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PDA Letter

Volume XLIV • Issue #10

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November/December 2008

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"Nontraditional" Host Cell Changeover Presented at 3rd Annual Micro Meeting

Emily Hough, PDA

Is it possible for firms to retrofit a facility dedicated one type of cell culture process for another to save time and money and increase flexibility? If you look at what Wyeth has accomplished by pulling off a "nontraditional" host cell changeover from a mammalian cell culture process to a bacterial process. The firm indicates that the successful changeover was helped greatly by sound risk management and consultation with the U.S. FDA.

Wyeth representatives **Kristin Murray** and **Stephen Reich** presented the case study "Utilization of a Risk Management Approach to Biopharmaceutical Host Cell Changeover" at *PDA's 3rd Annual Global Conference on Pharmaceutical Microbiology,* in Chicago, Ill., October 20–22. Murray, a Senior Manager of Global Regulatory Affairs, and Reich, a Risk Management Principal with the firm, explained that pursuit of this nontraditional changeover approach was driven by Wyeth's unique supply chain demands; which required the firm to expand capacity for the bacterial fermentation process at the same time the company was discontinuing a legacy mammalian cell culture process.

According to Reich, Wyeth's senior management looked at the two processes and realized that the existing mammalian suites also had the right production scale and capacity to support the bacterial product and, as such, the dedicated facility could be used instead of rebuilt to support the bacterial process. This decision would help the company reduce the capital expense required to start up the bacterial process.

"At that time, you could probably count on maybe two or three fingers the number of firms that have been able to execute host cell or expressions changeover to commercially licensed products, and actually Wyeth was one of them at that one point," said Reich. "But still this was still a very nontraditional proposal."

The company utilized sound quality risk management practices and sought feedback from the U.S. FDA Center for Drug Evaluation and Research (CDER) on their implementation strategy. Murray emphasized how important it was for the firm to work with the Agency in developing a "problem statement" for the risk management evaluations. "I cannot stress this enough, it included a lot of work with CDER in order to get through this."

continued on page 19

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Focusing in on microbiology
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Annex 1 Implementation Strategies

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Editor's Message

Pulling Off an Industrial "Switch"

It's not often you can pull out a *Seinfeld* reference for the *PDA Letter* (in fact, it probably has never been done before). But the cover story "'Nontraditional' Host Cell Changeover Presented at 3rd Annual Micro Meeting" covering a Wyeth case study about an uncommon host cell changeover from a mammalian cell culture process to a bacterial fermentation process got me thinking about the "Switch" episode. As Wyeth reported, the changeover procedure is very rare, possibly rarer then Jerry's attempted "Roommate Swith," discussed here by Jerry and his irrepressible sidekick George Costanza:

George: "The Switch?"

Jerry: "The Switch."

George: Can't be done.

Jerry: I wonder.

George:(Pounds table.) Do you realize in the entire history of western civilization no one has successfully accomplished the Roommate Switch? In the Middle Ages, you could get locked up for even suggesting it.

—*Seinfeld,* episode 11, 1995; transcript from *Wikipedia*, "The Switch"

But unlike Jerry, whose switch didn't work out as anticipated, Wyeth successfully implemented the changeover. Thankfully, the firm consulted with FDA, not George, and relied on sound quality risk management strategies as a guide instead of half-baked coffee shop plan.

Back to the micro meeting, which was the source of information for the cover story, the PDA Letter Editorial Committee deserves credit for recommending we cover this event in the last issue of the year—a mid-year change to the schedule. Be sure to check out the second report from the meeting, "FDA Investigator Looks Outside the Box for Microbial Contamination Control," by **Emily Hough.** Keep an eye on the next few issues for more coverage from that successful conference.

The issue also includes the results of a PDA cleaning survey in the "Science & Technology Snapshot," a preview of PDA's plan of action regarding the newly released FDA guidance on process validation ("Quality & Regulatory Snapshot"), and a great interview of a TRI instructor by the Institute's very own Stephanie Ko (in "TRI • Education").

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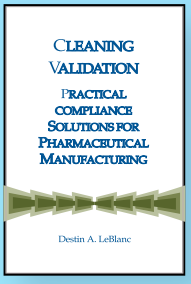
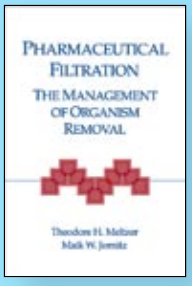


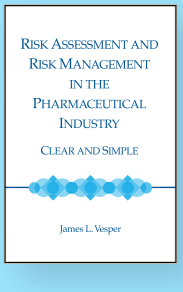
Cleaning Validation: Practical Compliance Solutions for Pharmaceutical Manufacturing
Author: Destin A. LeBlanc
Item: No. 17253
PDA Member: $265
Nonmember: $329

Filtration



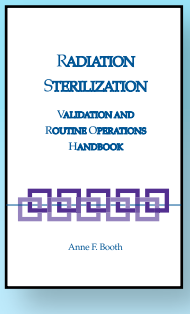
Pharmaceutical Filtration: The Management of Organism Removal
Authors: Maik W. Jornitz and Theodore H. Meltzer, PhD
Item: No.17235
PDA Member: $250
Nonmember: $309

Risk Assessment



Risk Assessment and Risk Management in the Pharmaceutical Industry: Clear and Simple
Author: James L. Vesper
Item: No.17219
PDA Member: $255
Nonmember: $319

Medical Device



Radiation Sterilization: Validation and Routine Operations Handbook
Author: Anne F. Booth
Item: No. 17277
PDA Member: $225
Nonmember: $279

Microbiology

Microbiology in Pharmaceutical Manufacturing, Second Edition, Revised and Expanded
Editor: Richard Prince, PhD
Item: No.17280
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Search Begins for PDA's Next President

John Shabushnig, PhD, PDA Chair

I want to announce that PDA President **Bob Myers** recently made the decision to retire. Bob has a long history of dedicated service to PDA, both as a volunteer and as staff leader. He will be leaving the staff in mid-2009. Please join me in wishing him well. Look for a recap of Bob's many accomplishments and a celebration of his retirement in an upcoming issue of the *PDA Letter*.

We have formed a search committee to hire our next President. The position description will be published on the PDA website in January. We will interview qualified candidates in the 1st quarter of 2009 and a decision is expected by mid-year. There is tremendous leadership talent within our Association. If you are interested in this important staff position, I would encourage you to send your resume to Tammy Giefer at tgiefer@eeihr.com.

Strategic Thinkers Needed

Maik Jornitz, PDA Chair-Elect

The Strategic Planning Committee requires your support and would like to ask for volunteers to work in specific topic task forces to analyze future requirements and formulate activity needs. Please contact **Maik Jornitz,** Strategic Planning Committee Chair, at Maik.Jornitz@Sartorius-Stedim.com to learn more about the different task force topics and/or to volunteer to work in one of the task forces. The space within these task forces is limited, therefore please take the opportunity to volunteer as soon as possible. Your contributions are highly appreciated.

2008 Election Voting is *E-xtraordinary!*

The online ballots for the 2008 Board of Directors Election has been a success! With the addition of electronic voting, participation in this year's election was twice as strong as past elections. PDA thanks all members who took the time to vote. PDA will announce the new elected Directors in the January issue of the *PDA Letter,* so stay tuned!

Science & Technology Snapshot

Sterilizing and Viral Filters Best Practices Updated with TR-26 & 41 Revisions

Kurt Brorson, PhD, U.S. FDA and Rich Levy, PhD, PDA

PDA members who work with sterilizing and viral filters will benefit from updated best practices with the 2008 revisions of PDA *Technical Report No. 26, Sterilizing Filtration of Liquids* and *Technical Report No. 41, Virus Filtration.* TR-41 already mailed with the September/October edition of the PDA Journal, and TR-26 will mail with the November/December edition.

TR-26 is intended to provide a systematic approach to selecting and validating the most appropriate filter for liquid-sterilizing filtration applications. The original TR-26, published in 1998, described the use and validation of sterilizing filtration to a generation of pharmaceutical scientists and engineers. The original technical report was developed in response to a need to document and harmonize filter validation studies, to recognize enhancements made in sterile filtration technologies and to include recent additional regulatory requirements established within the pharmaceutical industry. The document included references to regulatory documents, standards and scientific publications, all of which provided more detail and supportive data thought to be useful by the task force.

The new TR-26 Task Force of Revision was assembled in 2007 to document industry experience since 1998 with filter validation studies. Based on PDA member and industry feedback, a glossary, additional detail on filter applications and integrity testing, and a section on single use filtration systems were added. The task force was composed of European and North American industry and regulatory professionals, providing a diverse perspective, thus ensuring that the methods, terminology and practices of sterilizing filtration presented are reflective of sound science and can be utilized globally. This report underwent an 11-week global technical peer review that included feedback from the Americas, Asia-Pacific and Europe.

The publication of these two technical reports brings the total number printed in 2008 to five, with a sixth nearing completion. This is a doubling of the TRs published in the prior year.

The 2008 revision of TR-41 comes only a few years after its original publication, yet the update is significant. The new version includes viral validation protocols for both large virus retentive filters and small virus retentive filters, whereas the original addressed only the large virus filters. The document specifically addresses virus removal filters that retain viruses by a size-exclusion mechanism. It explains how they work, recommends how to elect the best filter for various applications, describes physical and biological characterization and test methods, and focuses squarely on filter validation. This document should be considered as a guide; it is not intended to establish any mandatory or implied standards. The team hopes to work with ASTM to use the report as a basis for a viral filter test standards.

In the technical report, large-pore virus filters are classified with the rating PR772-Log Reduction Factor (LRF) of six. Small-pore virus filers are classified with the rating PP7-LRF of four. To support both ratings, extensive physical and genetic characterization of both phages and an evaluation of their filtration properties were performed as part of a cooperative research and development agreement between PDA and the U.S. FDA. Both filter validation methods were tested at FDA and were found to be acceptable for testing small-scale models of filters. Viral retentive filters from four manufacturers were tested using the above methods, and the results are reported in the PDA Journal in September/October 2008.

The publication of these two technical reports brings the total number printed in 2008 to five, with a sixth nearing completion. This is a doubling of the TRs published in the prior year. PDA thanks all of the task forces, reviewers, members, and advisory board reviewers for contributing to one of our most productive TR years ever.

PDA Survey *Results*

Cleaning Validation Sampling Practices

Destin LeBlanc, Cleaning Validation Technologies

PDA conducted an online survey on the topic "Cleaning Validation Sampling Practices" during the summer of 2008. This is the third of a series of surveys the PDA has conducted on cleaning validation practices. The survey was designed by a team comprised of **Destin LeBlanc,** Consultant, Cleaning Validation Technologies; **Liz Dallison**, Principal Scientist, Analytical Control, Pfizer; **Jennifer Carlson,** Technical Manager, Corporate Quality Systems and Support, Genentech and **Paul Pluta** Editor-In-Chief, *Journal of Validation Technology* and *Journal of GXP Compliance*, Institute of Validation Technology. The results of that survey are summarized below.

It is important to note some details about the survey that impact the survey results. First, while there were a total of 92 participants, not all responded to every question. Unless otherwise specified, the percentages are based on those who responded to that specific question. Second, some of the responses in the results totaled more than 100% because more than one response was allowed per participant. Third, some questions had the option of "other," with the opportunity to write in a response. "Other" responses that were considered to be informative have been noted under the figures below. Finally, if there were no responses to a given choice, that fact is noted below the figures, but that choice is not given in the corresponding figure.

Survey Participation

Of the 82 respondents who indicated their country, 45% were from North America, 32% were from Europe and 13% were from other locations.

Participation by *department* was as follows: 47% from Validation, 18% from Quality Assurance, 11% from Technical Service, 10% from Quality Control/Analytical Support, 9% from Production/Manufacturing, 1% from Engineering, 0% from Regulatory, and 4% from "Other" departments.

68% of respondents were part of a multinational company, 13% were contract manufacturers, 10% were part of a regional company, 7% were the sole manufacturing location for their company, and 2% were "other." There were no responses from virtual companies.

A strong majority (68%) of respondents made finished drugs, followed by APIs (39%), combo products (10%), diagnostics (3%) and "other" products, including intermediates, biotech supplies and biotech raw materials (6%).

Nearly half of the facilities (45%) were commercial manufacturing facilities, 10% were clinical manufacturing facilities, 43% were both commercial and clinical products and 1% had "other" functions.

continued on next page

Journal *Preview*

Last Journal of the Year!

Walter Morris, PDA

Those considering investing in rapid sterility tests or not sure of the rapid methods' value should read the article by **Gary Gresset, Erwin Vanhaecke** and **Jeanne Moldenhauer,** a "technology/application" article appearing in the last Issue of PDA Journal Volume 62. Issue 6 is loaded with new research papers covering a wide array of topics. Notable papers include one by a group of researchers from the University of Barcelona on the uses of TOC and HPLC Analysis for cleaning validation and another by Millipore researchers on a novel challenge test for sterilizing-grade filter (serendipitously timed with the release of TR-26). As always, Issue 6 includes indexes for the year by author, keyword and contents summary.

Research

- Sonia Driss Chaieb, Jean-Claude Chaumeil, Sami Jebnoun, Naima Khrouf, Abderrazek Hedhili, and Souad Sfar, "Effect of High Calcium and Phosphate Concentrations on the Physicochemical Properties of Two Lipid Emulsions used as Total Parenteral Nutrition for Neonates"
- Kerry Roche-Lentine, Shawn Bates, and Nhung Nguyen, "Development of Serum-Free Media for the Cultivation and Recovery of Acholeplasma laidlawii used for Challenge Testing Sterilizing-Grade Filters Used in Biopharmaceutical Applications"
- Y. Madhusudan Rao, Ramesh Gannu, Y. Vamshi Vishnu, and V. Kishan, "Development of Carvedilol Transdermal Patches: Physicochemical, Ex- Vivo and Mechanical Properties Evaluation"
- Xiang-rong Zhang, Yi-fan Zhang, Jing Wang, Hai-bo Zhou, San-ming Li, and Da-fang Zhong, "Pharmacokinetics of Clarithromycin Citrate Salt after Oral Administration to Beagle Dogs and Food Effect on its Absorption"
- E. García-Montoya, M. Queralt, P. Pérez-Lozano, J.M. Suñé-Negre, M. Miñarro, and J.R. Ticó, "TOC (VCSN and VWP) and HPLC Analysis for Cleaning Validation in a Pharmaceutical Pilot Plant"
- Kamla Pathak, Shashi Kiran Mishra, and Anil K. Philip, "Passage Delaying Microbeads for Controlled Delivery of Loratadine"

Technology/Application

- Gary Gressett, Erwin Vanhaecke, and Jeanne Moldenhauer, "Why and How to Implement a Rapid Sterility Test"

PDA Survey on Cleaning Validation Sampling Practices, continued from previous page

By *manufacturing method for APIs*, 54% used biotechnology processes, 46% used organic synthesis, 10% used natural products extraction and 3% (one response) had an "Other" response, which was "egg-based" (presumably vaccine manufacture). The finished dosage forms manufactured by respondents are depicted in Figure 1.

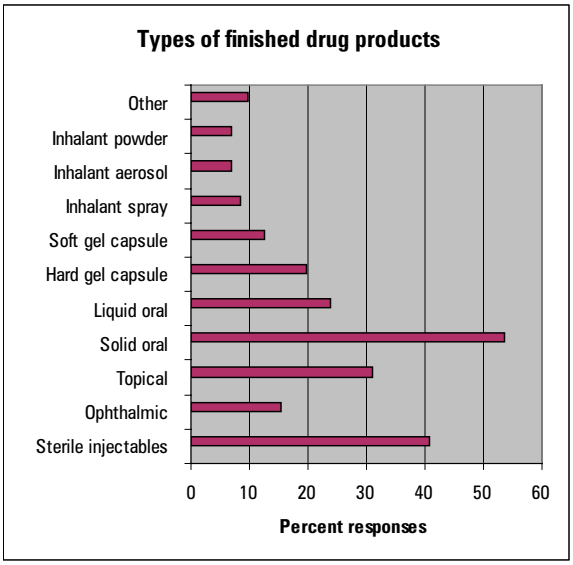
Sampling Methods for the API and for the Cleaning Agent

For measurement of *residues of the API* (regardless of the type of product), 96% used swab sampling, 76% used rinse sampling, 7% used solvent reflux sampling and 2% used placebo sampling.

For measurement of *residues of the cleaning agent* (regardless of the type of product), 67% used swab sampling, 74% used rinse sampling and 1% used placebo sampling.

Thus, for this survey, cleaning agents were sampled less frequently by swab sampling (as compared to the API).

Figure 1

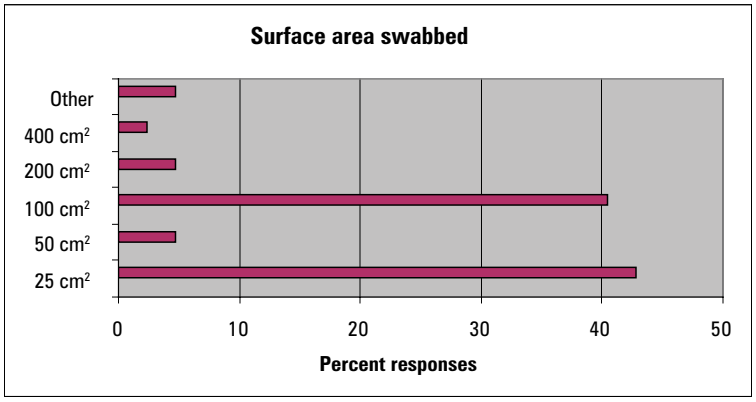


*"Other" responses included nasal spray, patches and vaginal creams.

Swab Sampling Practices for Measurement of Residues

For measurement of residues by swab sampling, the surface area values which most closely matched the surface area typically swabbed are given in Figure 2.

Figure 2



*Template vs. Eyeball method: For control of the swabbed area (regardless of the area specified), 56% trained samplers to swab an area without the use of a template (sometimes called the "eyeball" method), 40% used a template of some sort to control the specified sampling area, and 4% had "Other" responses, including no formal or specific control methods.

Figure 3

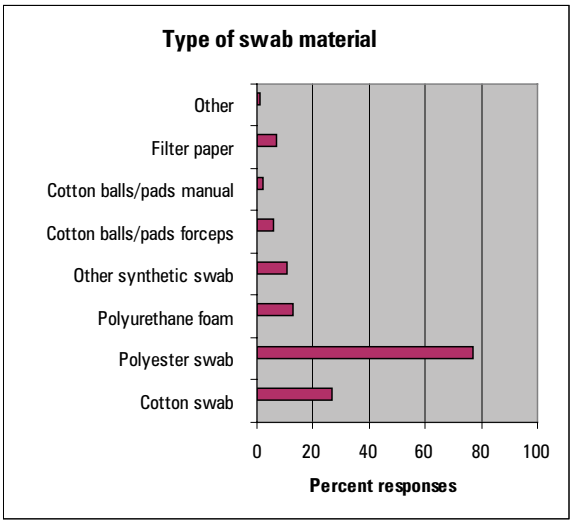
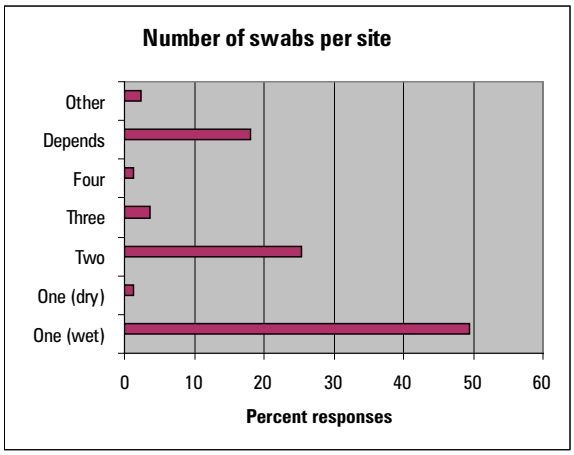
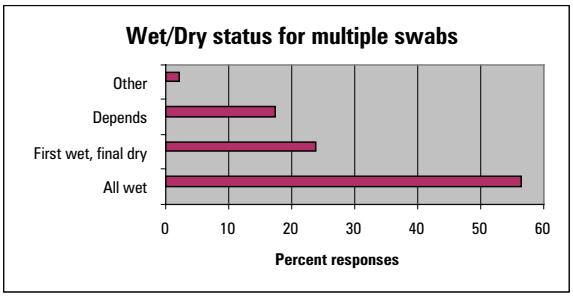


Figure 4



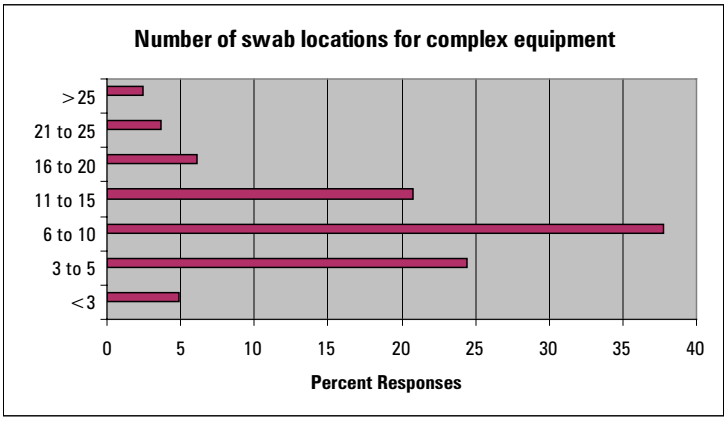
*Depends means the number used was specific to a given situation.

Figure 5



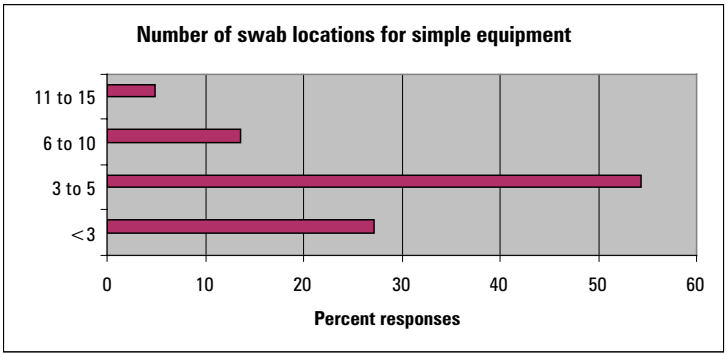
*No one responded that they were using a dry swab and then a final wet swab.
"Other" included a response that a wet swab was used first followed by a dry wiper.

Figure 6



* A range of "3 to 15" accounted for 83% of respondents (although that range was not a choice; it is a combination of the three most common responses). Note that in this survey, "complex" equipment was not defined or illustrated by an example.

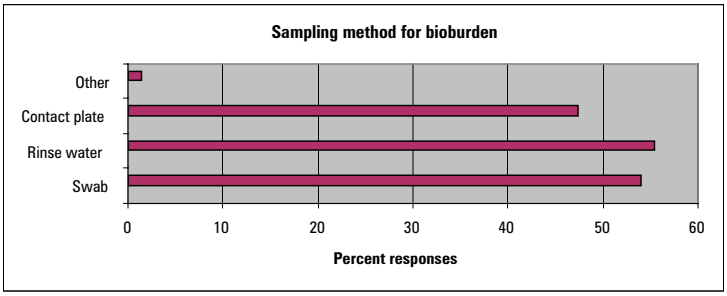
Figure 7



*A range of up to 5 locations accounted for 81% of respondents (although that range was not a choice, it is a combination of the two most common responses). No one responded that the number of swab locations was 16 to 20, 21 to 25, or >25. Note that in this survey, an example of simple equipment (a storage tank) was given.

Bioburden and Endotoxin Sampling Methods

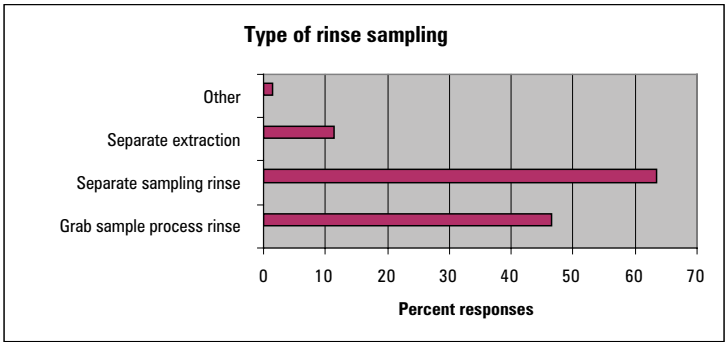
Figure 8



*The most common swab materials for bioburden were cotton (72% of respondents) and alginate (22% of respondents). 9% had "other" answers. For sampling for endotoxin, 95% of respondents used rinse sampling and 10% sampled by swabbing.

Rinse Sampling Practices

Figure 9



*"Other" included "it depends on the purpose."

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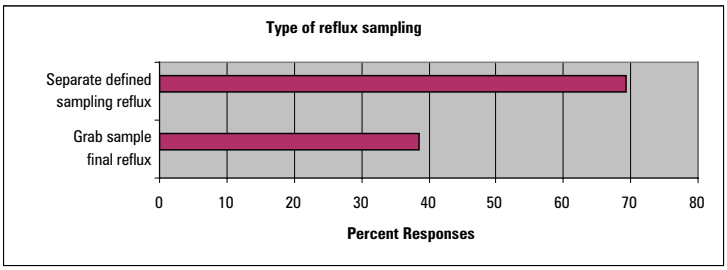
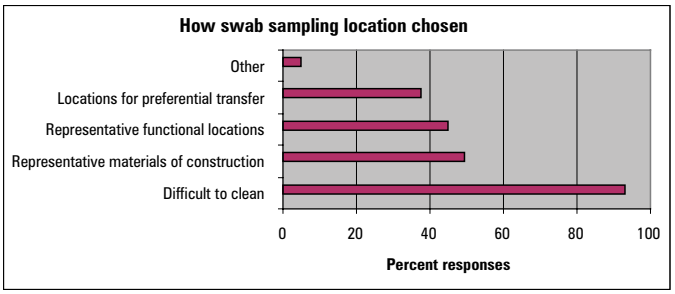
Reflux Sampling Practices

Figure 10



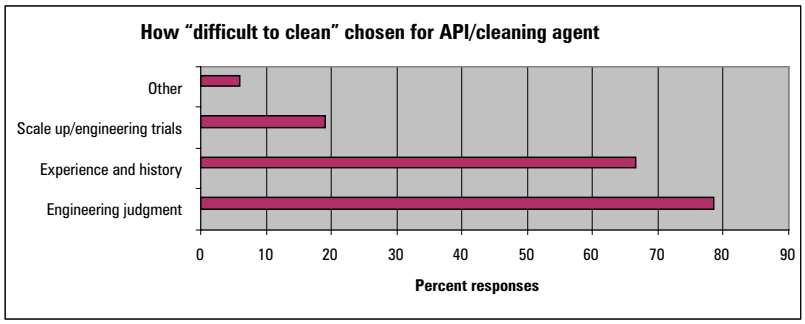
Swabbing Locations

Figure 11



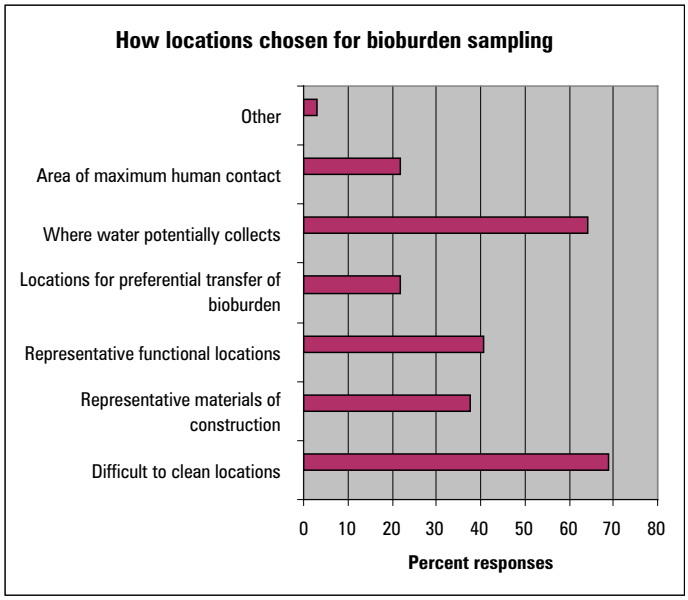
* It is clear multiple criteria are commonly used since three other answers each was given by about 35-50% of the respondents. "Other" included accessibility, risk analysis, and operator experience.

Figure 12



* "Other" included coverage tests. No one responded that they "don't select such locations."

Figure 13



* It is clear multiple criteria are commonly used since four other answers each was given by 20-40% of the respondents. "Other" included risk analysis and site SOP.

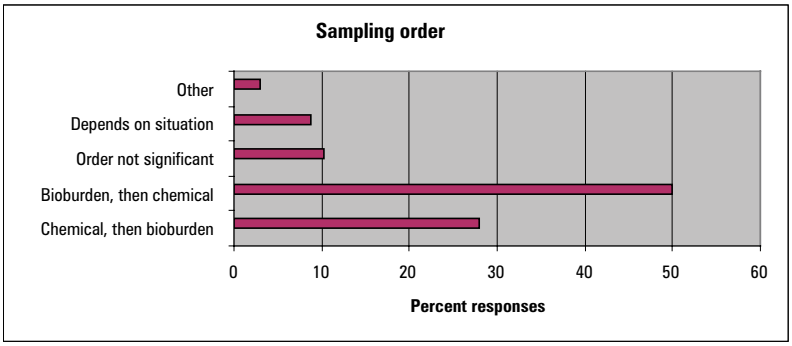
Other Sampling Issues

If the nominal swab sampling area was *not* available (for example, the specific part or location did not have 100 cm^2), 48% of the respondents had sampled that part or location and adjusted the limit accordingly, and 42% had sampled multiple equivalent parts or locations to achieve the nominal area specified. For 18% of the respondents, this situation (of not having adequate area to swab the nominal specified area) never occurred. 3% had "other" responses.

If sampling for both bioburden and a chemical species (API or cleaning agent) were to be performed, the order in which sampling was done is given in Figure 14.

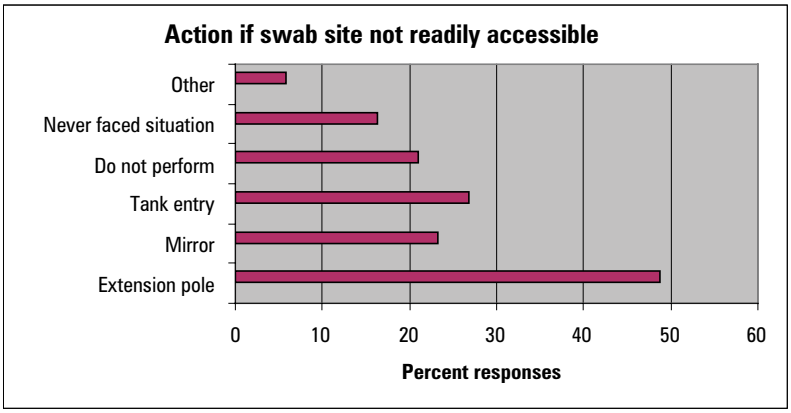
For *frequency* of requalification using a recovery study, responses are given in Figure 17.

Figure 14



* "Other" included having separate protocols for bioburden and API/cleaning agent measurements.

Figure 15



* "Other" included the use of rinse sampling.

Figure 16

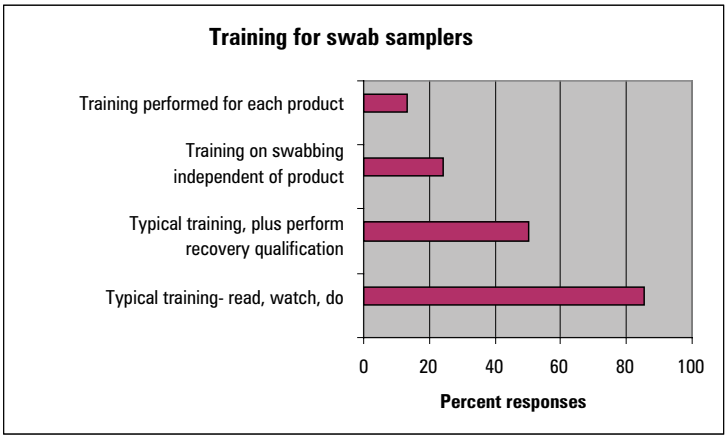
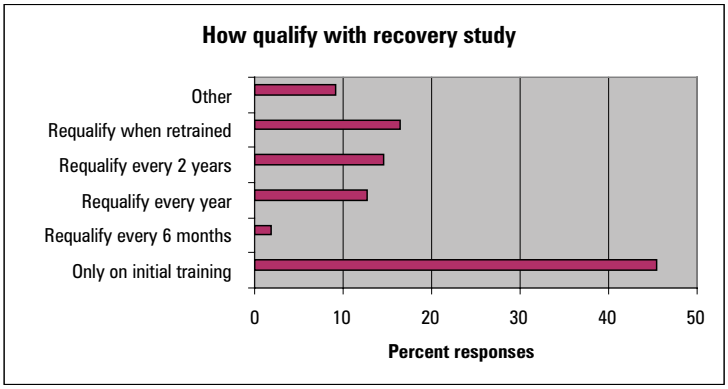


Figure 17



Considerations in Evaluating Responses

While this survey is not scientific in its selection of respondents, it does provide some basic information on current practices for sampling methods in cleaning validation for pharmaceutical manufacturing. Note that these questions were asked in the context of sampling methods *for cleaning validation*, and answers might not apply to those same sampling methods used for other purposes. Caution should be applied in using this data, since responses for different types of manufacturing situations (biotech vs. small molecule, or API manufacture vs. finished drug manufacture) may be different. However, in the selection of sampling methods, it should be recognized that no one method is ideal in all cases. The most important thing is that the sampling method is appropriate for its intended purpose. Design and use of recovery studies related to sampling methods will be covered in a separate survey.

PDA Interest Groups & Leaders

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

SECTION TITLE

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

SECTION LEADER

Frank S. Kohn, PhD *FSK Associates*	David Hussong, PhD *U.S. FDA*	Don E. Elinski *Lachman Consultants*	Sandeep Nema, PhD *Pfizer Inc.*	Robert L. Dana *PDA*

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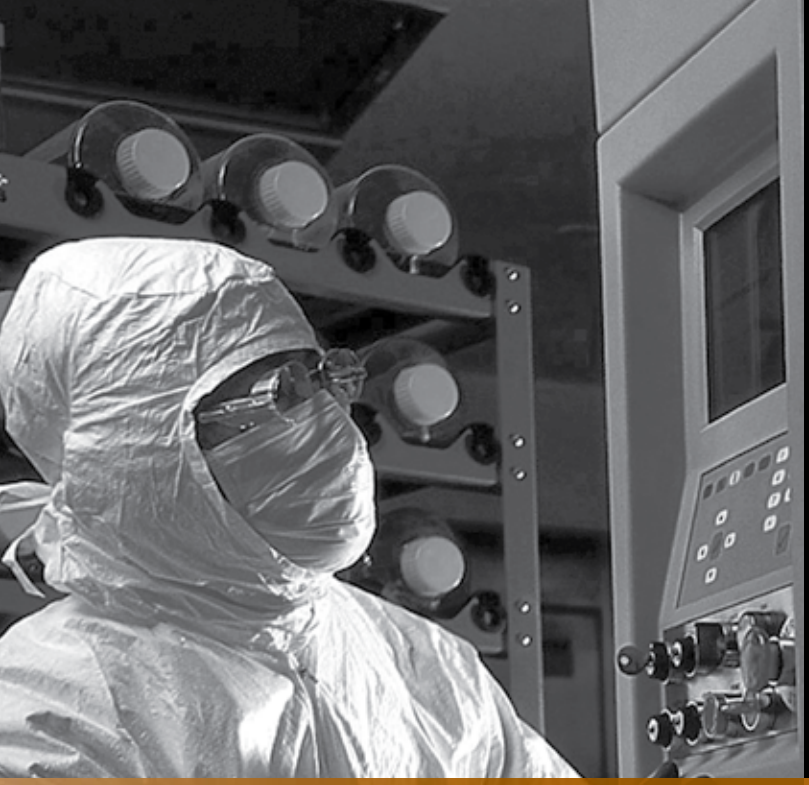

2009 PDA Annual Meeting

The Impact of the Microchip – Application of Modern Technologies in the Development, Manufacture and Testing of Bio/pharmaceutical Products

April 20-24, 2009

Las Vegas, Nevada

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Exhibition	April 20-21, 2009
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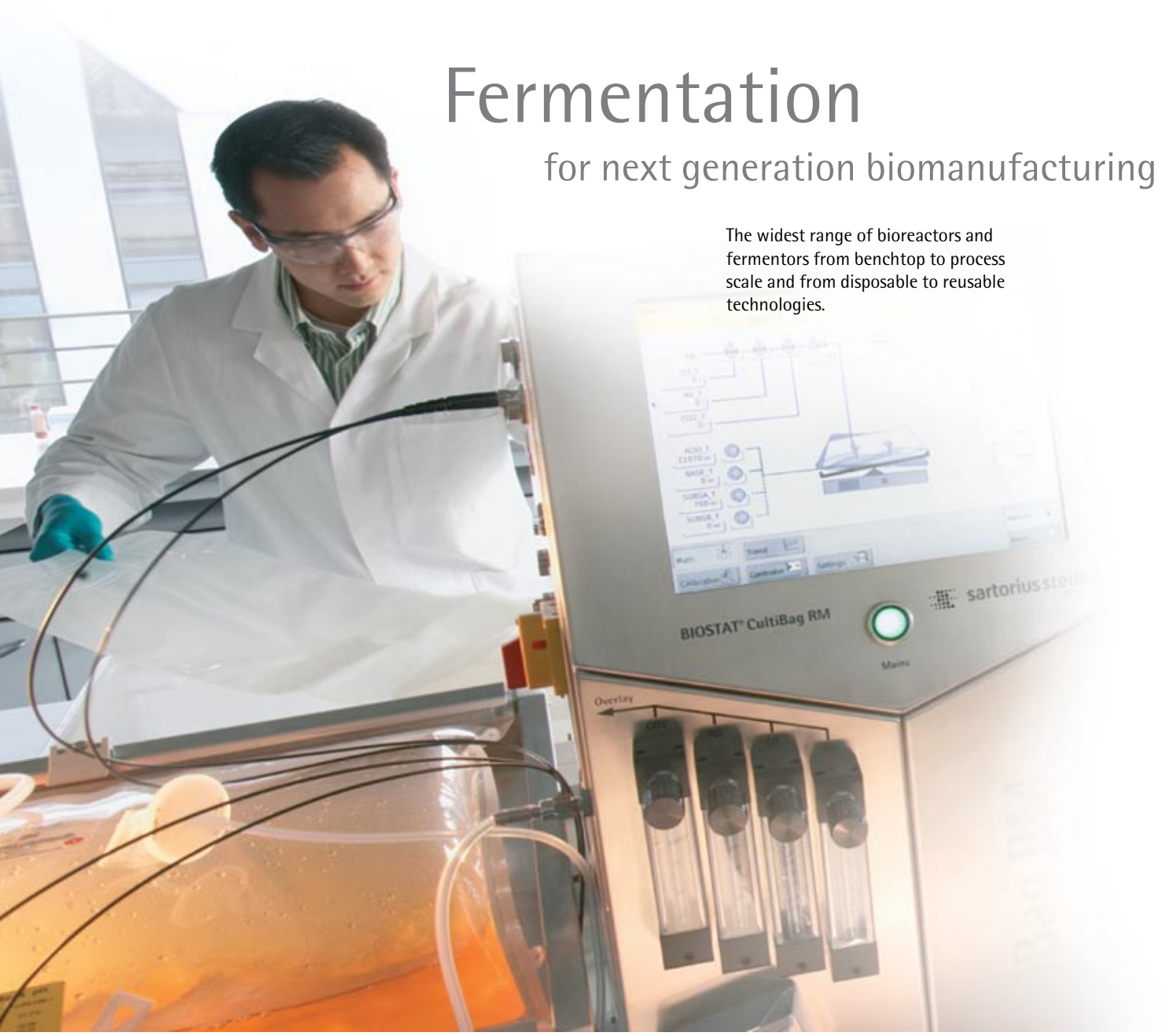

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"Nontraditional" Host Cell Changeover Presented at 3rd Annual Micro Meeting, continued from cover

The "problem statement" guided the changeover process by mapping out key considerations:

- Identifying how process components from the initial mammalian process could potentially carryover into the subsequent bacterial process.
- Ensuring that the appropriate control points were in place to mitigate those carryover risks.
- Demonstrating the effectiveness of those controls (validate process controls and additional changeover controls).

Shared Manufacturing Equipment

Reich noted that the similarities between the process was the impetus for the changeover. He said that they realized that the two systems were of the "right scale and dimensions and aspect ratio, etc., to support use after changeover for bacterial fermentation."

Reich said that the processes lined up with respect to the mechanics and equipment, so it was decided to share those systems.

He said that they did not share the inoculate material because "it is really quite easy to dedicate and dispose of—so there was no sense in trying to share that. Of course we also didn't share purification steps and purification hardware and that actually had the greatest implications and ramifications."

Reich said that to understand the "implications" and "ramifications" of the project, they organized their activities into a process flow diagram to sort out what they did and when. He said that "we identified critical points that were absolutely essential in assuring that we didn't have carryover from the mammalian process to the bacterial. So we looked essentially in three phases. Shutting down the mammalian process, including all the cleaning and decommissioning that we do, the changeover activities that we do in between products, and finally the bacterial process startup and capabilities of the bacterial process to mitigate any potential CHO process residuals that could have remained in that one."

Risk Assessment

The primary concern for the group was equipment cleaning. To develop this aspect, the team used quality risk management according to the guidance of ICH Q9. Different risk management/assessment tools were utilized. "The first was actually using the process flow diagram to help evaluate the sequence of events—to understand the exact order that we perform our steps in. We did use a Fault Tree Analysis (FTA) to identify all potential carryover pathways and associated controls. This goes back to my problem statement question, 'what could carry over and how?' A third step of the risk assessment was then using…Hazard Analysis and Critical Control Points (HACCP) to determine criticality and effectiveness of the controls we identified in the fault tree analysis. So FTA identified what could go wrong and how, and then we used a combination of FTA and HACCP to actually show the controls we had in place were being effective." ➤

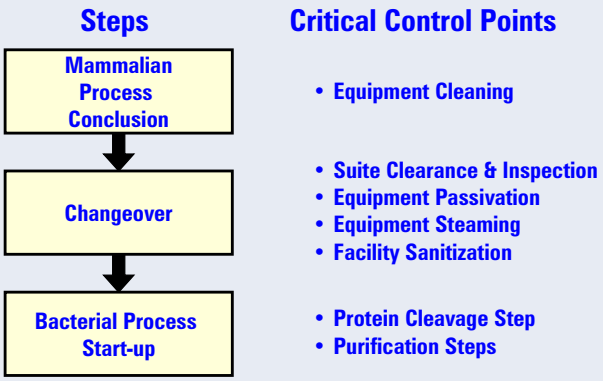
Fault Tree Analysis was one of the more effective risk assessment tools used in the carryover process. "The FTA starts with a high level fault that is rooted in your problem statement," said Reich. Wyeth's problem statement looked for ways to mitigate contaminants via carryover from the mammalian process to the bacterial.

Reich said that they utilized the FTA by deciding to map out problems in four ways, as they thought that carryover could take place one of four ways: either from environment, materials, equipment or personnel. "In typical fault tree fashion, you drill down each of these branches to get to a level where you have identified base-level faults that you've mitigated. For example, environment can turn into an analysis of looking at potential carryover from suite surfaces, the HVAC system, bio-safety cabinet systems and shared utilities and these can be drilled down even further."

Going the Extra Mile

Reich's presenter partner, Kristin Murray, said a "nontraditional" approach like this requires a firm "to go the extra mile." So Wyeth took some of their considerations off of the fault tree and fed them into HACCP. "The really nice thing about HACCP is, it is the best risk assessment tool out there to demonstrate the effectiveness of your controls. It emphasizes strength of controls rather than detection and for this changeover scenario, the bacterial process would not be capable of detecting really any of the CHO process components."

Changeover activities were organized in a PFD to serve as the basis for risk assessment



Demonstrating the effectiveness of the controls had to be done in two parts, according to Murray. "The first part is looking at process controls that we have as validated." Second, "we look at any additional changeover controls that we would need to put in place." Because the changeover process is highly nontraditional, Murray said, additional controls are needed to provide a very high level of assurance that we were not going to have mammalian process residuals carry over into a bacterial fermentation process."

Another problem was monitoring for the introduction of viruses into the bacterial process systems, which was not a concern for the mammalian process. For the latter, Wyeth conducted "extensive raw materials screening," said Murray. However, the bacteria process systems "are very different," she explained, "so if something carried over into our process we wouldn't necessarily be able to rely on downstream verification as a means of removal." To guard against the introduction of viruses in the bacterial process, the firm "needed to demonstrate an adequate level of our own activation ability as part of our decommissioning of our mammalian process and then also changeover processes that phase in between our mammalian process and our bacteria process."

Evolving Biological Facilities

Murray indicated that it is a clear strategy of Wyeth's to explore how facilities can be retrofitted for new products rather than rebuilding for every new product. Risk management and assessment tools allow the firm to devise effective mitigation methods to prevent carryover of residuals between processes.

Murray also stated her belief that cell line changeovers will become more common throughout the industry as technology continues to evolve and as contemporary supply chains require increased manufacturing flexibility.

Long-standing facility design paradigms are changing

Historical Facilities		Evolving Facilities
Intra-host cell systems (e.g. CHO to CHO) with same biosafety hazard level	⇨	Multi-host and/or biohazard levels in same facility
Dedicated Suites	⇨	Nondedicated suites where product changeovers are occurring more often and more rapidly Sharing of suites to manufacture different products concurrently in closed systems Sharing of suites between clinical and commercial manufacturing
Similarities in process capability and validation approach across processes	⇨	Process capability and validation may differ across processes

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FDA Investigator Looks Outside the Box for Microbial Contamination Control

Emily Hough, PDA

To what lengths and expense can your firm go to control contaminants? According to **Thomas Arista,** National Expert Investigator–Pharmaceutical/Biotechnology, U.S. FDA, you need to be thinking outside the box.

During his talk about the top inspection findings relating to microbial contamination, he provided a thought-provoking commentary about potential sources of contamination that often go unnoticed and uncontrolled by manufacturers. He asserted that firms cannot rely on just the regulatory requirements to establish sound microbial controls. He spoke at *PDA's 3rd Annual Global conference on Pharmaceutical Microbiology,* in Chicago, Ill., October 20-22.

Arista first addressed how microbial contamination enters a facility in the first place. "I am always interested in how we get the bad puppies inside an aseptic fill or manufacturing facility," he said. Since the industry works hard to design clean environments and controls for their facilities, he wondered why contaminants are found in them.

Specifically, Arista said, "I'm looking at environmental monitoring data, and I usually see the gram negative organisms or the gram positive organisms, especially the spore-formers." Seeing these, he said, this is "my first dot in connecting the cGMP dot" which indicates that "microorganisms are coming from the outside into your facility."

Noting that there currently are no requirements for or guidance on the monitoring of the outside environment and how the flow of personnel and materials into a facility can impact the internal environment, Arista wondered if operators and other personnel are even cognizant of the risks they can introduce by their morning routines. For example, he said, "maybe sometime in your life you had to take your dog or your cat to the vet or you had to walk the dog before you went to the office. This simple activity of walking your pet prior to going to the plant could be a source for microbial contamination. Connecting more cGMP dots."

Arista asked the audience members if they are required to wear dedicated factory attire, including shoes. He was pleased to see a number of people raise their hands. "Excellent," he said. "No rule says you have to have it. There are no requirements, again, for a factory for clothing, there is no requirements for one way personnel entry and exits out of a manufacturing area." However, he added, "I have seen more and more companies using them."

The FDA investigator next shared several examples of unique sources of contamination inside facilities.

In one case, a door used to enter an aseptic fill area was made of wood. Arista was pleased that no one in the audience, when asked, thought wood was an appropriate material for this environment. The photo he showed of the room revealed a dilapidated door with worn out laminate. The company passed filtered solutions through the doorway into the clean room, raising a number of questions: "The material has to go through that door. What's the data about that door? Where is the EM data for the door? Why is that door there?"

Arista then spoke about a case involving the use of a step stool by operators to do aseptic filtering. Operators were observed pulling the stool to the equipment, placing their hands near the underside, which did not have a cleanable surface. The investigator asked, "Why is this acceptable?"

In another case, Arista observed raw materials entering a clean room on wooden pallets. After raising the issue with the firm, they ceased the practice.

"So you see," said Arista, "it is not just the door, it's not just the step stool, but what is the thought process for something very basic, something so fundamental? And then why does it still exist? Why did FDA have to point this out to you? So you see now its something different other than a wooden door or a step stool. Where's quality?"

(l-r) Thomas Arista, FDA, Brenda Uratani, FDA, Kristin Murray, Wyeth, Stephen Reich, Wyeth, Patricia Hughes, FDA score a touchdown at the Microbiology conference. Kristin Murray and Stephen Reich are featured in the cover story.

Before delving into the top investigator observation, Arista mentioned environmental monitoring and risk management.

"Today," he said, "I've heard risk used at least a dozen times. Risk evaluation, I think, is key in determining your environmental monitoring. Some people still sample everything, and I think, good for you. You must have endless resources. The Agency will not and cannot say 'that is the wrong way to do it….Though, we would agree that a risk evaluation of all those data points is worthy of consideration to establish environmental monitoring.'"

- The step-stool is used in the clean room and it is not a smooth cleanable surface
- Personnel handling the step-stool during routine aseptic filling operations
- No bioburden data for the step-stool with an appearance of rust-like material
- Why is the step-stool with these conditions in the clean room?
- Where is the Quality Unit oversight?

- The wooden door is not a cleanable surface and it is in disrepair
- The entryway is used to transfer material into the clean room areas
- No bioburden data for the area
- Why is there the use of wooden doors?
- Where is the Quality Unit oversight?

Of interest to Arista when inspecting are:

- Where are the samples taken from?
- Who determines the sample? Is it objective or subjective?
- Why are sample locations valid?
- Where is the data?

The quality unit must also be involved in the environmental monitoring program to ensure it is objective and valid.

To demonstrate the importance of an independent check on the environmental monitoring program, Arista pointed to an inspection where he observed through a window an operator in an aseptic fill room spraying alcohol to clean a surface.

"And it wasn't a minute, within 30 seconds, here comes an agar plate. Cha-ching! Why did this event occur and is it a common practice that is unknown by quality? Connecting more cGMP dots."

Top Ten Inspection Trends

FDA investigator Thomas Arista presented the top ten recent inspection trends at PDA's recent micro meeting.

21 CFR 211.22 (d) The responsibilities and procedures applicable to the quality control unit are not [in writing] [fully followed].

21 CFR 211. 100 (b) Written production and process control procedures are not [followed in the execution of production and process control functions] [documented a the time of performance].

21 CFR 211.110(a) Control procedures are not established which [monitor the output] [validate the performance] of those manufacturing processes that may be responsible for casing variability in the characteristics of in-process material and the drug product.

21 CFR 211.160(b) Laboratory controls do not include the establishment of scientifically sound and appropriate [specifications] [standards] [sampling plans] [test procedures] designed to assure that [components] [drug product containers] [closures] [in-process materials] [labeling] [drug products] conform to appropriate standards of identity, strength, quality and purity.

21 CFR 211. 100(a) There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

21 CFR 211. 192 There is a failure to thoroughly review [any unexplained discrepancy] [the failure of a batch or any of its components to meet any of its specifications] whether or not the batch has been already distributed.

21 CFR 211.165(a) Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the [final specifications] [identity and strength of each active ingredient] prior to release.

21 CFR 211.25(a) Employees are not given training in [the particular operations they perform as part of their function] [current good manufacturing practices] [written procedures required by current good manufacturing practice regulations].

21 CFR 211.188 Batch production and control records [are not prepared for each batch of drug product produced] [do not include complete information relating to the production and control of each batch].

21 CFR 211.67(b) Written procedures are not [established] [followed] for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product.

Quality & Regulatory Snapshot

PDA Commenting on U.S. FDA Validation Draft, Workshops to Follow

Bob Dana, PDA

On November 18, the *Federal Register* contained a notice of the availability of the long-awaited draft guidance entitled, *Process Validation: Principles and Practices*. Jointly published by the Centers for biologics, drugs and veterinary medicine, the draft guidance outlines the general principles and approaches that the U.S. FDA considers to be appropriate elements of process validation for the manufacture of medicinal products, including active pharmaceutical ingredients (APIs).

Having anticipated the publication of this draft guidance for some time, we had assembled a task force who were prepared to develop PDA's comments on the draft guidance. The task force, co-chaired by **Hal Baseman,** COO, Valsource, and **Scott Bozzone,** Senior Manager, Pfizer, held their first meeting to organize the commenting process the same day the draft guidance was published. And a good thing it was that we were prepared, as the *Federal Register* notice only allowed a 60 day comment period, which is effectively significantly shorter because four U.S. holidays occur during the comment period—Thanksgiving, Christmas, New Year's Day and Martin Luther King Day. Comments are due to FDA on January 20, 2009.

The task force has identified subject matter experts who have specifically been asked to provide their input to the task force. In addition, the document has been made available to the general membership to provide comments through the PDA online commenting tool; go to https://store.pda.org/review/login.aspx or send an email to **Iris Rice** at rice@pda.org. Note that all comments must be received by December 10, 2009 to ensure consideration by the task force. The final PDA comments will be published in the February 2009 issue of the *PDA Letter* and will also be available on the website. This approach is new and part of our strategy for expanding the opportunity for our members to contribute to the comment process.

To ensure all our members are aware of the new draft guidance and its impact, we are currently in the process of developing a series of one-day public workshops to focus on the guidance. Plans, which are tentative at the time of this writing, are for these workshops to take place throughout the first half of 2009 in the following five locations:

Puerto Rico (February 18, 19 or 20)

San Francisco (March 3, 4 or 5)

Las Vegas in conjunction with the PDA 2009 Annual Meeting (April 23)

New Brunswick (May)

Chicago (June)

The Workshops will probably focus on changes in the content of the draft guidance, PDA's comments and implementation-related case studies. We are hoping to be able to have FDA participation in these workshops. Watch your mail and email for further information as it becomes available.

To further support our member needs, our Training and Research Institute will most likely offer training courses focused on validation strategies and applications associated with some of these workshops. Once again, stay tuned and watch your mail.

Don't miss the opportunity to be part of this new PDA initiative in 2009. If you would like to participate as a presenter in any of the workshops, or have ideas for a new training course, don't hesitate to contact us. You can contact me directly at dana@pda.org, or for training ideas or questions, contact **Gail Sherman,** our Vice President, Education at sherman@pda.org.

So, with this new development, we ring down the curtain on 2008. I'd like to take this opportunity to wish all of our members the very best for a wonderful Holiday season and the very best for the New Year.

Health Authority Report: Chinese Pharmaceutical Industry Evolution

Neil Wilkinson, David Begg Associates

[Author's Note: This article captures the presentation I delivered on behalf of **Tang Minhao,** Deputy Director of the Shanghai Municipal Food and Drug Administration at the *2008 PDA/FDA Pharmaceutical Ingredient Supply Chain Conference* in Washington, September 10–12. The presentation was originally given by Mr. Minhao for the State Food and Drug Agency (SFDA) at the PDA/FDA Quality Systems workshop in Shanghai, April 24–25, 2008. There it was agreed that I would present Mr. Minhao's talk on his behalf. These short notes represent my interpretation of the key messages given in the presentation, which is available at the "members only" section of www.pda.org.**]**

History has shown that harmful drug incidents occurred as the pharmaceutical industry grew in countries that now have a mature industry and regulatory systems. This includes the United States, European Union and other countries, where safety issues involving Thalidomide, the Devonport Incident (United Kingdom), Penn Pharmaceuticals recalls (Australia) have occurred. The lessons from these issues and the resulting legislation, guidances, enforcement programs and education has led to the maturity seen in the pharmaceutical industry and regulatory systems in these markets today. To put this into some context–this maturity has taken around 100 years of evolution in these markets!

China has only opened its borders around 25 years ago, its first drug law was not introduced until 1984 and GMP was introduced only in 1988–20 years ago. It is against this context that we see some of the current issues in the Chinese marketplace. Two other factors to consider are the level of average per capital GDP and changes in the structure of medical consumption of the people.

The Chinese pharmaceutical industry has been growing at a very fast rate over the last few years. Between 1998 and 2007, in the pharmaceutical sector:

- Output has grown from 137 to 668 billion Yuan
- Exports have grown from 3.4 to 24.6 billion USD
- Imports have grown from 1.5 to 14.0 billion USD

But against this incredible growth rate, many Chinese pharmaceutical companies are still mainly focused on cost. The cultural understanding and implementation of GMPs is still a "work in progress."

In line with the historical development of the pharmaceutical industry in other markets, there have also been local problems in China, involving:

- Qiqihar fake drug
- Anhui Huayuan xinfu injection
- Guandong Baiyi
- Shanghai Hualiang Methotrexate

…as well as others

Of course, there is also the Heparin incident which is still under investigation. It should be noted here that the onus is on the pharmaceutical manufacturer to assure the quality of its suppliers and the supply chain; the SFDA does not cover chemical industry materials for export. **[Author's Note:** In the European Union system, the onus is put on the drug product manufacturer to assure the quality of starting materials.**]**

As the pharmaceutical industry matured in other regions, the degree of economic maturity matched the degree of pharmaceutical supervision by the regulators. Similarly, China has been extending its regulatory processes for drug supervision and continues to move forward and catch up with other regions. Recent examples of this are:

- 1984 drug regulation/revised in 2001, includes GLP/GCP/GMP and GSP (Good Supply Practice) ➤

- 1988 GMP code, revised in 1992, 1998 and being updated to match global standards
- Many operations were closed after expiration of the "time limit" to meet GMP standards

The SFDA was formed in 2003 (from 1998 it was solely drugs). China is a large country, and the SFDA is a diverse organization with 31 provincial, 339 prefectural and 2321 county level constituent groups. At all levels there are drug control laboratories, including mobile testing trucks. The Chinese Pharmacopoeia has 15,000 drug standards and 686 medical device standards. The Shanghai FDA is a key part of the agency. SFDA is engaged in significant international collaboration and has various agreements/MOUs in place with the United States, European Union and others.

Regulatory systems at SFDA include:

- Registration of drug products and facilities
- Biologics release
- Packaging and labeling review
- Certification of pharmacists
- GMP and GSP certifications

Regulatory systems are continuing to evolve and develop, including:

- More focus on higher risk products
- Annual supervisions of blood products/vaccines
- Higher levels of inspections for parenteral products
- API certification system
- Evolving focus on GMPs /QbD

Another area that is also still evolving is that of "social responsibility of pharmaceutical enterprises." A "pharmaceutical culture" still needs to be evolved and matured for companies involved in pharmaceuticals in China. A business culture focused on cost is still prevalent. This needs to be changed to develop a culture that recognizes the specialty of pharmaceutical products and their uses/safety needs for the patient (e.g., medicines are higher risk than clothing/garments manufacture and supply). While obvious to a mature pharmaceutical region, this thinking needs to be embedded yet in China—China needs to learn from other countries and develop this basic fact.

In China, pharmaceutical enterprises need to bear these social responsibilities and provide *quality products* as their most important aim. As China moves forward and its pharmaceutical industry matures, SFDA understands that this is a work in progress, but are supportive of the need to make improvements/changes to the Industry and regulatory systems and develop the technical capability of the industry.

I would like to thank Tang Minhao for an interesting and stimulating presentation and providing me with the opportunity to deliver it on his behalf. I hope I did it justice.

[Editor's Note: PDA is working with the Shanghai FDA to provide training and other resources to regulators and industry in the Shanghai region. For more information on this program and the Quality Systems workshop held in Shanghai, see the October *PDA Letter,* pp. 8–9.**]**

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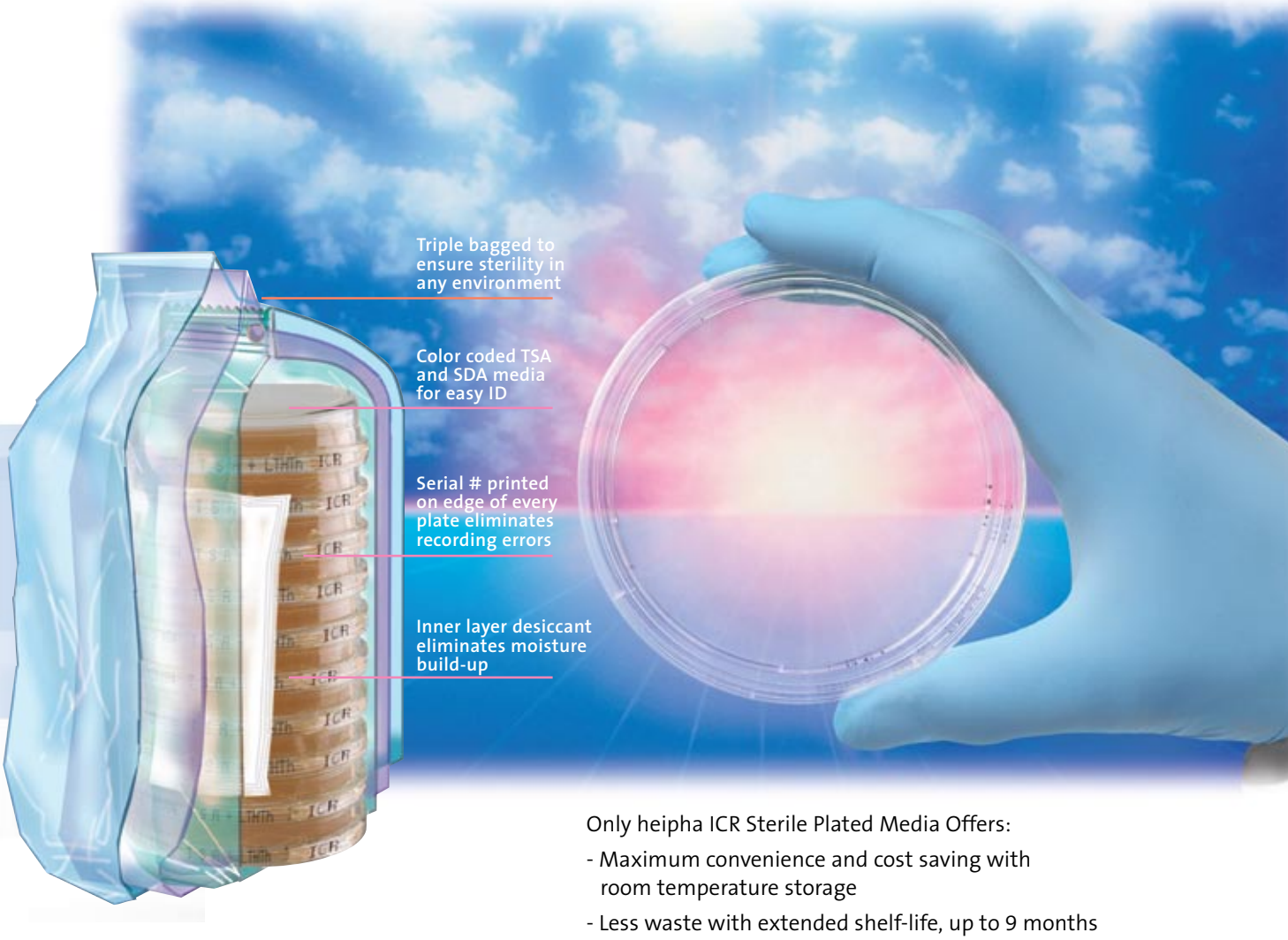

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Regulatory Briefs

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

International Harmonization

ICH Q4B Annexes Available for Comment

The U.S. FDA has published for comment four new annexes to the ICH Q4B on pharmacopeial harmonization:

Annex 4A: Microbiological Examination of Non-Sterile Products: Microbial Enumeration

Annex 4B: Microbiological Examination of Non-Sterile Products: Tests for Specified Microorganisms

Annex 4C: Microbiological Examination of Non-Sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use

Annex 5: Disintegration Test

Comments are requested and must be submitted by October 6, 2009 to be considered in the development of the final guidances.

Transatlantic Regulators Commit to Shared Cooperation

The European Commission, the EMEA and the U.S. FDA have acknowledged their commitment to regulatory cooperation and to intensifying their interactions in several new areas.

Meeting in London on September 30 and October 1, 2008, for the annual review of cooperative activities undertaken under the scope of their confidentiality arrangements, the European Union and United States authorities agreed to expand cooperation in the areas of advanced-therapy medicines and nanotechnology-derived medicinal products, as well as on the exchange of pharmacovigilance information. Having been in place for five years, both sides concur that the transatlantic cooperation activities continue to be successful in protecting and promoting global human and animal health, reducing the regulatory burden and costs so that innovative medicines can be brought to patients in a timely manner, while also allowing critical safety information about medicines to be shared between the United States and European Union regulatory authorities.

North America

Correction to Final Rule on GMPs for Finished Pharmaceuticals Published

The U.S. FDA published a notice of a correction to the Final Rule amending the GMPs for Finished Pharmaceuticals.

The original Final Rule was published with an error in the "Analysis of Impacts" section, which is corrected in this version. The correction does not materially affect the content or intent of the regulations.

Comments Requested on the Electronic Collection of Adverse Events

There is an opportunity to comment on a collection of information related to the use of MedWatchPlus Portal and Rational Questionnaire to collect electronically all adverse event, consumer complaint/product problem and medication use error data submitted to the U.S. FDA.

The comment request relates to whether the proposed collection of information is necessary, the accuracy of FDA's estimate of the burden associated with the data collection, ways to enhance the quality and utility of the information and ways to minimize the burden on respondents.

Comments are due by December 22, 2008.

U.S. FDA Draft Guidance on Electronically Creating and Submitting Product Labeling Files Available

The U.S. FDA has submitted a draft guidance on proposed collection of information. Entitled, *Draft Guidance for Industry on Providing Regulatory Submissions in Electronic Format—Drug Establishment Registration and Drug Listing: Availability: Registration of Producers at Drugs an Listing of Drugs in Commercial Distribution*; the draft guidance describes how to electronically create and submit structured product labeling files for establishment registration and drug listing information.

Available Draft Guidance from U.S. FDA on Potency Tests for Cellular and Gene Therapy Products Publicized

The U.S. FDA has announced the availability of a draft guidance for industry entitled, *Potency Tests for Cellular and Gene Therapy Products*. The draft guidance provides manufacturers of cellular and gene therapy products with recommendations for developing tests to measure potency. These recommendations are intended to clarify the potency information needed to support an IND or BLA.

Comments on the draft guidance are due by January 7, 2009.

US FDA Concept Paper to Aid Pharma Companies Enroll in Pilot Program

The US FDA has announced the availability of a concept paper entitled, *PDUFA Pilot Project Proprietary Name Review.* The concept paper provides information for pharmaceutical companies about how to evaluate proposed proprietary names and submit the data from those evaluations to the Agency for review under an anticipated pilot program. FDA plans to enroll participating firms in the pilot program in FY2009.

Comments on the pilot program may be submitted at any time.

QbD Pilot Program for Biotech Seeks Similar Answers as one for Small Molecules

Walter Morris and Emily Hough, PDA

Currently the U.S. FDA is looking for companies to participate in a Quality by Design (QbD) pilot program for biotechnology submissions. This program is intended to explore the use of expanded change protocol to describe specific tests, studies and acceptance criteria that demonstrate certain manufacturing changes will not have adverse effects. The Office of Biotechnology Products within CDER, is accepting the biotechnology submissions.

The biotech pilot follows on the recently concluded QbD pilot for small molecule drugs, which was conducted by the Office of New Drug Quality Assistance (ONDQA) from July 2005 to March 2007. FDA limited participation to 12 NDAs and/or supplements and received nine original NDAs and two supplements. As of July 31, 2008, eight submissions had been approved and three remained under review.

Two important, new concepts were fleshed out during the QbD pilot for small molecule products: the CMC Regulatory Agreement and the Comprehensive Quality Overall Summary (CQOS).

The CMC Regulatory Agreement was a paradigm-changing concept that grew out of the QbD/GMP for the 21st Century programs. It has been touted as an arrangement that would "bind CMC elements (for example, critical process parameters or critical quality attributes) and would define the boundaries of a design space within which manufacturers could implement changes with limited or no filing of manufacturing supplements."[1]

The concept has evolved from being called a "regulatory agreement" to a "Chemistry, Manufacturing and Controls Postapproval Management Plan" (CMC-PMP). A second, general guidance on post-approval changes is also in the works, but not specifically related to the QbD pilot program.

At the *2008 PDA/FDA Joint Regulatory Conference* in September, CDER Director **Helen Winkle** commented on the development of the CMC-PMP guidance. She noted the name change from regulatory agreement to CMC-PMP was done to placate legal concerns. "It won't be called a regulatory agreement," she said, because "that makes our lawyers nervous."

The CMC-PMP will be central to the QbD program, Winkle indicated, and once completed, will "allow those ➤

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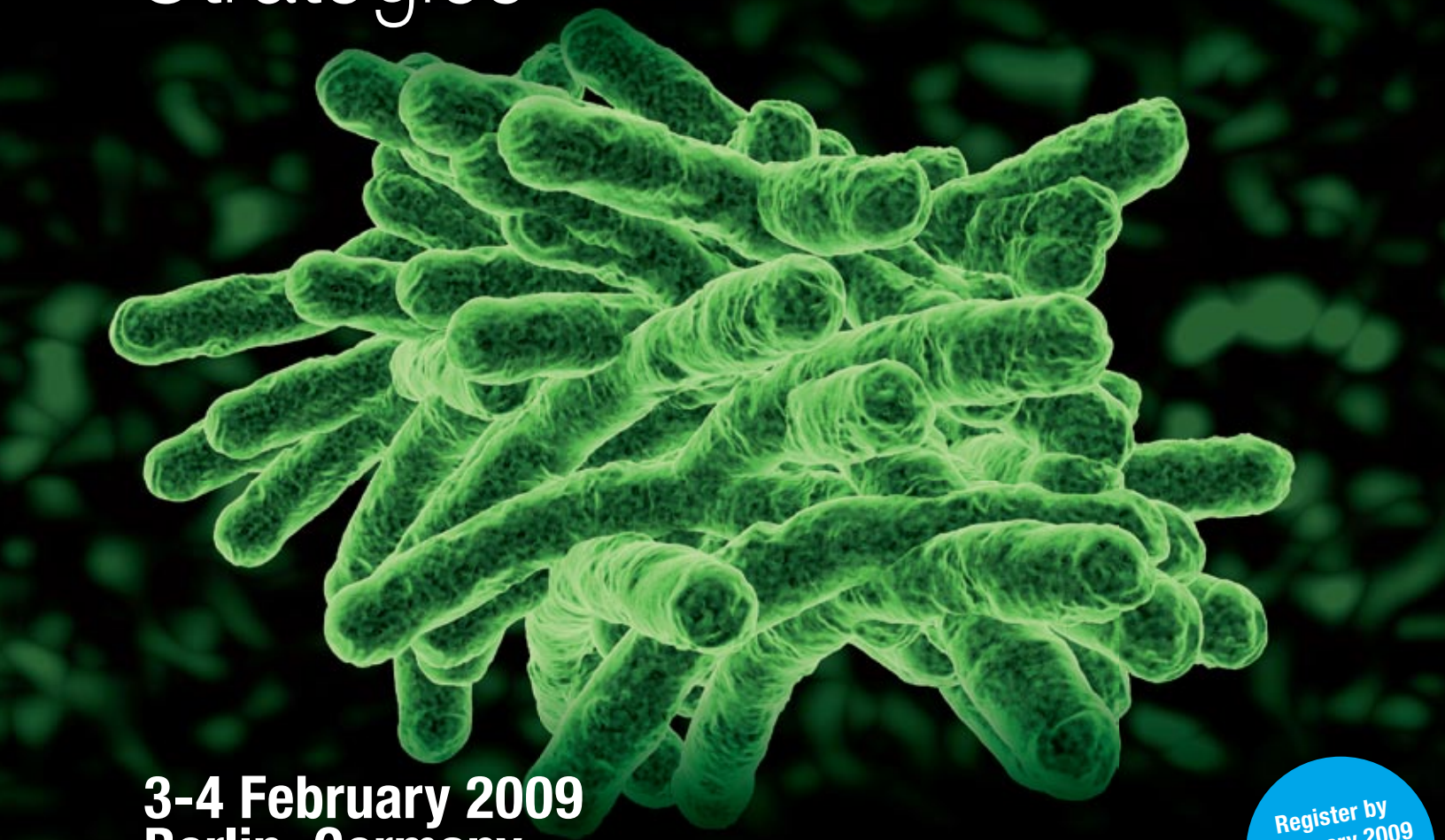

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- strategies to get such methods smoothly approved
- strategies to overcome the Variations hurdle
- the economics of Rapid Microbiology Methods
- dealing with deviations

type of submissions at any time, either premarket or post-market." It will formalize the "design space type of approach to manufacturing changes." Writing the guidance has been "difficult," she added. Right now, the Agency is "working on how to word it and on how to make that guidance work."

In a follow-up e-mail exchange with the *PDA Letter,* ONDQA Acting Deputy Director **Christine Moore**, PhD, explained that, during the ONDQA pilot, FDA "recognized the need for a customized framework to implement post-approval CMC changes in a QbD paradigm. Our vision is that the CMC-PMP will include a summary of the process and control strategy, a discussion of risk management approaches, and a plan for reporting different types of changes."

Important Goals of FDA's 21st Century GMP Initiative

- The most up-to-date concepts of risk management and quality systems approaches were incorporated into the manufacture of pharmaceuticals while maintaining product quality.
- Manufacturers were encouraged to use the latest scientific advances in pharmaceutical manufacturing and technology.
- The Agency's submission review and inspection programs operated in a coordinated and synergistic manner.
- Regulations and manufacturing standards were applied consistently by the Agency and the manufacturer.
- Management of the Agency's Risk-Based Approach encouraged innovation in the pharmaceutical manufacturing sector.
- Agency resources were used effectively and efficiently to address the most significant health risks.

Regarding the general guidance on post-approval changes, Winkle told the PDA/FDA conference that the document will "push on quality risk management and quality systems, and back away of from micromanagement, in my opinion, by the FDA of all sorts of changes."

In the follow-up correspondence, Moore said that the general post-approval changes guidance would expand the types of changes that could be reported in an Annual Report instead of through supplement, particularly those that are mostly administrative in nature. Examples include certain changes in laboratory testing sites, addition of in-process test specifications, replacement or addition of equipment that is the same design. According to Moore, the guidance is not specific to QbD type submissions and will be applicable to existing products.

Information gleaned through ONDQA's QBD pilot program on the CQOS was also valuable.

CQOS is also another important element of QbD. It has been defined as:

A comprehensive summary/account of information, knowledge, and understanding of the drug substance/product, from its early development to commercialization, emphasizing what is critical for a robust, reproducible process and consistent, reliable product quality. This would guide an applicant in gathering, organizing, and presenting systematically expected CMC information essential to regulatory action. Another benefit would be to facilitate a more relevant and focused scientific dialogue between reviewer and applicant.[2]

ONDQA's Moore said in her correspondence with the *PDA Letter* that FDA saw "highly varied approaches to the CQOS in the QbD pilot program. Because of their varied nature, the reviewers had mixed opinions on the value of the CQOS." She also noted that at this time the International Conference on Harmonisation is not actively pursuing expanding the concept of the CQOS, though it might be revisited at a later date.

All in all, ONDQA believes that the experience gained in the CMC pilot program was very valuable in helping shape pharmaceutical quality assessment system, and has provided valuable experience for industry as well.

FDA is hoping for more of the same with the CMC-QbD pilot program for biotechnology products. Submissions will include BLAs, NDAs or supplements reviewed by the FDA's Office of Biotechnology Products (OBP), and should demonstrate an applicant's increased knowledge of product attributes—linking the attributes to process parameters in an expanded change protocol. Comments on this pilot program can be submitted to FDA until December 31st**.**

[Editor's Note: For more information on the QbD pilot program consult the September/October 2008 issue of *International Pharmaceutical Quality* (www.ipqpubs.com).**]**

References

1. Koroneos, George. "FDA Proposes New CMC "Regulatory Agreement." Oct 13, 2005. http://pharmtech.findpharma.com/pharmtech/News/FDA-Proposes-New-CMC-Regulatory-Agreement/ArticleStandard/Article/detail/186954 (accessed September 2008).

2. Poochikian, Guirag, QOS: FDA Perspective," Proceedings of the AAPS/FDA/ISPE Workshop, North Bethesda, MD, October 5–7, 2005.

PDA Comments on FDA Parametric Release Guide and EU GMP Guidelines

For the comments grid, visit www.pda.org/regulatorycomments.

October 3, 2008

Division of Docket Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Reference: Draft Guidance for Industry on Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes; Federal Dockets Management System Docket FDA-2008-D-0391

Dear Sir/Madam,

PDA is pleased to offer comments on the FDA Draft "Guidance for Industry on Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes". PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by a committee of experts with experience in parametric release of terminally sterilized moist heat drug products including members representing our Regulatory Affairs and Quality Committee and our Science Advisory Board. PDA appreciates the opportunity to offer comments on this Draft Guidance and wishes to thank FDA for the opportunity to do so.

PDA endorses the need to maintain regulatory guidance documents in a state that emphasizes current technology, science and best practices. We also acknowledge the effort made by FDA in the publication for comments of FDA's Draft "Guidance for Industry on Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes". PDA strongly supports the inclusion of a risk assessment of the potential for the production and release of non-sterile products as one of the primary criteria in the support of a parametric release program.

With regard to the draft guidance document on parametric release, we have provided detailed comments identified by line number and have included a supporting rationale in the accompanying table. The following is a brief overview of the major points that PDA believes are most important to highlight to strengthen this guidance document:

- Chemical, biological, and/or physical indicators which may be used as load monitors lack the sensitivity to confirm that all critical sterilization cycle parameters have been met. An appropriately designed, correctly executed and effectively monitored sterilization process should be sufficient to mitigate the necessity for a laboratory test to confirm sterility, including laboratory testing of chemical and/or biological load monitors.
- Inasmuch as load monitors only demonstrate that a sterilization cycle occurred and do not have the sensitivity to demonstrate that all critical parameters have been met, classification of indirect monitors as defined in ISO 11140 provides no risk mitigation and should not be recommended.
- With regard to the content of submissions for parametric release, the Draft Guidance seems to focus primarily on existing products and seems to exclude new products from parametric release. We believe that with a properly executed assessment to identify and mitigate the risk of producing a non-sterile unit, new products (those for which there is no prior history of release via the sterility test) should also be eligible for approval using parametric release.

Again, PDA appreciates the opportunity to comment on this draft guidance document and provides these recommendations for your consideration. PDA believes that these comments will clarify and strengthen the guidance document to better serve the needs of both regulators and industry.

We would be pleased to offer our expertise in a public discussion and/or meeting with FDA to provide clarification of our comments. Should you wish to pursue that opportunity, or if there are any other questions, please do not hesitate to contact me.

Sincerely,
Robert B. Myers
President, PDA

31 October 2008

Ref: EU Guidelines to GMP,
Medicinal Products for Human and Veterinary Use,
Draft Annex 11, Computerised Systems
(08 April 2008, comments due 31 Oct 2008)

Dear Sabine and David:

PDA is pleased to have the opportunity to provide comments on the revisions to GMP Annex 11, Computerised Systems. Our comments were prepared by a group of member experts in this field after considerable discussion. Our comments are attached in the requested EMEA format.

In general the proposed revisions are acceptable and helpful. We have proposed some changes in order to make the guidance more useful. We particularly appreciate the following aspects of the revision which comport with international harmonization:

- Support of risk-based validation processes
- Validation measures which increase the quality and safety of critical systems.

If I can be of further assistance, please feel free to contact me, or our Director of Regulatory Affairs, Jim Lyda at: lyda@pda.org.

With very best regards,
Georg Roessling, PhD
Senior Vice President
PDA Europe

31 October 2008

Ref: EU Guidelines to GMP,
Medicinal Products for Human and Veterinary Use,
Draft Chapter 4, Documentation
(08 April 2008, comments due 31 Oct 2008)

Dear Sabine and David:

PDA is pleased to have the opportunity to provide comments on the revisions to EU GMP Chapter 4, Documentation. Our comments were prepared by a group of member experts in this field after considerable discussion. Our comments are attached in the requested EMEA format.

In general the proposed revisions are acceptable and helpful. We have proposed some changes in order to clarify and further improve the Chapter.

If I can be of further assistance, please feel free to contact me, or our Director of Regulatory Affairs, Jim Lyda at: *lyda@pda.org.*

With very best regards,
Georg Roessling, PhD
Senior Vice President
PDA Europe

Focus on Current Inspection Trends At PDA Delaware Valley Chapter Event

Sue Vogt Speth, PDADV Operating Committee Member (Ret. GSK)

The PDA Delaware Valley Chapter held a meeting on current inspection trends during its annual Vendor Night Extravaganza on Sept. 17, 2008. This year's meeting had by far the largest attendance in chapter history with 265 participants from local area pharmaceutical and biopharmaceutical industries at the Desmond Hotel and Conference Center in Malvern, Pa. The evening commenced with displays from 42 area vendor sponsors, another record increase in sponsorship for PDADV. Here, participants received hands on information about the latest technologies, resources and supplies, as well as the opportunity to speak with and discuss the latest and greatest tools of the trade with technical experts from our valuable suppliers.

Following the vendor displays, participants gained an understanding of the current inspection process as keynote speaker **Debra Pagano**, Senior Compliance Consultant, IHL Consulting Group, presented a lecture entitled, "Current Inspection Trends: What Are the Regulatory Expectations Globally And How Do We Meet Them?" Debra opened by providing the audience with an overview of responsibilities for the regulatory authorities and basic GMP requirements for manufacturing operations. She emphasized the importance of having procedures in place which identify, investigate and successfully correct any problems or issues that may occur, such as non-conformances or product failures. She explained how regulatory actions stemming from FDA-483 observations can delay product approvals as well as damage a company's reputation. Knowing regulatory regulations (such as the FDA, EMEA, MHRA, etc.) and guidelines are beneficial but may not be enough to adequately address expectations; Debra explained what FDA investigators are looking for based on top FDA 483, global observations and warning letters.

Debra provided the top ten CBER concerns, top five reasons for recall and a detailed analysis of non-conforming trends based on U.S. and EU inspections conducted by the FDA, as well as her personal review of the 2007 warning letters. The review Debra performed is certainly supportive of the top ten CBER concerns listed below.

10 Laboratory Controls – Changes

9 Stability

8 Testing and Release for Distribution
- Process Validation

7 Complaint Handling

6 Changes to an Approved Application – not reported to CBER

5 Biological Product Deviation Reporting
- Not reported/Not reported per regulation (i.e. 45 days)

4 Buildings and Facilities & Equipment
- Equipment not qualified
- Routine EM not performed
- Equipment not cleaned and maintained

3 Standard Operating Procedures
- Not being followed
- Do not address all facets

2 Quality Control Unit
- Inadequate Oversight by the QCU
- Inadequate review of production records
- No Procedures applicable to the QCU

1 Failure Investigations
- Lack of or inadequate investigation into unexplained discrepancies/deviations
- Investigation limited in scope

As always copies of the presentation were forwarded to all attendees by the PDADV Chapter President.

Referring a Colleague Could be a Win-Win!

Trevor Swan, PDA

A new feature now available online will allow you to quickly and easily educate a colleague about the value of PDA member resources. Simply visit the PDA website and click on "refer a colleague" under the membership section or visit www.pda.org/refer. Once you enter a colleague's information, an email from you will be automatically generated informing them of the PDA resources structured to support their work and advance their professional career.

Once your colleague has joined they will immediately have access to the tools needed to contribute to the advancement of the industry, influence regulation and propel their career. Participation on PDA Committees, Task Forces, Advisory Boards and chapters will all be open to them. Additionally they will begin receiving the finest industry publications including the *PDA Letter, PDA Journal of Pharmaceutical Science and Technology,* PDA Technical Reports and *International Pharmaceutical Quality (IPQ).* Membership discounts will also be immediately available to them.

Joining PDA is not only a reliable way to gain access to first tier scientific and regulatory resources and unparalleled networking opportunities, but it also a means joining and contributing to a distinguished community of industry leaders like yourself. Share the value of a PDA membership experience, refer a colleague to PDA.

To learn more about PDA's refer a colleague process or to discover more about volunteering with PDA, please visit www.pda.org/refer or contact **Hassana Howe** at howe@pda.org.

Congratulations!

Congratulations to our current winner, Abraxis BioScience's **Susan Prohn** from Grand Island, New York who won the Refer a Colleague $50 American Express Gift Card! Susan referred **Tony Giessert** who is now a new member of PDA!

Volunteer Spotlights

Gabriele Gori, PhD

Compliance Director, Quality Assurance, Bausch & Lomb

Education: Doctoral degree, Chemistry, University of Florence; Masters, Quality Management, University of Pisa

PDA Join Date: 1999

Areas of PDA Volunteerism: PDA Italy Chapter (secretary from November 2000–February 2005, president from February 2005–March 2007); Conference (organizer); Aseptic Processing and Quality Systems topics (speaker since 2001)

Professional Awards Won: PDA Distinguished Service Award (March 2007)

Interesting Fact about Yourself: My wife and I had twins —Massimiliano and Alessandro—in May this year, in addition to our 2 children Francesco (11 year old) and Veronica (8).

My hobbies are photography, gardening (I'm fond of orchids), swimming and scuba-diving: however - with the recent additions to my family - I have to say that babysitting is my most important hobby now!

Why did you join PDA and start to volunteer? After my first PDA meeting in Verona–Italy (in May 2000), I was intrigued with the ideas of creating a forum to discuss and influence the creation of regulations. This was the inaugural of the Italy Chapter.

Of your PDA volunteer experiences, which stand out the most? While no specific event stands out, I have enjoyed multiple instances where myself and my PDA colleagues have provided input to regulatory authorities, as well as many opportunities to provide practical guidance to other industry representatives

How has volunteering through PDA benefited you professionally? It has extended my knowledge of regulations and technology. It has also extended my network of experts to discuss and problem-solve common issues.

Which member benefit do you most look forward to? The ability to influence regulations and connect with other creative colleagues

Which PDA event/training course is your favorite? I enjoy the PDA/EMEA joint conference, and I am fond of Aseptic Processing and Sterilization Conferences and Training courses.

What would you say to somebody considering PDA membership? Join the fun. It is a great opportunity to become involved in a society dedicated to education and collaboration.

Norbert Hentschel

Director Compliance & Validation, Boehringer Ingelheim Pharma

Education: Chemical Technician

PDA Join Date: 1992

Areas of PDA Volunteerism: Organizing committees for several PDA events; Task Force member/chair; Biotech Advisory Board (Bio-AB) chair since April 2008

Interesting Fact about Yourself: As a contrast to my office job, I like to be in the nature. For example, I do enjoy mountain biking in the forests around my hometown or a hiking tour with my wife on the weekend. I also love to cook on weekends at home and on vacation, and to serve a good wine with the meal from my wine cellar.

Why did you join PDA and start to volunteer? I have joined PDA in 1992 after visiting a PDA conference in Basel, Switzerland. I liked PDA as it was an excellent information resource and platform to meet and discuss with other professionals. As a European PDA member, my first active involvement in PDA activities was to work in conference planning committees for European conferences.

Of your PDA volunteer experiences, which stand out the most? That's hard to say. I think the experience to work with other professionals on a common goal is always a memorable experience. It does not really matter on what project we worked on.

How has volunteering through PDA benefited you professionally? I have learned a lot from other members. To learn how people working for other companies or regulatory agencies look at things from another perspective than your own, does help to further develop your own perspective on things. Another thing is when you start working in a committee or Task Force the journey seems to be endless; but if you divide a long way into single steps and share the workload with a team you will reach your destination.

Which member benefit do you most look forward to? Independent from conferences and workshops the *PDA Letter* and the *PDA Connector* e-mail messages provide a concise overview on regulatory activities all over the world. Often it is sufficient to get just a heads up and to dive into the topic only if necessary.

Which PDA event/training course is your favorite? My favorites are workshops on specific topics of interest, e.g., process validation. I very much enjoy interaction with professionals from other companies.

What would you say to somebody considering PDA membership? Do it, you won't regret it.

Mark Staples, PhD

Consultant, Cusp PharmaTech Consulting LLC

Education: PhD, Biochemistry, University of Kansas

PDA Join Date: January 1, 1991

Areas of PDA Volunteerism: At the New England Chapter Level: Board Member-at-Large from 2005–2006; PDA New England Chapter President from 2003–2004; Treasurer from 1993–2002

Professional Awards Won: PDA Volunteer Award, Section Chair Award (Biotech Section, AAPS).

Interesting Fact about Yourself: I am an amateur photographer; I was the president from 2005-2008 of the Boston Camera Club. I won the Black and White Image of the Year Award from the New England Camera Club Council in 2007.

Why did you join PDA and start to volunteer? I've been in the biotechnology industry since the mid-1980's. The biotechnology industry was still evolving in the early 1990's, and PDA was actively helping stimulate discussion of the most pressing issues facing the industry.

Of your PDA volunteer experiences, which stand out the most? The PDA New England Chapter hit a low point in member interest 5–10 years ago, and it was very rewarding to be able to join other committed volunteers in making the Chapter a model for PDA Chapter management.

How has volunteering through PDA benefited you professionally? I have been able to build a network of professionals who, like myself, want to be actively involved in helping direct the course of the pharmaceutical industry through discussion of technological, operations and regulatory advances.

Which member benefits do you most look forward to? Opportunity to network with colleagues and the opportunity to see and comment on draft guidelines and whitepapers.

Which PDA event/training course is your favorite? Chapter dinner meetings

What would you say to somebody considering PDA membership? In the fast moving biotechnology and pharmaceutical industries, job security is a thing of the past and your own skills and knowledge can become obsolete in a few years. The risk of this situation can be alleviated by creating a strong network of fellow professionals and by taking full advantage of continuous education: both areas in which PDA excels. You gain greater career security by actively investing your time in your career, supported by the services and activities offered by societies such as PDA.

Shelley Preslar

Client Sales Executive, Invensys Process Systems

Education: BS in Marine Biology, University of North Carolina; MS Studies in Physiology, University of North Carolina; MBA in Global Management, University of Phoenix; PMP Certification, 2007

PDA Join Date: 2001

Areas of PDA Volunteerism: 2006 SEPDA (member); 2007 Original SEPDA Student Outreach Committee (chairperson); Speaker, committee member at numerous PDA conferences

Interesting Fact about Yourself: Honestly, I think one of the most interesting facts about me is that I was a Heavy Equipment Diesel Mechanic in the United States Marine Corps. It was difficult enough being a woman in the Marines, but I went into a very non-traditional job on top of that.

Why did you join PDA and start to volunteer? The company I worked for back in 2001 required all of us to become members in relevant professional associations for educational and networking purposes. PDA was one that I chose to join. As far as volunteering, that came a few years later. In my case, I was recruited by officers on the PDA Southeast (SEPDA) Board. There was a need to get some new people involved with our local chapter, and they came up with the idea of a student chapter organization. Well, those that know me are aware that I love a challenge, so I signed up as Chairperson for our Student Outreach Committee. Our task is to provide information, networking and mentoring for the students in our chapters. Our first school chapter is expected to be set up during this Fall Semester, with a second school targeted for Spring 2009.

How has volunteering through PDA benefited you professionally? I have been fortunate to meet many people from industry, consultant firms and regulatory agencies from across the globe. Many of my strongest ties have been formed as a result of my membership with PDA. The annual and local meetings offer wonderful networking opportunities. Even more important is the information provided during the technical sessions at these conferences. Speakers are chosen to give the most up-to-date information regarding technology, process ideas, regulatory requirements and more.

Which member benefit do you most look forward to? The Technical Reports are a great benefit. They provide the latest and greatest thinking on hot topics in our industry. PDA offers the ability to join working groups or interest groups to be a part of creating guidance documents. IPQ and the *PDA Letter* are also great ways to gain current information, and to see what is happening throughout our industry on a global scale.

Please Welcome the Following Industry

Meike Adam, F.Hoffmann-La Roche

Liliana Aguirre Rengifo, Pharmaservice SA de CV

Lisa Alexander, Millipore

Alexis Alexander, Novavax

Kathleen Alford, Alcon Laboratories

Heidi Allen, Centocor

Tish Anger, Apotex

Soulas Antoine, Kalibox

Liz Apodaca, Gen-Probe

Lisette Arias, Aramark Cleanroom Services

Frederic Ayers, Eli Lilly

Richard Bachelder, Ebewe Parenta Pharmaceuticals

Ryan Baker, Protein Design Labs

Deborah Baldwin, Stiefel Laboratories

Patricia Barco, Applied Biosystems

Corinne Bardgett, Sigma-Aldrich

Katarina Bartle, EMD Serono

Julie Basco, Catalent Pharma

Scott Bass, PharmaE

Florence Baudoux, GSK Biologicals

Anita Bawa, Genentech

Zoreh Bazzaz, Ministry of Health Iran

Stephen Beckerman, Shell Packaging Corporation

Trevor Bentley, Eli Lilly

Scott Berry, Genmab

Charles Biancon, BD

Darcy BIRSE, GE Healthcare

Kofi Boateng, CIBA Vision

Jason Bock, Teva Biopharmaceuticals

Daxa Bogdon, Genentech

Meow Hoe Boon, Health Sciences Authority

Stan Booth, Merck

Stacey Boushelle, Pfizer

George Bradbury, Shire

Yuval Brayer, Bio-Technology General

Paul Bridges, Genentech

Mirela Bubenik Bilicic, Pliva

Demi Buckley, Catalent Pharma

John Bucksath, ABC Laboratories

Eric Buenz, CaridianBCT

Tom Busby, Enzon

Audrey Butler, Ben Venue Laboratories

Tim Byas, Array Biopharma

Heidi Carley, Catalent Pharma

Anya Chamberlain, Emergent BioSolutions

Ken Cheng, Abbott Laboratories

Britt Juul Christensen, CMC Biologics

Jessica Chung, Johnson&Johnson

Wesley Church, GTC BioTherapeutics

Kathleen Cimbala, Baxter

Rakefet Cohen, Tena Pharmaceutical Industries

Ted Collins, UCB

David Collins, Eli Lilly

Joseph Connaghan, Special Process Services

Jeffrey Cook, Baxter Healthcare

Rosalyn Cooper, Amgen

Nathalie Cospin, UCB Pharma

William Crider, Crider

Jeff Curl, OSO Biopharmaceuticals

John D`Souza, CIBA Vision Sterile Manufacturing

Scott Dalton, Eli Lilly

Biswarup Das Gupta, GlaxoSmithKline

Kate Davenport, Baxter Healthcare

Isabelle Davidson, NewLink Genetics

Luc De Rycker, Cilag

Michael Delitala, Emergent BioSolutions

Louis Demers, Genentech

Cheryl Dennis, Banner

Katherine dePadua, Philips Respironics

Jerome Detreille, Catalent

Thomas DiBiase, Sanofi-Pasteur

Bertrand Digonnet, GlaxoSmithKline

Timothy DiLiberti, Astellas Pharma Technologies

Robin Diorio, Millipore

Alison Dodd, Eli Lilly

Younok Dumortier Shin, Bristol Myers Squibb

Ed Eichmann, BD-Pharmaceutical Systems

Lisbeth Eixarch-Queralt, Pfizer

Carla English, JHP Pharmaceuticals

Bruce Eu, Amgen

Janice Fajarito, BD Medical

Mehran Farhadpour, CIBA Vision

Justin Farrell, Eli Lilly

Isabelle Faure, AES Chemunex

Lili Fayazi, Novatrek

Alessio Ferrari, CTP Tecnolgie di Processo

John Finch, AMEC

Michelle Foster, CTD Quality Consulting

Amanda Foster, Sandoz

Jill Frazee, Emergent BioSolutions

Christa Fritschi, Schott Schweiz

Gretchen Fyock, Eli Lilly

Larry Galbraith, Biogen Idec

Patrice Galvin, Vicon Publishing

Larry Gatlin, Pfizer

Kaustubh Gavaskar, Baxter Healthcare

Melissa Germain, University of Florida

Maria Gibbs, Acambis

Germaynne Gibson, CIBA Vision Sterile Manufacturing

Anthony Giessert, Abraxis BioScience

Martin Gohlke, Dynavax

Jack Goodson, Jack Goodson Consulting

James Grace, Cold Chain Technologies

Anne Greene, Dublin Institute of Technology

Debra Greiner-Powell, Cytovance Biologics

Erwin Grill, Baxter Bioscience Manufacturing Sarl

Kirk Guckenberger, Eli Lilly

Leaders to the PDA Community

Vikas Gupta, Millipore

Rajiv Gupta, Abbott

Robert Gurley, Catalent

Jette Hansen, Novo Nordisk

Mette Hansen-Munch, SSI Statens Serum Institut

Larry Harneck, JHP Pharmaceuticals

Steve Harris, Biomerieux

Amber Harrison, Norwich Pharmaceuticals

Leeanne Haughton, CSL Limited

Nicolas Heaton, Sanofi-Aventis

Kristin Henney, Baxter Healthcare Corporation

Ulrich Herber, Accugenix

Josh Hobick, Dawson Logistics

Hanne Holmbom, H. Lundbeck

Kevin Hoopes, AstraZeneca

Brandon Horst, Colorado State University

Jaspaul Hothi, Health Canada

Keith Hovda, Poniard Pharamaceuticals

Yu Hu, Eli Lilly and Company

Hamedreza Inanloo Yaghmorloo, Ministry of Health Iran

Hajime Ishiga, Nipro Pharma

Patricia Izbicki, Bristol-Myers Squibb Company

Cynthia Jackson, Ciba Vision Corporation

Randall Jacobs, Allergan

Thomas Jacobsen, APP Pharmaceuticals

Jean-Marc Janssens, GSK Biologicals

Steven Jones, East Coast Validation Services

Walter Joppy, Johnson & Johnson

Sandra Juarbe, APP Pharmaceutical

Yun-Taek Jung, Korea Health IDI

Deborah Kamath, CIBA Vision

Sock Chin, Irene Kang, Baxter Healthcare

Kent Kashiwai, Teva Parenteral Medicines

Tomoko Katsuragi, Sato Yakuhin Kogyo

John Kelly, BD

Kheang Kho, MedImmune

Paul Killian, Millipore

Jong Kook Kim, Yooyoung Pharm

Geum Seok Kim, Yooyoung Pharm

Kenny Kim - Moo Young, APP Pharmaceuticals

Amy Kleiber, General Electric Healthcare

Keiichi Kotera

Sampath Krishnan, Amgen

Thomas Kristy, StarCast

Cornelia Kruettli, F. Hoffmann-La Roche

Austin Kuo, Eli Lilly

Chad Kurdziel, Schwarz Pharma

Katarzyna Lastawska, University of Warsaw

Mary Lavithis, CSL Bioplasma

Nadia Leden, AES Chemunex

Patricia Lee, Pall Life Sciences

Haike Leibiger, IDT Biologika

Mingxiang Li, Xoma

Hongyang Li, Eli Lilly

Alice Li, Genentech

Kimberly Lilly, Novavax

Johnson Lim, PII

Suyoung Lim, Johns Hopkins University

Randall Ling, CSL Behring

Roger Liu, Biogen Idec

Constance Long, BD-Pharmaceutical Systems

Catherine Lorimey, BD

Justyna Lubaska, Pliva

Brian Lynch, BD

Natasha Mach, Catalent Pharma

Sherri Main, Roquette

John Mandy, Pfizer

Cristina Marquez, Bristol-Myers Squibb

Juan Roberto Marquez-Eliza, Excellent Pharma Consulting

Luis Martinez, Baxter Healthcare

Margaret Mason, Millennium Pharmaceuticals

Alicia Mau, Afton Scientific

Jeremy Mauldin, Scott & White Hospital

Kathleen May, Catalent Pharma Solutions

Alain Mazurie, Plastef

Diane McKellar, Government of Canada

Dawn Melia, Merck

Alan Michiels, Bayer Healthcare

Barbara Miercke, Bayer Healthcare

Shannon Mikruk, Synthes

Melissa Miller, Sanofi Pasteur

Tadanari Miyatake, Hitachi America

Ray Mohan, CIBA Vision Sterile Manufacturing

John Moraga, Catalent Pharma

Ali Mostaghimi, Bayer Healthcare

Reginald Motley, West Pharmaceuticals Services

Anna Msella-Burgess, Eli Lilly and Company Pharmaceuticals

Christopher Mudd, Allergan

Navdeep Nagra, Sanofi Pasteur

Takeshi Nakagiri, Mochida Pharmaceuticals

Alex Naranjo, CIBA Vision Sterile Manufacturing

Mary Nasopoulos, CSL Limited

Douglas Nesta, GlaxoSmithKline

Hieu Nguyen, Catalent Pharma

Paul O'Hare, Autocal

Rod O'Keeffe, Ipsen

Danielle Oliver, Afton Scientific

Frank Olivero, ImClone

Katsuaki Orite, Eisai

Jamie Osborne, Siegfried

David Overcashier, Genentech

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

Please Welcome the Following Industry Leaders to the PDA Community

continued from previous page

Panteleimon Palamidis, Baxter Healthcare
Emilie Pan, Medimmune Vaccine
Richard Panton, Genentech
Young-Geun Park, Choong Wae
Sandra Parriott, BioMarin Pharmaceutial
Els Pasmooij, Amgen
Mark Pasmore, Baxter Healthcare
Svapnil Patel, Ikaria
Justin Pawlik
Timothy Pearcy, Biolyph
Jose Perez, Alcan Glass Tubing
P. Rohan Persaud, Merck
Eric Peryer, Baxter
Corey Peters, Bionostics
Zachary Peterson, Baxter
Tien Pham, HGSI
Ludovic Philippe, AES Chemunex
Terezinha Pinto, University Sao Paulo
Christina Pisanello, American Stelmi
Christina Pitts, Merial
James Plousis, Johnson & Johnson
Billy Pope, Pharme
Jacob David Porantharapilly, Novartis
Marta Portoles, Millipore
Alexis Proper, Dow Corning
Debra Purrington, Catalent
Ryan Raap, Amgen
Irene Ragel, CSL Ltd.
Thirunavukkarasu Ramasamy, Schering Plough
Delphine Ramos, HAL Allergy
Nancy Ramos, Baxter Healthcare
Jack Regan, Corgentech
Timothy Reinhardt, Pfizer
Paul Ricciatti, CIBA Vision
Anne Rigoulot, Sanfi Pasteur
John Rohloff, Replidyne
Nuphar Rozen-Alder, BD
Leilani Rubio, MedImmune
Allen Rudis, Charles River Laboratories
Jose Ruiz, IMA Edwards
Beth Ruland, Schering Plough
Robert Ruple, Imclone Systems
Wendy Saffell-Clemmer, Baxter
Sivakesava Sakhamuri, Bristol Myers Squibb
Mariam Salamatian, Pall
Amit Sareen, Lupin Limited
Gernot Scharf, F. Hoffmann - La Roche
Randy Schwemmin, Genentech
Carlos Segnini, Hospira
Lucien Sergile, Imclone Systems
Richard Shah, Gilroy Filtration
Sherwin Shang, Abbott Laboratories
Amit Sharma, Sartorius Stedim
Todd Sharratt, Micromedics
Michael Shaw, Mystic Pharmaceuticals
Brian Shontz, Cephalon
Eugene Shortall, Unilife Medical Solutions
Joshua Silverstein, Bionique Testing Labs
Heather Sinn, Agilent Technologies
Anthony Smiley, WL Gore and Associates
Barbara Thomas Smith, Lexicon Pharmaceuticals
Ronald Smith, Alcon Research
Terry Smith, Alcan Packaging
Jenny Smits, JHP Pharmaceuticals
Michael Snajkowski, CIBA Vision
Ed Sopp, Proteon Therapeutics
Walter Srsich, Sanofi Pasteur
Dorte Stockmann, Novo Nordisk
Jeanette Stabel, Novo Nordisk
Harald Stahl, GEA Niro
Terri Stepusin, GlaxoSmithKline
Paul Stevens, Amgen
Fred Stolz, Catalent
Trevor Streur, Cardiff University
Jon Strich, Xoma
David Sturdee, Clairvest Group
Eric Sweeney, Baxter
Erica Swierzowski, Regeneron
David Swindell, Stryker Biotechnology
Helle Sylvan, SSI Statens Serum Institut
Maricarmen Szendrey, Amgen
Dnyanesh Talpade, BD
Jo Thompson-Hehir, JTH Validation Services
Hiroshi Togashi, Daikyo Seiko
Paul Torres, APP Pharmaceuticals
Maridalia Torres, Food and Drug Administration
Jamie Travers, Medimmune
Kathleen Tucker, Dow Chemical
Brian Tufts, Baxter
Sam Turney, Genentech
Hideomi Ueda, Sato Yakuhin Kogyo
Gabriel Ugalde, Hospira
Francios Urvey, BD
Ton Van der Stappen, RIVM
Maria Vanni, Bausch & Lomb
Amber Violette, Talecris Biotherapeutics
Michael Waddington, Accugenix
Melissa Weakly, Amgen
Jason Willett, Veltek Associates
Bradley Wolk, Genentech Incorporated
Suh-Chin Wu, National Tsing Hua University
Jingjun Xie, NNE Pharmaplan China
Tzung-Horng Yang, Halozyme
Ping Yeh, Biogen Idec
Nes Young, Bristol Myers Squibb
Lisa Zhang, Sanofi-Aventis
Chunhua Zhao, Bayer Technology Services

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

Asia-Pacific

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Email: robert.caunce@hospira.com
www.pdachapters.org/australia

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Capital Area
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Contact: Allen Burgenson
Email: allen.burgenson@lonza.com
www.pdachapters.org/capitalarea

Delaware Valley
Areas Served: DE, NJ, PA
Contact: Art Vellutato, Jr.
Email: artjr@sterile.com
www.pdadv.org

Metro
Areas Served: NJ, NY
Contact: Lara Soltis
Email: lsoltis@texwipe.com
www.pdachapters.org/metro

Midwest
Areas Served: IA, IL, IN, KY, MI, MN, MO, ND, OH, SD, TX, WI
Contact: Peter Noverini
Email: peter_noverini@baxter.com
www.pdachapters.org/midwest

Mountain States
Areas Served: CO, ID, KS, MT, NE, NM, OK, UT, WY
Contact: Sara Hendricks
Email: scarry@att.net
www.pdachapters.org/mountainstates/

New England
Areas Served: CT, MA, ME, NH, RI, VT
Contact: Louis Zaczkiewicz
Email: zaczkiewicz@pdachapters.org
www.pdachapters.org/newengland

Puerto Rico
Contact: Manuel Melendez
Email: manuelm@amgen.com
www.pdachapters.org/puertorico

Southeast
Areas Served: AL, AR, FL, GA, LA, MS, NC, SC, TN, VA
Contact: Patrick Sabourin
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www.pdachapters.org/southeast

Southern California
Areas Served: AZ, CA, HI
Contact: Saeed Tafreshi
Email: saeedtafreshi@inteliteccorporation.com
www.pdachapters.org/southerncalifornia

West Coast
Areas Served: AK, CA, NV, OR, WA
Contact: John Ferreira
Email: jferreira@banzigersystems.com
www.pdachapters.org/westcoast

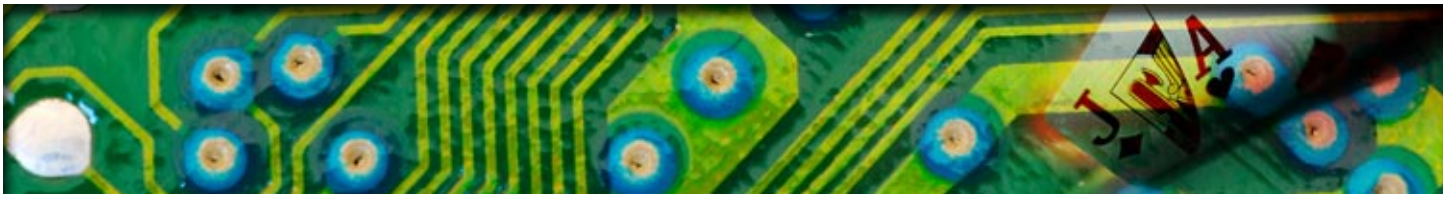
2009 PDA Annual Meeting: The Impact of the Microchip

Application of Modern Technologies in the Development, Manufacture and Testing of Bio/pharmaceutical Products

Las Vegas, Nevada • April 20–24, 2009 • www.pda.org/annual2009

Ian Elvins, Lonza Biologics, Chair, 2009 PDA Annual Meeting Program Planning Committee

When organizing the Conference, the program the planning committee sought to place an *emphasis on presenting innovative ideas* and practical tools for applying modern technologies to the development, manufacture and testing of pharmaceutical products and processes. Most of these tools and applications have been either fully or partly developed by small groups working within the companies represented at the Conference. Because of this, many of the best ideas may not be generally known within the industry. The intention of the Conference is to showcase these ideas so that other professionals, and ultimately the patient, can benefit. It is also clear that a technique developed in one area may find application (perhaps with minor modification) in totally different areas. Such applications may not have been obvious to the originators. Only by bringing together a diverse group of industry professionals at Conferences like the PDA Annual Meeting can these opportunities for cross fertilization of ideas occur. As always, the opportunity to network with a wide range of like minded individuals, in a relaxing setting such as the Red Rock Resort, offers tremendous added value. *Clearly, this is one occasion when "What happens in Vegas" definitely should NOT "Stay in Vegas!"*



Making Life Easy: the Microchip

It seems almost unbelievable to recall that prior to the mid 1980's the personal computer (at least in useful form) did not exist. No email, no Internet, no spreadsheets, no word processing remember secretaries hammering out reports on golf ball typewriters with carbon paper!). The speed and extent that the microchip has come to dominate every aspect of our lives has been so totally complete that we have difficulty remembering what life was like before. Our industry is no different. Computers and microchips can now be found in every aspect of the pharmaceutical industry; from discovery through to pharmacovigilance. I challenge you to think of any technologies in the development and manufacture of pharmaceuticals that are not controlled, monitored, analyzed or supported by a microchip. The victory of the silicon invasion has been total and we shall see evidence of this in the sessions presented at this year's Annual Meeting.

Difficult as it is to recall the days before silicon, it is worth making the effort in order to realize just what astonishing progress has been made in the application of microchip-based technologies. An industry professional that moved to Mars in 1985 and returned to Earth in 2008 would be amazed at just what is being accomplished with today's technology. This is precisely what the *2009 PDA Annual Meeting* aims to illustrate. The 2009 conference will be held April 20–24, in Las Vegas, Nevada.

Over the course of the conference we will be examining some of the latest tools and technologies that can add real practical value to the never ending quest for quality and consistency throughout the entire drug production and distribution chain. But that is not all. Indeed we seem to be riding an exponential curve towards ever more powerful and innovative technologies. Therefore we will also be taking a look at what the future may hold.

So what can we show our returning Martian? Here are a few examples of what the conference will have to offer:

Data Handling:

In the era prior to silicon, data handling meant poring over measurements recorded in notebooks. Now, the sheer volume and sophistication of data generated and recorded electronically means that much of it is never even seen by a human being. New ways to sort and analyze these mountains of data are essential if we are to make effective use of the power at our disposal. We will hear about some of the latest tools and how application of these help speed products to market and to the patient.

Process Control:

The modern biotechnology or API plant achieves a level of process control and monitoring that was inconceivable only a few years ago. Some of the industry's biggest players will present their latest experiences in plant/process automation and operation.

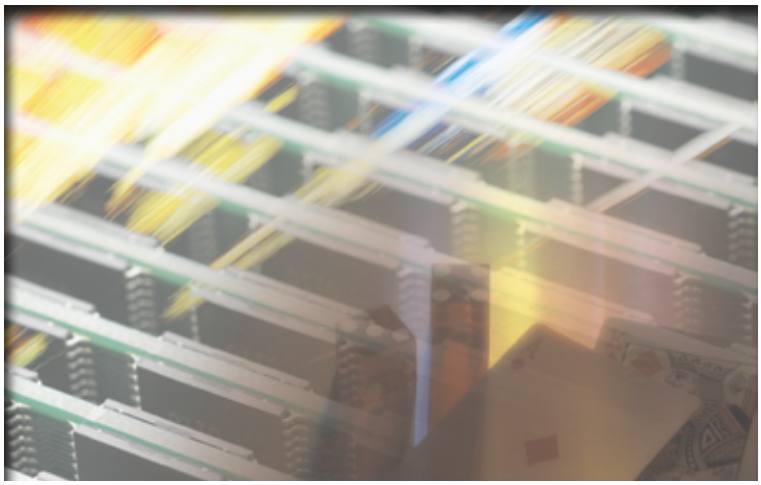
Quality Systems:

The huge progress made in other areas means that our QA groups must track and control much more than in the past. Additionally, the technology enables us to examine aspects of quality that could not be reached in the past. Sophisticated trend analysis can now give us warning of adverse trends far earlier than was ever possible in the past. This can only be achieved by maximizing our use of electronic tools

and systems. We will see how some companies are achieving new heights of quality through the latest systems for documentation, validation, training management and CAPA tracking.

Aseptic Processing:
The use of robotics and sophisticated visual inspection techniques are bringing us ever nearer to completely automated and isolated drug product filling processes in which that main source of contamination—the human being—no longer interacts with the product. We will see how the latest techniques can be applied to Blow-Fill-Seal, Vial and Syringe filling.

Laboratory:
It is in the laboratory that some of the most spectacular applications of chip based technology have occurred. Both chemical and biological analysis have progressed far beyond the days when measuring the area under a curve meant counting squares on a sheet of graph paper. In the microbiology area we will hear about some of the very latest rapid methods. In addition we will examine how the fully electronic laboratory is finally becoming reality.



There are many great ideas and tools that will be presented at this year's conference. I urge you to take a look at the conference brochure to see just what is on offer.

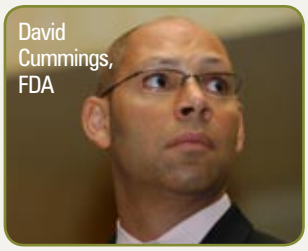
I look forward to welcoming you to Las Vegas for an exceptional *2009 PDA Annual Meeting!*

Faces and Places: 2008 PDA/FDA Joint Regulatory Conference

A1 Pharmaceutical Inspectorate and GHTF


John Thorsky, FDA


Tim Ulatowski, FDA


David Cummings, FDA

C1 Combination Products


Marsha Major, Centocor


Stephen Rhodes, FDA


Kimberly Trautman, FDA

IG3: Combination Products Interest Group


Michael Gross, Chimera Consulting


Lisa Hornback, Hornback Consulting


Kathleen Greene, Novartis

B2: Product Development


Steven Laurenz, Abbott


Anurag Rathore, Amgen

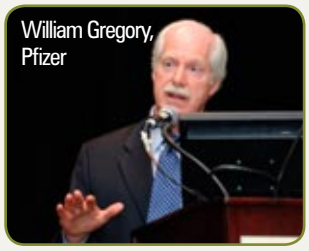

Paula Hudson, Eli Lilly

IG4: Clinical Trial Materials Interest Group


Vince Mathews, Eli Lilly


Amnon Eylath, Ariad Pharmaceuticals

B1: Product Safety Pharmacovilgilence


William Gregory, Pfizer


Louise Johnson, Aptuit

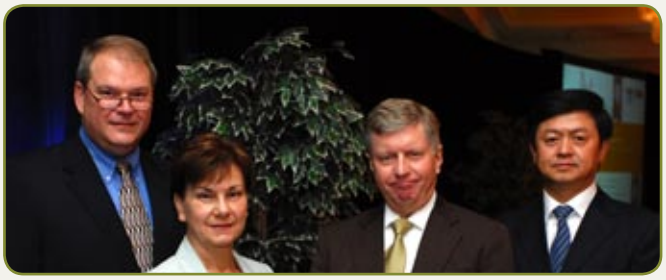
C2: Import Safety

(l-r) John Ayres, Eli Lilly; Maria Guazzaroni Jacobs, Pfizer; Jeff Shuren, FDA; Janeen Ann Skutnik, Pfizer; David Schoneker, Colocon

Transatlantic Initative

(l-r) Nick Buhay, FDA; Neil Wilkinson, David Begg Associates; Barbara Zinck, Zinck Consulting

Plenary 1



(l-r) John Finkbohner, MedImmune; Janet Woodcock, FDA; Roger Williams, USP; Tang Minhao, SHFDA

A4: International Harmonization: GMP Inspections, including PIC/s

(l-r) Martin Van Trieste, Amgen; Brian Hasselbalch, FDA; Chad Sheehy, Health Canada

C4: Customized Therapies

(l-r) Keith Wonnacott, FDA; Elizabeth Leininger, Elizabeth Leininger Consulting; Nakissa Sadrieh, FDA; Daniel Lobato, Shadle Consulting Services

P2: Implementing A Pharmaceutical Quality System – Transiting From an SOP-Based Quality System To a Comprehensive Quality System

P3: FDA Compliance Update

(l-r) Kate Cook, FDA; Martine Hartogensis, FDA; Deb Autor, FDA; Rick Friedman, FDA; Christopher Joneckis, FDA

(l-r back) Bob Dana, PDA; Joe Famulare, FDA (l-r front) Kimberly Trautman, FDA; Mary Anne Malarkey, FDA; Martine Hartogensis, FDA; Alyson Saben, FDA

Twenty Years and Counting: A Highlight of TRI Teacher John Ludwig

Stephanie Ko, PDA

He's a soft-spoken individual who loves watching his children play soccer, takes pride in mowing the grass, and warmheartedly reminisces the day he asked his wife to marry him. **John Ludwig** is the typical kind of person that you'd love to know, but his contributions as a veteran instructor for the Training and Research Institute are anything but typical.

John Ludwig, PhD, currently serves as the Executive Director of Analytical Research & Development for Pfizer, Inc. I met him in October 2008 when he was teaching at our New Brunswick Course Series in New Jersey. A casual conversation turned interesting when I asked him how many years he has taught for PDA. Quite unassumingly, he answered, "since 1989," to which I thought was simply remarkable.

We would like to share this interview with John as an example of the commitment, and caliber of our TRI instructors and how you can benefit by learning from them.

Stephanie: What were you doing when you first began teaching for PDA?

John: I was working as a Development Scientist III in parenteral formulation and process development for Burroughs Welcome Co. I taught a 3-day course on the basic principles of sterile dosage forms with Dr. Ken Avis. In the 1990s, I was asked by Mike Korczynski to help develop and teach the first Aseptic Processing course for PDA that included a hands-on laboratory component (2 week course). A number of wonderful people were involved in creating and teaching that course during the first few years including Ed Fitzgerald, Simon Rusmin, John Lindsay, Dave Matsuhiro, Mike Akers, Jim Cooper, Ed Trappler, and many more.

Stephanie: If you can recall, how were you selected as a PDA instructor?

John: When I completed graduate school, my major professor Dr. Ken Avis asked me if I would help develop and teach a new course for PDA on the basic aspects of sterile products. It started out as a 4 day course. I contributed during days 1-3. Dr. Avis instructed day 4 which was optional and usually a smaller group.

Stephanie: What is your current field of expertise?

John: I have a BS degree in Pharmacy and a PhD degree in Pharmaceutics from the University of Tennessee. I have worked extensively in parenteral formulation development, scale-up, and sterile fill/finish. For the past 5 years, I have also been responsible for biologics analytical research and development.

Stephanie: How many years have you been in this field?

John: 19 years

Stephanie: What positions have you held?

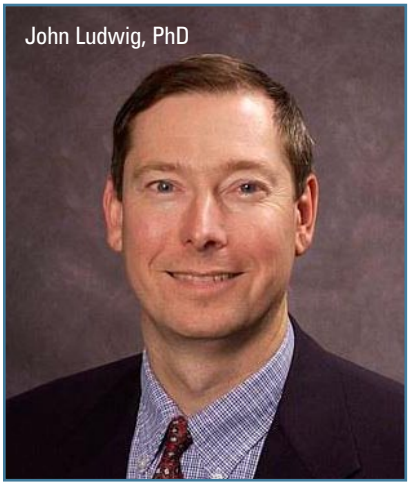
John: Development Scientist, Group Leader, Section Head, Director, Senior Director, Executive Director

Stephanie: What influenced you to choose this career path?

John: My father, Walt Ludwig, managed a process engineering group at Bristol-Myers in Evansville, Ind. I listened to him discuss what types of projects they were working on at the dinner table every evening, and gradually it dawned on me that the pharmaceutical industry was doing important work and was a clear avenue where one could contribute to public health in our society. I followed by dad's example and went to pharmacy school in order to get a firm basis in direct patient care as well as the science of medicines.

Stephanie: What makes your field unique?

John: In the parenterals field, we are accountable for always maintaining the highest technical and ethical standards. One contaminated vial could result in injury (or worse) to the patient.


John Ludwig, PhD

Stephanie: As an instructor, how do you continue to improve course content?

John: I keep a running file of interesting facts, new technologies, company surveys, scientific advances, compendial changes, etc. and update the course notes on a yearly basis.

Stephanie: How does teaching keep you energized in your profession?

John: Teaching for PDA is challenging and hard work, but at the same time very relaxing. I believe I learn just as much from the students as they hopefully learn from me. The Q&A in class and at breaks is often just as important as class time for exchanging ideas and discussing problems.

Stephanie: Describe your idea of the perfect student for your instruction.

John: The perfect student is excited about learning, and asks good questions (some of which I can't answer!).

Stephanie: What do you wish students would do more often?

John: Don't delay asking a question… speak up right then and let's see if we can find an answer. Also, if you've had an interesting experience or solved a difficult problem at your place of business bring the example forward to share with the class.

Stephanie: What advice would you give someone who is just starting to enter your field of expertise? ➤

PDA 2009

The Universe of Pre-filled Syringes and Injection Devices

27-30 October 2009, Venice, Italy

Call for Papers

Dear Friends and Colleagues,

This conference gives an update on all aspects of the application of parenteral products covering a broad range of topics. PDA is seeking presentations 30 minutes in length that address one of the following areas:

- Marketing and Business Development Issues Related to Parenteral Application Systems
- Materials, Components, Methods
- Supplier Quality
- User Studies
- Contract Manufacturing Issues and Quality Agreements
- Development, incl. PAT, QbD, Upscaling
- Process
- Manufacturing
- Packaging, Labelling, Sterialisation, Counterfeiting
- New Trends in Manufacturing
- Combination Products
- New Injection and Parenteral Application Concepts, New Containers and Systems
- Regulatory Trends and Inspection Issues
- Cases Studies

All submitted abstracts will be reviewed by the program committee for inclusion in the meeting or for poster presentation.

Abstracts must be non commercial in nature, describe new developments or work and significantly contribute to the body of knowledge relating to pre-filled syringe and injection devices. All abstracts will be reviewed by the Program Planning committee for inclusion in the meeting or in a poster session.

Please include the following information. Submissions received without full information will not be considered.

> **Title**
> **Presenter's biography**
> **Additional authors**
> **Full mailing address**
> **Phone number**
> **Fax number**
> **Email address of the presenter**
> **2 - 3 paragraph Abstract, summarizing your presentation**
> **Key objectives of your topic and what new information you will present that has not been presented elsewhere**
> **Explanation of specific take-home benefits your target audience can use immediately on the job**
> **Target audience (by job title or department)**

Send a copy of the Abstract and the presenter's biography (ca. 100 words in length) to Frederike Graeper at **graeper@pda.org.**

Poster abstracts must be received by February 16, 2009 to be considered

John: It's critical that you stay on a steep learning curve throughout your career. I've found that I'm happiest when I'm working slightly (sometimes completely) outside my comfort zone.

Volunteer for the most challenging assignments, and assemble the best team of scientists available to work with you on the project.

Stephanie: What is a common mistake you see happening too often in your field?

We work in a heavily regulated environment. There is a tendency at times to defer from common sense simply to try to conform to someone's interpretation of a regulation or guideline. My advice is to put yourself in the place of the patient and arrive at the best solution with that in mind. I've never seen an example where the regulations and guidelines didn't support a decision made in the best interest of the person who will be dosed with the drug.

Stephanie: What professional/ academic milestones have you achieved since you first began teaching?

John: I served as Chair of the AAPS Sterile Products Focus Group in 2004 and 2005. I also had the honor of Chairing the AAPS Arden Conference in 2007.

Stephanie: What new skills have you learned since you first began teaching?

John: I have become a much improved speaker as well as better able to think on my feet. The students PDA attracts to training classes are very bright and have unique experiences. They almost always ask questions that I've never thought about before. It's fun to think through possible approaches/answers real-time with the entire class.

Stephanie: What would you like to see happening in your field/industry?

John: I'm intrigued and encouraged by the QbD initiatives of the past couple of years. I'm very hopeful that by using enhanced process understanding and design space concepts the pharmaceutical industry will be able to make process improvements to commercial manufacturing processes without having to wait for regulatory approval. If we (industry and regulators) collectively work towards that end, my belief is we can be successful in enabling significant cost savings while maintaining high quality standards.

We hope this brief interview shows the pride that we have in our instructors and the standard by which they are chosen. You can be assured that our instructors *are* true experts and veterans in the field because they are passionate about teaching and sharing years of knowledge and experience with the students for their benefit and, ultimately, for the well-being of the patient.

[**Author's Note**: John Ludwig's 2-day course, "Sterile Pharmaceutical Dosage Forms: Basic Principles," is scheduled in St. Louis, MO from May 4–5, 2009.]

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Global Challenges For Investigational Medicinal Products Meeting In 2009

Rome, Italy • January 28–29 2009

Claudio Puglisi, Società Industria Farmaceutica Italiana, and Volker Eck, PhD, PDA

Investigational Medicinal Products (IMPs), also known as Investigational New Drugs, are under increasing attention from regulatory bodies. In Europe, as well as in the United States and Japan, regulations have been published to define some rules for developing and manufacturing IMPs. As companies in their attempt to reduce development times go global, it becomes obvious, that any company has to recognize and implement procedures to comply with very diverse expectations. PDA, in understanding the need to cope with global challenges, is organizing a conference and exhibition in Rome that will highlight important similarities and differences to be dealt with.

The conference will cover such topics as:

- Regulatory requirements in Europe and the USA
- Quality issues related to drug substances (APIs)
- Process development as well as changes and controls to this
- Product certification and the role of the Qualified Person in the EU
- Supply Chain issues in clinical trial material distribution
- Practical aspects of regulatory filings under the Investigational Medicinal Product Dossier regulation
- Challenges when sourcing from India and China

The conference is aimed to give as many answers as possible to prevailing questions you might have. To achieve this, a round table discussion with representatives from European and U.S. authorities will conclude the conference. Here, we want to give you exposure to a variety of viewpoints from regulatory bodies that should be of help to you when addressing questions or observations by assessors from different countries in your day-to-day work.

Plan for Next Year's Rapid Microbiology Methods Meeting

Berlin, Germany • February 3, 2009

Francesco Antonetti, PhD, Merck Serono and Volker Eck, PhD, PDA

Rapid Microbiology Methods (RMMs) from a scientific point of view have reached a mature state. However, use of such methodologies still is not as widespread as could be. PDA has now taken the initiative to bring together regulators from Europe with an invitation extended to the U.S. FDA and industry experts from around the world to highlight existing hurdles and experiences when establishing Rapid Microbiology Methods in a production environment.

The panel of speakers includes representatives from EMEA, MHRA and members of EDQM Working Parties to illustrate the expectations and the help these institutions can provide to any organization embarking into the use of RMMs. To do so, the first day will be dedicated to regulatory requirements and expectations.

The afternoon will give the opportunity to participate at one of the three workshops that will cover:

- Strategies on implementing RMMs for In-Process Controls and Environmental Monitoring
- Approaches on how to strategies to implement execute RMMS in new Marketing Applications
- Tactics on how to applying RMMs in existing Marketing Applications

Likewise, the second day is dedicated to illustrate from the previous day's presentations, industry's point-of-view, as well as to look at what questions have been raised by the authorities, how they have been addressed and what benefits have been gained. One very interesting and exciting lecture will address the implementation of RMMs to achieve Real-Time Release and the issues around obtaining approval from the authorities.

We invite professionals from regulatory affairs functions to join us at this event, and to discuss with the exquisite panel of subject matter experts from regulation and industry existing doubts about the usefulness and benefits that might be achieved. Also we invite anyone who is planning to embark in such a project to come and learn from the lecturers on what hurdles they might be confronted with, and the potential return of this investment which had been achieved in practical situations.

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