

Volume XLIII • Issue #6

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Stainless or Plastic?

A Look at the Trend towards Disposable Manufacturing Walter Morris, PDA

Application of disposable, or single-use, manufacturing and testing systems while not new technology—is one of the hottest manufacturing trends in recent years, particularly for bioprocessing. When one examines the benefits associated with these technologies, it is easy to see why. Single-use production tools offer a variety of advantages over stainless steel, including shorter process timelines and the elimination of risk from cross-contamination.

The trend towards disposables is evident with an increasing number of articles appearing in the trade literature highlighting the technology¹ and a growing number of industry conferences and events either partially or completely dedicated to the topic.² Indeed, the uptake of disposables has accelerated in recent years. It has been reported that nearly 97% of biopharmaceutical manufacturers use one form of single-use technology or another.³

In the last few months alone, several major single-use enablers have announced new lines of products, including bioreactors, sensors, bags, tubing, valves and connectors. These later generation disposable tools promise to provide biopharmaceutical manufacturers more capability and cost-savings.

This trend is prompting many single-use suppliers to form strategic collaborations with the goal of improving product lines and solving operational challenges. Closer collaboration is happening in the form of industry alliances, supply covenants and company mergers.

Careful examinations of the technology, however, reveal a number of challenges when it comes to applying single-use technology to downstream manufacturing processes, particularly with respect to processing scale, personnel training and waste management. These studies also predict savings far lower than the current zeitgeist suggests.

Through PDA's science and technology programs, conferences and educational offerings, the Association can help disposable enablers and end users work together to solve technical and other challenges to implementation.

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May Top 10 Bestsellers

SYSTEMS-BASED INSPECTION FOR PHARMACEUTICAL MANUFACTURERS

Systems-Based Inspection for Pharmaceutical Manufacturers

Edited by Jeanne Moldenhauer, PhD

Moldenhauer provides an overview of the regulatory background needed for FDA to perform inspections, a description of the six systems, including information on the expectations for the system and how a regulator might assess compliance, and aids for preparing for, handling, and concluding a regulatory inspection.

This book is of particular interest for companies that are preparing for their first inspection by FDA as well as for companies that want to benchmark their state of compliance against the industry. Published 2007. 398 pages. ISBN: 1-033722-03-7.

Top Ten Bestsellers:

- Systems-Based Inspection for Pharmaceutical Manufacturers Edited by Jeanne Moldenhauer, PhD Item No. 17243, PDA Member \$255, Nonmember \$319
- Quality Control Systems for the Microbiology Laboratory: The Key to Successful Inspections 40% Off By Lucia Clontz Item No. 17176, PDA Member \$195, Nonmember \$249
- Environmental Monitoring: A Comprehensive Handbook, Volume I, Volume II and Protocol CD Edited by Jeanne Moldenhauer, PhD Item No. 17239, PDA Member \$530, Nonmember \$659
- 4. Risk Assessment and Risk Management in the Pharmaceutical Industry: Clear and Simple By James L. Vesper Item No. 17219, PDA Member \$235, Nonmember \$289
- Encyclopedia of Rapid Microbiological Methods, Volume 1, 2, 3 Edited by Michael J. Miller, PhD Item No. 17252, PDA Member \$730, Nonmember \$899
- Technology Transfer: An International Good Practice Guide for Pharmaceutical and Allied Industries Edited by Mark Gibson Item No. 17218, PDA Member \$240, Nonmember \$299
- Microbiology in Pharmaceutical Manufacturing 40% Off Edited by Richard Prince Item No. 17185, PDA Member \$285, Nonmember \$359
- 8. PDA Technical Report 40, Sterilizing Filtration of Gases Item No. 01040, PDA Member \$75, Nonmember \$150
- 9. Chinese Drug GMP: An Unofficial Translation Including Related Sections of the Taiwanese, U.S., and ICH-API GMP Edited by Steven S. Kuwahara, PhD and Simon Xiuwei Li Item No. 17263, PDA Member \$240, Nonmember \$299
- Pharmaceutical Contamination Control: Practical Strategies for Compliance Edited by Nigel Halls, PhD Item No. 17246, PDA Member \$255, Nonmember \$315

Featured Titles:







Validation of Analytical Methods for Biopharmaceuticals: A Guide to Risk-Based Validation and Implementation Strategies Item: No.17264 PDA Member:\$255 Nonmember: \$315

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Editor's Message

The top news item in this issue is the recent release of a U.S. FDA guidance titled *Testing of Glycerin for Diethylene Glycol* and an associated MedWatch Safety Alert. Assistant Editor **Lindsay Donofrio** and I met with the CDER Office of Compliance Director and Deputy Director to discuss recent efforts by the Agency to protect the U.S. drug supply from DEG poisoning (page 30).

In January, PDA sponsored a conference on emerging manufacturing technology which inspired the theme of this month's issue: Hot Topics in Manufacturing. A session at the January conference on disposable bioprocessing was the catalyst for my article, "Stainless or Plastic? A Look at the Trend towards Disposable Manufacturing" (on the cover). **Michael Hanson**, a recipient of a PDA Journal student grant, provides a summary of his presentation at the emerging manufacturing technology meeting, "Use of Microarrays to Evaluate Cell Culture Processes" (page 24).

PDA's News & Notes marks the passing of former VP for Quality and Regulatory Affairs **Vicki Dedrick**, a friend to me and many others involved with PDA (page 8).

We have already received favorable comment on our celebration of TRI's tenth anniversary and the new Science & Technology Snapshot in the May issue (see below). We look forward to printing more Letters from readers in the future.

Letter to the Editor

It's a gorgeous Mother's Day here in northern New Jersey, and we spent a quiet morning on the patio reading. I read the May Letter from cover to cover, and not once did I put it down except for snatching another cream puff. In my view, this was a great issue for many reasons. It celebrates TRI's 10th and it helps promote TRI and its benefits to the industry. It was packed with a lot of refreshing ideas with a personal touch, including the humble beginning of TRI and its history in the eyes of those involved at day one, the dynamic duo story, the diverse staff articles selling the concept of TRI events co-sponsored with chapters, the career fair and the call-for-papers for the Journal and the Letter.

Last but not least, this issue covers it's-about-time-we-cover-them topics that perhaps should have received a lot more of our attention in the past. At least for me, the Science & Technology Snapshot approach turns an otherwise essential but sometimes "boring" subject into an eye-catcher instead.

Henry Kwan, PhD Kwan Consulting, LLC

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- Expanded upon ideas about what "risk-based" means and how it can be implemented
- · Developed a new sterilization process or method

We encourage you to submit a scientific abstract for presentation at the PDA 2008 Annual Meeting, which will be held April 14-18, 2008 at The Broadmoor in Colorado Springs, Colorado. Abstracts must be noncommercial in nature, describe new developments or work and significantly contribute to the body of knowledge relating to pharmaceutical manufacturing, quality management and technology. Industry case studies demonstrating advanced technologies, manufacturing efficiencies or solutions to regulatory compliance issues are preferable and will receive the highest consideration. All abstracts will be reviewed by the Program Planning Committee for inclusion in the meeting or in poster sessions. Please include the following information along with your abstracts and follow the steps identified in the All Academic abstract manager. Submissions received without full information will not be considered.

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

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PDA is seeking presentations 30 minutes in length, that present major challenges and practical approaches to resolution in the following areas:

Biotechnology Sciences

- Implication of ICH Q8, Q9, Q10
- Cell culture/line development
- Cold Chain Management
- Disposables for biopharmceutical manufacturing
- Innovative manufacturing
- Downstream processing
- Technology transfer
- Viral clearance/inactivation
- Contamination control
- Advances in aseptic filling
- Sterilization technologies

Quality Sciences

- Application of ICH Q8, Q9, Q10
- · Cleaning and multi-product manufacturing
- Compliance case studies
- Environmental monitoring
- Harmonization of quality issues
- Microbiological methods and trends
- Process Analytical Technologies (PAT)
- Quality management systems
- · Risk management and risk-based GMP
- Raw material and product impact
- Supplier quality management
- Validation of pharmaceutical and biopharmaceutical processes

Manufacturing Sciences

- · Aseptic processing new technologies
- Barrier/isolators/RABs
- Advances in dosage form deliveries
- · Blend uniformity and solid dose processing
- Blow-Fill-Seal
- CIP/SIP trends and innovation
- Contract manufacturing
- Design/management of multi-product facilities
- Production strategies in the global market
 environment
- · Industry manufacturing and product trends
- Parenteral primary packaging
- Pre-filled syringes and injectors

ABSTRACTS MUST BE RECEIVED BY JUNE 30, 2007 FOR CONSIDERATION

For more information, please contact Lu Castro, Senior Coordinator, Programs and Registration Services, PDA at +1 (301) 656-5900 ext. 122 or castro@pda.org.

PDA Saddened by Passing of Vicki Dedrick

It is with great sadness that PDA announces the death of **Victoria Dedrick,** who passed away on April 21, 2007. Vicki served as PDA's VP of Quality and Regulatory Affairs from February 2004 to April 2005.

PDA benefited from Vicki's fundamental strengths in the areas of international regulatory affairs, harmonization and quality assurance following a 25-year career as an executive in the pharmaceutical, biopharmaceutical and medical device industries.



Vicki Dedrick speaking with then-PDA Board Member Kathleen Greene at the 2004 PDA/FDA Joint Regulatory Conference.

Vicki helped strengthen PDA's ties with the Product Quality Research Institute, representing PDA on the Institute's Steering Committee and its Education, Communication and Assessment subcommittee. Vicki also was instrumental in working with the program planning committee on the agenda for the 2004 PDA/FDA Joint Regulatory Conference, the most successful one to date.

"Working with Vicki was one of the most rewarding working relationships I have ever had," PDA Regulatory Affairs and Science Coordinator **Iris Rice** said. "Vicki held high standards and expectations, and her work ethic was superior. She was a great teacher, and I will always be grateful for the way she taught me to strive for excellence. Vicki was loyal to PDA—she loved her job and she was highly dedicated to the growth and development of PDA."

"I was introduced to Vicki while walking to dinner at the 2004 International PDA Congress on a cold winter night in Basel," reminisced **Kathleen Greene**, a former PDA board member and friend to Vicki. "She was so interesting to talk with that I no longer minded the long walk in the cold. Vicki had a wealth of knowledge and knew what was important. She was always willing to share her experience and insight. I will miss her friendship and counsel."

"Vicki joined PDA at a transitional time and provided a steady and authoritative influence," PDA Managing Editor **Walter Morris** said. "As the editor of the *PDA Letter*, I always appreciated Vicki's dedication to communicating to the membership via the Letter and admired her strong ability to effectively use the written word to convey her messages."



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Our condolences go out to her family and friends.

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Sci-Tech Discussion Group: An Easy-to-Use Forum for Dialogue

Rich Levy, PhD, PDA

One of the many PDA benefits is the opportunity to share ideas and network with fellow members and nonmembers. In 1994, PDA collaborated with PharmWeb in the United Kingdom to establish an easy-to-use online forum devoted to discourse on subjects relevant to our members and to the pharmaceutical and biotech industries which PDA serves.

Specifically, the Sci-Tech Discussion Group is designed to provide a vehicle for the free exchange of information in the areas of international pharmaceutical manufacturing, process validation, quality control and regulatory affairs, emphasizing but not limited to sterile products technology.

The Discussion Group is open to anyone with an interest in pharmaceutical science and technology. A visit to the Sci-Tech Discussion Group website can include a review of the archives, which date back to 1996, for topics relevant to your interests or the posting of a specific question or commentary to the group. Most issues of the *PDA Letter* include a sample of the relevant and timely discussions found on the forum (see page 12 for this issue's discussions).

The Sci-Tech Discussion Group is only as successful as you make it. I hope you will consider rediscovering the excitement of learning about the challenges faced by our colleagues and join PDA in helping pharmaceutical scientists exchange ideas, knowledge and experiences.

If you have recommendations for improving the Discussion Group, please contact us at snapshot@pda.org.

Editor's Note: You can view and sign up for the Discussion Group at: www.pharmweb.net/pwmirror/pwq/pharmwebq2.html

Technical Report Watch

In Global Review: Drafts of the following TRs are under review by the global PDA membership. To learn how to comment on any one of the drafts, contact Genevieve Lovitt-Wood at gilovitt@mindspring.com.

- TR-26 (2007 Revision), Sterilizing Filtration of Liquids
- TR-14 (2007 Revision), Validation of Column-Based Separation Processes
- *Reprocessing of Biopharmaceuticals.* This TR will also be presented at the June 20 Biopharmaceutical Development and Manufacturing conference co-sponsored by PDA and the European Biopharmaceutical Enterprise.
- Aseptic Processing Risk Management

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

• Biological Indicators for Sporicidal Gassing Processes: Specification, Manufacture, Control and Use

In Board Review: Following technical editing, TRs are reviewed by PDA's advisory boards (SAB, BioAB). If/when approved, the PDA Board of Directors (BoD) makes the final decision to publish or not publish the document as an official PDA TR.

- Filtration of Liquids Using Cellulose-Based Depth Filters (SAB ballot)
- TR-43, Identification and Classification of Nonconformities in Molded and Tubular Glass Containers for Pharmaceutical Manufacturing (BoD ballot)
- TR-39 (2007 Revision) Guidance for Temperature Controlled Medicinal Products (Just BoD approved!)

Interest Group Briefing

PDA Interest Groups (IGs) have been around since 1995 and are a great way for individual members to become more involved with PDA. The IGs provide a vehicle for members with common interests (no pun intended) to interact with one another, exchange information, network and impact the positions of PDA and industry involving science, technology and the regulation of pharmaceutical and biopharmaceutical manufacturing.

Participating in IG meetings and activities is an excellent way to gain specialized information and contribute to important activities such as drafting PDA Technical Reports and Technical Bulletins and developing PDA positions on current regulatory initiatives.

There are currently over 20 IGs addressing the areas of quality systems and regulatory affairs, laboratory and microbiological sciences, pharmaceutical development, biopharmaceutical sciences and manufacturing sciences. The IGs meet in person at least once a year and conduct other meetings and activities, including focused training, periodically throughout the year.

Editor's Note: For a complete list of IGs and contact information, please see page 16 for "PDA Interest Groups & Leaders."

In order to best serve the needs of the membership, PDA IGs need to develop as new technology dictates, conduct their activities as appropriate and then retire when their work is done. The current IG supporting

continued on page 14

Leadership Opportunities

Participate in Upcoming Technical Report

PDA is seeking technical volunteers to actively participate in revision of the upcoming TR-33 *Evaluation, Validation and Implementation of New Microbiological Testing Methods.* Currently, we are seeking volunteers who are considering or are actively involved in the implementation of rapid microbiological methods in their corporations. The Task Force is chaired by **Jeanne Moldenhauer**, PhD. The team is forming now, and we encourage you to offer your time, skills and expertise to this project.

If you are interested in integrating your skills with this project, please contact Iris Rice, Coordinator, Scientific and Regulatory Affairs, PDA, at rice@pda.org. Please be prepared to offer a short biographical sketch outlining your areas of expertise and interest pertinent to the development of this project.

Task Force Corner

Biological Indicators Task Force: The group held a face-to-face meeting on May 16, hosted by member David Watling, PhD, at BioQuell in Andover, UK. This well-attended meeting was facilitated by co-chair Graham Steele, PhD, Steris, who presented comments received during their technical peer review. The task force held lengthy discussions in order to span regional differences on the subject and therefore ensure a global perspective was provided in the TR. Central issues discussed included differing regulatory expectations for log reduction and scientific determination of system D-value in a process that is inherently unable to provide a constant level of lethality. See "Technical Report Watch," opposite page, for the current status of the proposed TR, titled Biological Indicators for Sporicidal Gassing Processes: Specification, Manufacture, Control and Use.

TR-15 Revision Task Force: The task force met at PDA's Global Headquarters in Bethesda, Md., on May 2 to finalize their first draft of revised TR-15, *Validation of Tangential Flow Filtration in Biopharmaceutical Applications.* Their goal is to release the draft for "Global Review" in July. For more information,

continued on page 14

Sci-Tech Trends

Hot Topics in Manufacturing

This issue features two articles on manufacturing technology trends in bioprocessing. On the cover, PDA Managing Editor **Walter Morris's** article "Stainless or Plastic?" examines the industry's growing interest and use of disposable, or single-use, technology. The trend towards disposable manufacturing is evident with an increasing amount of media coverage and number of conferences on the topic. A number of new product lines are also appearing. The wide-spread interest in this technology is even prompting single-use suppliers to form strategic collaborations in hopes of improving products and solving challenges.

A second article written by **Michael Hanson**, University of Maryland, Baltimore County, titled "Use of Microarrays to Evaluate Cell Culture Processes" (page 24). explains how gene expression data can be utilized in the bioprocessing field. Technologies such as DNA microarrays have caused the accessibility of gene expression to increase steadily since the mid-1990s. Hanson discusses three specific uses of gene expression data, including for process development, as a regulatory gauge of risk and for process monitoring.

Recent Sci-Tech Discussions: Cold Chain Distribution and CIP and SIP Cycle

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

Cold Chain Distribution

Does anybody know about cold chain distribution for pharmaceuticals? Preferably, but not limited to, for European and Asian jurisdictions. References from other jurisdictions are also appreciated.

Respondent 1: The Parenteral Drug Association (PDA) has published a Technical Report (Technical Report 39) on cold chain and the transportation of temperature-sensitive pharmaceuticals. It is available through their website (www.pda.org). They also have a conference coming up on the subject in June. Details are also available through their website.

Respondent 2: This guidance may also come in handy, publicized by the Irish Medicines Board: http://www.imb.ie/uploads/publica-tions/194333_IND_003_01.pdf.

Respondent 3: Here are a few more references. *Keep it Cool: the Vaccine Cold Chain: Guideline for Immunisation Providers on Maintaining the Cold Chain* (Australia) http://www.dubboplainsdgp.com. au/pdfdocs/cool.pdf

Guidelines for Temperature Control of Drug Products during Storage and Transportation (GUIDE-0069) (Canada) http://www.hc-sc.gc.ca/dhp-mps/ compli-conform/gmp-bpf/docs/ gui-0069_tc-tm_e.html

Guidelines on Good Distribution Practice of Medicinal Products for Human Use (Europe) http://ec.europa.eu/enterprise/ pharmaceuticals/pharmacos/docs/ doc2001/may/gdpguidelines1.pdf

Recommendations on the control and monitoring of storage and transportation temperatures of medicinal products (UK) http://www.mhra.gov.uk/home/groups/ comms-ic/documents/publication/ con007569.pdf

"Cold Chain Management Briefing" (U.S. Army) http://www.usamma.army.mil/ Documents/CCM%20Brief.pdf

Notice to Readers: Guidelines for Maintaining and Managing the Vaccine Cold Chain (CDC) http://www.cdc.gov/mmwR/preview/ mmwrhtml/mm5242a6.htm

USP <1079> "Good Storage And Shipping Practices" www.usp.org

Good Distribution Practices (GDP) For Pharmaceutical Products (WHO) http://www.who.int/medicines/ services/expertcommittees/ pharmprep/QAS_068Rev2_ GDPdraft.pdf

CIP and SIP Cycle

We are the manufacturers of small and large volume parenterals by blow-fill-seal technology. Currently we are carrying out SIP cycles after filling of every three campaign batches of the same product. Is there any requirement that exists to carry out CIP and SIP after completion of every batch? If not required, kindly suggest the possible technical inputs required to support the philosophy of CIP & SIP after filling of three campaign batches. Please give the reference of any guideline supporting the inputs.

Respondent 1: [From U.S. FDA] Guide to Inspections Validation of Cleaning Processes: Determine the number of cleaning processes for each piece of equipment. Ideally, a piece of equipment or system will have one process for cleaning; however, this will depend on the products being produced and whether the cleanup occurs between batches of the same product (as in a large campaign) or between batches of different products. When the cleaning process is used only between batches of the same product (or different lots of the same intermediate in a bulk process), the firm need only meet a criteria of "visibly clean" for the equipment. Such between batch cleaning processes do not require validation. It indicates that cleaning must be between the batches.

Regarding SIP cycle: If sterile water is used for cleaning, the sterility may not be breached. The same may be demonstrated by media fill runs (SIP after 3 runs).

Respondent 2: Between-batch "cleaning" is not a requirement; it is unclear how the FDA guidance you referred to supports your statement that it is a "must." Some companies may clean between batches; other companies may utilize just a water rinse or a

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"vacuuming" between batches; in those latter cases validation is not required, nor is it an expectation that equipment even be visually clean following a water rinse or vacuuming (which is why I prefer not to call such steps "minor cleaning").

Also, I believe the FDA statement that validation is not required for such between-batch cleaning may be misleading. Such a statement is probably based on the fact that crosscontamination of the active is not an issue (except insofar as it changes the assay of the next product). However, that statement doesn't take into account adulteration from cleaning agents or bioburden. If those are not an issue, then perhaps validation is not required.

Furthermore, in their "new" program on top-down investigational technique, the FDA states something to the effect that for dedicated equipment (which is a special case of cleaning between batches), you will get a warning letter if there is a "lack of demonstration of effectiveness of cleaning." My question is what is a "demonstration of the effectiveness of cleaning"? My answer is that it is cleaning validation or cleaning verification.

Respondent 3: I fully agree with the last paragraph of [Respondent 2]. SIP will take care of your media fill. But to get the answer of CIP, you will have to understand the purpose of cleaning. I ask it in another way. [Why are] you cleaning after every three batches? We know in case of product change over, it is to avoid cross-contamination of previous product. But why at all in case of batch change of same product? Or in a dedicated facility?

As in case of product change over we calculate MACO, here also we can calculate MACO which will be based on safety limit, i.e., the safety of next batch from the degradants, oxidized material, repeated solvent/cleaning agent effect, etc., of built-up material of previous batches. In such cases, we are not interested in the carry over of API. (Being a sterile facility, bioburden is not an issue.)

So, in campaign manufacturing or dedicated facility, demonstrate the effectiveness of "partial" or "no" cleaning and the number of batches which can be manufactured before "complete" cleaning. (Your SOP can have any other terminology for "partial" and "complete" cleaning.) In such cases, forced degradation study of your product can give a lot of support while designing your protocol.

Task Force Corner, continued from page 11

contact Genevieve Lovitt-Wood at gilovitt@mindspring.com.

TR-26 Revision Task Force: Under the helm of co-chairs **Paul Stinavage,** Pfizer, and **Maurice Phelan,** Millipore, the TR-26 Task Force achieved their first milestone and met in Las Vegas, Nev., during the PDA 2007 Annual Meeting in March to review and finalize technical content on their first draft. The TR is now available for comment, and the team will be presenting for feedback at the New England PDA Chapter meeting on June 13.

TR-30 Revision Task Force: PDA has assembled a new task force to revise TR-30, *Parametric Release of Pharmaceuticals Terminally Sterilized by Moist Heat* (1999). Work on revising the task force will commence in June. Contact Genevieve Lovitt-Wood at gilovitt@mindspring.com for more information.

Disposable Processing Technology Task Force: PDA's Biotechnology Advisory Board is sponsoring the formation of a Disposable Processing Technology Task Force. Potential task force members met in March and May with PDA's Rich Levy. Contact rice@pda.org for more information. Thus, in any circumstances, you cannot avoid "Cleaning Validation." Because whatever process of cleaning you are carrying out should show documented evidence that it is consistent and safe to meet predetermined specification.

As far as the guideline is concerned, no guideline will give you the ready-made answer of your query. It is only the way you satisfy the expectations of an inspector from your document and work.

Interest Group Briefing, continued from page 11

infrastructure, which has served PDA and the IGs well over the years, faces some challenges which need to be addressed. To that end, we are in the beginning phase of a restage of the IG system. We are looking at ways to make the IGs more user friendly, provide more value to their members and become truly global in nature. For example, we are considering how 21st century electronic technology can contribute to that process, using tools such as a knowledge management system, e.g, Infostrength, and web-based communication, e.g., WebEx. We will be working with the IG leaders to develop and implement improved governance too, but we need input and ideas from PDA members to make the new system as effective and efficient as possible.

Your thoughts, suggestions and recommendations are important and will help ensure the new IG system delivers the member value we want and you deserve. What do you want and need from the IGs? **Please send your ideas to interestgroups@pda.org.** We look forward to hearing from you, and stay tuned for future IG snapshots, which will profile the individual IGs and introduce new ones.

PDA Interest Groups & Leaders

PDA Interest Groups are divided into five sections by subject matter. This aligns them for improved effectiveness, supports increased synergies and provides the opportunity for Interest Group members to play a more active role in Task Forces. The five sections are Quality Systems and Regulatory Affairs, Laboratory and Microbiological Sciences, Pharmaceutical Development, Biotechnological Sciences and Manufacturing Sciences. Any PDA member can join one or more Interest Group by updating their member profile (www.pda.org/pdf/join IG instruction.pdf). Please go to www.pda.org/interestgroups for more information.

North American Interest Groups

Section Leader	Frank Kohn, PhD FSK Associates	David Hussong, PhD <i>U.S. FDA</i>	Don Elinski <i>Lachman Consultants</i>	Sandeep Nema, PhD <i>Pfizer Inc.</i>	Robert Dana <i>PDA</i>
Section Title	Biopharmaceutical Sciences	Laboratory and Microbiological Sciences	Manufacturing Sciences	Pharmaceutical Development	Quality Systems and Regulatory Affairs
Related IGs and Group Leaders	Biotechnology Group Leader: Jill A. Myers, PhD BioPro Consulting mail: jmyers@bioproconsulting.com Lyophilization Group Leader: Edward H. Trappler Lyophilization Technology Email: etrappler@lyo-t.com Vaccines Group Leader: Frank S. Kohn, PhD FSK Associates Inc. Email: fsk@iowatelecom.net	Analytical Labs/ Stability Group Leader: Rafik H. Bishara, PhD Email: rafikbishara2@yahoo.com Microbiology/ Environmental Monitoring Group Leader: Jeanne E. Moldenhauer, PhD Email: jeannemoldenhauer@yahoo.com Visual Inspection of Parenterals Group Leader: John G. Shabushnig, PhD <i>Pfizer Inc.</i> Email: john.g.shabushnig@pfizer.com	Facilities and Engineering Group Leader: Christopher J. Smalley, PhD Wyeth Pharma Email: smallec2@lwyeth.com Filtration Group Leader: Russell Madsen The Williamsburg Group, LLC Email: madsen@thewilliamsburggroup.com Pharmaceutical Water Systems Group Leader Theodore H. Meltzer, PhD Capitola Consulting Co. Email: theodorehmeltzer@hotmail.com Sterile Processing Group Leader: Richard M. Johnson Fort Dodge Animal Health Email: johnsor4@fdah.com	Clinical Trial Materials Group Leader: Vince L. Mathews <i>Eli Lilly & Co.</i> Email: vlm@lilly.com Combination Products Group Leader: Michael A. Gross, PhD Cardiome Pharma Corp. Email: mgross@cardiome.com Packaging Science Group Leader: Edward J. Smith, PhD Wyeth Pharmaceuticals Email: smithej@wyeth.com Process Validation Group Leader: Harold S. Baseman ValSource, LLP Email: halbaseman@adelphia.net	Inspection Trends/ Regulatory Affairs Group Leader: Robert L. Dana PDA Email: dana@pda.org Quality Systems Group Leader: David A. Mayorga Global Quality Alliance, LLC Email: david@gqaconsulting.com

European Interest Groups

Related IGs and Group Leaders

Biotech Group Leader: **Roland Guenther** Novartis Pharma AG Email: roland.guenther@pharma. novartis.com

Visual Inspection of Parenterals Group Leader: Markus Lankers, PhD Rap.ID GmbH Email: markus.lankers@rap-id.com

Roger Seiler Sartorius SA Email: roger.seiler@sartorius.com

Filtration

Group Leader:

Production and Engineering

Group Leader: Philippe Gomez Sartorius SA Email: Philippe.gomez@sartorius.com

Prefilled Syringes Group Leader: Thomas Schoenknecht, PhD

Nanotechnology Group Leader: D F Chowdhury Aphton BioPharma

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Technology Transfer

Group Leaders: Volker Eck, PhD PDA Email: eck@pda.org Zdenka Mrvova Zentiva Email: zdenka.mrvova@zentiva.cz

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Stainless or Plastic?, continued from cover

New Products

Mr. McGuire: I want to say one word to you. Just one word.

Benjamin: Yes, sir.

Mr. McGuire: Plastics.

— *The Graduate* (1967), Embassy Pictures

Forget the robotic arms, sophisticated online measurement devices and shiny stainless steel machinery, the hottest products on display at the 2007 INTERPHEX trade show in New York (April 24-26) were made from plastic—bags, impellers, tubes, connectors, sensors, etc.—at least it seemed that way to this observer. On top of the many vendors showing off their disposable wares in the exhibition, the large trade show included a number of presentations on single-use technologies and their applications.

Notable new disposable product launches in New York were made by Millipore Corporation and Pall Corporation—two longtime PDA supporters.

Millipore, for example, unveiled its latest generation disposable bioreactor, which can be applied to the mixing of pharmaceutical ingredients and to the preparation of process solutions. The unit purportedly offers "mixing efficiency in a contained system, saving valuable process and validation time."

Millipore also displayed its newest crimping solution for use with singleuse assemblies. The product combines a patented crimping tool and tubing pinch pipes pre-mounted on the tubing of the disposable assembly. Millipore states that the crimping tool's patented design "first crimps the metallic pinch pipe ensuring a proper seal, then cuts the tubing into two sterile fluid paths."

Pall Corporation introduced its first "integrated single-use manufacturing solution" and new single-use containers. In an announcement issued April 25, a company spokesperson stated that the new containers "were specifically developed to address some of the most pressing concerns manufacturers have about expanding implementation of single-use technologies, specifically issues about leachables and extractables and bag handling."

New Partnerships

Besides a continual string of new product releases, many of the product enablers are pursuing new partnerships and in many cases merging outright.

Sartorius AG-maker of several singleuse products-has been particularly active in forming new partnerships. The company is in the process of completing a merger with Stedim S.A., which was formally announced Feb. 22. The combined company will be called Sartorius Stedim Biotech S.A. In one press announcement, Stedim's "attractive market share in the market of disposable bag systems for pharmaceutical applications" was mentioned as a primary reason for the partnership. In another release, Stedim was credited as a "pioneer for disposable bag systems for biopharmaceutical applications." Both companies are longtime PDA supporters.

In a May press release, Sartorius publicized that it had strengthened and extended an existing supply agreement with TC Tech Corp., a division of Thermo Fisher Scientific Inc. Specifically, the agreement stipulates that TC Tech will supply Sartorius with disposable process containers up to the end of 2007 and with disposable process containers assembled with Sartorius filter capsules up to 2012. In turn, Sartorius will supply TC Tech with filter units for a further five years.

The Thermo Fisher Scientific-TC Tech connection was itself created via mergers in 2006, when Fisher acquired TC Tech early in the year, and then Thermo and Fisher merged at year's end. This past April, GE Healthcare bolstered its bioprocessing equipment line-up with the acquisition of Wave Biotech. GE's primary interest in Wave was the latter's single-use bioreactor system—the Wave Mixer—and sterile tube fuser.

Another deal involved W.L. Gore and Associates' purchase of privately-owned Amesil in February, marrying Amesil's non-reactive fluid transport, containment and sampling solutions with GoreTM PharmBio Products' line of single-use freeze-drying and filtration products.

And New Alliances

All of the aforementioned vendors have joined together with other single-use suppliers to form the Bio-Process Systems Alliance (BPSA), which operates under the umbrella of the 70-year-old Society of the Plastics Industry.

Overall, 35 companies were listed as members of the Alliance in 2006. Their goal is to:

- Grow the market nationally and internationally by facilitating adoption of single-use components and systems
- Establish guidelines and standards for the use and disposal of single-use process components and systems
- Educate customers, regulatory bodies and non-government organizations on the benefits of using single-use systems

Subcommittees reflecting these points of interest have been formed.

In the May 2007 *BioProcess International* supplement on disposables,⁴ BPSA Guidelines and Standards Committee Chair **Jerold Martin** (Pall Life Sciences) provides an update on "one of the core activities" of the Alliance, "to educate and develop guides that safeguard the quality of drugs produced using" disposable technology. The first project undertaken by the committee was to identify and publish a comprehensive list of consensus quality tests for the qualification, validation and use of single-use products. Next, the committee plans to develop guides addressing single-use system components, sterility claims, extractables and leachables and systembased issues.

The End of Stainless Steel?

In light of the healthy pipeline of new product announcements and the burgeoning alliances/partnerships among enablers, the trend seems to clearly suggest stainless steel might become a relic of twentieth century biopharmaceutical manufacturing. *BioProcess International*, for one, optimistically predicted "The End for Stainless Steel?" in a June 2006 article.⁵ But a close look at the state of the art, particularly in the realm of large scale mammalian cell culture production, shows that any notion of steel's demise is probably premature.

For sure, biopharmaceutical companies are increasingly exploring single-use solutions, particularly when planning new bioprocesses. Many are finding, however, that plastic is not always practical or desirable. At the 2007 INTERPHEX show, speakers in sessions dedicated to single-use technology addressed different implementation scenarios.

Jennifer LoMonaco and Todd

Rumsey, both engineers with Biokinetics, presented a case study called "The Economics of Single-Use Systems: A Media Prep ROI Analysis" which compared the capital and operational costs of using a stainless steel tank and a single-use media mixing system.

A quantitative analysis showed that the disposable option required a \$771,665 (USD) capital investment compared with a capital outlay of \$958,710 for the stainless steel system. Pipe installation for clean-in-place and steam-in-place were cited by LoMonaco and Rumsey as the primary reason LoMonaco and Rumsey considered the overall difference in cost between the stainless steel and single-use systems to be "negligible."

for the capital cost differential between the single-use and steel systems.

Projected annual operating expenditures were essentially the same for the steel and the plastic systems at about \$5 mil. per year. Regarding individual operating expenses, Biokinetics estimated that the cost of "bags and tubing" would be twice as high for the disposable system than for the steel system (the former using bags for media prep and storage, the latter for storage only), but "vent filters" and "manpower" would be significantly more expensive annually for the steel.

In presenting the results of the study, LoMonaco and Rumsey considered the overall difference in cost between the stainless steel and single-use systems to be "negligible." Armed with this information, the company that hired Biokinetics ultimately decided to forgo installing either system; instead the company continues to purchase the media from a vendor.

According to Rumsey, the client does use disposables in its buffer hold and intermediate product hold applications, as do other Biokinetics clients. Filtration (liquid and air) and sampling are other areas where the firm's clients are frequently utilizing single-use technology.

A Plastic Ceiling?

Another presentation at INTERPHEX on the topic, entitled "Case Study for Applying Single Use/Disposable Technology in Vaccine Manufacturing," was given by FLUOR engineers **Craig Sandstrom,** PhD, and **Miranda Baladi.** Over the last few years the firm has been commissioned to evaluate disposable options for vaccine and other biopharm processes. The case study presented drew primarily from one large, recent conceptual study for a small-scale vaccine process, but also pulled from other similar studies done by the firm.

In presenting their findings, Sandstrom and Baladi discussed a number of key practical considerations that might not be evident to those considering a single-use approach to manufacturing.

For one, companies need to be particularly careful in training operators who will weld the plastic tubing. Some of FLUOR's clients have reported difficulties with welds, particularly for larger diameter tubing. Reliability issues usually boil down to the preparedness of the operators using the systems.

"I've been looking at the tubing connections for quite some time, and, in my mind, that is probably one of the biggest practical, technical challenges with the bags," Sandstrom said during a follow-up telephone conversation. Because there is always a possibility the weld will fail, he advises users to have a contingency plan. "If you know it has failed when you made it, you hate to throw anything away."

When considering a disposable manufacturing system, firms are confronted with the practical limitations in scale and flow rates. Companies currently have greater flexibility with stainless steel systems because required flow rates dictate the pipe size. Sandstrom explained: "If I want to have a 20,000L tank with a 3" or 4" outlet, that is not a problem. I can get those." A bag with a 4" outlet, on the other hand, currently is not available. In their slides, Sandstrom and Baladi showed that the largest diameter plastic tubes available are $1\frac{1}{2}$ ", which equates to a flow rate of 120L/minute.►

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The size of single-use bioreactor bags is also limited. Currently, state of the art for large scale mammalian facilities producing therapeutic monoclonal antibodies is 15 to 25,000L bioreactors, with vessels and product tanks in the thousands of liters. The practical upper limit of bags for single-use solutions is 1000L, although contract manufacturer and single-use bioreactor supplier Xcellerex, Inc. is working on a 2000L bag.

Sandstrom commented on the discrepancy in scale between stainless steel and plastic. There is an "order of magnitude difference between your large-scale commercial manufacturing and what disposable bioreactor vendors are looking at as an upper scale. Can they make an order of magnitude increase in size in the future? I cannot tell you right now 'yes' or 'no,' but today the answer is no."

Another consideration is the robustness of the systems. Sandstrom estimates some of the single-use bioreactors on the market now have a product life expectancy of 5-10 years. Many of FLUOR's clients, however, are looking at useful facility lives of 20 years.

Although the case study involved a small-scale vaccine process, the firm that commissioned the conceptual evaluation has not yet committed to the technology. Sandstrom noted that the company was "surprised that single use would not save them a lot more money." The fact that a single-use bioreactor does not lend itself to highly The practical upper limit of bags for single-use solutions is 1000L, although contract manufacturer and single-use bioreactor supplier Xcellerex, Inc. is working on a 2000L bag.

automated facilities as well as stainless steel systems adds to the operational cost.

Sandstrom believes "disposable technology is a great technology when applied in the right applications: a small-scale facility with volumes of a 1000L or less and where you want a lot of flexibility." For clinical trials, initial product launch and pilot and contract facilities, "disposable technology is almost impossible to beat," he said. "There is tremendous advantage." In fact, he is currently working on a project where disposable technology is "a perfect fit."

However, Sandstrom concluded, "if you are doing large scale antibody manufacturing, running at a relatively high utilization rate and doing the same thing today, planning to do the same thing tomorrow and continue on for the next 10 or 20 years, it may not make as much sense to use disposable technology."

Disposables and PDA

Talks on disposables are making the agenda of PDA meetings. For example, at the Association's global conference on Emerging Manufacturing and Quality Control Technologies, Jan. 29-31, 2007 in San Diego, Calif., a session was dedicated to disposable bioreactors. Speaking were **Millie Ullah**, PhD, Sartorius North America, and Xcellerex President **Parrish Galliher**.

Galliher founded Xcellerex in 2003 to provide contract process development and manufacturing services to the biopharmaceutical industry. Before long, the company's innovative scalable, single-use manufacturing technology prompted it to become a vendor as well as a user of single-use technology. In 2005, Xcellerex received the "Technology of the Year in Biologics Manufacturing" award from research/consulting firm Frost & Sullivan for the FlexFactoryTM integrated manufacturing platform and XDRTM disposable stirred tank reactor.

Its long history in the business and its expanding capabilities were some of the reasons Sartorius's Ullah was invited to speak at the PDA conference. She provided an overview of the benefits firms can realize from single-use bioreactors. Her conclusion is provided in the box on this page.

In March, **Robert Repetto**, Wyeth, and **Roberta Landon**, Millipore and BPSA, met with PDA's **Rich Levy** to >

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Advantages of Single-Use, Disposable Technology Millie Ullah, Sartorius

Drug developers need to manufacture large quantities of material in the shortest period of time in order to meet their goal of getting their drug into the clinic. Often there is limited time available for scale-up and optimization of the process. Single-use, disposable processes and components offer many advantages for drug developers:

- 1. Disposable components are sterile and ready to use when supplied, which eliminates the need for cleaning and sterilization. Therefore decreasing the requirement for water and steam generators.
- 2. Eliminating Cross Contamination. Disposable components are single use only and therefore not used for subsequent operations, eliminating the chance of cross contamination or product carry-over between process runs.
- 3. Shorter Timelines. Long set-up times for equipment installation are avoided because the need for stainless steel equipment is reduced or eliminated.
- Reduction in Complex Systems Costs. Systems are less complex, reducing engineering requirements and eliminating clean-in-place or steam-in-place operations and associated services and pipe work.
- 5. Validation Benefits. The use of disposable components greatly reduces the complexity of validation. As there are substantially fewer reusable components, fewer items need to be tracked and extensive validation studies for sterilization and cleaning can be eliminated.
- 6. Rapid Reconfigurations of Systems. By eliminating most, if not all, hard piping and stationary tanks, disposable components allow for operations to be more rapidly reconfigured for new process runs.

Discarding of disposable materials is a common concern. The used cultivation bags can be sterilized by autoclaving and then destroyed by incineration. The bag films are made from environmentally compatible materials when incinerated. This is sometimes less critical for the environment than the cleaning of conventional bioreactors with alcohol, acids and basic solutions. An additional safety factor is the fact that no cell or protein residues are released into the wastewater cycle.

formulate a vision of a PDA disposable manufacturer task force. Understanding that group's like BPSA are already active in this area, the three agreed PDA's task force would augment those efforts rather than reproduce them. Certainly, the PDA task force could provide a voice for single-use product end users.

As this issue of the Letter goes to press, the task force leaders are currently creating a scope of efforts which will be submitted to the BioAB and SAB for approval. The scope will probably include a technical report, meetings and workshops, and training activities at PDA's new Training and Research Institute in Bethesda, Md., to provide more TRI training for end users, particularly in the area of tubing welds. This training will undoubtedly include the latest disposable equipment from manufacturers as part of the hands-on laboratory training.

Notes:

- 1. For example, *BioProcess International* published with the May edition its fourth supplement on single-use/ disposable technology in four years. *BioPharm International* and *Genetic Engineering & Biotechnology News* both have published several articles on the topic since the beginning of the year.
- 2. For example, PDA started the year with a conference on Emerging Manufacturing Technology, featuring a session on single-use systems. INTERPHEX 2007 included sessions on the topic. IBC Life Sciences is offering a conference in June.
- 3. Hélèna Pora, PhD, "Disposables: Keeping Pace with Today's Disposable Processing Applications," *BioPharm International*, April 2007.
- 4. Jerold Martin, "An Update of the Bio-Process Systems Alliance's Latest Activities," *BioProcess International*, May 2007.
- 5. Pietro Forgione and Mark Van Trier, "The End for Stainless Steel?" *BioProcess International*, June 2006.



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Use of Microarrays to Evaluate Cell Culture Processes

Progress Report from a PDA Journal Student Grantee Michael Hanson, University of Maryland, Baltimore County

Introduction

The accessibility of gene expression data has increased steadily since the mid-1990s with the advent and utilization of various technologies, such as DNA microarrays and Reverse Transcription Polymerase Chain Reaction (RT-PCR). These tools have been applied primarily in the medical field, for example, to profile various types of cancer tissues. Here it will be described how gene expression data can be utilized in the bioprocessing arena. The three specific uses to be discussed are for process development, as a regulatory gauge of risk and for process monitoring.

Process Development

During upstream bioprocess development, several stages of optimization are required. Traditionally, in the first stage, the production cell line is chosen and genetically engineered to efficiently produce the product of interest. Next, an appropriate growth media is formulated and suitable bioreactor culture conditions are established. Here the goal is usually to maximize yield while maintaining quality specifications of the active pharmaceutical ingredient (API). However, with the capability to monitor changes in gene expression, we can use information obtained during media development and bioreactor optimization and apply it to reengineer the production cell line. Then, this upstream development paradigm becomes iterative, or cyclic. A great example of this was carried out by researchers at the Bioprocessing Technology Institute in Singapore where DNA microarray studies identified four genes that are critical to the onset apoptosis, or programmed cell death.¹ Based on this information, cell lines with the ability to avoid apoptosis were developed, enabling an increase in product titer.

Disposable bag reactor technology is gaining momentum as a formidable contender to traditional stirred-tank vessels.

Cell Culture Process Changes

From the discovery phase, through the clinic and into commercial manufacturing, biopharmaceutical processes are continually being refined to improve yields and meet market demands. Some process changes that occur late in the clinic stage and post-approval require regulatory consent. Postapproval changes are categorized as major, moderate or minor based on the impact the process change could have on product quality attributes. From a regulatory perspective, it has proven difficult to classify process change severity in this way. This PhD project, a collaborative effort with researchers and regulators at the U.S. FDA, was conceived as an internal way to increase the foundation of knowledge about cell culture process changes and to see if production cell transcriptome data can be indicative of process change severity. Several relevant cell culture process changes have been chosen for study.

Disposable bag reactor technology is gaining momentum as a formidable contender to traditional stirred-tank vessels. Because of the mechanism of mixing and sterility issues, traditional electrochemical probes for dissolved oxygen (DO) concentration and pH have not been successfully implemented into these systems. Fluorescence-based optical sensors have emerged as a solution to this setback. As shown in Figure 1, an optical sensor consists of three principle components, the latter two are located external to ►

Figure 1



Fluorescence-based optical sensor schematic. Optical sensors generally consist of a fluorophore immobilized inside the reactor vessel, and LED(s) and a detector, both exterior.

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June 26-27, 2007 PDA Technical Report No. 1 2007 Revision Chicago, Illinois

September 24-28, 2007 2007 PDA/FDA Joint Regulatory Conference (Conference, Courses and Exhibition) Washington, D.C.

October 15-16, 2007 2007 PDA Visual Inspection Forum Bethesda, Maryland

October 29-November 2, 2007

PDA's 2nd Annual Global Conference on Pharmaceutical Microbiology (Conference, Courses and Exhibition) Bethesda, Maryland

November 1-2, 2007 PDA/FDA Co-Sponsored Conference Series on Quality Systems Bethesda, Maryland

November 6-8, 2007 PDA Extractables/Leachables Forum Bethesda, Maryland

Training

Lab and Lecture events are held at PDA TRI, Bethesa, Maryland unless otherwise indicated.

August 2-3, 2007 Environmental Mycology Identification Workshop

October 1-5, 2007 Rapid Microbiological Methods

October 15-19 and November 5-9, 2007 Aseptic Processing Training Program

October 17-18, 2007 Visual Inspection Training Course

October 23-24, 2007 Fundamentals of D, F and z Value Analysis

October 25-26, 2007 Validating a Steam Sterilizer October 31-November 2, 2007 Advanced Environmental Mycology Identification Workshop

Lecture Courses

October 8-10, 2007 Advanced Pharmaceutical Filtrations and Filters

Course Series

June 11-13, 2007 Baltimore Training Course Series

October 15-17, 2007 Philadelphia Training Course Series Philadelphia, Pennsylvania

November 27-29, 2007 San Diego Course Series San Diego, California

Chapters

June 13, 2007 PDA New England Chapter Facility Tour, Networking and Dinner Meeting Burlington, Massachusetts

June 13, 2007

Delaware Valley Chapter Dinner Meeting Malvern, Pennsylvania

July 18, 2007 Puerto Rico Chapter Educational Conference Location TBD

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September 11-12, 2007 Industrial Freeze Drying and Spray Drying Cologne, Germany

September 12-13, 2007 Technology Transfer Basel, Switzerland

October 9-10, 2007 Cleanrooms/Isolators/RABS Co-sponsored by PDA and R3 Nordic Berlin, Germany

October 17-18, 2007 Pharmaceutical Cold Chain Berlin, Germany

October 25, 2007 Supplier Quality and GMPs Rome, Italy (postoned from June 11, 2007, Bologna, Italy)

November 7-9, 2007

Modern Aseptic Production Co-sponsored by PDA and R3 Nordic Stockholm, Sweden

November 13-15, 2007 Berlin Course Series Berlin, Germany

November 15-16, 2007 Cork Course Series

Cork Ireland

November 27-28, 2007 The Universe of Pre-filled Syringes Berlin, Germany

December 4-7, 2007 Practical Aspects of Aseptic Processing Training Basel, Switzerland

December 10-11, 2007 PDA/FDA Co-Sponsored Series on Quality Systems Dublin, Ireland

December 12-14, 2007 Dublin Training Course Series Dublin, Ireland

January 23-24, 2008

Investigational Medicinal Products: How to Get the GCP/GMP Interface Right Paris, France

February 20-21, 2008

PDA/EMEA Joint Conference Budapest, Hungary

Asia

July 5, 2007 PDA Japan Chapter J-Pharmaceutical Affaires Law Update Tokyo, Japan

September 23, 2007

PDA Japan Chapter Conference with US Task Force before 2007 PDA/FDA Joint Regulatory Conference Washington, D.C.

November 13-14, 2007

PDA Japan Chapter Annual PDA Japan Chapter Meeting Tokyo, Japan the vessel. These are:

- 1. An analyte-sensitive fluorophore that is encapsulated in a patch, which is affixed to the inside of a transparent reactor vessel
- 2. Light-emitting diode(s) (LED) for fluorophore excitation
- 3. A detector for emission quantification

As the patches are illuminated, cells are also exposed to light of varying wavelengths, in some cases ultraviolet. Cells are also continually exposed to the sensor patch. Thus, the first process change we chose to study was the implementation of optical sensors into a high throughput bioreactor (HTBR). Three configurations of sensors and light exposure were tested: The first process change we chose to study was the implementation of optical sensors into a high throughput bioreactor.

instrumentation has no impact on cellular physiology at the transcript level.²

The second process change that was explored was the addition of a common industrial inducing agent, sodium butyrate, into the cell culture medium. As demonstrated in studies by others,

Process Change	Genes	Gene Sets	Pathways
Optical Instrumentation	0	N/A	N/A
Butyrate Addition	116	29	1
High Osmolality	25	95	9

The impact of different process changes on individual genes, functional groups and biological pathways. Group and pathway analyses were not carried out for the implementation of optical sensing.

- 1. Patches (+) and light (+)
- 2. Patches (–) and light (+)
- 3. Patches (-) and light (-)

There was no difference in hybridoma viable cell density or culture viability between the three configurations at any time point (p < 0.05). Also, no genes were found to change in expression when comparing configuration one and three (p < 0.001). Therefore, it was concluded that the optical sensor

butyrate caused an arrest in cell growth, purportedly due to the retention of cells in the G1/G0 phase of growth. Possibly related to this change in cell state was an immediate increase in culture pH and a decrease in oxygen uptake rate. Almost a two-fold increase in monoclonal antibody (MAb) production resulted as well. Of the approximately 17,000 genes analyzed by microarray analysis, 116 changed in expression. Of these, 90 increased in expression while the remaining 26 decreased. Most of the analyzed genes can be grouped into functional groups and biological pathways based on their roles within the cell. Like the genes, 29 of these groups and 1 pathway changed in activity as a result of sodium butyrate addition.

In fed-batch processes, concentrated feed solutions are added. To control pH, acidic gas and a basic solution are also added. All three of these additions combine to steadily increase media osmolality over the duration of a culture. Due to the prevalence of this situation, the third process change employed was an increase in media osmolality by sodium chloride addition. The experiment was carried out with two sets of cells: those maintained in regular media and others that were adapted to high-osmolality media. Although the increase in osmolality drastically inhibited cell growth, specific MAb productivity increased significantly. Protein production increases are not uncommon as a cellular response to stress. While only 25 individual genes changed in expression due to the osmolality increase, 95 functional groups and 9 pathways were affected. This suggests a general stress response where the genes involved carry out many different roles within the cell.

Until now, three different process changes had been employed with varying impacts on cell culture behavior and gene expression, as summarized in Table 1. How to interpret these array data with respect to regulatory risk is unclear and still being investigated. In terms of severity, what is more important, individual genes or groups?

Critical Process Parameters and Quality Attributes

Ultimately, what is most important is how any process change impacts quality attributes of the product. For this reason, testing of the product resulting from each of these process changes has begun. Size exclusion chromatography showed no evidence of fragmentation

Table 1



Relationships between some critical process parameters (CPP) and critical quality attributes (COA).

With current rates of technological improvements coupled with our increasing understanding of complex biological networks, these hurdles may not be so daunting.

or aggregation of MAb produced while monitoring optically. More rigorous analyses are being carried out on the remaining process change samples.

In the literature in recent years, some specific critical process parameters (CPP) have been identified that influence critical quality attributes (CQA) of the product, as shown in Figure 2. What is unclear is whether these parameters are general or product-specific. An essential part of the Quality by Design paradigm is that these process parameters can be monitored and controlled. Ultimately, it would be remarkable if similar types of relationships as those shown in Figure 2 could be established between gene expression data and CQAs. Thus, by monitoring the levels of certain genes, one could define and inhabit a process space in which quality product is being produced.

There are several drawbacks or hurdles to this theoretically attractive idea.

First, relationships must be established between gene expression and product quality attributes. Second, gene expression measurements are nowhere near real-time. By today's standards, it would take a day to realize the process is outside of its design space. And lastly, although we can monitor gene expression levels, we cannot control them (not finely, at least not yet) to keep the process within the design space. These drawbacks make the concept of using gene expression data as a surrogate indicator of product quality to seem theoretical at best. However, with current rates of technological improvements coupled with our increasing understanding of complex biological networks, these hurdles may not be so daunting.

Summary

Knowledge gained from gene expression experiments has been practically applied to process and cell line development. We (UMBC) have established an ongoing collaboration with FDA (CDER) to study the impact of relevant process changes on gene expression patterns and product quality attributes. And in the future, gene expression data could be used as a surrogate indicator of product quality in cell culture systems.

Acknowledgements

The author would like to thank Antonio Moreira, PhD (UMBC); Govind Rao, PhD (UMBC) and Kurt Brorson, PhD (FDA), for advising in the research described here and PDA for partial funding of the work in the form of the *PDA Journal of Pharmaceutical Science and Technology* Pre-doctoral Fellowship.

References:

- 1. Wong DCF *et al.* 2006. Targeting early apoptotic genes in batch and fed-batch CHO cell cultures. *Biotechnol Bioeng*, 95(3)350-61.
- Ge X *et al.* 2006. Validation of an optical sensor-based highthroughput bioreactor system for mammalian cell culture. *J Biotechnol*, 122, 293-306.

About the Author

Michael Hanson is a graduate research assistant at the Center for Advanced Sensor Technology, Department of Chemical and Biochemical Engineering, University of Maryland, Baltimore County (UMBC), Baltimore, Md. This article is a summary of his presentation at PDA's Emerging Manufacturing and Quality Control Technologies Global Conference, which was held on January 29, 2007, in San Diego, Calif.

Comment on this Article. Contact morris@pda.org.

FDA Warns Drug Manufacturers to Guard against DEG Poisoning Walter Morris, PDA

In May, the U.S. FDA released the guidance *Testing of Glycerin for Diethylene Glycol* and issued a MedWatch Safety Alert to remind manufacturers to be extra vigilant in testing their supplies of glycerin and other ingredients that could potentially be contaminated with diethylene glycol (DEG). While the guidance is meant to reinforce existing safeguards against a DEG problem in the United States, its primary purpose is to raise awareness of continued threats to the glycerin supply from unethical suppliers in foreign markets.

Reports of several hundred deaths in Panama resulting from DEG contamination prompted the FDA's actions. A May 10 *New York Times* article titled "Poisoned Medicines" provides a detailed and disturbing account of the problem with DEG contamination from China to Panama.

The Times article revealed that a U.S. company had received 50 tons of counterfeit glycerin in 1995 related to a poisoning in Haiti. FDA was unaware of this situation until the Times reporters began researching the story. FDA is now considering options for requiring all companies to report findings of DEG-tainted supplies.

PDA met with CDER Office of Compliance Director **Deborah Autor**, Esq., and Deputy Director **Joseph Famulare** to discuss FDA's growing concern in light of continued problems abroad.

When asked about the timing of the guidance and the MedWatch Safety Alert, Autor commented, "First and foremost, there hasn't been a diethylene glycol poisoning incident that we know of in this country for 70 years, so that is good. Nonetheless, in light of recent events outside the United States, we think there is a continued risk of such contamination. So in the wake of that, we prepared this guidance document emphasizing the importance of testing glycerin in such a way that DEG contamination will be identified."

The current actions are similar to those taken by FDA following poisonings in Haiti over a decade ago. At the time, the Agency and its counterparts in Europe and Japan were developing a guidance on GMPs for APIs (Q7A) via the International Conference on Harmonisation. The situation in Haiti heavily influenced the content of Q7A, including inclusion of section 17 on shipping controls, which is referenced in the new DEG guidance. Besides testing, companies can avoid problems with DEG by securing their supply chain.

"We prepared this guidance document emphasizing the importance of testing glycerin in such a way that DEG contamination will be identified."

"Once you start going through brokers, changing hands, that is a signal that a U.S. supplier has to look for and control as much as possible through its systems of purchasing and its own quality systems," Famulare stated. "GMPs form a basis for that, but beyond that companies really need to be wary."

The DEG guidance reinforces the importance of testing and supply change control to ensure the absence of DEG in glycerin and other components like propylene glycol. Firms are to reference the U.S. Pharmacopeia monograph for glycerin, which includes a limit test for DEG. "The USP actually added a test for detecting DEG in the glycerin monograph. It is pretty apparent after that incident you could have tested glycerin for all of its attributes and still not have discovered that DEG was present or totally substituted for the product," Famulare explained. "So what we wanted to do in this DEG guidance is make it crystal clear in following the cGMPs here in the United States, one of the specific identity tests is the DEG test. As a result of our effort, the USP is even going to further clarify that point in terms of making sure it is specifically listed as an identity test. It is in there now, but it needs a little more clarity. So they will be working through their process. We certainly clarify that in our guidance."

While not specifically applicable to excipients like glycerin, ICH Q7A provides sound advice for testing all pharmaceutical ingredients. Referencing the document, Famulare discussed sampling: "So how many containers you sample and where you sample is a decision you have to make as a company on a risk basis, but it should be based on what you know about your supply chain. The emphasis is also on making sure you are getting your materials from a reputable supplier, that you verify the supply chain to the degree you can. To the degree you have confidence in your suppliers, you can adjust your representative sampling, but we still want that sampling and testing done because it is a potentially fatal issue."

When asked if there is an imminent risk to U.S. medicines, Autor replied, "I don't feel there is an imminent threat to the U.S. market. But I do think it is possible for a component like this to come in the United States, which is why there needs to be the appropriate testing as well as appropriate process and label controls to prevent this from

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PDA Comments on EMEA GMP Guide

For the complete comments, including the comments grids, go to www.pda.org/regulatorycomments.

April 25, 2007

Ms. Sabine Atzor European Commission Enterprise DG, Pharmaceuticals Rue de Genève, 1 1049 Brussels Belgium

Mr. David Cockburn European Medicines Evaluation Agency 7 Westferry Circus London E14 4HB United Kingdom

Dear Ms. Atzor and Mr. Cockburn:

PDA is pleased to provide comments on the proposed revision to Chapter 1 of the GMP guide to include reference to quality risk management (QRM) principles. PDA is an international professional association of 10,000 individual member scientists having an interest in the fields of pharmaceutical manufacturing and quality. Our comments were prepared by a committee of experts in the area of

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\checkmark	Via Electronic Mail
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John Shabushnig, PhD Plane Inc.	/ westerry circus
Secretary:	United Kingdom
Lisa Steens, PhD Roder Mailhorn Compution	·····
Thesunc.	Dear Ms. Atzor and Mr. Cockburn:
Maik Jornitz Satorius Comoration	
Immediate Past Chair:	PDA is pleased to provide comments on the proposed revision to Chapter
Nikki Mehringer	1 of the GMP guide to include reference to guality risk management (QRM) principles
En City and Company President	individual member scientists basing an interest in the fields of
Robert Myers	pharmaceutical manufacturing and quality. Our comments were prepared
DIRECTORS	by a committee of experts in the area of quality, and approved by our
Rebecca Devine, PhD	Regulatory Affairs and Quality Committee as well as the PDA Board of
Regulatory Consultant	Directors.
Katheen Greete Novaris Pharmaceuticals Corp.	
Yoshihito Hashimoto, Msc	Our comments are embraced by the three general concepts:
Chyoda Corporation	success an organizational unit he set un for this function
Vetex Pharmaceuticals	QRM principles should be an aspect of the reviewer functions, not
Tim Marten, Ophil	just GMP and quality, and thus should be reflected in a CHMP
Steven Mendivil	guidance and
Angen	The ICH Q9 guidance is optional and not a requirement
Any 3cott-Billman GaocSmithKine	Attached please find our comments in the approval EMEA format. If I can
Eric Sheinin, PhD	be of further assistance, please feel free to contact me.
U.S. Pharmacopeia Gall Solar	
GE Healthcare	With kind regards,
Laara Thoma, PharmD University of Tennesson	A 44
Martin Van Trieste	16 Africant and a second secon
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Schaeler, P.L.L.C.	PDA Europe
Editor, PDA Journal of Pharmaceutical Science	roessling@pda.org
and Technology:	A DE
Lee Arsolit, PhD University of Iowa	

quality, and approved by our Regulatory Affairs and Quality Committee as well as the PDA Board of Directors.

Our comments are embraced by the three general concepts:

- 1. QRM is based on principles (a way of thinking), and does not suggest an organizational unit be set-up for this function.
- 2. QRM principles should be an aspect of the reviewer functions, not just GMP and quality, and thus should be reflected in a CHMP guidance and
- 3. The ICH Q9 guidance is optional and not a requirement

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Risk Based Approach and Risk Management in Pharmaceutical Manufacturing Processes

13 November 2007

The FDA is keen to encourage companies to adopt risk management techniques in their manufacturing operations. The recent initiative GMP in the 21st Century A Risk-Based Approach advocates the use of these techniques. This course will provide participants with a regulatory and historical background to pharmaceutical risk assessment and the use of risk assessment and risk management tools. It will comprise of a combination of formal presentations, group exercises and group discussion sessions. Group exercises will allow attendees to learn about risk assessment tools by using them to solve hypothetical problems, based on real life experiences of the course tutor. Following the risk assessment exercise, each group will be asked to develop a control philosophy to manage the risks identified. **Instructor: Trevor Deeks**, *Emergent BioSolutions*

Fundamentals of Pharmaceutical Filtrations and Filters

13-15 November 2007

Filtration is used to separate unwanted particles, both viable and nonviable, from drug preparations. This highly-interactive training course is intended to provide a fundamental understanding of pharmaceutical filtrations and filters. The course will enable the participants to concentrate on the use of filters for the most demanding and critical operations for the manufacture of aseptic products.

Instructor: Maik W. Jornitz, Sartorius Instructor: Theodore H. Meltzer, PhD, Capitola Consulting



This course will address the FDA Draft Guidance for the manufacture of drugs for Phase I trials and compare its recommendations with Annex 13 of the EU GMPs. The course is designed to be highly interactive with the opportunity for the audience to ask questions and to exchange views with other participants struggling with similar conundrums. Students will participate in an exercise to provide solutions to specific quality problems observed in the day-to-day quality operations in their companies. **Instructor: Karen Ginsbury**, *Pharmaceutical Consulting Israel*, *Ltd.*

Development of Qualification and Validation Protocols – A Risk Management Approach

15 November 2007

The objective of this course is to provide instruction for the development and writing of qualification and validation protocols and summary reports utilizing up-to-date risk management and objective-based approaches. The course is designed to be in lecture format, encouraging group participation, questions, and answers throughout. It will be an interactive workshop, designed to develop the test methodology and acceptance criteria for a process/system validation protocol and program.

Instructor: Hal Baseman, ValSource, LLC

Check **www.pdatraining.org** for new courses being added to the European Training Course Series in Berlin!

PRACTICAL ASPECTS OF ASEPTIC PROCESSING

4-7 December 2007 / Basel, Switzerland www.pdatraining.org/paap

For those looking for a comprehensive overview of current aseptic processing practices, this course is it. You will learn what is necessary to build an effective aseptic process, including: facility design, velocity testing and airflow studies, HEPA certification, microbiological issues and how to manage environmental control systems. Hands-on experience with proper gowning procedure and sanitization is also included. Instructor: John Lindsay, Aseptic Solutions Inc. Instructor: Peter Koger, Veltek Associates, Inc.

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Contact: Jessica Petree, Manager, Lecture Education email: *petree@pda.org /* Tel: +1 (410) 455-5800 After 30 June, please call +1 (240) 482-1658

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Delaware Valley Chapter Meeting Focuses on QbD

Sue Vogt Speth, PDADV Operating Committee Member; GlaxoSmithKline

Over 100 participants from local area pharmaceutical and biopharmaceutical companies attended the PDA Delaware Valley Chapter (PDADV) meeting on Wednesday, April 18, at the Desmond Hotel and Conference Center in Malvern, Pa. **Dominic Ventura**, PhD, VP of Technology, Wyeth Pharmaceuticals, shared his extensive implementation experience with Quality by Design (QbD). Ventura's lecture was entitled "Implementation of Quality by Design Concepts in a Risk-Based Approach."

Attendees gained an understanding of how definitions and strategies evolve during the implementation process, how to use risk assessment to reap the benefits of strategy alignment across multiple disciplines, and how to establish the design space and transfer it from laboratory through pilot to full-scale production. Using these methodologies for successful product filings was discussed. Ventura explained the role of risk-management tools and their use in the establishment of critical and noncritical process and quality parameters. He also discussed the relationship of Process Analytical Technology and QbD. At the close of his remarks, Ventura entertained questions and shared ideas with the attendees.

Enrich Your Career – Become a Volunteer

Hassana Howe, PDA

As a not-for-profit professional association, PDA is run by and for its members. The success of PDA depends on members like you to contribute both ideas and abilities. By getting involved and volunteering your time and talents, you will not only help advance the industry, but you will also enrich your career.

Participate in a shared commitment to the global advancement of science, technology and regulation with the following volunteer opportunities.

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Identify global regulatory issues and interact with regulatory agencies by volunteering with the Regulatory Affairs & Quality Committee. Assist with topic and speaker selection for PDA meetings on the Program Planning Committee. Enhance PDA membership by welcoming new PDA members and enriching the PDA membership experience on our Membership Committee.

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By joining a PDA Task Force, you will contribute to the development or revisions of highly-valued industry guidances or the preparation of PDA comments on global regulatory issues, while networking with experts from industry, academia and/or government agencies. For a complete list of Task Forces, please visit the "Quality/ Regulatory Affairs" section of the PDA website (www.pda.org).

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Advisory Boards help PDA identify issues of interest to the industry and assist in developing strategic planning for researching these issues. Advisory Boards provide insight by studying and preparing written documents, including articles, technical bulletins, technical reports and surveys to be published in PDA resources.

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- Program Advisory Board (PAB)
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PDA Interest Groups provide a forum for members to exchange ideas, network and directly impact the advancement of pharmaceutical and biopharmaceutical science, technology and regulation. Not only are Interest Groups an excellent source of specialized information, but they also serve as a springboard for involvement in leading-edge activities such as the drafting and final publication of PDA Technical Reports and PDA Technical Bulletins.

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- Quality Systems & Regulatory Affairs

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Bioassay Development and Validation October 15-16, 2007 **Instructor: David Lansky, PhD**, Lansky Consulting, LLC

Systems-Level Risk-Based Assessment for Electronic Records Regulatory Requirements - NEW COURSE! October 15-16, 2007 Instructors: Carolyn Apperson-Hansen, Cleveland

Clinic and Scott Revolinski, Nuclear Safety Associates

Achieving cGMP Compliance During Development of a Biotechnology Product October 16, 2007 Instructor: Joseph G. Habarta, PhD, J. Habarta Consulting Computer Products Supplier Auditing Model: Auditor Training October 16-17, 2007 Instructor: Charles M. Waite, Process Design Consultants, Inc.

Fundamentals of Lyophilization October 16-17, 2007 **Instructor: Edward H. Trappler**, Lyophilization Technology

Sterile Pharmaceutical Dosage Forms : Basic Principles October 16-17, 2007 Instructors: Michael J. Akers, PhD, Baxter Pharmaceutical Solutions, LLC and John D. Ludwig, Pfizer, Inc.

Approaches to Performing Internal Audits as Part of a Total Quality System for Pharmaceutical Product Development and Manufacture *October 17, 2007* **Instructor: Joseph G. Habarta, PhD**, J. Habarta *Consulting*

www.pdatraining.org/philadelphia

Contact: Jessica Petree, Manager, Lecture Education Tel: +1 (410) 455-5800 After June 30, please call +1 (301) 656-5900, ext.151 Email: petree@pda.org

Chapter Contacts

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

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2007 PDA Visual Inspection Forum

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- Particulate identification
- Sources in manufacturing environment and their control

All submitted abstracts will be reviewed by the Program Planning Committee for inclusion in the meeting or for poster presentation.

Visit www.pda.org.visinspect to submit your abstract. Abstracts must be received by June 30, 2007 for consideration.

Case studies are particularly desired. Commercial abstracts featuring promotion of products and services will not be considered. After June 30, 2007, you will be advised in writing of the status of your abstract. PDA will provide one complimentary registration per presentation. Additional presenters are required to pay appropriate conference registration fees. All presenters are responsible for their own travel and lodging, with the exception of health authority speakers.

Please include the following information and follow the steps identified in the All Academic abstract manager. Submissions received without full information will not be considered.

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- → 2-3 paragraph abstract, summarizing your topic and the appropriate forum (case study, discussion, traditional, panel, etc.)
- ----> Audience take-home benefits
- ----> Rationale

For more information, please contact:

Lu Castro, Senior Coordinator Programs and Registration Services Email: castro@pda.org Tel: +1 (301) 656-5900 ext. 122

ATTENTION EXHIBITORS

PDA is seeking vendors who provide excellent products/services in support of this conference. Space is limited and is available on a first come, first served basis. To reserve your space, please contact Cindy Tabb at tabb@pda.org or +1 (301) 656-5900 ext. 222.

PDA Welcomes New Members

Cristina Alves, Hovione Tomoyasu Andoh, KNC Laboratories Kuang Anna, Baxter Louis Antinori, Pfizer Salvatore Arrigo, Medarex John Avellanet, Cerulean Associates Jim Bacon, Talecris Biotherapeutics Jonathan Bellush, Wyeth Eileen Benham, NutraMax Products Carmen Betancourt, KaloBios Pharmaceuticals Eileen Bohler, Pfizer Nicolas Bralet, Becton Dickinson Stacey Calautti, Merck Linda Carducci, Global Biologics Supply Chain Phillip Carter, Baxter Tuba Celebi, Sanovel Estela Celi, Teva Pharmaceuticals Charlene Chan, Amylin Ohio Ross Chester, SAR Enterprises Veronique Chiavazza, sanofi pasteur Mohanganesh Chintha, Biological E. Katia Chohbane, OPi Nishchal Chudasama, Bristol-Myers Squibb Jesse Ciras, MBL Bella Cohen, Abbott Laboratories Mary Conzo-Dupre, Genzyme Douglas Cusato, Helvoet Pharma Eva Czerwiec, ImClone Systems Tracy Davis, Invensys Charles Davis, SAIC-Frederick Mark Davis, UPS David de Chaves, Shire Sue Deady, Abbott Laboratories Bruce Donnelly, Johnson & Johnson James Donohue, Tyco Healthcare Kieran Doyle, Cross Vetpharm Group Jeri Dugan, Genentech Eric Edgcomb, Baxter Matthew Egan, Tyco Healthcare Marianne Erickson, University of Missouri Robert Ferris, Novartis Brian Flynn, Fastent Search and Recruitment John Frey, Genzyme Biosurgery Yuji Fujita, Chiyoda Ikuo Fukasawa, Asubio Pharma Fumiaki Fukui, Toray Industries Toshiyuki Furutani, Tanabe Seiyaku Tsutomu Futagami, Nippon Electric Glass Daniel Gagnon, UPS Laurence Girard, sanofi pasteur Christine Gladwell, Baxter Eamonn Gleeson, Amgen Miguel Gomez, Watson Laboratories Maaike Gons, N.V. Organon Tara Gooen, U.S. FDA Lisa Gough, Amgen Helen Grad, Baxter Harvey Greenawalt, Averion Life Sciences Jamie Grossi, Sartorius Jens Peter Gundorf, Novo Nordisk Amilcar Guzman, Amgen Elaine Haines, Amgen Therese Hall, Bayer Nigel Hamilton, sanofi-aventis Mette Hansen, Novo Nordisk Nanette Hanson, Genentech Peter Harris, B & V Testing Cate Hass, Validation Resources Michelle Herrick, Formatech Elisabeth Hesser, KV Pharmaceutical Maija Hietava, Maijatek

Michelle Hoekstra, CSL Behring Alex Hollenbeck, Total Quality Birgitte Holst, Novo Nordisk Jianfeng Hong, Baxter Hiroshi Hosomi, Kyowa Vacuum Engineering Anne Huffman, Abraxis Bioscience David Hunden, Eli Lilly Ron Iandoli, Genzyme Masahiro Ikeda, Sankyo Sandra Illich, Wyeth Akira Ishii, Kyowa Vacuum Engineering Javalakshmi Iyer, Baxter Benigno Jean-Francois, sanofi pasteur Ryan Johnson, Allergan Steve Jordan, PDL BioPharma Marcia Kafkakis, Baxter Toshiki Kameyama, Terumo Yosie Kaneda, Taisho Pharmaceutical Shinichi Kaneda, Terumo Fumikazu Kato, Seikagaku Sato Katsuhiko, Eisai Paul Kester, Port City Group Hiroyuki Kikukawa, Sumitomo 3M Tara King, Merck John Knutsen, Bristol-Myers Squibb Mel Koch, University of Washington Venkat Koganti, Pfizer Tomonori Konse, Sankyo Sabrina Kordys, Gorbec Pharmaceutical Services Takahiro Kumonaka, Terumo Jerry Kurian, Lisa Ampoules & Vials Debbie LaBelle, Watson Laboratories Steven Lasko, Nastech Sueanne Lee, Genentech Annie Lee, Novartis Lynette Lenti, Abraxis BioScience

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Kostas Liaros, Famar Andy Lin, Cell Genesys Wei Liu, Elan Drug Delivery Edwin Lopez, EL-Blocks Karen Luzzi, Wyeth Shigeru Makizaki, Hisamitsu Pharmaceutical Tadahiko Masuda, Banyu Pharmaceutical Kimberly Matheson, sanofi pasteur Glenn Mattei, Becton Dickinson Helen Mayfield, Amylin Pharmaceuticals Jennifer Maynard, Bayer Patricia Mazur-Hopkins, Lonza Kevin McCarthy, Tyco Healthcare/ Mallinckrodt Tony McCourt, Bristol-Myers Squibb Linda Metcalf, Eli Lilly Lalit Misra, Sharon Bio-Medicine Makoto Miyazaki, Kaneka Cristiano Moretti, Autocal Ireland Atsuhide Mori, Astellas Pharma Susumu Morishita, Kyowa Vacuum Engineering Doina Morusca, Invensys Validation Technologies Phang Mui Foong, Ansell Gina Mullane, Charles River Laboratories Akihiro Nakajima, Meiji Dairies Mitsuhiro Nakamura, Millipore Eiji Nakanishi, Ajinomoto Emily Nelson, TalentWave Elena Nieczkoski, Array Biopharma Nobutaka Ninomiya, Ajinomoto Yoshitaka Nishita, Ono Pharmaceutical Donald Nolde, Cold Chain Technologies Hiroyuki Ootsuki, Terumo Jorge Ortiz, GO Pharmaceutical Consulting

Young shin Park, KBCC Ronak Patel, Medfil Accounts Payable, Intermune Waleska Pena-Fornes, Amgen Robert Perks, Baxter Jonathan Petersen, Schering-Plough Thaddeus Prusik, Temptime Eric Puentes, Amgen William, Quinn, Novo Nordisk Leticia Quinones, Bristol-Myers Squibb James Renaud, Amgen Ric Reordan, XOMA Kristi Reuss, Orthovita Elliott Rice, Novo Nordisk William Robinson, Commissioning Agents Benjamin Romero, Bristol-Myers Squibb Raymond Rugebregt, JM Hyde Consulting Daniel Rzegocki, Celator Pharma Lucie Sabourin, Canadian Blood Services Yoshihiro Saitou, Meiji Daries Takashi Sakaguchi, Eisai Lawrence Salerno, Retractable Technologies Marcelo Sanchez, Servycal Raquel Santos, Amgen Ricardo Santos, Cisabrasile James Sayer, Biogen Idec Mark Schlieper, Canadian Blood Services Arvind Sharma, Dabar Pharma Steven Sharples, Hospira Arthur Shaw, Pfizer Stacy Sherling, Eli Lilly Daniel Shertok, PDL Biopharma Katsushi Shintaku, Ono Pharmaceutical Seiichi Sibuya, Daikin Applied Systems

Kathryn Simon, Diosynth Biotechnology Narinder Singh, Q Validation Paul Smith, Teva Parenteral Medicines Michael Smith, Alcon Laboratories Puay Eng Soon, Alpha Biologics Valerie Soubeyrand, SIPPEX **Rainer Stegmeier**, Abbot Laboratories Gary Stein, Abraxis BioScience David Stephens, MRI Chattanooga Nicholas Sticco, Bristol-Myers Squibb Margaret Stotts, Array BioPharma Paul Strittmatter, Shire Fumi Suzuki, Merck Naoto Takamatsu, Invitrogen Hideki Takayama, Takata Seiyaku Hiroshi Takeno, Denka-Seiken Tokuhiro Tamura, Eli Lilly Masahiko Tanahashi, Toray Industries Doina Teoreanu, SNC Lavalin Pharma Takaaki Terahara, Hisamitsu Pharmaceutical Thea Terblanche, Bodene Stephan Thebault, Genentech Mark Thompson, Wyeth Yoshiaki Tobe, Daikin Applied Systems Yasuo Tokuda, Kyowa Vacuum Engineering Jose Torres, Amgen Elisa Tovera, Amgen Jeri Tumulty, Martec Cedric Vachette, sanofi pasteur Susan Vargo, Amgen Ganesh Vedantham, Amgen Sandrine Vernier, Institut Straumann Ann Villalobos, Johnson & Johnson

If your information appears inaccurate in this list, please visit www.pda.org to update your profile or email changes to info@pda.org.

PDA/FDA Conference Offers Something for Everyone

Washington, D.C. · September 24-28, 2007

Susan Schniepp, Hospira

The PDA/FDA Joint Regulatory Conference has been a premier meeting and tradition for over 15 years and has established itself as a must-attend industry event. This year's conference promises to continue and enhance this illustrious tradition by offering relevant and timely sessions.

With the adoption of ICH Q8 (pharmaceutical development) and Q9 (quality risk management) guidelines and the emergence of ICH Q10 (pharmaceutical quality systems), industry and regulatory authorities will come together at the 2007 conference to discuss the regulations and form a consensus on their applications in light of the Quality by Design (QbD), riskbased approach to quality systems and design space concepts. The program, developed jointly between industry and the U.S. FDA volunteers, is entitled Evolution of the Global Regulatory Environment: A Practical Approach to Change.

Attendees will have the opportunity to participate in unique sessions focusing on a wide variety of topics pertinent to today's regulatory and quality environment. The information discussed and presented in these targeted sessions will assist participants in rethinking, reinterpreting and reapplying the current regulations to fit the cGMPs for the 21st century paradigm with respect to their individual company policies. Panel discussions will focus on the impact these initiatives have on manufacturing, quality and regulatory functions during product life cycle.

The opening plenary session will set the tone for the conference by exploring approaches on how to sell QbD within an organization. Industry speakers will present case studies on their company's methods for adopting and implementing the QbD model. Other



The PDA/FDA Gala event will take place on Tuesday, September 25, at the Historic Carnegie Library, home of the National Music Center.

plenary sessions will focus on obtaining first-cycle approval for NDAs, ANDAs and BLAs by employing the concepts in the guidance *Good Review Management Principles and Practices for PDUFA Products.* The final day will feature two unique sessions. The first will discuss global GMP compliance issues and the second will feature an all-FDA panel, which will offer insight on today's hot topics and the future direction of the Agency. Many of the other sessions will incorporate an industry and regulatory speaker followed by a panel discussion where multiple representatives from the Agency's Centers will partake in answering audience questions. Session titles include:

- Analytical Laboratory Challenges
- Rapid Method Implementation: Beyond Microbiology
- Regulatory and Quality Issues with Biologically-Derived Materials
- Biosimilars
- Change Management: Regulatory and Industry Perspectives
- Understanding Risk Management Applications
- Dedicated Facilities and Potent Compounds
- Pharmaceutical/Biotechnology Case Studies in Six Sigma Application

As you can see, this conference offers something for everyone. We hope you will join us for what promises to be the most exciting PDA/FDA meeting to date.

FDA Warns Drug Manufacturers to Guard against DEG Poisoning, continued from page 30

occurring in the supply of raw materials. Unlike food requirements, there is a requirement for drugs that raw materials be tested and suppliers be qualified, so I think the situation for drugs is much better than it could be."

FDA has increased its own vigilance in the wake of the Panama DEG poisonings. "In 2006 after the Panama incident, the Agency put into place an import alert to require all glycerin received from a supplier other than the country of the manufacturer—so all transshipped glycerin—to be sampled and tested to confirm the absence of DEG," Autor said. "So we have done a lot in this country to try and prevent this issue." In 2001, FDA placed a similar import alert on all imports of glycerin shipped from China.

"But ultimately," Famulare emphasized, "it is the manufacturer's responsibility to ensure the ingredients used are pure, safe, effective for their intended use. The DEG guidance is really reinforcing that, because the manufacturer is really the first line of detection. The Panamanian issue just highlighted this."



Conference Exhibition Sept. 24-26 Sept. 24-25

Training Course Sept. 27-28

PDA/FDA Joint Regulatory Conference

Evolution of the Global Regulatory Environment: A Practical Approach to Change **WASHINGTON, D.C.**

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PDA Presents Technology Transfer Today

Basel, Switzerland · September 12-13, 2007 Jim Lyda, PDA

Mark your calendar for the first PDA conference dedicated to Technology Transfer (TT) since 2002! This meeting will offer a forum for discussing today's best practices when moving products between manufacturing sites within a company and to and from third-party manufacturers. The conference will also present strategies for coping with the introduction of new technology and other issues we confront while operating in a rapidly changing world of buyout, consolidation and strategic product changes.

Speakers will include:

- **Siegfried Schmitt,** PhD, GE Healthcare
- Hans Groeger, PhD, F. Hoffmann-LaRoche

- Jan Gustafsson, Novo Nordisk
- Peter Mayer, Vetter Pharma
- Claudia Nardini, Kedrion
- Peter D. Smith, PAREXEL Consulting (former FDA inspector) And more to come...

Topics will include:

- Overview of TT Today
- Regulatory Perspective–What is required? What is not?
- Planning and Organization
- Outsourcing Strategies
- Registration–Planning for complexity
- Drug Substance Transfer (case study)
- Drug Product Transfer (case study)
- Managing New Technology

• Inspection and Compliance Concerns

Note on Format: This conference will start at 1:00 p.m. on Wednesday, September 12, and conclude the following day, Thursday, September 13, at 12:00 p.m. This two half-day format will allow for easy travel to Basel on the morning of the first day and easy departure the following afternoon.

We look forward to seeing you in Basel!

For more information go to www.pda.org/europe.

PDA/R³Nordic Conference: Modern Aseptic Production

Södertälje (Stockholm), Sweden · November 7-8, 2007 Volker Eck, PhD, PDA

R³Nordic and PDA will host a conference on modern aseptic production issues at the end of this year. The meeting will be held November 7-8, 2007, at the Swedish AstraZeneca site of Södertälje—close to Stockholm.

The conference includes a visit to the Nexium plant in Södertälje, one of the most modern blow-fill-seal production facilities. A complete program agenda will be published soon and posted on the R³Nordic and PDA websites (www. r3nordic.com and www.pda.org).

In addition to the conference, an exhibition will offer participants the opportunity to interact directly with providers of the latest technologies. For all inquiries, please contact PDA's **Volker Eck** at eck@pda.org.

Confirmed conference contributors:

Johann Kurz, PhD, Austrian Ministry of Health

Tor Gråberg, Swedish Ministry of Health

Kurt Nordén, Biovitrum, Stockholm, Sweden



Other contributors will include a researcher from the Royal Institute of Technology (KTH) School of Biotechnology in Stockholm, representatives from AstraZeneca and Novo Nordisk Engineering, and other pioneers in modern aseptic production solutions.

> Program Planning Committee: (I-r) Bengt Ljungqvist, PhD; Berit Reinmüller, PhD; Volker Eck, PhD; and Stefan Köhler, Co-Chair (not pictured, Johann Kurz, PhD, Co-Chair)

Co-Sponsored Conference Series on Quality Systems



Join regulatory representatives and industry experts at the PDA/FDA Co-Sponsored Conference Series on Quality Systems to learn how your company can manage change more effectively and instill a continuous improvement philosophy. Industry case studies for modern quality systems will include:

- Developing a Pharmaceutical Quality System
- The Lifecycle Approach
- Key Enablers of the Pharmaceutical Quality System

Additional topics of discussion will include:

HD

- Management Responsibilities
- Change Management
- Corrective Action/Preventive Action
- Process and Product Quality Management

www.pda.org/qualsys

November 1-2, 2007 Bethesda, Maryland



December 10-11, 2007 Dublin, Ireland



April 21-22, 2008 Beijing, China April 24-25, 2008 Shanghai, China



Faces and Places: Annual Meeting Sessions Draw Record Crowd





Anurag Rathore, PhD, Amgen, and Stephen Tyler, Abbott Industries, present Process Analytical Technology case studies



(L-R) PDA Chairman Vincent Anicetti, Genentech, and PDA President Bob Myers join attendees at the Opening Plenary Session



Dan Denney, Jr., PhD, Genitope Corporation, presents the meeting's keynote address on personalized medicine



Annual Meeting Program Chair Michael Eakins, PhD, welcomes attendees and introduces the keynote speaker



(L-R) Stefan Sundström and Stefan Köhler, AstraZeneca Engineering and Support, delivered their presentation "Airborne Particles within Aseptic Processing"



(L-R) Harold Baseman, ValSource; Mark Roache, Bayer Healthcare and Miguel Montalvo, Expert Validation Consulting, pose after the Process Validation Workshop



2nd Annual Student Symposium: (I-r) Stuart Cantor, U. of Maryland; Salil Desai, U. of Iowa; Laura Thoma, PDA Board; Janja Intra, U. of Iowa; Vince Anicetti, PDA Chair; William Riordan, U. of Wisconson, Madison; Lee Kirsch, PDA Journal; Henry Kwan, Consultant

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(L-R) Solomon Alade, PhD, Alcon Research, and Richard Taylor, Bayer Healthcare, participate in the session "Case Studies on Application of ICH Guidelines"



Meeting attendee asks question during Plenary Session 3



(L-R) Daniel Norwood, PhD, Boehringer Ingelheim Pharmaceuticals; Edward Smith, PhD, Wyeth Pharmaceuticals and Dana Guazzo, RxPax, present the Packaging Science Interest Group session



(L-R) 2008 Annual Meeting Program Chair Maik Jornitz, Sartorius, shakes hands with Peter Barton Hutt, Covington and Burling, following the feature presentation in Plenary Session 3



Mycoplasma Task Force Co-chair John Geigert, PhD, BioPharmaceutical Quality Solutions, speaks to a full room of members sporting the group's new t-shirts, which read "PDA Mycoplasma Task Force"



PDA Journal Editor Lee Kirsch, PhD, University of lowa, discusses the recent efforts of the National Institute for Pharmaceutical Technology and Education with attendees



(L-R) Session Moderator Rich Levy, PhD, PDA; Bruce Bird, PhD, Pfizer and Terrence Tougas, PhD, Boehringer Ingelheim Pharmaceuticals, presented updates on the Product Quality Research Institute

Faces and Places: Not Everything that Happens in Vegas... Stays in Vegas









The Annual Meeting Gala is always an attendee favorite with hundreds of participants looking forward to the event each year. This year was no exception. Here guests unwind with a night of food, games and dancing.





Here to help...a number of FDA alum attend the Annual Meeting (Front, I-r) Amy Scott-Billman, Rebecca Devine, Gail Sherman, (back row, I-r) Jim Lyda, Robert Darius, David Chesney, Paul McKim, Kirsten Vadheim



The showgirls stole the show at PDA's Las Vegas meeting

PDA authors sign their books

Sue Schniepp, (left) Understanding the United States Pharmacopeia and National Formulary Demystifying the Standard Setting Process

Ted Meltzer, PhD, (right) *Pharmaceutical Filtration: The Management of Organism Removal*



Michael Miller, PhD, (right) Encyclopedia of Rapid Microbiological Methods

Steven Kuwahara, PhD, (left) *Chinese Drug GMP: An Unofficial Translation Including Related Sections of the Taiwanese, U.S., and ICH-API GMP*

Faces and Places: Annual Meeting Exhibits Show Off Latest Products, Services and Technologies































Introducing New Education Advisory Committee

Gail Sherman, PDA

I am pleased to report that the new TRI Education Advisory Committee has been named. We are very excited to have a committee of this caliber to work with TRI to ensure the continued success of PDA's educational programs. The committee will have the following responsibilities:

- 1. Advise TRI on the design, development and implementation of a full training curriculum for the industry, academia and regulatory health authorities in both hands-on laboratory training and lecture series in the PDA areas of core competency—sterile processing, biotechnology and microbiology.
- 2. Develop for TRI use courses related to the hot topics and new technologies in today's industry and forward.
- 3. Align with PDA's Interest Groups, committees, advisory boards and chapters worldwide to ensure a common understanding of education provided by PDA.
- 4. Assist in promotion of TRI educational offerings and cross promotion with other PDA programs and events.

The new committee was approved by the PDA Board of Directors in March 2007, and it had its first teleconference in May. A schedule of teleconferences and face-to-face meetings will be developed.

The committee members, who come from a broad range of experiences and functions, are:

Eddie Ballance, Eisai Vivian Bringlesmark, PAREXEL Consulting Alison Demarest, Meridian BioGroup Igor Ferlon, Probiomed, SA Jennifer Gaudet, Stryker Biotech Wendy Gould, Pfizer Sheila Magil, BioProcess Technology Consultants, Inc. Gregory Meyer, Compliance Media Garth Mussey, Ben Venue Laboratories, Inc. Anurag Rathore, Amgen Cynthia Romero-Arroyo, Ortho Biologics Mark Trotter, Sartorius Corporation Barbara van der Schalie, SAIC Elizabeth Wenske, University of Kansas Amy Scott-Bilman, GlaxoSmithKline Eric Sheinin, Consultant

If you would like to get involved in the subcommittees to work on curriculum development in PDA's areas of competency, please let me know.

Visit www.pda.org/pdaletter

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

Synergy. Strength. Leadership. Cambrex Bioproducts is Now Part of Lonza

Following the acquisition of Cambrex Bioproducts, Lonza is now your leading supplier of cutting edge rapid detection products for endotoxin, bacteria, and fungi including:

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Lonza

After evaluating 25 vendors, the European Medicines Agency (EMEA) selects TrackWise as its enterprise Quality Management System (QMS).



Claus Christiansen... Integrated Quality Management Auditor for the EMEA, gave these reasons for the selection:

- "Quick and smooth implementation."
- "Overall breadth of the TrackWise solution."
- "Ease of configuration."
- "Ability to integrate with existing software."
- "Audit trail and electronic signature."
- "Pharmaceutical industry experience."

"Manages critical quality processes and global risk analysis."



The Ultimate Quality Management Software

ABOUT THE EMEA

The European Medicines Agency coordinates the evaluation and supervision of medicinal products for its 25 European Union (EU) member states. It has implemented TrackWise to replace paper based and spreadsheet systems used by the agency to manage its quality processes. Implementation took only four months, meeting set timetables and budget goals.

ABOUT SPARTA SYSTEMS' TRACKWISE SOFTWARE Sparta Systems is the recognized global leader for enterprise quality and compliance management software. Over 200 companies and 300,000 users rely on TrackWise, including quality assurance, manufacturing, customer support and regulatory professionals. TrackWise is a complete solution with unlimited flexibility to meet the precise needs of each customer. Sparta Systems also offers full support services and best practices for implementation.



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