The following comments are provided for the Agency's consideration.

Point #1 Scope (Section 1.3)

Point #2 Design Space (Line 51), Approved Design Space (Line 77)

Attachment: Comment Grid

Page 2: PDA Comment ICH Q8

The following comments are provided for the Agency's consideration.

Point #1 Scope (Section 1.3): The scope states this guideline is intended to provide guidance for drug products and may be applicable for other types of products. However, the specific case examples contained within the document provide a slant more towards small molecules. For this guideline to be applicable to protein drug products and biological products, then the guideline would benefit from including specific guidance through examples in an appendix for these types of products. This will assure manufacturers of the more complex protein products would be able to more easily apply the principles contained within the guideline. Further, the evolution of the development of the formulation for large molecule drug products (typically protein drug products and biological products) normally takes place during the development of the drug substance. Since this document does not apply to drug substances, there is a gap in how this document can be applied for those drug products. Inclusion of drug substances in the scope would be preferred.

The guideline makes no differentiation between generic and innovative products. While the Common Technical Document is primarily for innovative products, it would be beneficial for the guideline to include some clarification on this issue.

The issue of scale-up is not addressed either in the body of the document or in the glossary. It would be beneficial for the guideline to include some clarification on this issue.

Point #2 Design Space (Line 51), Approved Design Space (Line 77): The term "design space" is first used in Line 51. Understanding "design space" as a concept is crucial to a complete understanding of this guideline and the benefits contained within. It would be preferable to include the definition within the body of the text where the term is first used in addition to the definition in the glossary. The concept of design space would also benefit from a more detailed definition and description. It is not clear if the design space refers to product specifications or to processing parameters. Also, the intended inter-relationship between the design space, the critical processing parameters and product release specifications is not clear. PDA supports the recent discussions at the PQRI Workshop on Specifications. At that meeting, the concept of separation of release specifications based on clinical relevance (critical quality attributes) from critical processing parameters internally controlled during manufacturing was advanced.

Clarification is needed for the mechanism by which a design space becomes an approved design space by different regulatory authorities. There should be assurance across the three regions concerning consistent interpretation of the design space.

Changes outside of the design space could be implemented according to protocols demonstrating parity with original processes. Thus, regulatory flexibility would be realized. Process knowledge must be demonstrated for a firm to take advantage of this regulatory flexibility. We would suggest the addition of a fourth bullet point stating manufacturing process improvements, outside of the approved design space (described in comparability exercises) could be implemented without further regulatory review.

Point #3 Initial Concept to Final Design (line 143): Line 143 states "The summary should highlight the evolution of the formulation design from initial concept up to the final design." It is unclear what is meant by the initial concept. The term "Initial concept" should be replaced by the term "initial early development" for greater clarity. The term "final design" should be replaced by the term "commercial formulation". The sentence would then read "the summary should highlight the evolution of the formulation design from the initial early development formulation up to the commercial formulation".

Point #4: Test Methods: The guidance is silent regarding the test methods utilized throughout pharmaceutical development. Some comments on analytical methods should be included. Those methods that support critical process parameters should be demonstrated to be reliable, accurate and robust as early as possible in the development stage.

PDA would be pleased to offer its expertise to assist in the clarification of its comments, and the continued evolution of this important Guideline. We look forward to working with FDA, industry and other professional associations to develop a world class document.

Yours sincerely,

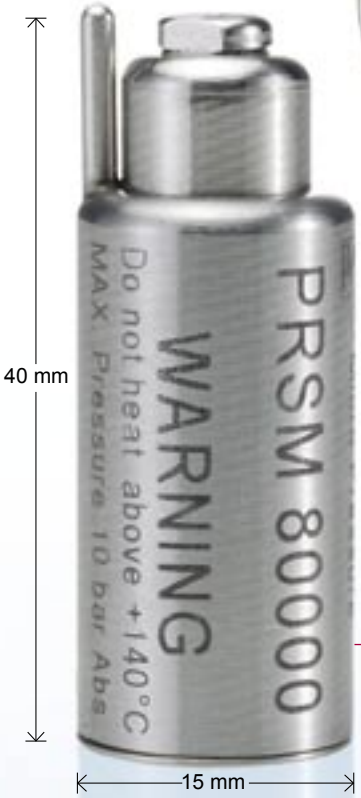
Lance K. Hoboy
Vice President, Finance & Strategic Planning, PDA

Go to www.pda.org/regulatory/regcomments.htm for this letter and the comments grid.

Thermal Validation Solutions

Temperature, Pressure & Humidity

For over 50 years Ellab has focused on manufacturing the highest quality temperature, pressure and humidity monitoring systems. The ValSuite software enables a complete solution integrating real-time monitoring, wireless data logging, and automated calibration in one validated software platform for applications requiring compliance with FDA guidelines and international GMP standards.



TrackSense Pro loggers are unmatched in accuracy, performance and versatility

Ideal for thermal validation applications, such as steam or EtO sterilization, mapping rooms and stability chambers. Dramatically reduces setup time and improves productivity.

Calibration Baths & Temperature Standards

The bath and temperature standard can be integrated into the software for automated multi-point calibration.

E-Val Flex

Real-time thermocouple monitoring system.

TrackView

Network data acquisition software designed for plant wide data acquisition and alarming.

Thermal Validation Solutions

ellab
Building Confidence

www.ellab.com • info@ellab.com • Phone no. USA 303 425 3370

Globe Trekking: My Recent Visits with PDA's Chapters

Kelly Coates, PDA

As PDA Manager, Membership & Chapters, one of my privileged responsibilities is to visit our members and Chapters around the world. The last few months have been an exciting time for me as I began traveling the globe to attend PDA and Chapter events. I was able to meet many PDA members and see firsthand how PDA Chapters help to bring the best of PDA to their local communities.

Capital Area Chapter Dinner: Jason Mangler shows off GE Ionics new TOC Analyzer (left). Naomie Baer chats with Debra Pagano (left).

PDA International Congress

My travels began with a trip to Rome, Italy, in March for the PDA International Congress. This was my first opportunity to meet many of our European members. The Italy Chapter did an excellent job assisting with the event and making us all feel welcome in their part of the world.

PDA Capital Area Chapter

On March 23, I attended my first Chapter event along with **Gail Sherman,** PDA Vice President of Education and Director of TRI. The PDA Capital Area Chapter dinner meeting in Gaithersburg, Md., included an informative presentation, "Preparing for PreApproval Inspections," by **Debra Pagano,** IHL Consulting Group, Inc. This topic was obviously a hit, since it drew a record number of attendees for the Chapter. As an added bonus, I was able to meet the Chapter's scholarship winners, **Jaime Miller** and **Erin Voss,** both students at the University of Maryland Baltimore County, who were also recognized at this event.

PDA Annual Meeting

My next trip was to the main PDA event of the year: the PDA Annual Meeting in Chicago, Illinois, April 4-6. I was delighted to attend the PDA Honor Awards dinner, where 24 members were honored for their achievements and commitment to PDA. I also participated in my first Chapter Council Meeting with Chapter representatives from around the world. We discussed Chapter activities, the upcoming Chapter Handbook and new initiatives to collaborate with PDA TRI. Another successful event was the New Member breakfast, during which I was able to talk with new PDA members and listen to Board member Kathleen Greene's talk about the benefits of PDA membership.

PDA Delaware Valley Chapter

On April 12, I drove to Malvern, Pa., along with PDA TRI's Gail Sherman and Strother Dixon to attend the PDA Delaware Valley Chapter's dinner meeting, which focused on sterile components and containers. Chapter President **Art Vellutato, Jr.** was recognized at this meeting for his contributions to the Chapter. After dinner, **Maurice Phelan,** Millipore Corporation, presented "Disposable Manufacturing Solutions."

PDA Southern California Chapter Seeks Board Nominees

The PDA Southern California Chapter is seeking nominees for its Board of Directors. The positions of President, Vice President and Secretary are open this year. All current PDA members in the Southern California region are eligible. Take advantage of this opportunity to get involved in your local PDA Chapter. Chapter officers not only serve the industry, PDA and their local community but also gain the following benefits:

- Interact with other industry leaders in areas of interest
- Develop leadership and managerial skills
- Enhance communication and networking skills
- Become a leader who is dedicated to the industry

For more information or to announce your candidacy, please send your contact information, the position you are interested in and a short professional summary to Kikoo Tejwani, PDA Southern California Chapter President, at kikoo.tejwani@bbraun.com.

Delaware Valley Chapter Annual Meeting: Participants discuss a paper (left). Thomas Quinn introduces Art Vellutato, who was recognized for his service to the Chapter (right).

Todd Snell (top), Myron Dittmer and Jorge Ferreira at the New England Chapter Dinner

PDA New England Chapter

My latest trip was to Boston, Mass., on April 20. There I met with New England Chapter leaders **Myron Dittmer, Louis Zaczkiewicz** and **Mark Staples, PhD**. It was hard to miss the enthusiasm and motivation exhibited by this Chapter. After a tour of the local Genzyme facility, there was a networking dinner where **Jorge Ferreira,** Washington Group International, as well as **Todd Snell** and **Jack Prior,** both from Genzyme, talked about biotechnology issues related to the Genzyme facility.

Throughout my travels, I have been impressed by the enthusiasm of PDA's members and volunteers. Their commitment to the industry and the mission of PDA are exemplary. I greatly value the time that I have spent with all of you, learning more about what you do and how we at PDA can help you do it better. I also look forward to many more exciting travels to come.

The *PDA Letter* is published monthly by PDA, exclusively for PDA members. Subscriptions are not available. Articles in the PDA Letter may be reproduced with permission—contact the *PDA Letter* Editor for details.

PDA Letter **Editor**
Walter Morris
+1 (301) 656-5900, ext. 148
morris@pda.org

Advertising
Dorothea McGuire, Sales
+1 (301) 656-5900, ext. 150
mcguire@pda.org

Layout
Lisa Baehr

Printing and Distribution
H&N Printing and Graphics, Inc.

PDA Global Headquarters
3 Bethesda Metro Center, Suite 1500
Bethesda, MD 20814 USA
Tel: +1 (301) 656-5900
Fax: +1 (301) 986-0296
E-mail: info@pda.org
Web site: www.pda.org

PDA Office of European Director
R-1059.747 Postfach
Schwarzwaldalle 215
CH-4002 Basel, Switzerland
Tel: +41 61 321 56 30
Fax: +41 61 321 83 48

PDA European Office
287 Avenue Louise
BE-1050 Brussels, Belgium
Tel: +32-2-643-2045
Fax: +32-2-645-2671

PDA Training and Research Institute
c/o UMBC Technology Center
1450 S. Rolling Road
Baltimore, MD 21227 USA
Tel: +1 (410) 455-5800
Fax: +1 (410) 455-5802
E-mail: info-tri@pda.org

New England Chapter Hosts Genzyme Tour and Dinner Meeting

Louis T. Zaczkiewicz, Washington Group International

The PDA New England Chapter (NEPDA) and the Boston Chapter of the American Society for Quality (ASQ-Boston) held a joint tour and dinner meeting focusing on biotechnology as it relates to the Genzyme Allston Landing Manufacturing Facility on April 20, 2005. Over 80 people attended this event, with representatives from the biotech, pharmaceutical and device industries.

Genzyme's facility, completed in 1994, was initially designed to produce only one product, Cerezyme, from cell culture through fill-finish. Over the years, Genzyme has significantly upgraded and improved the facility. They now manufacture four commercially approved products there: two biologics and two drugs.

The dinner meeting opened with a welcome from **Myron Dittmer,** NEPDA President. **Kelly Coates,** Manager, Membership & Chapters, PDA, talked about the benefits of PDA membership. **Richard Levy,** PhD, PDA chair-elect, then spoke briefly about the recent personnel changes occurring at PDA.

Next, **Jorge Ferreira,** Director, Aseptic Processing and Fill/Finish Technologies, Washington Group International, gave a presentation called, "The Extra Work that Goes Into Building a Manufacturing Facility When it is FDA-Regulated." This talk took us through the GMP regulations through the facility operation and covered the phases of design and engineering, construction, commissioning and validation. Overall, we learned that GMP compliance is not "extra work;" it is a mandatory level of quality that is a diligent response to industry requirements to help ensure the safety, quality and efficacy of drugs.

The next speaker, **Todd Snell,** Associate Director of Corporate Quality for Genzyme, presented, "An Ongoing Program to Assess Key Quality Elements at Genzyme Manufacturing Sites." Genzyme's program consists of a quality program built upon the successes of the "Five-Star" safety program. The key to this program is a self-rating that each department uses to categorize its level of quality, measured as a rating from one to five. A three-star rating corresponds to meeting regulatory requirements. A four-star rating could include adding statistical process control (SPC) to a department's operation.

The last speaker, **Jack Prior,** Associate Director of Technical Support Services, Genzyme, spoke on "Strategies for Monitoring and Troubleshooting Biopharmaceutical Operations." His presentation covered process data bottlenecks, statistical process control, chromatography troubleshooting and data systems.

We gratefully acknowledge **Bill Martin** from Genzyme who organized the tour guides, speakers and the facility tour. We also thank the event sponsors, Washington Group International, Masy Systems and Commissioning Agents for their financial support that made this event possible.

Chapter Contacts

The following is a list of the PDA Chapters, organized by the area of the world they are located. Included are the Chapter name, the area(s) served, the Chapter contact person and their e-mail address. Where applicable, the Chapter's Web site is listed. More information on PDA Chapters is available at www.pda.org/chapters/index.html.

Asia Pacific

Australia Chapter
Contact: Greg Jordan
E-mail:
greg.jordan@au.maynepharma.com

India Chapter
Contact: Darshan Makhey, PhD
E-mail:
dmakhey@nicholaspiramal.co.in

Japan Chapter
Contact: Katsuhide Terada, PhD
E-mail: terada@phar.toho-u.ac.jp
Web site: www.j-pda.jp

Korea Chapter
Contact: Woo-Hyun Paik
E-mail: whpaik@hitel.net

Southeast Asia Chapter
Contact: K. P. P. Prasad, PhD
E-mail: prasad.kpp@pfizer.com

Taiwan Chapter
Contact: Shin-Yi Hsu
E-mail: shinyi.hsu@otsuka.com.tw
Web site: www.pdatc.org.tw

Europe

Central Europe Chapter
Contact: Erich Sturzenegger, PhD
E-mail:
erich.sturzenegger@pharma.novartis.com

France Chapter
Contact: Jean-Louis Saubion, PhD
E-mail: ufch@wanadoo.fr

Italy Chapter
Contact: Gabriele Gori
E-mail: gabriele.gori@bausch.it
Web site: www.pda-it.org

Prague Chapter
Contact: Zdenka Mrvova
E-mail: zdenka.mrvova@zentiva.cz

Spain Chapter
Contact: Jordi Botet, PhD
E-mail: jbotet@stegroup.com

United Kingdom and Ireland Chapter
Contact: Frank W. Talbot
E-mail: ftpharmser@aol.com

Middle East

Israel Chapter
Contact: Sigalit Portnoy
E-mail: sig@taro.co.il

North America

Canada Chapter
Contact: Hein Wick
E-mail: hwick@hwmr.ca
Web site: www.pdacanada.org

Capital Area Chapter
Areas Served: MD, DC, VA, WV
Contact: Barry A. Friedman, PhD
E-mail:
barry.friedman@cambrex.com
Web site: www.pdacapitalchapter.org

Delaware Valley Chapter
Areas Served: DE, NJ, PA
Contact: Art Vellutato, Jr.
E-mail: artjr@sterile.com
Web site: www.pdadv.org

Metro Chapter
Areas Served: NJ, NY
Contact: Nate Manco
E-mail: natemanco@optonline.net
Web site: www.pdametro.org

Midwest Chapter
Areas Served: IL, IN, OH, WI, IA, MN
Contact: Madhu Ahluwalia
E-mail: madhu@cgxp.xom

Mountain States Chapter
Areas Served: CO, WY, UT, ID, NE, KS, OK, MT
Contact: Cathie Wilkerson
E-mail:
cathie.wilkerson@rtx-inc.com
Web site: www.mspda.org

New England Chapter
Areas Served: MA, CT, RI, NH, VT, ME
Contact: Myron Dittmer, Jr.
E-mail: mdittmer@hyaluron.com

Puerto Rico Chapter
Contact: Silma Bladuell
E-mail: bladues@wyeth.com

Southeast Chapter
Areas Served: NC, SC, TN, VA, FL, GA
Contact: Lisa Eklund
E-mail: lisa.eklund@hospira.com
Web site: www.pdase.org

Southern California Chapter
Areas Served: Southern California
Contact: Kikoo Tejwani
E-mail: kikoo.tejwani@bbraun.com
Web site: www.pdasc.org

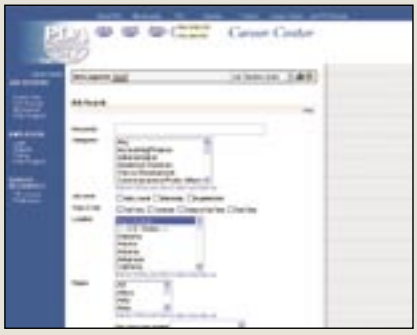
West Coast Chapter
Areas Served: Northern California
Contact: Peter Rauenbuehler
E-mail: pbr@gene.com
Web site: www.wccpda.org

THE HOTTEST JOBS SERVED UP JUST FOR YOU

www.pda.org/careers

THE **HOTTEST JOBS,** THE TOP EMPLOYERS ARE WAITING FOR YOU ON:
www.pda.org/careers

PDA
An International Association For Pharmaceutical Science And Technology



LOG ON TO:

> Create, edit, and store your resume and cover letter for employers to see
> Control the information displayed through our confidentiality feature which lets you omit your personally identifiable information
> Search and apply to a variety of careers—ranging from entry level to executive level positions
> Receive email notifications when new jobs are available (Available to PDA Members only)
> Schedule in-person interviews at PDA Career Fairs

PDA HEADQUARTERS

3 Bethesda Metro Center

Suite 1500

Bethesda, MD 20814 USA

TEL: +1(301)656-5900

FAX: +1(301)986-0296

Introducing the 2005 PDA/FDA Joint Regulatory Conference

Louise Johnson, Vice President, Quality, Vertex Pharmaceuticals; Program Committee Chair

The PDA/FDA Joint Regulatory Conference continues to be a much-anticipated event and an essential part of continuing education for the pharmaceutical and biopharmaceutical industry.

This conference has established a formidable reputation for providing the latest updates on the domestic and international regulations and guidances that impact manufacturing science and technology, quality systems, as well as drug and process development. Creating a forum for collaboration and education, this conference provides networking opportunities between FDA and the pharmaceutical and biopharmaceutical industry.

This year's conference theme is: *The Product Life Cycle: Quality by Design, Implementation and Continuous Improvement*. The plenary sessions complement the multitracked conference format; together they provide forums to explore the evolution of quality systems and product quality from development through commercial maturity.

"Quality by Design" topics include: FDA's critical path initiative,ICH Q8 Product Development updates, specification setting and risk management. Implementation issues will be explored in sessions on combination products, process validation and critical process parameters, to name a few. Management responsibilities, FDA inspection/quality trends and PAT case studies are samples of some of the "Continuous Improvement" topics.

Additionally, the committee has gathered expertise from outside the industry to provide unique insights that will challenge industry and FDA's thinking. For example, **Arthur Trepanier,** Senior Process Improvement Specialist at Lockheed Martin Missile and Fire Control Division will present a Lockheed Martin Case Study on the implementation of Lean Six Sigma.

At the breakfast, lunch and coffee break sessions, you will be able to discuss key issues and meet new colleagues and old friends. As is our tradition, this conference will be held in Washington D.C., a city noted for its dynamism, history and beauty.

Please join us for what promises to be an outstanding conference. You will be taking home current, pertinent and relevant information that will enhance your career as well as your understanding of emerging FDA and industry thinking on the *Product Life Cycle: Quality by Design, Implementation and Continuous Improvement*.

Visit the 2005 PDA/FDA Joint Regulatory Conference Exhibition Hall for free!

Exhibitor List

(as of June 8, 2005)

Accugenix, Inc.
Aurical Company
bioMerieux
BioProcess International
Bioscience International
Charles River Laboratories
Chemir Pharma Services
Commissioning Agents, Inc.
Cryovac - Sealed Air Corporation
Ciba Specialty Chemicals
Drumbeat Dimensions, Inc.
Dupont Qualicon
Ferro Pfanstiehl Laboratories
Genesis Machinery Products
Genomic Profiling Systems
GxP Partners
Lighthouse Insruments
Lloyd's Register Serentec, Inc.
Millipore Corporation
Molecular Epidemiology, Inc.
NNE US, Inc.
Novatek International
Pall Life Sciences
Parexel Consulting
Pharmaceutical Formulation & Quality (PFQ)
PML Microbiologicals
PSI
Quality is Learned, Inc.
Qumas
Sartorius Corporation
Sparta Systems, Inc.
Texwipe (ITW)
Thomson Scientific
Validation in Partnership Limited
Vectech Pharmaceutical Consultants, Inc.
Veltek Associates, Inc.
Vetter Pharma-Fertigung GmbH & Co. KG
VTS Consultants, Inc.
Working Words, Inc.

PDA Training and Research Institute *presents:*

Biotechnology: Overview of Principles, Tools, Processes and Products

Overview

Biotechnology combines disciplines such as molecular biology, biochemistry, chemistry, microbiology, chemical engineering and computing. This course presents a broad understanding of this rapidly advancing science and its applications to the pharmaceutical industry.

Who Should Attend

Manufacturing
- ✓ Director
- ✓ Manager/Leader/ Supervisor
- ✓ Operator/Technician

Engineering
- ✓ Director
- ✓ Manager/Leader/ Supervisor
- ✓ Engineer

Research and Development
- ✓ Director
- ✓ Manager/Leader/ Supervisor
- ✓ Scientist/Researcher

Benefits of Attending

Gain a basic understanding of the theory, principles, techniques and potential of biotechnology in order to:

- Effectively develop or improve a biopharmaceutical product process
- Efficiently apply the fundamental tools of biotechnology

Learning Objectives

At the completion of this course, participants will be able to:

- Define biotechnology and provide examples of current applications of biotechnology and its products to the pharmaceutical industry
- Discuss the fundamental tools and how they are used in biotechnology
- Explain the biopharmaceutical product development process
- Describe the key steps in a biopharmaceutical manufacturing process

Key Topics

- Scientific principles used by the biotechnology industry
- Overview of the tools used (recombinant DNA, genomics and gene arrays, proteomics, bioinformatics, etc.),
- Biopharmaceutical product development,
- Biomanufacturing strategies (protein expression, fermentation, cell culture, downstream processing and purification),
- Types of products and their applications in medicine.

Baltimore, Md.

August 9-11, 2005

PDA # 280

Venue

PDA Training and Research Institute
1450 South Rolling Road
Baltimore, MD 21227 USA
Tel: +1 (410) 455-5800
Fax: +1 (410) 455-5802
E-mail: tri@pda.org

Faculty

Dr. Antonio R. Moreira, Executive Vice President of SPI USA, Inc. and Vice Provost for Academic Affairs and Professor of Chemical and Biochemical Engineering at the University of Maryland, Baltimore County (UMBC).

Registration Fees

Member	**$2,230**
Nonmember	**$2,425**
Government	**$895**
Health Authority	**$895**
Academic*	**$895**
Student*	**$340**

** Must be a PDA member to receive this rate.*

For more information and to register online:

Visit www.pda.org/tri

Or, print out a registration form and fax or mail to:

PDA
P.O. Box 79465
Baltimore, MD 21279-0465 USA
Tel: +1 (301) 656-5900
Fax: +1 (301) 986-1093

To learn more about other *Career-long Learning*™ opportunities visit www.pda.org.

Picky about particulates?

Manic about microbes?

Count on Biotest

The HYCON® System for Environmental Monitoring: RCS Air Samplers, APC Particle Counters and Contact Slides.

APC Airborne Particle Counters and RCS Microbial Air Samplers combine to give you a clear picture of airborne contamination. Biotest Diagnostics Corporation offers a full line of reliably accurate, technically-advanced, hand-held, air monitoring devices. When you're picky about maintaining air quality standards, count on Biotest. Call today or visit our website at www.BiotestUSA.com.

Biotest

CE

Biotest DIN EN ISO 9001 HYCON

BIOTEST DIAGNOSTICS CORPORATION
66 Ford Road, Suite 220, Denville, New Jersey 07834
Phone: 973.625.1300 • 800.522.0090 • Fax: 973.625.9454
www.BiotestUSA.com

This September,

the leading minds in Pharmaceutical Manufacturing, Quality Assurance, Compliance and Regulatory Affairs will be in Washington D.C...

Will you?

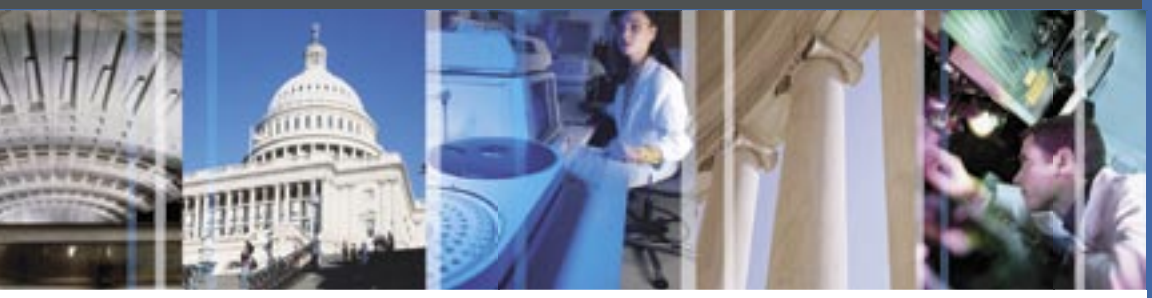
Since 1986, the PDA/FDA Joint Regulatory Conference has been the essential source for gaining valuable insights and success strategies from top FDA, industry and academic experts in an unbiased, science-based forum.

Specifically designed for mid- and upper-level pharmaceutical and biopharmaceutical professionals, this year's conference will present new information you can apply immediately to make your product development and continuous improvement processes more predictable, reliable and less costly.

2005 PDA/FDA *Joint Regulatory Conference*

The Product Life Cycle: Quality by Design, Implementation and Continuous Improvement

September 12-14, 2005



PLUS

Free visitor passes to the exhibit hall, the perfect venue to build relationships and learn about the latest products, services and technologies.

Eight interactive courses from the PDA Training and Research Institute, designed to improve processes, performance and the bottom line.

PDA
An International Association For Pharmaceutical Science And Technology

FDA

Register today!

www.pda.org/pdafda2005

Renaissance Hotel
Washington, D.C.
Conference - Sept. 12-14, 2005
Exhibition - Sept. 12-13, 2005
PDA TRI Courses – Sept. 15-16, 2005