Science • Technology • Quality • Regulatory • Community

PDA Letter

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In This Issue...

PDA Parenteral Drug Association

Connecting People, Science and Regulation℠

The "Product Quality Review" vs. The "Annual Product Review" —Are They the Same?

Expectations of the Authorities

Joerg Neuhaus, PhD, Pharmaceutical Inspector, Joachim Leube, PhD, Bayer Biologicals, and James Lyda, PDA Europe

In October 2005, the European Commission updated "Chapter 1: Quality Management" of the EU GMP to include new requirements for a Product Quality Review (PQR). New section 1.5 requires that a PQR normally be performed annually. Some of the requirements in section 1.5 also are found in Part II of the EC GMP Guideline relating to APIs (formally referred to as ICH Q7A).

The new PQR provisions became effective on January 1, 2006. Now, manufacturers are expected to conduct PQR's based on at least six months of data; in the future, 12-month reviews will be expected. Based on this timetable, all companies subject to the requirement should have a PQR system of some type in place by now.

To many observers, the PQR requirement sounds much like the "Annual Product Review" required by the U.S. FDA GMP's under 21 CFR 211.180(e). However, there are important differences: the PQR clearly places much more of a burden on the manufacturer. While some companies had existing quality-related systems which facilitated prompt compliance with the PQR, other companies need to develop new procedures and review systems to meet this requirement.

The depth and scope of the PQR can result in an extremely powerful quality management tool, if performed correctly. The PQR should uncover key problems and demonstrate how a company deals with them. As such, the PQR offers benefits to both the manufacturer and inspectors. The former will be able to demonstrate its policies and commitment to quality through the PQR. The latter can use the PQR as a valuable "entry point" for the conduct of the inspection.

The PQR requirements will add to the workload of manufacturers and/or marketing authorization holders (MAHs). However, the required resources are easily manageable if the PQR is designed and planned efficiently. The inverse is true, also: the workload will increase dramatically if the PQR system is poorly planned and conducted. The PQR can save money by avoiding failure

continued on page 35

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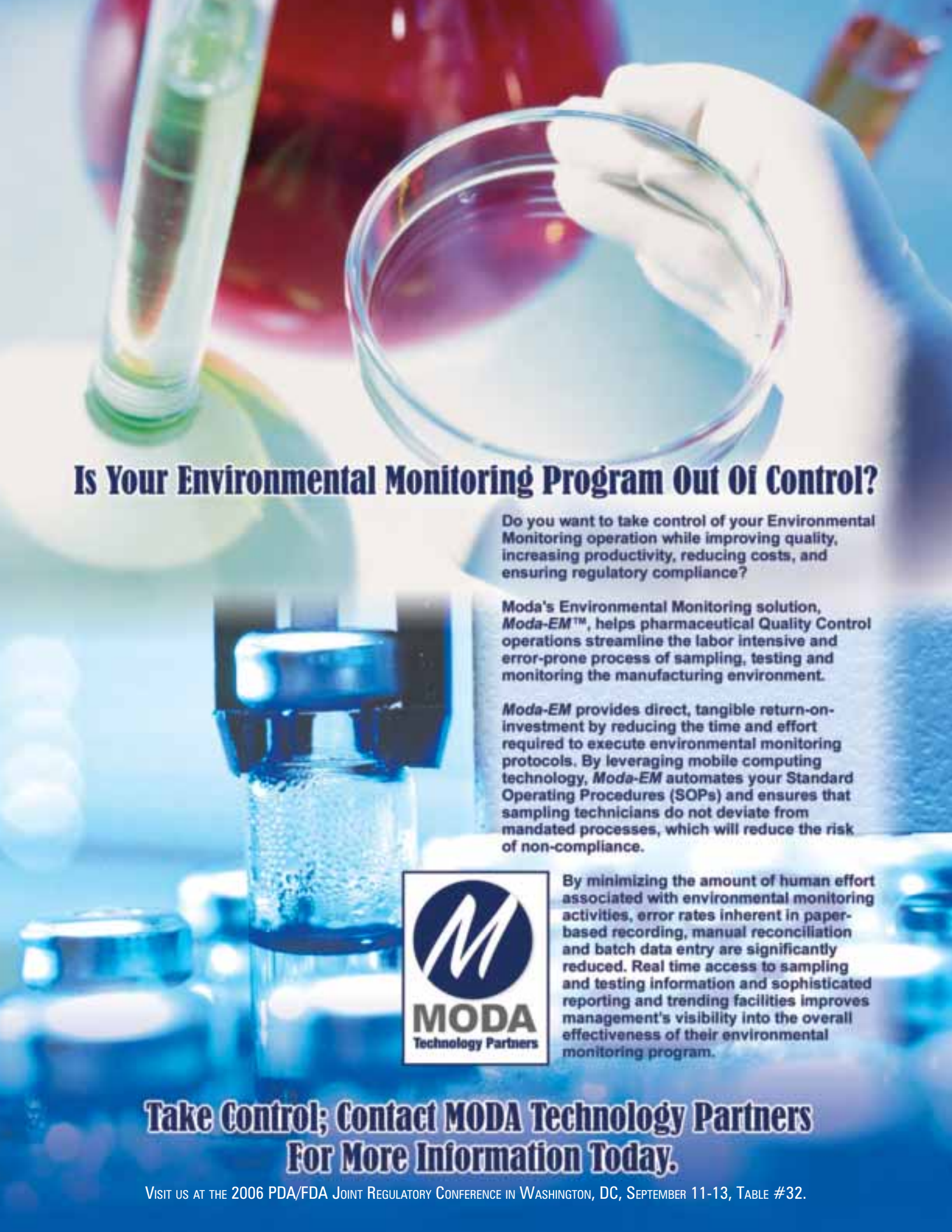

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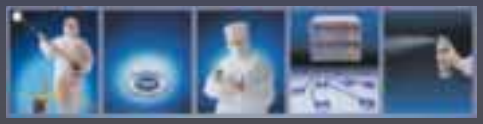

Innovative Clean Room Products

ARC Benefits Focus of PDA/FDA Conference Breakfast Session

Deborah King, Syntegra, LLC

In 1996, PDA was challenged by FDA to provide a practical solution to the growing burden of pharmaceutical company compliance. PDA's solution was a stakeholder-created technology process audit checklist and system, published as Technical Report No. 32: *Auditing of Suppliers Providing Computer Products and Services for Regulated Pharmaceutical Operations*. The efficiencies envisioned with the publication of TR#32 were realized in the creation of the Audit Repository Center (now known as the Audit Resource Center), or ARC. The ARC is alive and growing today, having been recently relaunched. Originally, TR#32 was published with FDA involvement to improve audit efficiency. ARC-certified audits obtained from the resulting audit repository meet many regulated company's audit needs, while also limiting the "noise factor" for technology suppliers exposed to multiple audits yearly.

Stakeholder perspectives will be presented on September 13 at a "Breakfast Session" during the PDA/FDA Joint Regulatory Conference. Two ARC participating firms will discuss the benefits of the TR#32/ARC process. **Peter Miller,** Director of IM Quality Assurance, will talk about the experiences of Bristol Myers-Squibb, and **Charles Steiniger,** Director of Quality Assurance, will share the perspective of Sparta Systems, Inc.

"ARC continues to strive to reestablish a valuable resource to the pharmaceutical industry," states BMS's Miller. "BMS continues to be a strong supporter of a structured approach to computer supplier auditing through group audits and the ARC's efforts."

In addition to manufacturer benefits, technology developers enjoy increased speed-to-sales closure while reducing the number of audits to which they are subjected. The TR#32 data collection tool provides a clear and thorough examination of suppliers' practices and provides observations to allow the determination of the audited technology's appropriateness for its intended use.

"Participating in PDA audits is a respected way for Sparta Systems to demonstrate its compliance with industry standards for developing software. Completing this audit helps our customers and prospective customers reduce risk and save significant cost and time commitments in lieu of conducting their own audits," says Steiniger.

In this manner, both subscribing and supplying companies can reduce their audit costs by as much as 50% through participation in the ARC program.

New audits are currently being performed, certified and added to the repository, or library. After a dormant period, the number of audits currently in the library has increased by one-third and the number of subscribing companies purchasing those audits has increased by 50%. Once filed, the audits become available for all subscribers to use, thus eliminating the need for duplicative process audits.

PDA's ARC licensee is SynTegra, LLC, a Germantown, Maryland company. SynTegra is responsible for managing and growing ARC while maintaining the high standards of PDA. The company has revised and simplified the business model to make it easier and more economical for both manufacturers (called "subscribers") and their technology providers (called "suppliers") to work together. As most readers know, companies spend great amounts of time and money on FDA-mandated audits. All too often, those audits are repetitions of work previously done by others. By subscribing to the PDA-licensed SynTegra ARC, pharmaceutical and biotechnology companies can obtain the required data—completed by PDA-certified auditors using the published TR 32 process—for a significantly lower investment than performing their own onsite audit. As an extra quality check, all audits are validated or certified by a SynTegra in-house expert, before placement in the audit center "library."

Certified audits are placed in the audit center's library, where they are made available to subscribers. Confidential information is protected from disclosure to any entity other than the suppliers' prospective customers, thus safeguarding the supplier's valuable intellectual property.

The ARC also serves as a third-party broker in getting audits completed. When a requested audit is not yet available in the ARC, SynTegra contacts the technology provider to develop the relationship and schedule an audit.

[**Editor's Note:** For the opportunity to learn more, attend the breakfast. For a list of available audits, contact Deborah King, Audit Center Coordinator, at +1 (301) 216-2434 or DKing@SynTegraLLC.com.]

PDA Parenteral Drug Association Bookstore

Bestsellers

Technology Transfer: An International Good Practice Guide for Pharmaceutical and Allied Industries

Edited by Mark Gibson

A comprehensive overview and guide to the technology transfer process for pharmaceutical drug substance and products and the corresponding analytical methods and tests from R&D to production.

Item No. 17218 PDA Member $215 Nonmember $269

New feature: The table of contents and first chapter are available for download at www.pda.org/bookstore.

Risk Assessment and Risk Management in the Pharmaceutical Industry: Clear and Simple
by James L. Vesper
Explores the phases of the risk management process and examines how the various tools can be applied in identifying hazards and evaluating their potential impact and affects.
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Environmental Monitoring, Volume I, Volume II and Protocol CD
edited by Jeanne Moldenhauer, PhD
Describes methods for developing and operating an appropriate, sustainable microbiological program both in the lab and during production. Numerous useful protocols are included on CD.
Item No. 17239 PDA Member $480 Nonmember $599

Quality Control Systems for the Microbiology Laboratory: The Key to Successful Inspections **20% OFF**
by Lucia Clontz
Produce timely, compliant results through each phase of microbiology laboratory work using this guide that focuses on current issues and inspection trends.
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PDA Archive on CD-ROM – PDA Archive Retrieval Index (2006 version)
Fully-searchable four disk CD-ROM archive includes all PDA Journal articles, Technical Reports and Monographs, Technical Bulletins and select Conference Proceedings.
Item no. 01101 PDA Member $395 Nonmember $590

Encyclopedia of Rapid Microbiological Methods, Volume I, II, III
edited by Michael J. Miller, PhD
Focuses on regulatory and compendial initiatives currently in place that help pharmaceutical microbiologists and managers implement RMM in their facilities.
Item No. 17252 PDA Member $660 Nonmember $815

Good Manufacturing Practice Regulations, 21 CFR Parts 210-211, Sub-Parts B thru K Set of 10 programs – Shepherd Training CDs
Narrated by Dick Shepard
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Item No. 11014 PDA Member $1500 Nonmember $1695

Technical Report No. 39, Cold Chain Guidance for Medicinal Products: Maintaining the Quality of Temperature-Sensitive Medicinal Products Through the Transportation Environment
Provides guidance to both the pharmaceutical industry and regulators on the essential principles and practices for shipment of products which require controlled temperatures during transit.
Item No. 01039 PDA Member $75 Nonmember $150

Practical Safety Ventilation in Pharmaceutical and Biotech Cleanrooms
by Bengt Ljungqvist, PhD and Berit Reinmuller, PhD
Describes factors concerning risks of airborne contaminants in pharmaceutical cleanrooms.
Item No. 17233 PDA Member $225 Nonmember $249

Technical Report No. 42, Process Validation of Protein Manufacturing
Focuses on validation of biopharmaceutical processes used to manufacture therapeutic proteins and polypeptides produced from recombinant or non-recombinant cell-culture expression systems.
Item No. 01042 PDA Member $75 Nonmember $150

EM of Manufacturing and Storage Areas for Non-Sterile Oral Solid Drugs: A Survey

Don Elinski, Lachman Consultants

Although not universally deemed a CGMP requirement, many pharmaceutical manufacturers of oral solids have adopted some degree of design, monitoring and control of manufacturing and storage areas for viable organisms and, in some cases, nonviable particulates.

This trend has been driven over the years by corporate mandate, often due to multinational corporations attempting to adhere to the most stringent standard—the EU Zone Classification. EU CGMP 5.19 is interpreted by some to require a manufacturer to utilize a Zone D Classification, which involves closed processing, gowning requirements and airlocks to provide added assurance of environmental control. U.S. CGMPs as sometimes interpreted by FDA also has contributed to this trend, particularly the interpretation of 21 CFR Sections 211.42, 211.46, 211.56, 211.63, 211.67 and 211.113, which can be cited to require such action.

In an attempt to gauge current industry practice in this area, PDA surveyed a sampling of oral solid manufacturers to develop benchmarking data. Unfortunately, only fourteen firms responded to the survey, producing results that are statistically not valid. Therefore, the PDA Science Advisory Board voted to refrain publishing the results as a technical report. Because the results provide insight into industry practice, the SAB recommended that the results be shared with the PDA membership via the *PDA Letter* and website. The complete survey and its appendices are available at www.pda.org.

Because of the anonymous nature of the responses, one cannot make substantive judgments about the overall compliance of the facilities described herein to CGMP. One can, however, use the data in comparison to one's own facility to format acceptable scientific risk-based standards for the design, monitoring and control of nonsterile oral solids manufacturing and storage areas.

All of the data received (14 survey responders) were analyzed as follows:

- The results were calculated based on how many people answered each question.
- Multiple-choice questions were coded differently than yes/no questions. Each of the multiple-choice questions were broken down, including every option given in the question and tallied. Then, the number of respondents that chose a particular option was divided by the total number that responded to that question. Yes/no answers were coded by having "yes" represented by "1" and "no" by "0," and then taking the average for the question. The average represents the percentage of respondents that said "yes."
- Many of the multiple choice questions did not indicate whether it was possible to select a single option or whether a respondent was able to select multiple options. Therefore, there are many questions that result in a sum over 100%, because a respondent(s) selected multiple options for that particular question. Furthermore, some questions may total 99% or 101%, the result of rounding.
- The questions related to finishes used in particular rooms and results are shown in Appendices 1 and 2.

The complete survey and its appendices are available at www.pda.org.

Of the 14 responders, the majority were ethical producers of tablets (86%) and capsules (79%). A surprisingly large population of responses (72%) indicated that they also produced food supplements. Eighty three percent of the populations indicated that their practices were driven by normal industry practice for these types of dosage forms, with 33% indicating that they were following written corporate policies.

Facility design questions in the survey were broken down according to the type of processing area. These consisted of: compounding/processing rooms, corridors, equipment storage rooms, equipment washrooms, material storage areas located within the tablet/capsule processing areas, weighing subdivision and sampling areas and packaging areas.

In **compounding and processing areas,** rooms are designed as classified but are not monitored as such. If nonviable particulates are monitored, this appears to occur only when the area is not in use for production and may actually occur only at filter installation. Rooms are tested for viable organisms periodically (three to four times yearly) when not in production. The typical compounding/processing room carries a negative pressure differential at greater than 0.05 % WG as a design specification. Monitoring of the pressure differential in most cases is accomplished via a building monitoring system. Supply air in these areas is through HEPA filters located either centrally in the air ducts or in the ceiling of the room itself. No special precautions are taken during room/equipment cleaning for the ➤

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protection of the HEPA filters. Air returns are usually in the lower wall surfaces. Dust collection is accomplished via a central system, which is on continuously. When HEPA filters are changed in compounding/processing areas, the usual testing to IEST standards including air velocity, air change rate and DOP, or equivalent leak testing, is done. Additional sampling in these areas may include temperature and humidity monitoring with an out-of-limit excursion affecting batch release decisions.

Predominant finishes for **all areas in tableting and encapsulation** are epoxy for walls and ceilings and possibly floors. Responses regarding floor finishes were mixed, with some utilizing some type of rock or terrazzo. Metal doors made primarily of steel are used in these areas, with some responders using aluminum or some other type of metal. Floor drains may be located in compounding/processing areas, but are usually open only during cleaning activities.

Corridors generally follow the same indications and finishes as above, with perhaps a lessened frequency for viable organism monitoring. Generally, processing equipment is not used in corridor areas. The use of centrally located ASHRAE filters is higher than in processing areas. Air returns may be in ceilings or upper wall surfaces in corridors. Dust collection is not usually located in these areas. Some responders appear only to monitor for temperature in corridors. Floor drains are not usually seen in these areas. If the corridors are classified, airlocks separate them from unclassified areas. Double-door airlocks are used for material transfer in classified operations. Corridors are subject normally to daily cleaning.

Equipment storage rooms are, for the most part, dedicated and may or may not be classified. Nonviable particulate testing does not normally occur in these rooms, but viable testing for microorganisms may occur periodically (three to four times annually). Negative pressurization is maintained in these areas and is monitored by means of a building monitoring system. Air supply is accomplished through HEPA filters located centrally away from the room. Air returns are in the ceilings or along upper wall surfaces. No dust collection occurs in these areas. HEPA filter installation and testing is as per compounding/processing areas. Temperature control is more predominant in these areas. Floor drains are not a usual fixture for these areas, and if present, are open only for cleaning activities.

Material storage within tableting and encapsulation areas occurs in rooms of classified design…

Equipment washrooms may be designed as classified but are not monitored or operated as such. Most responders do not test for nonviable particulates, but do monitor them periodically when not in production on an infrequent basis (quarterly at most). Washrooms tend to be designed negatively pressurized at greater than 0.05 % WG. A building monitoring system usually monitors this parameter. Air supply is accomplished through HEPA filters located centrally away from the room. Air returns are in the ceilings or along upper wall surfaces. Dust collection in these rooms is not normal, but if it is used, it is on continuously. HEPA filter installation and testing follows other areas where HEPAs are used. Temperature and humidity controls are normal in these areas as well as floor drains, which remain open at all times.

Material storage within tableting and encapsulation areas occurs in rooms of classified design, but these rooms are usually not monitored or operated as such. Viable testing for microorganisms and nonviable particulate testing is not normally done in these areas. No pressure differential is usually kept. Air supply is accomplished through HEPA filters located centrally away from the room. Air returns are in the ceilings or along upper wall surfaces, but may be located in lower wall surfaces, as well. HEPA filter installation and testing follows other areas where HEPA's are used. Temperature and humidity controls are normal in these areas with excursions addressed during batch record review. Floor drains are usually not available in these areas.

Weighing/subdivision rooms generally are classified as Class 100,000. Periodic testing for nonviable microorganisms occurs in these areas periodically (usually annually) with testing for viable particulates occurring more frequently (every one to three months). All testing occurs when the area is not in production. Weighing/subdivision areas tend to be designed negatively pressurized at greater than 0.05 % WG. A building monitoring system usually monitors this parameter. These rooms have air supplied through HEPA filters mounted in the ceiling with air returns in the lower wall surfaces. No special precautions are taken to protect HEPA filters during cleaning. HEPA filter installation and testing follows other areas where HEPAs are used. Temperature and humidity controls are normal in these areas, with excursions addressed during batch record review. Floor drains are not normal in weighing and subdivision areas.

Packaging areas are generally nonclassified. It appears they are not tested for nonviable particulates, but may be tested periodically (annually) when not in production use for viable

microorganisms. If packaging areas are pressurized, they tend to be designed negatively pressurized at greater than 0.05 % WG. A building monitoring system usually monitors this parameter. Air supply is accomplished through ASRAE filters mounted centrally away from these rooms. Air returns are in the ceilings or along lower wall surfaces. Temperature and humidity controls are standard in these areas. Floor drains are not usually present.

External housekeeping contractors are most frequently used for cleaning corridors and storage rooms, with less likelihood of use for other production areas. Most areas are cleaned on a daily basis and include cleaning ceiling, walls and floor surfaces with an antimicrobial agent. Housekeeping is not allowed when materials are exposed in a room.

A slight majority of firms surveyed produce in a campaign mode (multiple batches without intervening cleaning). Campaigns can run for a fixed number of batches or a set period of time, whichever is exceeded first. After the campaign, the equipment receives more extensive cleaning and disassembly than after an individual batch. Room cleaning may utilize the same housekeeping as if the rooms were cleaned for an individual batch, or it may be more intensive.

Frequency of environmental monitoring for "objectionable organisms" ranges from one to four times per year in processing areas, filling rooms or booths and in weighing areas with lesser frequencies being more common in other areas. The results of such monitoring are considered in batch release decisions. Aerobic monitoring follows the same frequencies as for objectionable organisms. Fifty percent of the responders did indicate aerobic monitoring at least quarterly in packaging areas. Action/alert limits are set using historical data/statistics or are set at no more than 100 CFU/plate.

The survey also addresses equipment cleaning practices.

The author would like to acknowledge Jim Agalloco of Agalloco & Associates for the creation of the survey instrument and thank PDA for the collation of the data.

[**Editor's Note:** The survey results are available at www.pda.org.]

PDA Parenteral Drug Association Bookstore

What's New

New PDA-DHI Co-Published Technical Book

Risk-Based Software Validation: Ten Easy Steps

By David Nettleton and Janet Gough

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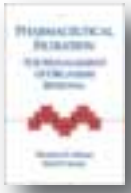

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Recent Sci-Tech Discussions: Environmental Monitoring, Terminal Sterilization and Precipitation

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

Recently, while visiting a contract manufacturer, we were told that the settle plates for environmental monitoring (EM) are prepared by quality control (QC) but exposed by manufacturing staff to reduce entry of personnel in the cleanrooms. The argument sounds logical and makes sense. On the other hand, GMP documents (including EU-GMP) state that EM is a part of the QC responsibility. I would request forum members to give their opinion on the acceptability of such a practice in light of the regulations and of the practicality.

Respondent 1: Yes, it sounds logical, but are the settle plates kept every day for monitoring? If yes, then the production staff can be made aware of the criticality of handling the plates and the right angle face of the plates, so as to enhance maximum chances of the microbe to fall on the plate and proliferate. It is a passive method. If you are not doing the plates exposure everyday, then you must be having the authorized list of personnel who have been authorized to go inside the sterile area. That will not really cause much difference in viable and non-viable counts at rest or in dynamic conditions.

Respondent 2: The question really is not one of practicality, but one of accountability. There are many practices that might be considered more practical than the current practice. For example, it might make much more sense to have QC report directly to the head of manufacturing. However, this might also make it difficult for QC to be objective. Manufacturing personnel should not be taking EM samples. They should be focusing on manufacturing. The EM samples, as a whole (surface, active viable air, active non-viable air and personnel), are the only checkpoints on the performance of the staff in the controlled areas, and I would be very concerned about temptation in a facility where this check on performance was being conducted by the people being monitored. I have heard several manufacturing directors try to make the case that their personnel should be the ones taking these samples. Practicality, training (this argument runs that the microbiologists assigned to the task are the most poorly trained in the microbiology department, and so most contamination events are due to technician error), and motivation seem to be the most common arguments. However, ignoring a debate on the value of these arguments, there is no getting around the desirability of having people independent of the manufacturing chain of command taking, handling and reporting these samples.

Respondent 3: It is a QC responsibility that the sampling be performed, and performed properly; but this is a function often delegated to production staff to perform according to the QC standard operating procedure (SOP), and with QC oversight that they are doing the sampling properly.

Respondent 4: If quality can verify placement, and operators are trained in handling and placement of settling plates, the EM program is still under quality and should be okay.

Respondent 5: As the issue sounds logical, it should be acceptable that the settle plates are exposed by sterile area production personnel, provided following conditions are met: (1) The same simulation should take place during media fill trials. (2) The production personnel should know the designated locations for the exposure of plates. (3) The exposure time limits to be known by the production personnel. Above all, they should have enough demonstrative training on the overall activity of receiving the plates into the sterile area, their exposure, their collection after exposure and finally returning them outside.

Respondent 6: Environmental monitoring is indeed a part of QC responsibilities and is a check that activities are performed in production areas that do not increase the viable counts. This check must be independent to be objective and to give a true picture of the situation. I fully agree with the views of Respondent 2 on this.

Respondent 7: Please consider that the operators are not the only ones subject to temptation, as a QC person placing plates is also now part of the process and is monitoring his or her own activities as well. Therefore, the same temptation exists for him or her.

Respondent 8: Yes and no, but mainly no. The QC independence from the manufacturing chain of command is a critical safeguard—you cannot argue that the ideal situation involves unsupervised personnel in a tasking situation monitoring their own performance. It is just not a wise manner

in which to operate. I do agree that if you find thumbprints in the agar, or other evidence of QC mistakes, the operators may be motivated to correct them before the plates get to the lab. No system is completely foolproof, but some are much better than others.

Respondent 9: Yes, but if you remember my original note, I included verification of placement, thus, not unsupervised. I also believe that as with other processes, if validation is conducted with operators placing plates and routine audits of the placements, and the technique of the operators is in place, the system can work, even though, as you correctly point out, "the more control the safer you are." The hard part, I suppose, is always the balance and judging the commitment and competency of all parties to find the balance that allows us to achieve what is ultimately the goal of a quality product.

Could someone please refer me to a regulation where the revalidation of a terminal sterilizing system is described? Specifically, I am looking for a schedule for revalidations; i.e., one year or six months or less. As well, what is the minimum requirement for such a revalidation? Thanks very much.

Respondent 1: I prefer to use the term revalidation as only a reference when discussing assessment of changes made to the system. When referring to time-based evaluation, I prefer to use the term periodic monitoring. There is a European guidance that discusses yearly monitoring for autoclaves. If you are not concerned with European guidances, then you set your own minimum requirements based on the robustness of the change control, preventive maintenance, and other quality systems in place that control your terminal sterilization equipment and procedures.

Respondent 2: Sterilizers, autoclaves, depyrogenation tunnels, etc., are normally done on an annual basis. There are, of course, exceptions but this is the best *industry standard* we have.

Respondent 3: If you remember the defunct proposed 21 CFR 212,"CGMPs for LVPs," from 1978, this called for requalification of sterilizers "at least annually." These proposed regulations died, but industry leaped upon them, and it became standard (dare I say "current" under CGMP) to perform sterilizer revalidations annually. There may even be mention of it in some FDA guidelines.

Can anybody help us by solving precipitating in diclofenac injections? Do we not know why the precipitate is happening in only few ampoules, and not in all?

Respondent 1: You have the kind of problem that challenges scientists to justify why they get paid. But, such problems do happen. The problem may be defined as limited, random or failed containers. You must do all you can to identify the precipitate compound/material. Limited contamination of containers or equipment is one of the typical causes of such problems. I am aware of at least two possibilities. One is the residue of cleaning or sanitizing agents in the packaging line. When this happens, the contamination will get only into the first few packaged containers. This residue contamination may cause incompatibility and precipitation. Another possibility for such contamination is that some problem in your ampoule washing machine may lead to incomplete cleaning of a few ampoules, leaving residue in some ampoules. Also, check for possible problems with the water supply. A third possibility is leaching of heavy metal ions from some ampoules. This would seem unlikely. It may be that just a few ampoules were briefly exposed to high temperatures, or some such factor. I think you really need to identify the precipitate and its chemistry to know what may have happened.

Respondent 2: The quality of steam vapor used for autoclaving can also generate these troubles. Another suggestion is autoclaving the good ampoules and bad ones and see if the number of particles increases. If this happens, then incompatibilities are the most probable explanation.

Call for Volunteers

The PDA Mycoplasma Task Force, co-chaired by Barbara Potts (Genentech) and John Geigert (BioPharmaceutical Quality Solutions) is seeking technical volunteers to participate in four important subgroups:

1) Standardization of mycoplasma removing filters
2) Inactivation/removal of mycoplasma from pharmaceutical processes
3) Emerging mycoplasma issues from insects and plants
4) Standardization of mycoplasma test methods

We encourage you to make a difference for our membership and our industry. Please contact Iris Rice (rice@pda.org) to volunteer. Please provide a short bio and indicate on which subgroup you would be interested in serving.

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Message from the Editor

Walter Morris, PDA

60 Years of PDA Contribution: Parenteral Science, Technology and Regulations

Sixty years ago, the Parenteral Drug Association was formed in New York City by six founders who wanted to build an organization of professionals to help the pharmaceutical industry meet the scientific and regulatory challenges associated with large-scale, industrial parenteral production.

Needless to say, the science and technology used in the industry has changed significantly since 1946. From advancing technologies for sterilization, filtration and information systems to implementing modern barrier systems, isolators and robotics, PDA's talented and diverse membership has been at the forefront of change.

To understand PDA's ongoing role in the advancement of sterile product manufacture, all one has to do is look at an agenda from a PDA annual meeting or the line-up of courses sponsored by our Training and Research Institute (TRI) or review our publications catalogue.

When the schedule for the *PDA Letter* changed to 10 issues annually, PDA decided to dedicate the first "double edition" of each year—the July/August issue—to the Association's core area of contribution. This year, we are proud to publish three diverse features on sterile products/aseptic processing that address scientific, technological and regulatory issues. The first one challenges the practice of hold time validation in "Time-Out for Hold Time Validations" by **Rainer Newman,** Johnson & Johnson (p. 20). In "Automating Aseptic Processing to the Max" (p. 24), we present two case studies of advanced aseptic processing designs: "Aseptic Processing: The Handai Way," by former PDA Chair **James Akers,** PhD (Akers, Kennedy and Associates Inc.), **Mashito Kawata** (Osaka University) and **Kazuhito Tanimoto** (Shibuya Kogyo, Ltd.) and "Aseptic Processing: The Vetter Way," a discussion between PDA and Vetter's **Jörg Zimmermann.** The last feature, "The Risk of Microbiological Contamination" (p. 34), by **Anthony Cundell,** PhD, a Consulting Microbiologist, elaborates on recent regulatory actions and changes in the industry that might have raised the risks of contamination.

That's not all! In the Science and Technology section we have reprinted a number of recent Sci-Tech Discussions on issues important to parenteral manufacturers (p. 13).

Besides the regulatory briefs that we include in most issues, our Quality and Regulatory Affairs sections features a contribution from German Inspector **Jeorg Neuhaus** on complying with the EMEA's new Product Quality Review requirement (cover).

PDA's Senior Chapters Liaison, **Henry Kwan,** files his first report on chapter activities in the Membership Resources section (p. 40). In addition, the section includes a summary and photos from the May 2006 conference on validation, sponsored by the Italy, France and Spain Chapters (p. 42).

This issue also includes six pages of photos from the 2006 Annual Meeting (pp. 46-51), at which PDA celebrated its 60th Anniversary with one of the best attended annual meetings in years. The conference included sessions on rapid microbiological methods, barrier systems, and groundbreaking manufacturing science for traditional and biologically-derived parenteral products. In June, PDA continued its series of training workshops on the U.S. FDA guidance on aseptic processing in Prague, Czech Republic. Later this year, PDA is sponsoring conferences on pre-filled syringes and microbiology in the United States.

Finally, the July/August issue serves as PDA's "show issue" for the upcoming PDA/FDA Joint Regulatory Conference (pp. 44-45). Conference Chair **Cindy Rockel** (Millipore) introduces the keynote speakers, the exciting networking events are described and the TRI courses and conference Exhibitors are listed.

We hope you find this special issue of the *PDA Letter* useful and informative. Thanks for reading!

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VISIT US AT THE 2006 PDA/FDA JOINT REGULATORY CONFERENCE IN WASHINGTON, DC, SEPTEMBER 11-13, TABLE #35.

Time-Out for Hold Time Validations

Rainer Newman, Johnson & Johnson

The sterile hold vessel is validated for five days, and we want to extend it to eight days. What do we have to do?

The vessel hold time is validated at 48 hours. We exceeded this by 4 hours. Do we have to reject the product?

We have 21 tanks; do we have to do a hold time validation on each one?

Questions such as these arise as the result of the common practice of validating the time period for holding sterile in-process vessels, including process tanks and lyophilizer chambers, used during aseptic processing. Certain regulatory provisions contribute to the perception that the time per se for sterilized vessels must be validated. 21 CFR 211.111, "Time Limitations on Production," for example, requires "time limits for the completion of each phase of production." The 2004 FDA aseptic processing guidance calls for the establishment of "time limits for holding sterile…containers and closures." Further along, the guidance says that "time limits established for various production phases should be supported by data."[1]

Our industry's belief that "time" alone is critical and must be validated is counterproductive and not very scientific. Of course, no one believes in "spontaneous generation" (the theory living organisms can arise from inanimate materials). Even so, it seems we do continue to struggle with the fact that any sterile material will remain so indefinitely until, and unless, contamination from a living organism is introduced. While we implement and validate a host of controls and procedures to sterilize and hold our in-process vessels, both before and after placing in-process materials into them, oftentimes operators and quality professionals, as well as regulators, get caught up worrying about the time period itself. In our validation activities, we should place much less emphasis on the actual time period—the hold time validation—and increase our efforts to validate the activities and events that the vessel is subject to before, during and after the hold period. Once we accept that we only need to validate these contamination prevention procedures, we can move away from this concept of "hold time validation."

Once we accept that we only need to validate these contamination prevention procedures, we can move away from this concept of "hold time validation."

Under current expectations and practices, aseptic manufacturers typically validate a specified hold period (usually denominated in hours or days), which is called "hold time validation." They usually do this by keeping sterile media in a sterile tank for a predefined amount of time before examining the media to determine if the acceptance criteria were met, i.e., non-turbidity. Then, for additional assurance, the validated hold time is adjusted downward to include a "safety margin" by requiring the operational hold time limit to be something less than the time applied during the validation. This eventually leads to the situation where the operational hold time is exceeded, with the usual result that the deviation is accepted on that basis that it was within the validated time. Sometimes, of course, even the validated hold time is exceeded. It is common for regulators to request the data from this process hold validation and to see reports when there are deviations.

Instead, the sole focus should be on "process hold validation"—the demonstration that the conditions under which a vessel is held and the measures employed to control and monitor that vessel during the hold period are adequate to prevent contamination. This process would abandon the unscientific demonstration of "how long" sterile media remains sterile.

Of course, it is imperative to first conclusively determine that the materials involved are sterile. This involves ensuring that:

1. The interior of the vessel is sterile (typically via SIP with saturated steam).
2. The materials introduced into the vessel are sterile (typically sterile filtration).
3. The transfer of the sterile materials into and out of the vessel does not introduce contamination during the transfer (usually achieved through maintaining a closed, sterilized system that has been treated as part of the SIP process and/or sterilized connection made aseptically).

Once sterile starting materials are confirmed via rigorous validation procedures, the process hold validation effort can proceed. Good risk management should be incorporated into the validation design at the outset. Failure Modes and Effects Analysis (FMEA), or a similar assessment process, should be used to identify the risks inherent in the system that could cause the failures such as the following:

1. Loss of container integrity, including seal leaks, vent filter damage, loss of positive pressure, etc.

2. The existence of contaminants and the means of introducing contaminants into the vessel.

Of these two risk areas, maintaining integrity is a much more robust and controllable activity than is preventing the existence and introduction of contaminants, largely because the former can be known and controlled with high degree of certainty, while microbiological detection and control is, at best, a delayed estimation of the true conditions. Although it remains good compliance and good practice to employ high levels of microbial control and detection of potential contaminants, a zero CFU environmental result only demonstrates the likelihood of continued good control; it does not represent additional proof of continued assurance of sterility. A good environmental result cannot confirm sterility, but an undesirable result will certainly raise questions about the continued assurance of sterility.

With these concepts in mind, it becomes clear that what manufacturers are trying to demonstrate with hold time studies has little to do with time and much to do with equipment and process activity. As noted earlier, because system integrity is essentially an absolute factor and is relatively easy to establish, control and monitor, it should receive most of our attention in designing a hold validation, as well as during routine use. In other words, the main focus should be on eliminating the possibility of introducing a contaminant by controlling and measuring vessel integrity factors. The validation should address equipment integrity, procedures and processes (including the environment) that might affect the equipment.

Since the outside of the vessel and the surrounding environment are not typically sterile, we must assume any breach in vessel integrity will result in a reduced assurance of sterility. Nevertheless, it remains common sense, a regulatory requirement and good aseptic technique to store vessels in an environmentally acceptable area and to handle them in an aseptically acceptable manner.

In my opinion, the critical monitoring and control points are those that maintain and indicate continued vessel integrity, because a loss or degradation of these critical indicators would imply a risk of potentially introducing a contaminant. Depending on the vessel and its intended method of maintaining integrity, these critical indicators include:

- Sterile gas over-pressure
- Vent filter integrity
- Component integrity (e.g., gaskets, head bolts, valves, and other penetration sealing systems)

Of these, the over-pressure and filter integrity are typically the most obvious and important. Where a vent filter is employed, the filter and the tank integrity are paramount; where over-pressure is used, loss of pressure is usually indicative of failures in almost anything else relevant to maintaining sterility.

…it becomes clear that what manufacturers are trying to demonstrate with hold time studies has little to do with time and much to do with equipment and process activity.

So, what should a process hold validation look like? Below, I have outlined a feasible seven-step validation:

1. Ensure the sterilization of the vessel and whatever is intended to be placed into it have been sterilized via a robustly validated method.
2. Determine a hold period that the process requires. The above discussion notwithstanding, there does need to be an upper limit, not because time is a risk *per se*, but because more time means greater opportunity for an integrity-compromising event to occur. Furthermore, regulators require specified hold times, are accustomed to seeing holds defined in terms of time and are especially uncomfortable with long and undefined periods. (Stability of the in-process materials is also a major concern, but not the focus of this article.)
3. Determine the equipment, devices, processes and procedures involved in filling, moving, storing, and dispensing material from the vessel.
4. Based on equipment and process steps, perform a risk assessment and rank the risks for failure potential, i.e., for losing integrity.
5. Determine the most appropriate equipment and method to control and monitor the vessel during the hold period.
6. Conduct tests and stress the environment and actions in alignment with the risk level. For example:
   a. If it is planned to store a vessel at an overpressure of +5psi (35 kPa), then validate the capability to hold at +2psi (14 kPa). Constantly monitor the pressure.
   b. If vessel movement is involved, include that movement in the validation, but in a more stressful way. For example, if normal operation of the vessel involves moving it once to another location and back, move it *five times* during the validation.
7. Confirm that the vessel and the contents have remained sterile.

Can the concept of bracketing be applied to process hold validation when a large number of tanks are involved? I believe so, given that bracketing for containers is acceptable in medial fill designs. One would have to evaluate the various vessels (components, construction, purpose, etc.), group together vessels with similar controls and risks, and apply a risk-based method to justify the bracketing. This approach will help firms identify common control and monitoring parameters that make sense for a given grouping. Installation qualification and operational qualification of each tank would still be required.

To return to the opening questions, I might respond:

The sterile hold vessel is validated for five days, and we want to extend it to eight days. What do we have to do? If time by itself is a non-factor when holding a sterile vessel, adding (or deducting time as a safety margin) has no meaning. Safety margins should be based on stressing the system in terms of the risks discussed above, not in terms of time. Evaluate what elevated or additional risks are introduced by the extended time period, challenge those and ensure continued ability to meet the acceptance criteria.

The vessel hold time is validated at 48 hours. We exceeded this by four hours. Do we have to reject the product? No, as long as all the critical control factors are all within the validated parameters. Determining this constitutes the principle component of an investigation that I would, barring any negative outcomes, judge as being otherwise in compliance without additional risk of non-sterility. Clearly this does not address other issues resulting from the extended hold period, such as the aforementioned stability. This approach complies with the regulations, as 21 CFR 211.111 states: "Deviation from established time limits may be acceptable if such deviation does not compromise the quality of the drug product. Such deviation shall be justified and documented."

We have 21 tanks; do we have to do a hold time validation on each one? If we use the concept of bracketing, and there is a logical and rational grouping, plus a specific confirmation of integrity for each tank, no, you do not have to validate the hold time for each one.

Reference

1. FDA Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice, September 2004. p.17 and p. 20.

About the Author

Rainer Newman serves as Executive Director of Technology Support at Johnson & Johnson and has over 30 years of experience in the pharmaceutical industry. He is active in a number of professional associations and currently sits on the *PDA Letter* Editorial Committee. He is a veteran of the U.S. Army and served in Vietnam.

Recommended Resources

For more information or to purchase these publications, visit www.pda.org/bookstore.

Environmental Monitoring, Volume I, Volume II, and Protocol CD
These two volumes, with more than 50 chapters written by subject matter experts worldwide, describe methods for developing and operating an appropriate, sustainable microbiological program for production and the laboratory. Numerous useful protocols are included on CD.

Cleanroom Microbiology for the Non-Microbiologist, Second Edition
The book also introduces the types, sources, control and elimination of organisms encountered in the manufacture of sterile products as well as the applications for bacterial detection, avoidance of contamination and cleanroom design considerations.

Cleanroom Clothing Systems People as a Contamination Source
This is the first comprehensive scientific analysis of cleanroom clothing systems for particulate shedding. This book provides detailed specifications on various "clean" garment systems.

PDA Technical Report 13 Revised, Fundamentals of an Environmental Monitoring Program
The purpose of this document is to identify microbiological and particulate control concepts and principles as they relate to the manufacture of sterile pharmaceutical products. It expands substantially upon the first edition.

Points to Consider for Aseptic Processing - *PDA Journal of Pharmaceutical Science and Technology:* 2003 Supplement Volume 57 Issue 2
The document represents over 18 months of dedicated work by the Task Force members. It presents the issues framed as problem statements with both a recommendation and a rationale for the recommendation provided.

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Automating Aseptic Processing to the Max

Using Isolators and Robots in Japan, RABS and Robots in Germany

Increasingly, regulators are expecting high-tech designs for aseptic processing in order to achieve greater sterility assurance for parenteral product fill and finish operations, with the primary goal being the limitation of human interventions.

Just recently, the U.S. FDA's **Robert Mello,** PhD, reinforced this view at an industry conference on biotechnology (AAPS, June 19-21), where he emphasized that CDER wants to see "people taken out of the process" whenever possible in aseptic processing. PDA contacted CDER's **Richard Friedman** to confirm the expectations of the Center. He stated:

"There is significant uncertainty inherent in manual or semi-automated aseptic operations. As aseptic processes become more automated and protected, there should be a corresponding reduction in uncertainty. Many of the factors in traditional semi-automated and partially protected aseptic operations are difficult to measure and interpret, so risk assessment is to some extent confounded. It is particularly difficult to measure the everyday performance of people. While these manually oriented processes are not easily characterized, modern technologies like robotics and isolators tip the balance away from dependence on people and toward measurable processing characteristics. The more mechanically dependent processes also provide better data for trending which will facilitate continuous process improvement. In modern aseptic processes, design, control, and maintenance of equipment become primary, and the potential of an operator to pose a direct contamination risk should increasingly become secondary."

Friedman was the lead author of FDA's 2004 aseptic processing guidance, which emphasizes the regulatory and quality advantages of using advanced design approaches.

The following two articles demonstrate how advanced technologies, like isolators, Restricted Access Barrier Systems and robotics, are being applied to meet this goal.

PDA wants to hear about your advanced aseptic processing facility. Please contact the *PDA Letter* editor at morris@pda.org and include "advanced aseptic processing" in the subject line. Your case study will be considered for inclusion in the 2007 July/August issue of the Letter on aseptic processing/sterile products.

Aseptic Processing: A Vetter Way

Walter Morris, PDA

Vetter Pharma-Fertigung GmbH & Co. KG, a contract manufacturer based in Germany, boasts modern aseptic fill/finish operations that rival the best in the world.

A variety of advanced technologies works seamlessly together like a fine orchestra to create a symphony of high productivity, improved quality and solid compliance that soothes the concerns of all Vetter's customers. These technologies include Restricted Access Barrier Systems, continuous particulate monitoring devices, active air sampling via gelatin filtration, and robotics.

It was the foresight, creativity and commitment to higher standards of Vetter's senior officials, not a corporate reaction to regulatory actions and customer specifications, that has resulted in "automation to the max," according to Vetter's **Jörg Zimmermann,** Head of Production, Langenargen. The firm strongly believes its processes offer the maximum product contamination and environmental controls, with the minimum operator interference with the product possible. In addition, the processes have proven after numerous inspections—both pre- and post-approval—to be compliant with all relevant GMP requirements.

continued on page 25

Aseptic Processing: The Handai Way

Jim Akers, PhD, Akers Kennedy and Associates; Kazuhito Tanimoto, Shibuya Kogyo Co. Ltd.; and Masahito Kawata, Handai Biken

[**Editor's Note:** This article is excerpted from "Aseptic Processing, the Japanese Way," which appeared in the June 2006 edition of *Pharmaceutical Manufacturing* (vol. 5, is. 6). This excerpt is reprinted with permission of the authors and Putman Media, which retains all rights to the article and photos.]

While the global pharmaceutical industry tends to be conservative in nature, its implementation of newer technologies for aseptic processing has been impressive—and nowhere more so than in Japan. Shibuya Kogyo (Kanazawa, Japan), in conjunction with La Calhene (Vendôme Cedex, France), introduced isolators for aseptic manufacturing to the Japanese market in 1994. Over the last dozen years, more than 40 isolator-based production lines have been installed and validated throughout the country.

Isolators are used in a wide variety of applications, including both large- and small-volume parenterals, lyophilized products, powder fills, combination products, medical devices as well as more typical liquidfills into a single

continued on page 30

Aseptic Processing: A Vetter Way, continued from page 24

Over a decade ago, the firm set out to build one of the most modern and automated fill/finish operations in the world at its new Langenargen site. The first consideration was how best to separate the operators from sterile products, components and equipment. At the time, isolators were starting to gain a foothold in the pharmaceutical industry for aseptic filling. After careful study and consideration of its processes and products, however, Vetter took a different path, choosing to employ Restricted Access Barrier Systems (RABS).

As a contract manufacturer with the objective to serve many clients and manufacture a variety of products, Vetter believed RABS offered the kind of flexibility the company would require. In addition, RABS could easily be retrofitted to the firm's older processes at its facilities in Ravensburg, Germany. RABS is also in use at the company's newest facility in Ravensburg, which will add four additional commercial clean rooms to Vetter's existing 12.

While the RABS separate the operators from the process, Vetter's use of robots to move sterile components between processing equipment removes operators from the process.

A robotic arm places vials in the lyophilizer

Zimmermann explains that RABS is not an automatic choice: "In one of the steps of the design phase, we sit together and say, 'This is the product, this is the new process, and what is the best cleanroom design for both?' If we were doing a product next which would need special handling, we might use an isolator, especially if operator protection would be an issue."

Vetter puts a lot of effort into ensuring that the RABS properly fits the filling lines. They start with a life-sized model of the line based on basic process designs. To determine the best set-up of the RABS, Zimmermann explains, "We determine where operators have to reach, where they have to do manipulations and what does the barrier have to look like to do that. It is something where you have to do a lot of forward thinking, but in the end you get a process that can operate with the door closed." That final point is very important.

With the doors shut during an entire fill, Vetter's RABS acts almost like an isolator, save for being hermetically sealed. Zimmermann created a scale to rate Vetter's RABS. If a conventional cleanroom with the operator directly in the ISO 7 area doing manipulations on open products is a 1 and a fully sealed isolator is a 10, Vetter's RABS "would rank as a 7 or 8." On top of this highly effective barrier, Vetter maintains an ISO 7 environment outside of the RABS, with operators completely gowned with gloves and goggles.

While the RABS separate the operators from the process, Vetter's use of robots to move sterile components between processing equipment removes operators from the process. Zimmermann says that with the robots, two operators are necessary per line, but without the robots, five per line.

The rationale for using the robots, however, is the critical nature of the jobs they perform. The robots function at the steps of the process where human intervention is riskiest, such as moving trays of syringes or vials from the dry heat tunnel to the filling line. "If you can avoid human interventions there, it gives you more protection for the product."

The company chose to use robotics in the aseptic process when it first committed to building the Langenargen facility. "Initially when the lines were designed with the robots, in 1993-94, people were still a little hesitant to depend on robots and rely on software. I think we have come a long way since then. The robots were already quite good when we installed them, but they have been trained and have the logic behind them to do their tasks." Surprisingly, Zimmermann says the robots rarely fail. "I think I've had in the last two years a robot fail once, requiring a stoppage of the line for maybe an hour or two." Twice a year,

Vetter maintains the robots, which requires about half a day of work.

Zimmermann told a recent ISPE conference that the technical availability of the line is "95%, usually in excess of 98%. So in the time that I have assigned for the fill, I will have almost no failures due to mechanical malfunctions or robot malfunctions." Not knowing for sure, Zimmermann believes Vetter's technical availability rate is quite good and impressed the audience at the ISPE conference.

In addition to the RABS and the robots, Vetter has over 10 years experience using continuous particulate monitoring systems and active air sampling with the gelatin filtration method, both of which are becoming common throughout the industry. Zimmermann notes that both systems can be retrofitted "relatively easily to existing lines," and the firm has done so for each of its cleanrooms. Active air sampling is combined with traditional settle plate sampling. The former allows the company to correlate counts to air volume; the latter allows for correlation to exposure time and surface area, he said.

On top of the highly automated and modern fill lines, Vetter has an aggressive "quality on the floor" approach that utilizes Six Sigma principles and draws in support from manufacturing and other divisions of the company. At the PDA 2006 Annual Meeting in April, Vetter's Bernd Renger, PhD, Director of Quality Control, discussed "quality on the floor." While the new approach means higher investments of time, capacities and training, the company has witnessed solid returns in terms of prevented or easily closed deviations, complaints and other issues.

Vetter is extremely satisfied that its operations are meeting the highest quality and compliance standards. Of more than 1,000,000 units filled during medial fills at the Langenargen plant (through Aug. 2005), the company had only one contaminated unit. The environmental monitoring data for the ISO 5 area is impressive with two deviations in 2002, one in 2003, four in 2004 and four in 2005 (out of an average of 14,000 samples per year). Its regulatory record is excellent as well. Zimmermann states that an investigator during a 2005 inspection deemed the fill/finish line as "low risk."

Vetter clearly has raised the bar in aseptic processing. Overall, the company is certain it has made the right decisions in investing heavily in advanced processing and control technologies and innovative quality systems. These decisions have helped the company achieve higher productivity, improved quality and an impeccable compliance record.

Vital production statistics at Vetter

Langenargen site

Operations:	5 filling lines
Container Formats:	Vetter LyoJect syringes, cartridges, various liquid prefilled syringe sizes, vials
Filling speeds:	70-200 units/minute (depending on the container format)
Stoppers:	various designs
Production types:	Recombinant proteins and conventional drug substances.

Company-wide

Sites:	Ravensburg, Langenargen and Ravensburg Vetter Sued
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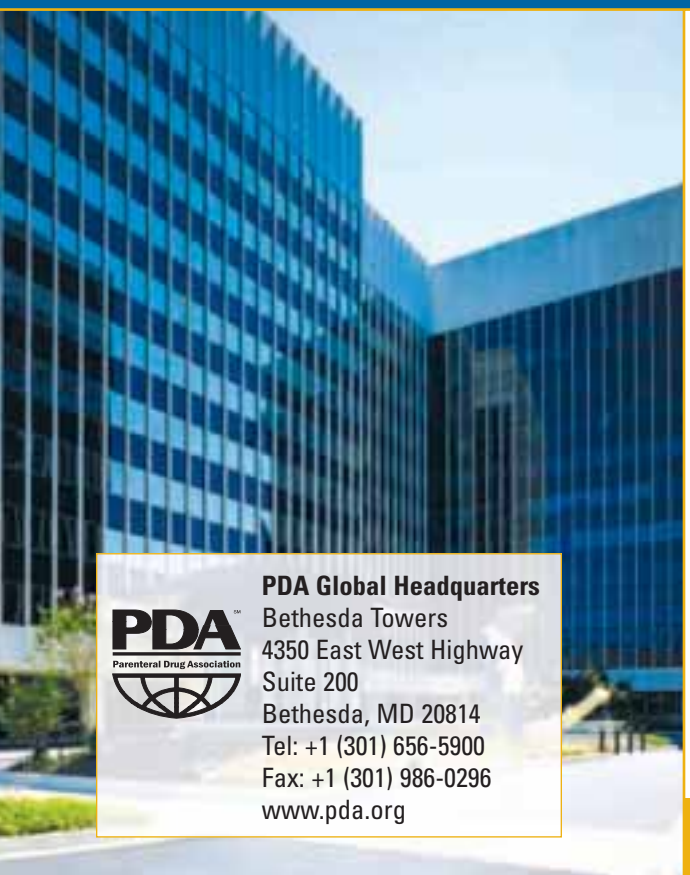

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Millbrae, California

August 11, 2006
PDA Midwest Chapter
2nd Annual Golf Outing
Wheeling, Illinois

October 10, 2006
PDA Southeast Chapter
PDA Southeast Chapter Fall Meeting and Vendor Show
Chapel Hill, North Carolina

Aseptic Processing: The Handai Way, continued from page 26

container. In addition to advanced aseptic processing environments such as isolators, Japanese firms have been more aggressive than some of their international counterparts in the adoption of factory automation and robotics.

A Case in Point: Handai Biken

The following case study serves as an excellent example of a modern Japanese aseptic processing facility. This aseptic processing manufacturing line is installed at the Handai Biken facility in Kagawa, Japan, and is dedicated to the aseptic bottling of vaccines in vials. The Kagawa facility was built and the equipment installed in 2004, and commercial production of vaccines commenced in 2005. The facility can produce lyophilized and liquid-filled vials.

All product filling, lyophilization and stoppering at the site are conducted in vertical unidirectional airflow isolators, which are designed and operated to comply with IS0 14644 Class 5 requirements. The environment surrounding the isolators complies with ISO Class 7 requirements. Handai Biken developed user requirement specifications (URS) for this project, in order to minimize the risk of contaminating the biological products. The production systems are designed to minimize particulate contamination as well as human intervention. Additionally, a number of design features were implemented to ensure high yields and minimal line stoppages.

The project consists of five isolator sections:

1. Between the tunnel and filler (3.9 m^3 total enclosed volume)
2. Filling/stoppering machine (4.8 m^3)
3. Rubber stopper supply system (16.9 m^3)
4. Lyophilizer conveyor (3.9 m^3)
5. Automatic lyophilizer loading/unloading (17.0 m^3)

The total enclosed isolator volume for these five sections is 47.4 m^3. To facilitate vapor hydrogen peroxide decontamination, the isolators are divided into two sections. The first section, which consists of the isolators described in items 1-4 above, has a total enclosed volume of 30.4 m^3, while the second decontamination group consists only of the fifth isolator.

Decontamination is accomplished by VHPM1000S vapor phase hydrogen peroxide generators sourced from Steris Corp. (Mentor, Ohio). The isolator network is divided into two sections for decontamination, in order to ensure that the total volume and surface area to be treated is within the capacity of the vapor phase hydrogen peroxide generators.

All product filling, lyophilization and stoppering at the site are conducted in vertical unidirectional airflow isolators.

The isolators are equipped with dehumidification units to reach the relatively low humidity levels required by the Steris vapor phase hydrogen peroxide generators prior to the decontamination process. Decontamination of the isolators was validated using *G. stearothermophilus* biological indicators on stainless steel coupons with a population of 10^6 spores per indicator. The acceptance criterion for decontamination was complete kill of all biological indicators placed within the isolators.

Following are functional descriptions of each major piece of process equipment on the line:

Vial washer: The vial washer uses hot water for injection and, in typical washer designs, this results in the formation of water vapor under the top cover of the machine. Handai Biken engineers were concerned about the negative air pressure that would develop within the top cover. With Shibuya, they developed a doubleshell washer system, in which positive HEPA-filtered air is supplied between the outer and inner shells of the machine cover to preclude the entrainment of particulate matter from the surrounding environment. This ensures that the vials are washed and handled in a clean, high particulate air quality environment.

Dry heat tunnel and interface isolator: The dry heat tunnel is equipped with a fully dry-heat-sterilizable cooling zone, which can be sterilized by dry heat at 170°C for 20 minutes during changeover periods. This sterilization process is fully validated. A vial counting system is used in front of the inlet to form a single row and ensure the smooth feeding of glass with minimum pressure on the glass pack. Rows are fed intermittently to ensure that no horizontal pressure is applied to vials already moving on the conveyor. Thus, minimum horizontal pressure is required to feed each row of vials onto the conveyor, which eliminates "crashing" of glass and prevents particulate formation, or vial breakage resulting from hard glass-to-glass contact.

Aseptic filling machine/rubber stopping machine and isolator: Fill mass (volume) is controlled by means of eight mass flow meters, each of which supplies a single fill point or needle. All filling data are digitized and stored electronically. This enables the system to record the precise fill data including mass, vial number and time and to display this data on the control panel. A full summary of all filling data for each filled unit can be printed out on a daily basis. All product contact

Vital production statistics at Handai Biken

Filling speeds:	400 vials/minute for 2-mL vials and 200 vials/minute for 7-mL vials. In the future, the system will be equipped to handle 10-mL vials
Container type:	Glass vials, 2 mL and 7 mL
Stopper types:	Five types of rubber stoppers are used: lyophilization stoppers for both 2-mL and 7-mL vials, and three different types of conventional stoppers for 2-mL vials
Aluminum caps:	Two types, one for 2-mL containers and another for 7-mL containers
Product types filled:	A clear vaccine solution with a mean viscosity of 2 cp., and a vaccine suspension, which will sediment without mixing

Stoppers removed by robotic arm from the autoclave are then unloaded into stopper bowls, obviating the need for human intervention.

parts within the mass flow meters are composed of 316L stainless steel. The mass flow meters can be fully cleaned and sterilized in place.

Handai Biken engineers specified that, in addition to the mass flow metering system, fill weights must also be taken gravimetrically. Eight load cells can perform the fill-weight function in approximately ten seconds. The gravimetric weight check system was originally used at 15-minute intervals throughout the filling operation. Because the flow-metering system proved to be extremely accurate and reliable, the engineers decided that it was not necessary to check fill volumes gravimetrically throughout the filling process. Actual mass flow fill accuracies have been +/- 0.5%, which is well within the +/- 1% validation acceptance criterion. Therefore, fill volumes are now checked by the load cells only for reference purposes during set-up.

The fill machine's cantilever construction allows for all maintenance to be performed from outside the isolator enclosure. Also, there is no equipment located under the filling needles, which allows air to flow undisturbed to the air returns on the floor of the machine. This design ensures undisturbed unidirectional airflow through the critical aseptic zone.

Rubber stopper supply system: The rubber stopper supply system is one of the most important design features of this entire processing system. Handai Biken and Shibuya Kogyo recognized that one of the most frequent interventions required in aseptic vial processing lines is to stage rubber stoppers and manually place them into the stopper feed hopper. In a filling system capable of line speeds of up to 400 vials per minute, stopper supply can be labor intensive, and batch processing of stoppers would require significant storage space after autoclaving. It was also determined that, at the stopper consumption rate required for this filling system, the use of a rapid transfer port or "Beta-Bag" system might not be practical.

To resolve these issues, Shibuya provided a stopper washing system that washes each stopper individually to ensure gentle handling and minimal particulate generation. The stopper washing system automatically feeds the stoppers into custom-designed stainless steel stopper cans, which are perforated for good steam penetration during autoclaving. These cans are fed automatically into a dedicated autoclave in which all stoppers are sterilized using a validated moist heat process.

After the cycle is complete, the autoclave is automatically unloaded using robotics, and the sterile stopper-filled cans are accumulated within a

conveyor inside the stopper supply isolator. Robots lift the cans and tip the stoppers into the hoppers as required. Empty cans are returned to the autoclave, which serves as a pass box for transfer of these empty cans back to the loading side of the autoclave, where they are prepared for their next use.

This automatic stopper preparation and feed system offers a tremendous advantage over more conventional manual systems. The combination of automation and robotics eliminates the potential ergonomic problems of conventional isolators and minimizes contamination risk by avoiding the use of gloved interventions. And, since no autoclave bags or wraps are required for the operation, the approach eliminates a great deal of waste that would normally have to be removed from the isolator. This system has proven to be efficient and extremely reliable in day-to-day production operations.

The implementation of the stopper supply system also required robots capable of withstanding vapor phase hydrogen peroxide decontamination. These robots do not contribute to particulate contamination, which would be considered significant in an ISO Class 5 environment. In fact, studies have determined that they would be suitable for use in an ISO Class 4 environment.

These robots were co-developed by Shibuya Kogyo Co., Ltd. and Fanuc Robotics (Rochester Hills, Mich.)

As far as PDA knows, Honda's Asimo isn't working at a Japanese aseptic processing facility—YET! (Courtesy Honda Motor Co., Ltd.)

specifically for use in aseptic processing environments where resistance to cleaning and disinfection agents as well as low particulate generation are very important.

Lyophilization/aluminum cap sealing: Half-stoppered vials are conveyed from the stoppering unit to the lyophilizer all within isolators. All loading and unloading of the lyophilizer is fully automated and requires no operator intervention. The fully stoppered vials, once unloaded, are conveyed to an aluminum cap applying and sealing station. This station is located within a unidirectional HEPA-filtered clean booth that meets ISO 5 conditions.

The isolator-based aseptic filling line described in this article was conceived and built in Japan using equipment sourced nearly exclusively from Japanese vendors. We believe the filling system described here is fully state-of-the-art and will meet all global production quality and validation requirements.

An important trend in aseptic manufacturing will be the elimination of human contamination and ease of operation in separative environments such as isolators. The use of carefully designed automation and robotics can both reduce contamination risk by eliminating many interventions and also improve productivity and reliability. We can envision a future in which the need for human operators for direct intervention in aseptic operations will be eliminated.

About the Authors

James E. Akers, PhD, is president of Akers Kennedy & Associates, Inc. and has over 21 years experience in the pharmaceutical industry, working at various director level positions within the industry and for the last decade as a consultant. A former Chair and board member for PDA, Dr. Akers remains active in PDA, as well as in USP and ISPE.

Kazuhito Tanimoto is currently a deputy manager within the pharmaceutical engineering department of Shibuya Kogyo, Ltd. He has a wide range of expertise in the design and engineering of various types of isolator systems for a wide range of pharmaceutical manufacturing applications.

Masahito Kawata is currently a production manager of Kan-onji Institute at the Research Foundation for Microbial Diseases of Osaka University (Biken). He has worked primarily in the quality assurance field in Biken, especially in microbiological assessment, has managed the isolator filling line installation at Biken's new facility.

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The Risk of Microbiological Contamination

Anthony Cundell, PhD, Consultant

There is a perception in the pharmaceutical industry that the frequency of microbial contamination, especially of sterile products, has increased in recent years. For example, the number of sterile drug products recalled was fewer than ten a year from 1983 to 1998 jumping to 55, 30, 50, 52, and 30 in 1999, 2000, 2001, 2002, and 2003, respectively. As reported in a trade magazine interview, Richard Friedman, CDER, U.S. FDA, believes that problem detection in sterile product manufacturing appears higher both for pharmaceutical companies and the FDA. However, Russell Madsen, The Williamsburg Group, believes isolated events triggered recalls for a lack of sterility assurance and were not reflective of a negative trend within the industry. Madsen cited a recall of disposable sterile alcohol wipes manufactured by a third party and included in drug products kits distributed by multiple companies as an example of one reason for increased recalls. Both observers are partly right in their explanations.

Regulators and the industry are placing more emphasis on compliance with the manufacture and testing of sterile products resulting in increased product rejections and recalls for current Good Manufacturing Practices (CGMP) violations that may impact sterility assurance and not necessarily actual microbial contamination of product.

A detailed examination of the 2003 sterile product recalls as reported in the March 2004 "The Gold Sheet" revealed that 30 of those involving injectable products were for reasons of a lack of sterility assurance (Table 2). The two cases of frank microbial contamination were with injectable products manufactured by sterile product compounding companies (Lee Pharmacy and Urgent Care Pharmacy) that were designed as a Class I recall, seriously impacting human health, and not by pharmaceutical manufacturers. All the remaining recalls were designated as Class II recalls. As sterile products manufactured out of compliance with CGMPs may be defined as adulterated under the U.S. Federal Food, Drug, and Cosmetic Act (F, D & C) it is often difficult to discern whether citing for a lack of sterility assurance expose recipients of sterile products to significant risk. The February 2005 issue of the "The Gold Sheet" reported a sharp decline in the number of injectable products recalled in 2004 versus 2003, i.e., 38 versus 8 product batches. In 2004 there were two Class I recalls, six Class II recalls, and one Class III recall related to sterility issues with injectable products (Table 3). In the fall of 2003, American Pharmaceutical Partners recalled one lot of preservative-free potassium acetate IV use after dilution due to *Bacillus licheniformis,* while in July 2004, Parenta Pharmaceuticals recalled preservative-free ephedrine sulfate pharmacy bulk packs due to a sterility failure.

Damage to packaging components and improper container-closure assembly were reasons for product recall for lack of sterility assurance in both 2003 and 2004. This indicates an inattention to detail during the aseptic filling process. The loss of environmental control was demonstrated by a Class 100 filling room exceeded non-viable particulate limits (2003) and a media fill failure (2004) also provided grounds for product recall.

The author believes that a number of advances in the pharmaceutical industry and medical practice may increase the risk of microbial contamination of pharmaceutical products. These advances include:

- Changes in the pharmaceutical industry from small-molecule therapeutic agents made by chemical synthesis using traditional pharmaceutical manufacturing methods to complex-molecule therapeutic agents often made using cell culture, and manufactured with complex purification and bulk aseptic processing steps.
- The development of novel drug delivery systems such as nasal sprays, transdermal patches, and drug-coated transplanted medical devices that may increase patient risk to microbial contamination due to their invasiveness within the human body.
- The sourcing of active pharmaceutical ingredients from manufacturing facilities in third-world countries with increased risk of potential product contamination.
- Pressure to reduce product release cycle times driving reduced microbial testing plans and the implementation of rapid microbial methods that may not be truly equivalent to compendial testing methods.
- Lower relative investment in pharmaceutical operations over the past decade than research and development and marketing.
- The growth of off-label dosage regimes and patient populations out-stripping product specifications.

With pharmaceutical drug products, epidemiological evidence of product causing human infection is sparse or non-existent because the frequency of occurrence of recipient infection is so low. With the exception of a few well-publicized cases (e.g., the contamination of an inhalation solution with water-borne bacteria that overcame the preservative system), the epidemiological significance of contaminated drug products is largely unknown but would represent little or no public health risk compared to food-borne illness.

Continued on the bottom of page 35

The "Product Quality Review" vs. The "Annual Product Review"—Are They the Same?, continued from cover

costs, through process optimization and by the extension of preventive maintenance and calibration periods. So, it is beneficial to plan the PQR in an optimal way.

General Requirements

The general requirements of the PQR are described in section 1.5 of the EU GMP. Regular periodic or rolling quality reviews of all licensed medicinal products, including export-only products, should be conducted with the objective of (1) verifying the consistency of the existing process and the appropriateness of current specifications—for both starting materials and finished product, and (2) highlighting any trends and identifying product and process improvements. Such reviews should normally be conducted and documented annually, taking into account previous reviews, and they should include at least reviews of:

- Starting materials and packaging materials used for the product, especially those from new sources
- Critical in-process controls and finished product results
- All batches that failed to meet established specification(s) and their investigation
- All significant deviations or non-conformances, their related investigations, and the effectiveness of the resultant corrective and preventative actions taken
- All changes carried out to the processes or analytical methods
- Marketing Authorisation variations submitted/granted/refused, including those for third-country (export-only) dossiers
- Results of the stability monitoring program and any adverse trends
- All quality-related returns, complaints and recalls, and the investigations performed at the time

Section 1.5 does provide for the grouping of PQR's by product type, e.g., solid dosage forms, liquid dosage forms and sterile products, where scientifically justified.

- Adequacy of any other previous product, process or equipment corrective actions
- Post-marketing commitments for new Marketing Authorisations and variations to Marketing Authorisations
- Qualification status of relevant equipment and utilities, e.g., HVAC, water, compressed gases, etc.
- Technical agreements to ensure that they are up to date

Evaluation of the Results, The QP

Section 1.5 states that the manufacturer and MAH, where different, should evaluate the results of this review and should make an assessment whether corrective and preventative action—or any revalidation—should be undertaken. Reasons for such corrective actions should be documented, and the agreed corrective and preventative actions should be completed in a timely and effective manner. In addition, there should be management procedures for the ongoing management and review of these actions. The effectiveness of these procedures should be verified during self-inspection (audit).

The Qualified Person responsible for final batch certification, together with the marketing authorisation holder, should ensure that the quality review is accurate and is performed in a timely manner. Finally, Section 1.5 does provide for the grouping of PQR's by product type, e.g., solid dosage forms, liquid dosage forms and sterile products, where scientifically justified.

Contractors and Manufacturers Outside the EU

Where the MAH is not the manufacturer, there should be a technical agreement in place between the various parties that defines their respective ➤

The Risk of Microbiological Contamination, continued from page 34

In the United States, food-borne diseases have been estimated, in a recent study, to cause between six and eight million illnesses and up to nine thousand deaths annually (Mead et al. 2000). Although the pharmaceutical industry should not be complacent, contrast these numbers to the few isolated cases where pharmaceutical products have caused infection in patients.

As companies increasingly use risk-based approaches to the prevention of microbial contamination in sterile drug products, they can gain insight into risk areas by reviewing drug product recalls and FDA warning letters that involve actual or potential microbial contamination.

[**Editor's Note:** The article was excerpted from a longer essay by Dr. Cundell, titled "Risk-Based Approach to Pharmaceutical Microbiology," which appeared in the PDA/DHI book, *Encyclopedia of Rapid Microbiological Methods, Volume 1.* Visit www.pda.org/bookstore for more information and/or to purchase the book. Dr. Cundell is now Director of Pharma. Science, Microbiology at Schering-Plough. He was an independent consultant when he wrote the chapter and the views expressed are his own.]

responsibilities in producing the quality review. The MAH is ultimately accountable for the PQR. For manufacturers who export into the EU, there must be some provision to assist the importer/MAH in the completion of the PQR. So, for companies that export to Europe, most or all of the activities associated with the PQR will have to be implemented and coordinated through a technical agreement.

Compared to the Annual Product Review

The long-standing FDA requirements for the annual product review can be found in 21 CFR 211.180:
(e) Written records required by this part shall be maintained so that data therein can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures. Written procedures shall be established and followed for such evaluations and shall include provisions for (1) A review of a representative number of batches [Note: generally considered to be all batches], *whether approved or rejected, and, where applicable, records associated with the batch, and (2) A review of complaints, recalls, returned or salvaged drug products, and investigations conducted under § 211.192 for each drug product.*

The PQR exceeds the requirements of the FDA annual product review in several key ways:

- All batches are covered
- The history of previous periods is included
- The consideration of starting materials, process, process environment and process output equals product and discrepancies
- Key elements of the quality management system must be considered, too
- Product groups are tied to identify rare problems.

Expectations in Future Regulatory Inspections

The PQR should be a meaningful evaluation and interpretation of all information available about the manufacturing process, its process environment and its output. To do this, the PQR should be a valuable summary of information. It is not intended to be a meaningless listing of huge amounts of data. Nor will the reported observation, "Nothing has changed since the previous review," be a sufficient summary. It should be demonstrated that the raw data fed into the PQR has been collected and evaluated in a reliable way (e.g., the availability of data, the completeness of inclusion to the PQR, evaluation algorithms, etc.). The raw data do not need to be attached to the PQR provided the above criteria are met.

The PQR should cover at least a one-year period to be able to detect long-term trends. This is applicable to a system of rolling reviews, as well. A long-term evaluation and interpretation should be part of the system. A well-implemented Product Quality Review system will promote quality management at its best.

For questions regarding this article, contact:

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Germany
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Note: This article is based on the day-long PDA training course, "The Product Quality Review: What is in it? How do you do it?" presented by Dr. Neuhaus and assisted by Dr. Leube. For future dates of this course, watch the PDA Letter or check www.pda.org.

[**Editor's Note**: A committee of PDA volunteer experts prepared comments on the proposed version of PQR section 1.5, and the comments were submitted to the EMEA on June 30, 2004. PDA proposed changes to the draft of 1.5 which were intended to: make the section harmonized with the FDA regulations; lessen the validation and qualification determinations; delete stability study reviews, limit stability rules to section 6, 'Ongoing Stability;' and delete the section describing the responsibilities of the Qualified Person (i.e., the PQR is a quality review and should be accountable to the quality organization). As the final version of the PQR requirements show, very few of PDA's recommendations were accepted. Copies of PDA comments can be found at: www.pda.org/regulatory/RegComments.html.]

PDA welcomes Volker Eck, PhD, to its European staff

PDA continues its strategic move to enhance its European operations. With Volker Eck joining its European staff PDA takes another step in this direction.

Volker Eck has an impressive scientific and industrial background. Chemist by education he received his PhD from Freie Universität Berlin, Germany, for his studies on the physicochemistry of phospholipid bilayers and vesicles. After working in the Max-Planck Society as a research fellow, he joined Schering AG, Berlin, Germany, in 1983 where he served as Department Head of Quality Assurance for Diagnostics in the company's pharmaceutical Research and Development Branch. In the year 2000 he joined the then Pharmacia & Upjohn and later Pfizer Inc. research centre in Nerviano, Italy, where he served as Director of the Analytical Research & Development department. His last assignment was with Nerviano Medical Sciences Srl, a contract manufacturing organisation spun-off from Pfizer Inc., where he served as Director for the Analytical Development & Quality Control department.

continued on page 41

PDA Comments on EDQM Particulate Contamination Document

29 June 2006

Dr. Peter Castle
EDQM, European Pharmacopoeia Commission Secretariat
226 Avenue De Colmar, B.P. 907
F-67029 Strasbourg Cedex 1
France

Ref.: Particulate contamination: Sub-visible particles (100-ml preparations) (RZ/PH/2006-01586L, Strasbourg, 23/05/2006)

Dear Dr. Castle:

The Parenteral Drug Association (PDA) is the largest international scientific professional association dedicated to the science and technology of parenteral medications. I am writing to you in regard to the EDQM proposal, cited above, to reclassify 100 ml containers as LVPs, thus complying with Japanese Pharmacopoeia (JP) particle criteria. We thank EDQM for your efforts to ensure the transparency of the change process, and for soliciting industry opinion about the proposed change.

Due to the limited time provided for review and comment, PDA cannot offer hard data showing the implications of such a change on marketed products. However we can provide, as you requested, our general opinion of the proposed change. Our views which follow have been developed through a quick, but deliberative process involving our Regulatory Affairs and Quality Committee, with approval by the PDA Board of Directors.

1. Patient Risk:

Patient risk should remain the key motivation for any change to the pharmacopoeial particulate standards. The particulate limits for SVPs are based on the recognition that patients are exposed to a much smaller volume of drug or medical solution for SVP preparations as opposed to LVPs. Thus, the particulate risk to the patient (if any) is much smaller for SVPs. By that criterion we are unaware of any risk information, either presented by EDQM or available in the literature, to justify this change.

2. Harmonisation:

While the proposed change may result in harmonization with the JP standards, it will result in a failure to harmonize with the USP standards. Since there is no underlying evidence of patient risk, we find the argument for harmonization to be unpersuasive. Rather, under these circumstances, the recognized and published standards should be given a 'grandfather' status and recognized as having precedence over a new harmonization decision.

3. Impact on the supply of marketed products:

It is reasonable to presume that all 100ml preparations currently marketed in Europe will be subject to the new standards along with the related testing and manufacturing obligations. It is probable that some lots, particularly of protein and… biologic products, will be rejected unnecessarily. This could result in the shortage of medically imperative products. PDA is a scientific organization and we do not routinely factor costs into our technical recommendations. In this case however we believe it is prudent that the costs associated with unnecessarily rejecting product previously considered acceptable be taken into account in the risk/benefit analysis.

In summary, it is our recommendation that this proposal not be adopted at this time pending a more inclusive and detailed consideration of the associated benefits and risks.

Thank you again for the opportunity to support your activities. Please contact me if you have any questions.

Very best regards,

Georg Roessling, PhD
Senior Vice President
PDA Europe
E-mail: Roessling@pda.org

PDA Parenteral Drug Association

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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/regulatory/RegNewsArchive-2006.html.

Europe

Active Substance Master File Procedure, Comments Until August 30

In May, the European Medicines Agency (EMEA) posted the draft *Guideline on Active Substance Master File Procedure.* The guideline is intended to assist applicants/marketing application holders in the compilation of the active substance section of their dossiers for a medicinal product. It is also intended to help European Drug Master File (EDMF) holders in the compilation of their EDMF. The guideline is not intended to give instructions to the Competent Authorities/EMEA in the administrative and scientific handling of EDMFs and related filings.

The public comment period closes August 30 (EMEA/CVMP/134/02 Rev 2, CPMP/QWP/227/02 Rev 2, Consultation, 27 April 2005).

EMEA's Korteweg Recognized as "Quality Leader"

EMEA announced that staff member Marijke Korteweg has been awarded the prestigious title of "European Quality Leader of the Year 2006" by the European Organization for Quality. Korteweg is an advisor to EMEA in the area of Integrated Quality Management . The award was presented in recognition of her continuous striving for quality and improvement over two decades in the European medicines system. Korteweg holds a PhD in chemistry and biochemistry and is a Fellow of the Institute of Quality Assurance. She joined EMEA in London in 1997.

New, Faster Scientific Advice Procedure

The EMEA announced its "New Framework for Scientific Advice & Protocol Assistance," which introduces significant changes to the way the Agency provides scientific advice on the research and development of new medicines. The Framework was released for public consultation in September 2005 and came into effect on July 1, 2006. Updated EMEA scientific advice and protocol assistance guidance will be published on the EMEA website.

EU Agrees to Meet With FDA on Voluntary Genomic Data Submission

On May 31, EMEA reported an agreement among the European Commission, EMEA and the U.S. FDA to a procedure for joint briefing meetings with sponsors following voluntary submission of genomic data. Much of pharmacogenomic data are of an exploratory nature and are not required to be submitted to health authorities in most cases. However, voluntary submission of such data is encouraged as a means to ensure that regulatory authorities are familiar with the issues arising from the integration of pharmacogenomics in drug development.

North America

FDA Issues Updated Counterfeit Report

FDA's Counterfeit Drug Task Force has issued their 2006 updated report. The report contains recommendations for FDA actions to further safeguard the nation's drug supply from the threat posed by counterfeit drugs. The report recommends a number of actions be taken, including:

- Stakeholders work to expeditiously implement the widespread use of electronic pedigrees
- FDA provides technical assistance to the U.S. Congress if legislation regarding electronic pedigrees is considered
- Stakeholders continue to move toward implementation of RFID, phasing in its use with products that are most vulnerable to counterfeiting and diversion being given first priority
- FDA continues to facilitate RFID implementation, working with stakeholders
- FDA completes its RFID Impact Study and publishes the results
- Stakeholders explore the use of RFID for tracking medical countermeasures
- FDA works with manufacturers and other stakeholders in their efforts to develop appropriate messages, symbols or statements for labeling of drug products and packaging that contains an RFID tag as they pertain to privacy issues and consumer education
- FDA works with private and public sector organizations in their efforts to educate consumers about RFID

Acting Commissioner Von Eschenbach has endorsed the report and its recommendations. Furthermore, Dr. Von Eschenbach has directed that, as recommended in the report, a draft Compliance Policy Guide be issued for public comment, with the intent to finalize this Compliance Policy Guide by December 1, 2006. Accordingly, FDA has developed Draft Compliance Policy Guide 160.900, entitled "Prescription Drug Marketing Act - Pedigree Requirements under 21 CFR Part 203."

A New Focus on Chapters

Henry Kwan, PhD, Kwan Consulting, LLC

In the beginning of 2006, following the vision of Bob Myers, President of PDA, and with the support of the Board of Directors, a new Senior Chapter Liaison position was created at PDA. I accepted the challenge to serve PDA in this role as a consultant. Although it is a part-time role for me (I continue to pursue my independent pharmaceutical consulting practice), my commitment to the responsibilities of the position is indeed fulltime.

The primary mission of the Senior Chapter Liaison is to help support the activities of the North American and Asian chapters by ensuring that proper communication between the PDA Global Headquarters in Bethesda, Md., and the chapter leaders occurs. I will accomplish this by attending their events and by remaining in constant communication with the chapter leaders. PDA Sr. VP Europe, Georg Roessling, PhD, performs this role for the many PDA chapters in Europe.

In the Senior Chapter Liaison role, I work very closely with Marc Povell (povell@pda.org), who joined PDA in March as Manager, Membership & Chapters, reporting to Lance Hoboy, Vice President, Membership Services and Administration. Marc has five years of experience in membership and chapter relations from another nonprofit professional society. Marc will provide logistical and day-to-day support to the chapters and their leaders, including support of chapter-related websites, maintenance of chapter membership lists and event calendars, help with membership surveys, etc. He is also will ensure that all relevant PDA brochures, catalogs and event promotional items are expeditiously supplied to the chapters for distribution at their events in order to help them promote PDA membership and *Career-long Learning*.

So far in 2006, chapters in North America, Europe, Australia, and Asia have sponsored 20 meetings. Below is a brief recap of some of these events sponsored by our North America chapters. While just a sampling, this review is intended to provide a flavor of what the chapters are doing to bring exciting topics and expert speakers to their membership. As you shall see, the scope of the topics is quite broad, and they represent some of the most pertinent issues facing the pharmaceutical industry now.

[**Editor's Note:** Please see "The Future of Validation...Now" on page 42 for a discussion of the proceedings at the May meeting on the future of validation in Barcelona, Spain, hosted by the PDA Spain, Italy and France Chapters.]

New England Chapter

On February 8, over 90 people attended a New England Chapter dinner meeting, and many of the attendees enjoyed a trip to Genomic Profiling System's manufacturing facility in Burlington, MA, where The Growth Direct™ Test, an automated, rapid microbial system, was demonstrated. Featured dinner speakers included:

- **Don Straus,** PhD, CSO and Vice President of Research at GPS, who talked about The Growth Direct™ Test
- **Michael Waddington,** Vice President of Laboratory Operations at Accugenix, Inc., who discussed the identification of microorganisms using comparative DNA sequencing.

On May 17, the New England Chapter boasted record attendance of over 150 people for their conference titled, "FDA Inspections." Several representatives of the U.S. FDA participated, including **Stephen Souza,** Supervisory Investigator, who presented, "FDA's High Risk Drug & Systematic Approach to Inspections," and **Anthony Warchut,** Investigator, who participated in the panel discussion. The other featured dinner speakers were:

- **Michelle Sceppa,** Principal of MSceppa Consulting, who presented, "CGMP Pitfalls in the QC Laboratory—Preparing the QC Lab and Staff for an FDA Inspection"
- **Mark Lookabaugh,** Senior Consultant, PAREXEL Consulting, (recently retired from FDA as Compliance Branch Director at the New England District office in Stoneham, MA), who presented, "Responding to a Form FDA 483 or Warning Letter"

Metro Chapter

On January 18, the Metro Chapter successfully hosted its "First Annual FDA and Vendor Show," which was attended by about 120 people. A three-hour vendor show was capped with a dinner presentation by **Dan Gabicki,** Drug Specialist, New Jersey District, U.S. FDA.

On March 1, over 60 people attended a dinner talk titled, "Qualification and Validation of Pharmaceutical Water Systems," delivered by **Nancy Tomoney,** Northeast Regional Project Manager, PharmaSys, Inc

On April 5, about 55 people attended the "PDA Metro Chapter Day: Update on Current Microbiology Issues." The program was excellent and included the follow expert speakers:

- **Len Mestrandrea, PhD,** Senior Science Advisor, Pfizer Global Manufacturing, "Bacterial Endotoxin Testing and Areas to Audit"
- **Kimberly McFarland,** Associate Director, QC Microbiology, Imclone Systems, Inc., "Guidelines for Managing and Organizing

a Pharmaceutical Microbiology Department"

- **David Milligan,** Director of Technical Sales, Getinge-la Calhene, "The Maintenance and Validation of a Sterility Test Isolator"
- **Jim Agalloco,** Agalloco & Associates, "Aseptic Processing Risk Assessment: The Akers-Agalloco Method"
- **Tony Cundell,** PhD, Director, Pharmaceutical Sciences, Microbiology, Schering-Plough Research Institute**,** "Status and Explanation of In-Revisions USP Microbiology General Chapters"
- **Dennis Guilfoyle,** PhD, Pharmaceutical Microbiologist, Northeast Regional Laboratory**,** U.S. FDA, "Risk Analysis for Non-Sterile Drugs Contaminated with Microorganisms"

As you can see, both the New England and the Metro chapters have been very active in putting on substantial programs at their events in just the first few months of the year. They both are planning at least three additional events for 2006. What a great job they have done, indeed!

In addition, the Australia Chapter is planning a meeting on cold chain management on Aug. 17 and one involving the Australian Therapeutics Goods Agency on Nov. 16. The biannual PDA Asia-Pacific Congress will be held in Tokyo from November 13-15, and is supported by our Asian chapters. In future periodic updates, we will cover events that are sponsored by other chapters.

On behalf of PDA, I would like to acknowledge the volunteer efforts and the contributions made by all of the chapter leaders, as well as the guest speakers who took time out of their busy schedules to support PDA's chapters and membership. I encourage all PDA members to step up their efforts to contribute to the chapters, as a volunteer, a sponsor and/or a prospective speaker at chapter events.

[**Editor's Note:** While still consulting, Henry can be reached regarding PDA chapters and membership at his PDA email address, kwan@pda.org.]

Announcements, continued from page 36

Volker has been a member of PDA since 1996. He has been an invited speaker to many events of PDA and other professional and scientific organisations. Volker is one of the founding members of PDA's Italy Chapter and a member of the Chapter Board. He is also Co-Chair of PDA's Technology Transfer Interest Group and member of the Science Advisory Board of PDA. He has helped to organise international meetings and training courses of PDA in Italy and elsewhere with success.

In joining PDA Europe, Volker will be helping PDA to serve its existing European members better. In his role as Senior Director of Science and Technology, reporting to the Senior Vice President of PDA Europe, Georg Roessling, he will contribute to the strategic objective of PDA to continuously grow in Europe by facilitating to hold exquisite meetings and training courses, that offer sound science and insight into advanced technologies.

To contact Volker, e-mail him at: eck@PDA.org

Guide the Direction of PDA and Gain Visibility within the Bio/Pharmaceutical Industry

PDA's Board of Directors seeks members to serve on a newly established Membership Advisory Board to ensure that PDA maintains the highest level of technical and regulatory relevance to its 10,000+ members by identifying programs, products and services that meet the professional needs of those members.

This is an opportunity to interact with both seasoned and senior-level professionals as well as younger rising stars within the pharmaceutical and biopharmaceutical community. Serving on the Membership Advisory Board will also provide you with a broader understanding of the industry professions, activities and issues.

For additional information or to express your interest in this volunteer opportunity, please contact Lance K. Hoboy, Vice President at +1 (301) 656-5900 ext. 114 or hoboy@pda.org.

The Future of Validation…Now

Jim Lyda, PDA

What is the future of validation? PDA's Spain, Italy and France Chapters tackled this question at a two-day conference called "Process Understanding & the Future of Validation," May 23-24, 2006, at the Barceló Hotel Sants, Barcelona.

Conference speakers addressed and assessed the impact of risk-based GMP, process analytical technology (PAT), process understanding/design space and the unfolding trilogy of the International Conference on Harmonisation quality guidances Q8 (pharmaceutical development), Q9 (risk management) and Q10 (quality systems) that will impact the validation activities in the pharma and biopharmaceutical industries.

PDA Spain Chapter President **Jordi Botet**, STE Compliance Services, opened the conference, and conference chair **Carina Sonnega**, Biotechnology Consulting, France, closed the event. In between, the attendees were treated to a selection of world-class presenters who covered the validation landscape from its peaks to its valleys.

PDA expresses sincere appreciation to the following presenters:

- **Joerg Neuhaus,** PhD, Pharmaceutical Inspector, Bezirksregierung Köln, Germany
- **Hal Baseman,** Valsource LLP and Head of the PDA Validation Interest Group, USA
- **Volker Eck,** Nerviano Medical Science and Officer of the PDA Italy Chapter
- **Trevor Deeks,** Skanska Pharmaceutical Group, UK
- **Harald Stahl,** Niro Pharma Systems, Germany
- **John Richmond,** Bruker Optics, UK
- **Letizia Caccialupi,** Boehringer Ingelheim, Germany

Session 1, The Future of Validation – Regulatory Change, Pharma Quality and ICH (l-r): Jordi Botet, STE Compliance Services; Hal Baseman, Valsource LLP & Head of PDA Validation Interest Group; Joerg Neuhaus, Pharmaceutical Inspector, Bezirksregierung Koeln; James Lyda, PDA Europe.

- **Joachim Leube,** PhD, Bayer Biologicals, Italy
- **Morten Munk,** CMC Biopharmaceuticals and co-author of PDA Technical Report 42, Denmark

Special thanks go to the following presenters for relaying the latest ICH and harmonization content to the conference and its attendees:

- **Fritz Erni,** PhD, Novartis Pharmaceuticals and member of the ICH Q8 Expert Working Group, Switzerland
- **Neil Wilkinson**, AstraZeneca and member of the ICH Q10 Expert Working Group, UK
- **Joyce Ramsbotham**, Solvay Pharmaceuticals and EFPIA topic leader, The Netherlands.

Of all the messages delivered at this conference, one was the clearest: validation will and shall look different in the future. Regulatory agencies will give the industry much more flexibility, but to attain this flexibility, industry will have to change its way of doing business. The "tick the box" mentality will not work in future.

A full-day course on EMEA's "Periodic Quality Review," delivered by Drs. Neuhaus and Leube, preceded the conference and was particularly informative and valuable.

[**Editor's Note:** A complete review of the PQR begins on the cover of this issue.]

Finally, thanks are due to the PDA volunteer members who made up the scientific planning committee that worked so diligently to design this conference:

- **Jordi Botet,** STE Compliance Services, Spain
- **Jean Louis Saubion,** UFCH and President of the PDA France Chapter
- **Volker Eck,** Nerviano Medical Sciences, Italy
- **Joachim Leube,** Bayer Biologicals, Italy
- **Claudio Puglisi,** SIFI, Italy
- **Phillipe Gomez,** Sartorius, France
- **Paulo Curto,** DOC, Italy
- **James Lyda,** PDA Europe
- **Georg Roessling,** PhD, PDA Europe

Where will you be October 12-13?

Jim Lyda, PDA

If you are involved in the regulated pharmaceutical industry, you will want to be where the following European regulators will be…

Johannes Blümel, *Paul Ehrlich Institute*
Emer Cooke, *EMEA*
David Cockburn, *EMEA*
Michael Deats, *MHRA, UK*
Richard Funnell, *MHRA, UK*
Tor Gråberg, *Medical Products Agency, Sweden*
Jirí Holý, USKVBL, Czech Republic
Gerald Heddell, *MHRA, UK*
Dries de Kaste, *RIVM, Netherlands*
Susanne Keitel, *BfArM, Germany*
Catherine Lefèbvre, *AFSSAPS, France*
Thomas Lönngren, *EMEA*
John Lynch, *Irish Medicines Board*
Jacques Morénas, *AFSSAPS, France*
Carlo Pini, *ISS, Italy*
Paul Sexton, *Irish Medicines Board*
Milan Šmíd, *State Institute for Drug Control, Czech Republic*
Martin Terberger, *European Commission*
Jason Todd, *DEFRA, UK*
Anne Marie Vangsted, *DMA, Denmark*
Rudolf Völler, *GMP Inspector, Germany*

…at the 2006 PDA-EMEA Joint Conference, "Understanding the European GMP Environment" in London.

Four Plenary Sessions

"Understanding the EU Regulatory Framework I": Speakers in the opening session will explain the foundations on which GMPs in the European Union are based, starting with the legal origins of directives and regulations, and how legislation is made in the EU. Participants will learn how lawmaking occurs, and how it is then implemented in EU Member States. The role of Europe's various review and oversight organizations (e.g., EMEA, EU Commission and EDQM) and how they interact with national bodies will be reviewed. The various options for making regulatory submissions and the consequences for inspections will also be clarified. The role of EMEA, how the national inspectorates perform GMP inspections, both domestically and overseas, and how and when they occur complete this session. The topics are:

- Legislation and How it is Made
- Regulatory Framework and Key Players
- Inspections and How they Occur

"Understanding the EU Regulatory Framework II": Speakers in this session will discuss how EU regulation is implemented in the Member States and how industry can assist in shaping the future GMPs. Distinct requirements of EU Member States will be elucidated, including those in the UK and the Czech Republic, a relatively new EU Member State. The topics are:

- European GMP and its Implementation in Member States
- New Member State Agency Implementation of EU GMPs
- Industry's Role in the Development of Regulatory Controls

"Consistent Implementation of EU GMP": The challenge of implementing GMPs across all Member States, the background and training of inspectors, and the role of EMEA in achieving a consistent approach to inspecting will be addressed. Speakers will cover the role of PIC/S and of inspectors from MRA countries in harmonizing GMPs more widely. An industry view of how to establish consistent implementation of GMPs along with a quality system across a global company will be presented. The topics are:

- How Inspectors Can Make the System Work
- How Regulators Can Make the System Work: An Example of Good Practice
- How Industry Can Make the System Work: An Example of Good Practice

"Manufacturing and Inspections: Present and Future": Speakers in the closing plenary session will outline the EU inspection and manufacturing environment of today and project its evolution into the future. Current responsibilities of EU GMP inspectorates from a national, European and international perspective will be discussed, as well as the various ways EU regulators contribute to international cooperation. Industry and regulatory representatives also will address the importance of global harmonization of quality systems expectations, regulatory change management processes and the criticality of moving to science- and risk-based approaches to GMPs and quality decisions. EMEA will close the conference by outlining some of the difficult challenges of the future, including better supply-chain control, nationally and internationally, as well as the optimal use of resources. The topics are:

- Present: Evolution of the EU Inspectorate Perspective and Current Hot Topics
- Present and Future: How Industry has Evolved from National to Global
- Global Harmonization
- Future Challenges

In Addition, Nine Concurrent Sessions:

- Contractor Management
- Dedicated Facilities
- The Role of the Qualified Person
- Investigational Medicinal Products
- Counterfeiting
- Veterinary GMPs
- Quality Standards and Emerging Countries
- GMPs for Starting Materials
- New Technologies

See you in London!

The Foundation for Business Success: Continuous Improvement Throughout the Product Life Cycle

PDA/FDA Joint Regulatory Conference • Washington, D.C. • September 11-15, 2006

Cindy Rockel, Millipore

This year's PDA/FDA Joint Regulatory Conference once again promises to deliver unprecedented program content, focusing on the industry's emerging adoption and implementation of FDA's 21st Century initiatives and the ICH Q8, Q9, Q10 guidances.

The open plenary sessions will combine academic and regulatory perspectives highlighting industry's continuous challenge to effectively integrate the highest-quality standards, based on sound science, into best business practices. **Daniel Diermeier,** PhD, IBM Distinguished Professor of Regulation and Competitive Practice, Northwestern University, will speak about how this is being accomplished in pharmaceutical and biotech firms. His message will focus on the strategic importance and value for quality from nonmarket forces such as public health, regulatory and economics perspectives.

Dr. Diermeier will also participate with CEOs **Joshua Boger,** PhD, Vertex Pharmaceutical, Inc. and **Guy Villax,** Hovione, on an interactive panel to discuss how these senior executives have strategically positioned quality in their companies.

Dr. Boger and Mr. Villax offer different perspectives on the topic, as the former represents a public company, and the latter heads a private operation. They will share their common challenges and benefits to developing the quality culture they want instilled in their companies. Both CEOs will discuss how they achieve corporate alignment between their roles, the roles of their executive team, the quality unit and operations.

The plenary sessions and the complementing regulatory affairs, quality systems and manufacturing tracks are designed to engage the conference attendees in an unmatched discussion with other industry executives and top FDA officials.

Additional plenary sessions will focus on the implementation of ICH Q8 and Q9. An update on Q10 will be provided. The closing plenary will combine commentary from FDA and a continuous improvement model represented by an internationally known electronics company.

The conference will also feature 12 Interest Group meetings and an Exhibit Hall, with representatives from technology providers to pharmaceutical services. Following the conference, the PDA Training and Research Institute will provide a comprehensive slate of lecture courses for *Career-long Learning*SM.

TRI Courses

In conjunction with the 2006 PDA/FDA Joint Regulatory Conference, the PDA Training and Research Institute (PDA TRI) is offering ten courses aimed at keeping you and your facility in full compliance and abreast of the latest guidelines.

A Comprehensive Guide to OOS Regulations
September 14

API – Qualification & Validation of API Facilities and Processes
September 14-15

Applied Quality Systems
September 15

Auditing Techniques for cGMP Compliance
September 15

Development of Qualification and Validation Protocols – A Risk Management Approach – New Course!
September 14

Failure Mode Analysis – New Course!
September 15

Introduction to Change Control
September 14

Preparing for and Managing FDA Inspections – New Course!
September 14-15

Statistical Tools Supporting Quality Risk Management and Analysis (ICH Q9) – New Course!
September 15

Elements of Risk Management
September 14-15

2006 PDA/FDA Conference Gala Extravaganza Best Yet!

This year's *PDA/FDA Joint Regulatory Conference* has several events designed to allow you to interact with others in your field, making it easy to strengthen and expand your professional network.

Refreshments in Exhibits Area

Between sessions, be sure to tour the Exhibit Area as you sip coffee with friends. You'll have the opportunity to evaluate and compare the latest pharmaceutical and biopharmaceutical technologies at these informative and interactive exhibits. **Monday:** 10:00 – 10:30 a.m. and 3:00 – 3:45 p.m. **Tuesday:** 10:30 – 11:00 a.m. and 2:30 – 3:00 p.m.

Interact with PDA Interest Groups

One of the best networking experiences at PDA conferences are the Interest Group Sessions. They offer the ideal opportunity to get answers to your questions from peers and colleagues. 11 Interest Group are scheduled for this year's conference. **Tuesday:** 7:30 – 8:45 a.m. and 4:30 – 5:15 p.m. **Wednesday:** 7:30 – 8:45 a.m.

Monday Night Reception

Take another glance around the exhibit tables as you and your peers relax after the first day of the conference. The mood will be light as you enjoy the evening refreshments while browsing the exhibits. **Monday:** 5:15 – 7:15 p.m.

Art, Music and Excitement – An Unforgettable Gala Extravaganza

Top off your PDA/FDA experience at Tuesday night's gala event, which will be the best networking opportunity of the week! This exciting event will take place at the **National Museum of Women in the Arts** and has something for everyone. Kick up your heels in the Great Hall to one of Washington's **dazzling dance bands** or **try your luck at one of the many casino tables** featured on the Mezzanine level. Need a break from the fun and games, or a quiet place to converse with friends and colleagues? Visit **the many art galleries** that the museum offers. The featured exhibit will be ***Dreaming Their Way: Australian Aboriginal Women Painters,*** a groundbreaking exhibition of art by indigenous women of Australia. **Museum docents will be on hand to answer questions** regarding these breathtaking pieces. Tickets are $25 (a portion of which is tax deductible) and are available through registration. Tickets are limited, so be sure to purchase yours in advance! **Tuesday:** 7:00 – 9:30 p.m.

2006 PDA/FDA Joint Regulatory Conference

List of Exhibitors

(as of July 6, 2006)

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Accugenix	25
AES - Chemunex, Inc.	39
Amadeus International	57
Associates of Cape Cod, Inc.	78
Bioscience International	37
BioVigilant Systems, Inc.	30
Clarkston Consulting	79
CSSC, Inc.	42
Drumbeat Dimensions, Inc.	40
DuPont Qualicon	31
EMD Chemicals, Inc.	23
Genesis Machinery Products	46
Lighthouse Instruments, LLC	45
Micron Video International	61
Millipore Corporation	27
Mission 3	34
Moda Technology Partners	32
Molecular Epidemiology, Inc.	28
Novatek International	36
Pacific Bridge Medical	76
Pall Life Sciences	20
Parexel Consulting	22
Phoenix Imaging	33
Pilgrim Software, Inc.	18
PML Microbiologicals	29
Quality is Learned, Inc.	21
Sartorius Corporation	38
Sparta-Systems, Inc.	41
Texwipe (ITW)	35
Title 21 Software	6
Veltek Associates, Inc.	44
Vetter Pharma-Fertigung GmbH & Co. KG	43
Working Words, Inc.	24

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In Focus: PDA's 2006 Annual Meeting - Honor Awards Dinner

Most of PDA's 2005 Honor Award winners were in attendance to receive their award at the 2006 Annual Meeting: (back row, l/r) PDA Chair Vince Anicetti; Howard Drake, Service Appreciation; Jim Lyda, Distinguished Service; Rich Levy, Frederick J. Carleton Award; Michael Miller, Distinguished Service; Dennis Jenke, Frederick D. Simon Award; Ed Fry, Distinguished Service; Maik Jornitz, Distinguished Editor/Author; Laura Thoma for Ken Avis, PDA Science Trailblazer; David Matsuhiro, James P. Agalloco Award; Sypros Fetsis, Chapter Volunteer Award (middle row, l/r) PDA Past-Chair Nikki Mehringer; Randall Tedder, Chapter Volunteer Award; PDA President Bob Myers; John Geigert, Gordon Personeus Award; Louise Johnson, Distinguished Service; Kunio Kawamura, Honorary Membership; Russell Madsen, Honorary Membership; Awards Committee Chair Jennie Allewell; Martin Van Trieste, Distinguished Service (front row, sitting l/r) PDA Science Trailblazers: Bengt Ljungqvist, Berit Reinmuller, Ted Meltzer and Julius Knapp

PDA President Bob Myers congratulates Russ Madsen for winning PDA's most prestigious award, Honorary Membership

PDA Honor Award winners not in attendance or not pictured:

Toshiaki Nishihata, Distinguished Service
Jeanne Moldenhauer, Distinguished Editor/Author
Lisa Hollis-McCulley, Chapter Volunteer Award
Thomas Quinn, Chapter Volunteer Award
Byong-Ho Youn, Chapter Volunteer Award
James Agalloco, Chapter Volunteer Award
Joachim Leube, Chapter Volunteer Award
Maggie Sparhawk, Chapter Volunteer Award

Bob Myers introduces Kunio Kawamura, winner of PDA's most prestigious award, Honorary Membership

Bob Myers toasts PDA's Science Trailblazers: (l/r) Bengt Lujungqvist, Berit Reinmuller, Ted Meltzer and Julius Knapp; Laura Thoma representing Kenneth Avis (deceased); Irving Pflug not able to attend

PDA's Sr. VP Rich Levy poses with Past-Chair Nikki Mehringer and current Chair Vince Anicetti

PDA Board Member John Shabushnig (l) and Paul Stinavage enjoy the refreshments prior to dinner

Former PDA President Ed Fry receives the Distinguished Service Award

PDA's Honor Awards

In Focus: PDA's 2006 Annual Meeting - Sessions

PDA Chair Vincent Anicetti, Keynote Speaker Dr. Susan Desmond-Hellman (Amgen), and PDA President Bob Myers

2006 Annual Meeting Chair John Geigert

Charles Arntzen, PhD, Arizona State University, discusses plant expression systems for large-scale vaccine production

Charles Van Beveren, PhD, Favrille, Inc., talks about the production of patient-specific monoclonal antibodies for non-Hodgkin's lymphoma therapy

Pfizer Research Microbiologist Monique Reisterer speaks in a Manufacturing Science session

PDA's Rich Levy (l) poses with Opening Plenary Session speaker Norbert Hehme, GlaxoSmithKline, who addressed the challenges posed by the influenza pandemic to the vaccine industry

Ursula Busse, PhD, Medicago, explains how to produce biopharmaceuticals in alfalfa

PDA consultant for Chapters, Henry Kwan (l), answers questions following a session

Students at the 2nd Annual Meeting Student Symposium pose with PDA Journal Editor Lee Kirsch (back row, 3rd from left) and PDA Board Member Laura Thoma (right of Dr. Kirsch)

Closing Plenary Session (l/r): PDA's Rich Levy, FDA's Barry Cherney, and 2007 Annual Meeting Program Chair Michael Eakins

PDA Honorary Member Russell Madsen (l) and Cardinal Health's Tony Pavell (rear center) answer questions following presentations during the Process Validation Interest Group session

Attendees at the closing plenary session heard FDA's take on QbD for biopharmaceuticals

Markus Lankers, PhD, Rap-ID Particle Systems, outlines the most common contamination in lyophilized products

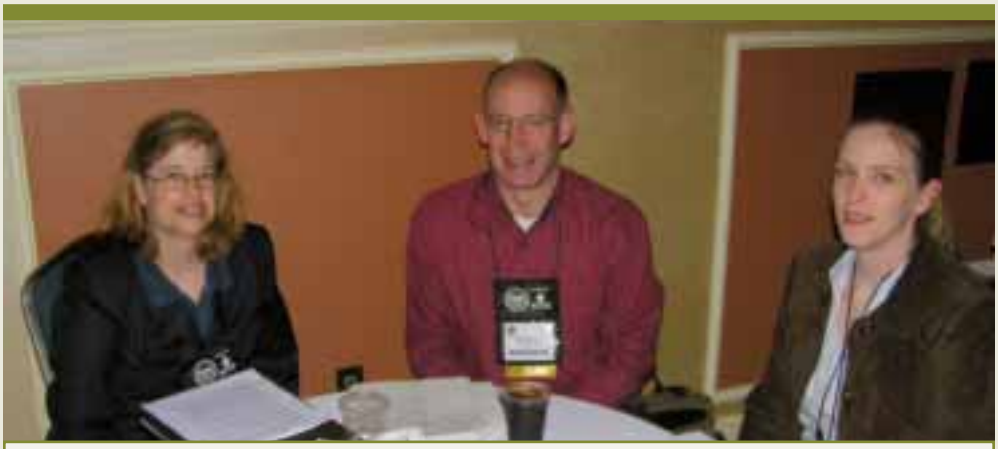
PDA Board Member John Shabushnig (r), talks with PDA Science Trailblazer Julius Knapp (center) and another conference participant

ATS Compliant Solutions' Thomas Hayes speaking in a Manufacturing Science session

In Focus: PDA's 2006 Annual Meeting - Exhibitions, TRI & Networking

Long-standing PDA VIPs (l/r): Ted Meltzer, Jules Knapp and Fred Carleton

PDA authors (l/r) Ted Meltzer, Maik Jornitz and Michael Miller



Three Chapter Leaders, One Company: Sara Hendricks, President-Elect, Mountain States Chapter; Rusty Morrison, Treasurer/Secretary, New England Chapter; Angel Colucci, Communication Chair, Southeast Chapter. All with Commissioning Agents, Inc.

Tim Cser, EMD, and Christine Steele, HollisterStier, take in a poster between sessions

Gregory Meyer, President, Compliance Media and TRIAB member, engages students during TRI's "Elements of Risk Management" course following the Annual Meeting. The course will be offered again at the upcoming PDA/FDA conference.

Exhibitors and poster presenters entertained many visitors during the 2006 PDA Annual Meeting Exhibition

Planning Nearly Complete for Joint ISPE/PDA Conferences on ICH Q8/Q9

Challenges of Implementing Q8 and Q9 – Practical Applications • Bethesda, Dec. 6-7 • Brussels, Feb. 12-13

Bob Dana, PDA

Recently, ICH published two new quality-based documents that will have a major impact on how the pharmaceutical industry and those who regulate the industry will do business. The ICH Harmonized Tripartite Guidelines, *Pharmaceutical Development, Q8* and *Quality Risk Management, Q9* both reached Step 4 of the implementation process in November 2005. FDA has recently issued a new guidance on both ICH standards. Clearly, there is much going on in this area.

In discussing how to best meet the members' needs for learning about the ICH documents, we decided to approach the International Society of Pharmaceutical Engineering (ISPE) to explore the possibility of partnering to develop and present a series of workshops addressing Q8 and Q9. Early in 2006, a kickoff meeting was held between ISPE and PDA staff, and it was quickly determined that such a partnership was both possible and desirable. Using the resources of both organizations, it seemed possible to develop a unique series of workshops devoted specifically to Q8 and Q9.

A Planning Committee, co-chaired by Joe Phillips of ISPE and Bob Dana of PDA, was formed and tasked with the responsibility to develop these workshops. The intention was to go beyond focusing on just what were contained in the Guidelines to include a discussion of what wasn't and why. To that end, we decided to enlist members of the ICH Expert Working Groups who actually wrote the Q8 and Q9 documents. Doing so provided a unique perspective for these workshops. As many as 12–14 representatives of the Expert Working Groups will have participated in the development and presentation of these workshops.

The Program Committee has developed what we believe is an outstanding program for these two-day workshops. Regulators and industry representatives from Europe, Japan and the United States will describe the challenges involved with the implementation and application of the Pharmaceutical Development and Quality Risk Management guidance in their respective areas.

In the session entitled, "Q8 Implementation Challenges—A Regulatory Perspective," FDA and European regulators will consider such things as: how to conduct science- and risk-based assessments of submissions, how to balance expectations for a quality by design-based submission and approval of a quality product without raising the bar, how to provide regulatory flexibility while still assuring product quality, and how to handle legacy products. In a counterpoint to this session, industry representatives will provide their perspective of the challenges associated with the implementation of Q8, including a review of the potential benefits, such as enhanced process capability and robustness, better integration of review and inspection systems, and the achievement of greater flexibility in specification setting and in the management of pos-approval changes. Similar sessions will address the challenges associated with the adoption and implementation of Q9.

One session will be devoted to the Japanese perspective on Q8 and Q9, with speakers representing the Japanese health authority and industry.

Through the extensive use of case studies, attendees will learn from regulators and industry alike about actual experiences with the FDA's CMC Pilot Program, EFPIA's pharmaceutical development model and the implementation of strategies for quality risk management. Panel discussions featuring both regulators and industry speakers will allow ample opportunity for dialogue and interaction between the panelists and workshop attendees. Representatives from both ISPE and PDA will also provide updates regarding what each association is doing relative to Q8 and Q9. The workshop will conclude with a panel of regulators from the three ICH regions providing a look into the future to see what the world might look like ten years from now. The workshops will be structured with no parallel sessions, so all attendees will have the benefit of attending each session and hearing all the presentations. To see details of the Workshop Program, visit the PDA Web site at www.pda.org or the ISPE Web site at www.ispe.org.

Following the successful PDA model developed after the publication of the ICH Q7A Guideline, the workshops will be held in multiple locations. The initial workshop will take place in Washington, D.C., Dec. 6–7, and will be repeated in Brussels, Belgium on February 12–13, 2007. Planning is now getting underway for a third session to be held in Japan later in 2007.

The ability of ISPE and PDA to join forces to co-sponsor these workshops provides a significant opportunity for members of both organizations to come together for an unparalleled educational and networking opportunity. The partnership enables both

PDA Continues to Explore the Pre-Filled Universe

Patty Kiang, PhD, Genentech, Inc. and Program Planning Committee Chair

Strong, sustained growth is predicted for pre-filled syringes and injection devices in the next decade, especially in the area of biopharmaceuticals. By examining the scientific aspects and regulatory impact of these devices, ***The Universe of Pre-Filled Syringes & Injection Devices*** will provide guidance on patient safety and product integrity, as well as manufacturing and development as they relate to pre-filled syringes and injection devices. This two-and-a-half day interactive forum will feature five plenary sessions covering topics aimed at helping pharmaceutical and biopharmaceutical professionals ease into the transition from vials to pre-filled syringes:

- **Materials, Methods and Technologies**—Explore the advantages and disadvantages of different types of materials used for pre-filled syringe construction, as well as the challenges of elastomeric components.
- **Development Considerations**—Get insight into the development and manufacturing of pre-filled syringes and the role of extractables and leachables as key components in the stability and behavior of drugs.
- **Manufacturing Case Studies**—Hear real-life solutions involving aseptic filling technology, transferring products to dual- or single-chamber pre-filled syringes or to an auto-injector.
- **Process Technology**—Examine the latest developments in technology for silicone testing, visual inspection and developing an aseptic production site
- **Regulatory Implications**—Learn about the latest FDA perspective on the cGMP and other regulatory requirements for pre-filled syringes and injection devices

In addition to the plenary sessions, participants will have the opportunity to interact directly with global industry and regulatory experts at the exhibitor booths and during two breakfast sessions. The first will cover the issue of syringe safety; the second is dedicated to injection pens and auto-injectors.

For more information about The Universe of Pre-Filled Syringes & Injection Devices, or to register, visit www.pda.org/prefilled.

Planning Nearly Complete for Joint ISPE/PDA Workshops on ICH Q8/Q9, continued from page 52

organizations to leverage their strengths to provide high-level scientific forums which will be mutually beneficial to our members and the global pharmaceutical and biopharmaceutical communities. We are looking forward to seeing many members of our organizations at one of these workshops.

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Vice President's Message

Gail Sherman

Moving Pangs

Last month, in highlighting the great first half of 2006 TRI experienced and previewing the second half (including the course series at the PDA major conferences in Washington, London and Tokyo, stand-alones in St. Louis and Boston, and, of course, all of our lab courses), I also touched on PDA's plans to move the TRI facility and consolidate our U.S.-based staff in Bethesda, Md. Since this move is going to consume us for the next six months, it might as well consume you, as well. I will continue to update the progress of the move to Bethesda in the Letter or on the PDA website.

As I said last month, preparation for this move is exciting and a bit scary at the same time. I've never been involved in a move of this magnitude before. Yes, I have moved offices and homes (though maybe this is easy compared to that), but never laboratories with all of the equipment and "stuff" that it takes to keep them up and running. The more involved I get, the more I learn from all of the questions being asked, as well as the answers that sometimes fall out of the sky! You know, like "Where's the HVAC? How much electricity do we need? Where are the drains and where do you want the water?" We are deliberating what kind of walls should be put up in the clean room, what the floors should look like, and what colors are good in different areas, because after all, while we must be functional, we must also look good (do you think they will let me paint the walls red?). And then there are the training rooms and the design and equipment needed for functionality. Then there are the important issues of what equipment to keep, what to leave, what we need to function, and what would be nice to have. Also issues such as what works, what doesn't, and how it is all incorporated into the planning process and the space. I think I will start lists. And maybe we'll organize a yard sale or a donation to the Smithsonian. So, who has a spare autoclave lying around that would look perfect in our new TRI lab? Some of what we are planning is a dream (ah, we can all dream), but much of it is practical and driven by necessity.

But seriously, the last few weeks have proved to be challenging—deciding what we need to do to move forward, what our floor plans and office space should look like, and when we should shut down our current facility and start up the new one. And, someone told me that I needed to do a budget for 2007 with all the new and existing courses that these labs will soon accommodate, and if you've been reading my column since last year, you know how much I love budgets!

This entire process is giving me a much greater and realistic appreciation of what you and your companies go through when changing facilities. Design, requisitioning, change control, etc., are not easy!

So, by the time you read this, we should have a plan and a build-out concept approved. Hopefully, we will have our permits and approvals to move forward (I learned about permits the hard way when rehabbing a 100 year-old row house in Baltimore with some friends). And, we should be seriously organizing, pitching and consolidating all of our stuff to move. Maybe the budget will even be finished, too!

So does anyone have any navy blue lab coats they'd like to send our way (that have all their buttons)?

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