*Science • Technology • Quality • Regulatory • Community*

# PDA Letter

Volume XLIV • Issue #4

www.pda.org/pdaletter

April 2008

## In This Issue…





PDA Parenteral Drug Association

*Connecting People, Science and Regulation®*

# Ensuring *T* is an Effective Part of *CAPA*

**Kristina R. Spitler, Almac Clinical Services**

The pharmaceutical industry has been buzzing with discussions around Corrective And Preventive Action (CAPA) as regulators expect companies to be better at root cause analysis, yet relatively little focus has been given to the role that *training* and *retraining* should play.

It is not uncommon for firms to forgo extensive root cause analyses in favor of sending employees to retraining sessions. Companies need to vigilantly ensure that "operator error" is not just an excuse for unexplained problems and that retraining is not just a convenient "fix."

### When Retraining is Just a Band-Aid

I've known cases where retraining events are too quickly applied as a corrective action and actually mask problems and hinder discovery of true root causes.

Recently, U.S. FDA investigators cited a pharmaceutical firm for sending analysts to retraining whenever out-of-specification (OOS) results were obtained. The problem per the FDA 483 was that the process on which they were retrained had no impact on preventing the same problem from occurring in the future.

The investigators observed that the retraining was not specifically linked to the OOS result and that "analyst error" might not have been the root cause of the failure in the first place:

> *The analysts were retrained on the analytical method itself, but there was no documented training regarding continuing the analysis knowing that he or she made an extraction error or that there was a problem with the disintegration of these two capsules during the analysis….*
>
> *The investigation did not address the reason why these two capsules did not dissolve adequately. The analyst's interview did not determine if the capsules were taking longer than normal to disintegrate before adding diluting solvent A, or if the capsules took longer to dissolve because he/she added diluting solvent A without making sure the capsules had disintegrated. The first scenario (the capsules taking longer than normal to disintegrate) would not indicate analyst error, but a possible process related error that would have required the investigation to be extended outside of the laboratory, e.g., investigation of the process and historical data to determine root cause.*[1]

Such short-sightedness exacerbates the underlying problem and brings greater attention to an already poor training process.

***continued on page 19***

# 2008 PDA/FDA Joint Regulatory Conference

## Harmonization, Implementation and Modernization: Achieving a Future Vision

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

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

*www.pda.org/pdafda2008*

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

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

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


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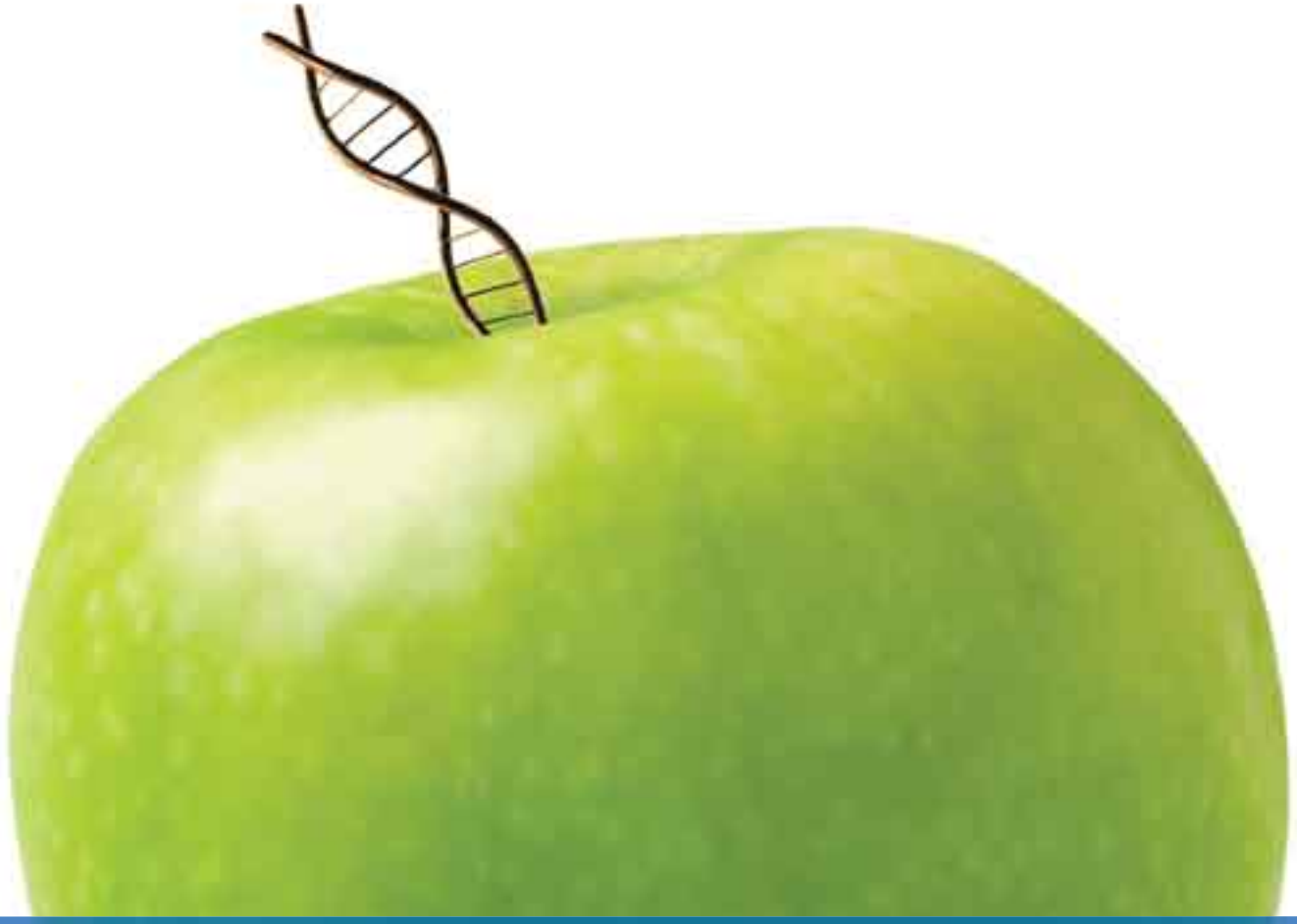
*Effective training programs should serve as an integral piece of the CAPA puzzle.*

***Coming Next Month:***
***European Regulatory Update***



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Applied Biosystems

## Editor's Message

Following up briefly on last month's cover story, the U.S. FDA announced as we were going to press with this issue that it plans to open field offices in China. **Emily Hough** is at the Food and Drug Law Institute conference in Washington, D.C. as I write this and has informed me that FDA Commissioner **Andrew Von Eschenbach,** MD, stated the plan is still pending the assent of the Chinese government and that FDA would like to open offices in other countries as well. Keep an eye on the *PDA Letter's* "Quality & Regulatory" section for more information on this ongoing story.

After reading this month's cover story "Ensuring *T* is an Effective Part of *CAPA,"* readers might want to go back and evaluate the effectiveness of their training programs. The article updates one published in the Letter in April 2006, and includes additional U.S. FDA inspection observations regarding personnel training. **Kristina Spitler,** the author, will be presenting a paper at the 2008 PDA Annual Meeting on the topic and will be speaking at the *2008 PDA Biennial Training Conference* in New Orleans.

For those of you who pay attention to the "Upcoming Issue" information we include on the Table Of Contents page, the article on media fills and risk management has been delayed and will appear in the July/August issue, which we reserve each year for articles on aseptic processing/sterile products. It is a great article by two well-known PDA volunteers, and I look forward to publishing it.

Back to this issue: Emily Hough wrote a timely article based on the recent PDA conference on cold chain shipping. Membership's **Hassana Howe** and **Trevor Swan** provide this month's "Tales From the Trail." **Gail's "**TRI Talk" outlines lots of new "stuff" for TRI, and much more! We hope you enjoy the issue!

### Visit www.pda.org/pdaletter

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

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


# PDA Letter

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# 2009 PDA Annual Meeting

## The Microchip: Impact on the Pharmaceutical/Biopharmaceutical Industry

# Call for Papers

**April 20-24, 2009 | Las Vegas, Nevada**

Friends and Colleagues:

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

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

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

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

[redacted]

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

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

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

[redacted]

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

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

Please include the following information with your abstracts:

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

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Science & Technology Snapshot

# Task Forces: Connecting Members and Nonmembers to Solve Everyday Challenges

**Rich Levy, PhD, PDA**

Another benefit of belonging to PDA is the opportunity to share ideas, debate and establish documented industry best practices. To enable that end, specific task forces are sanctioned by PDA Advisory Boards. Each task force is composed of PDA members and nonmembers devoted to transforming the group's scope statement into a PDA technical report—what PDA calls a best practices guide. Each technical report, if approved by the relevant Advisory Board and the PDA Board of Directors, will be published as part of our *PDA Journal of Pharmaceutical Science and Technology*. While most task forces address new topics of interest, other teams come together to address needs for revision in content which arise over the course of a technical report's life cycle.

**Here are some task force facts:**

- Number of current Advisory Board approved task forces: 38
- Number rewriting existing technical reports: 8
- Number of task forces in preapproval stage: 8
- Number of technical reports published in 2007: 3
- Projected number of technical reports to publish in 2008: 6

Current task forces cover classical pharmaceutical and biotech subjects.
You can view the entire PDA task force list by visiting www.pda.org/taskforce.

**Some of the current PDA Task Forces include:**

- Analytical Methods Validation for Biopharmaceuticals
- Audit Criteria Standardization
- Blow-Fill-Seal – A TR in partnership with the Blow-Fill-Seal Society
- Cell Substrate Characterization
- Cleaning Validation for BioTech Products
- Disposable Manufacturing Technology
- Fundamentals of an Environmental Monitoring Program
- Nonconformities in Ampules, Syringes and Injection Devices
- Nonsterile Environmental Monitoring
- Mycoplasma – Detection, Filtration and Alternative Methods
- Pharmaceutical Waters
- Dry Heat Sterilization – TR-3 revision
- Steam-in-Place
- Most Heat Sterilizer Systems
- Parametric Release – TR-30 Revision
- Viral Safety Topics

Ideas for topics are generated by PDA Advisory Boards, PDA Interest Groups and individual PDA members. If you would like to volunteer to lead, participate in or act as a reviewer for task force deliverables, please contact us at snapshot@pda.org.

# Technical Report *Watch*

**In Production:** *A new technical report is to be included with the May/June issue of the PDA Journal.*

**TR-45, *Filtration of Liquids Using Cellulose-Based Depth Filters***

This report was written to provide guidelines for the selection, validation and use of cellulose-based depth filters in pharmaceutical and biopharmaceutical applications that is useful in all regulatory environments. This report also provides information on physical and performance characteristics of cellulose-based depth filter products in sheet, lenticular cartridge (modules) and capsule configurations.

The report does not always address region-specific regulatory expectations, but provides up-to-date scientific recommendations for use by industry and regulators in establishing a filtration policy. This report should be considered a guide and it is not intended to establish mandatory standards for filtration. It is intended to be a single-source overview that complements existing guidance documents listed in the reference section.

# Leadership *Opportunities*

## PDA's Interested In Your Feedback

The Task Force working on *PDA Technical Report No. 33, Evaluation, Validation and Implementation of New Microbiological Testing Methods* would like to hear viewpoints from the perspectives of rapid and alternative microbiological methods vendors. We are looking for one-page reviews of your methods, including relevant applications and the science behind the technology.

The Task Force would also like for the PDA membership to provide information on how their company has qualified, gained approval and implemented a rapid or alternative microbiological method.

Please provide your feedback and comments to the Task Force chairs:

**Michael J. Miller,** PhD, *Eli Lilly and Company*
mjmiller@lilly.com

**Jeanne E. Moldenhauer,** *Excellent Pharma Consulting*
jeannemoldenhauer@yahoo.com

We appreciate your time and feedback to this important project!

# In *Print*

## Risk Analysis In Aseptic Processing

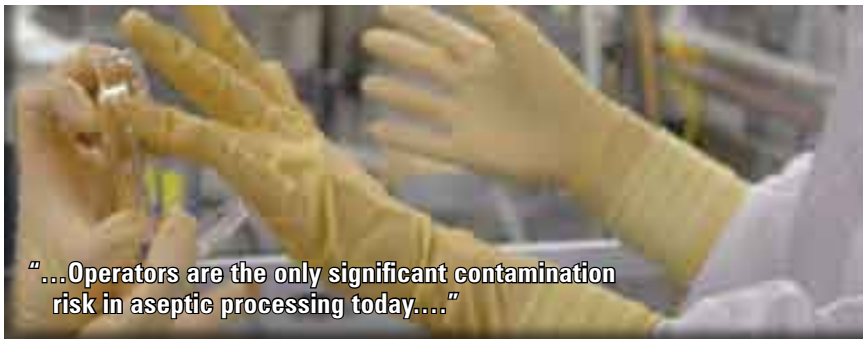
*From "Microbiological Risk Assessment in Pharmaceutical Production Operations" by James Akers, a chapter in Volume 1 of the two-volume* Microbiology in Pharmaceutical Manufacturing, Second Edition, *edited by Richard Prince, PhD.*

Certainly it is possible to use a form of HACCP-like risk analysis in aseptic processing. However, the processes and facilities currently used for aseptic processing are so uniform in design and performance that other methods may actually be more suitable. There are three principles in microbial risk within aseptic processing environments that are generally agreed upon by the majority of industry experts:

1) Contamination risk is almost completely related to human activity. Operators are the only significant contamination risk in aseptic processing today. It follows then that risk management is primarily related to the work of personnel. There are three principle ways by which the risk of human contamination can be abated. The first and arguably most effective risk abatement measure is the implementation of separative technologies designed to eliminate direct operator intervention into the most critical (and therefore most risk intensive) environments in aseptic processing. Examples of separative technologies are isolators and RABS systems, although the separation afforded by RABS can be variable since some RABS concepts allow for direct human intervention. A second means for abatement of risk from the work of operators is to replace these employees or at least reduce their need to intervene through the use of machine automation or robotics. Examples of automation reducing intervention include use of automated container sterilization and feed systems, automatic fill volume or weight checking, and automated loading and unloading of lyophilizers. It is possible to use extensive automation and separative technologies together and, in fact, such operations, in the author's opinion, represent the future of aseptic processing. Finally, managers of aseptic operations should always be on the lookout to improve the smoothness and efficiency with which their manufacturing processes operate so that interventions can be minimized or eliminated.

***continued on next page***

*In Print, continued from previous page*




2) The most probable route of contamination of product in aseptic processing is via the airborne route. Mechanical transfer of microorganisms from surfaces is rather inefficient as microbial recovery studies have shown. Since these contamination aerosols are principally associated with humans it follows that the further operators can be kept from the critical zone the lower the contamination risk. The Akers-Agalloco risk analysis method assumes that the probability of contamination falls off in proportion to the distance an operator is from the aseptic critical zone (the critical zone defined as an area, always ISO 5 in particulate air quality, in which product is filled into a container and/or assembled).

3) Since contamination is principally airborne, the shorter the exposure time of product, containers, closures or devices, the lower the risk of contamination. This simple notion has been a chief consideration in deposition risk analysis models proposed for evaluation of aseptic processes. While it seems obvious that this concept has merit, it should not be interpreted to mean that there is some uniform background level of contamination in an ISO 5 room. *In aseptic processing contamination is heterogeneously distributed and personnel-associated.*

## Practical Means Of Contamination Risk Abatement In Aseptic Processing

1) Always consider operators to be mobile contamination generators. Studies have shown that qualified operators wearing even the most effective gowns and working with sound aseptic practices can slough >1000 CFU/hour. The rate at which operators slough microorganisms will increase with the intensity of their production activity. Therefore, the less work operators do near the critical zone, and the less rapid and intense their movements, the better. Work that therefore requires an operator to strain physically is inherently risky. Heavy and physically demanding work is not compatible with aseptic operations. Although the risk of operator contamination is reduced significantly by separative technologies, good aseptic practices are still required. No skin should be exposed at any time in aseptic processing. Double-gloving is a requirement in modern aseptic processing and often gloves are taped to the gown gauntlet to avoid separation. Consideration could also be given to sterile sleeve covers which cover the glove-gauntlet interface.

2) In conventional cleanrooms, air exchange rates should be sufficient to handle the contamination emitted by the number of workers who will be present during an operation. Since cleanrooms are classified (or, in the case of the EU Annex 1, scheme graded), it may be tempting to think that all ISO 5 rooms (or their EU equivalent) are equal in terms of contamination control capability. This, however, is not the case at all. A room that provides only 60 air changes an hour and has a personnel load of five operators will be inherently higher in contamination risk than a room that provides 500 air changes an hour and has the same personnel load. The well-known statement that "the solution to pollution is dilution" applies quite well to cleanroom operations. In a CDC report on contamination control, they reported that the time required to achieve a contamination removal effectiveness of 99.9% at an air exchange rate of 20/hour was 21 minutes. However, raising the air exchange rate to 50/hour reduced the time to reach a 99.9% removal efficiency level to eight minutes. Obviously, these are much lower air exchange rates than would be used in aseptic processing fill rooms and critical zones. However, these data give a clear indication of the advantage of more rapid exchange of air (CDC). Air exchange rates and contamination removal efficiency are far more important risk metrics than the widely discussed smoke studies used to visualize airflow. Smoke studies, while marginally useful, are largely subjective and do not directly measure the removal of contamination, which is the prime consideration in risk abatement.

3) Manual aseptic connections should always be avoided. It is commonplace in modern aseptic processing systems for the entire wetted path to be cleaned and sterilized in place. Systems and processes that rely on personnel to make connections are inherently higher risk and require significantly added contamination control.

4) Machine set-up and adjustment is often considered the most

risk-intensive element of aseptic processing. The less work involved in executing the set-up, the better. In fact, no set-up at all is the best available alternative. Another advantage of isolator systems is that, typically, set-up is accomplished prior to vapor phase hydrogen peroxide decontamination, which means that the risk of contamination is effectively obviated by this reliable and reproducible sporicidal treatment. Older equipment may require very extensive set-up, and there may be no practical solution other than upgrading the equipment to this very substantial risk.

5) Employee comfort is always vital in aseptic processing. Working environments that are warm and humid are particularly high risk since they can result not only in discomfort but also perspiration. If perspiration is observed in any cleanroom, contamination risk is elevated. Humidities in the higher end of the traditional 50% ±10% range long used in cleanrooms may not be sufficient in all cases from a control perspective. Also, temperatures in the range of 16.5–18°C are typical in many production facilities.
6) Visible moisture is always unacceptable in any environment where contamination control is critical. All aseptic environments must always been clean and exceptionally dry. Moisture provides an opportunity for microorganisms to survive in what is otherwise an environment not conducive to microbial survival. Microbial growth is impossible in the absence of water: "dryness" is an often-overlooked critical process parameter from a contamination control standpoint.
7) Qualification of employees is always a critical consideration in aseptic processing, however it is not truly an element of a risk management program, nor is it part of a validation program. Rather, employee qualification is really a testing program at the conclusion of job skills training. GMP requirements include both training on regulatory requirements and job skills. Logically, job and process knowledge can only be gained when some basic training in the area of microbiology as it relates to contamination control is also included. One often hears in discussions about personnel qualifications the view that these employees are almost considered *validated* by the act of participating in a successful media fill test. This is, of course, not at all the case! Just because an operator performed an assigned job task in a media fill test and recoverable contamination was not detected at a given time does not mean that employee can function with suitably low risk over a sustained period of time. How well an operator performs can only be ascertained by watching him/her work day in and day out. Obviously, given the very low sensitivity of service sampling, particularly on a flexible service such as a gown, any tendency toward higher than normal incidence rates in personnel monitoring is a critical concern and a clear indicator of contamination risk.

# Recent Sci-Tech Discussions: Environmental Monitoring

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

**Are there any circumstances under which an incomplete media fill can be considered valid without repeating it? We have a new injection facility, we are carrying out the media filling. We have carried out three media fills of smallest pack size, during the first media filling of our largest pack size, the media filling was stopped due to the tunnel breakdown. Only 60% of filling was carried out. Can we consider it a complete media fill and incubate the vials, or else we have to repeat?**

**Respondent 1:** Yes, you must totally simulate what happens during your normal production single shift.

**Respondent 2:** Be glad that that the tunnel breakdown occurred during validation and not during production. You will have to perform a root cause analysis of the tunnel breakdown, then take the appropriate Corrective And Preventive Actions. This could serve as documented evidence to invalidate this media fill run.

In your validation plan you have specified the number of injections to be filled. Using only 60% of that number will not be acceptable, even if the number of injections filled > 3000 and the number of contaminated units = 0.

**Respondent 3:** Write it up and repeat. It cannot be used as it doesn't cover the range you intended

**Respondent 4:** You need to determine the cause of the tunnel failure and rectify before repeating the study with the full quantity stated in your protocol.

One thing to bear in mind though is that if you had a similar problem during routine production, you most likely wouldn't reject the product you had filled—it would be, after all, "good" product that simply didn't meet your yield requirements, therefore you should incubate these vials and fully investigate any contaminated units observed, after all, if the tunnel hadn't broken down you would have continued filling to completion. In view of this, the partial fill should be incubated, read and written up as such with a deviation to the protocol to describe the fault, rectification and repeat run.

You would probably have trouble defending it to an inspector if you discarded the "good" vials from the original study even though there were not enough to fulfill the requirements of the protocol.

**Respondent 3:** Two issues here, they contradict each other

1) If you claim it as valid you are only validated for its revised scope.
2) As you didn't comply with the protocol how can it be valid? From an inspectors view perhaps you cut it short deliberately?

**Respondent 5:** What do you mean by "incomplete"?

**Questioner:** Dear [Respondent 5], Incomplete media filling, I mean that the batch size of Media Filling that we have defined in the protocol was not completely filled, can it be considered valid.

**Respondent 5:** My opinion is that your media fill run is invalid. You did not meet the criteria set out in your protocol.

**Respondent 6:** Depends on the reason. If you can provide an adequate explanation and your QA can complete an investigation and sign of on a deviation report which should include an impact report which demonstrates that the deviation from the protocol could not have an impact on the integrity of the batch, you should be okay. However, in the case of a sterile product I am pushed to think of a deviation that might be okay. For other dosage forms it would be easier.

**Respondent 3:** In this case I believe the study is valid (dependant on *why* it was cut short *but* that now becomes the validated batch size not the extended batch size represented by the other two runs.

**Respondent 7:** According to me, no, because then the real purpose of defining the size of the fill gets defeated. However could I know the reasons for such incomplete filling. Probably then I could give a better opinion rather than a straight forward no.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Conference | Exhibition

# PDA Interest Groups & Leaders

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

## SECTION TITLE

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

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| | | | | |
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*Ensuring T is an Effective Part of CAPA, continued from cover*

I've heard of other situations where the retraining provided as a corrective action is often identical to the original training, which apparently was not effective to begin with. Doesn't this seem like a vicious cycle with no real corrective action at all? You've probably heard the saying, "The definition of insanity is doing the same thing over and over again and expecting different results." Perhaps we all need to do some investigation into our CAPA systems to see how often we are perpetuating insanity.

At a recent industry conference, I listened to a trainer from a large pharmaceutical company talk about an exercise where her training department performed such an investigation. They examined their company's CAPA system to identify all incidents of retraining in a given time period. They found it staggering to discover that some operators had been retrained on the exact same procedure multiple times in the period reviewed. The retraining was administered as a corrective action because the cause of the deviation was categorized as "operator error;" and the common assumption being if the operator makes a mistake, they must need retraining.

As a result of the training department's study, the firm realized that the standard operating procedure (SOP) was unclear and misleading, causing the operators to become easily confused. Only after the SOP was clarified *and* the operators were retrained *differently* did the vicious cycle cease.

**Retraining should not:**

- Mask the real problem
- Hinder discovery of the real root cause
- Replicate original training
- Proceed without analysis
- Be a "band-aid" for problems making training nothing more than a "formalistic, useless exercise to satisfy a regulation" (per preamble quote from Commissioner on 211.25)

**Retraining should:**

- Address the root cause of the problem
- Address the part of the function or process where knowledge deficit is the issue
- Encompass an effectiveness evaluation to ensure **training** corrections fix **training** problems

### Effective Training as a Preventive Action

If we really want training to have a corrective *and preventive* effect, we need to carefully examined retraining events to ensure that they rectify the original problem—if it truly is a training problem at all. Repeating the original training process as if all operator errors are the result of knowledge deficits is missing the mark in a number of cases and contributes to ineffective CAPA systems.

Imagine the outcome if we quit trying to just correct deviations with training and start *preventing* them with training. A proactive approach will yield far better results than a reactive one.

Before applying the "training fix," it's beneficial for a firm's quality unit and training department to confer and determine what type of retraining will actually solve the root cause of the deviation. Retraining should address the root cause of the deviation and the part of the function or process where knowledge deficit or skill competency is the issue.

In addition, companies need to evaluate the effectiveness of their retraining efforts to ensure that the corrective action had the desired effect.

Read through some warning letters and 483 observations referencing training and you'll notice that training completion and training effectiveness do not necessarily go hand in hand. The FDA has cited a variety of cases where employees are trained on excessive numbers of SOPs in a given day, training needs are not adequately assessed, training is not sufficient to produce competency, untrained personnel are training others—basically training is not effective. The bottom line is that it takes more than a sign-in sheet to demonstrate employee qualification.

> "The Commissioner intends that the training be meaningful to the employee, not a formalistic but useless exercise to satisfy a regulation."
>
> www.fda.gov/cder/dmpq/preamble.txt

To have an effective training system, you have to start at the foundation, the regulatory expectations. In the U.S. Code of Federal Regulations, personnel qualifications are discussed in 211.25, 58.29, 606.20 and 820.25. If you read each of them, they essentially set forth very similar requirements. The Medicines Healthcare Regulatory Agency "Orange Guide" speaks of training in chapters 2.8–2.12, and we should also look at what the International Conference on Harmonisation has to say in Q7A (GMPs for active ingredients). If these are all studied, the requirements essentially span ten common principles.

1) Find the "magic" combination of *education, training and experience, or any combination thereof* commensurate with assigned functions
2) Ensure training enables personnel to perform *assigned functions*. It certainly takes different levels of education, training, and experience to perform all of the many functions in our industry, and the key is ensuring that the combination is well suited to the function

3) Provide training in *particular operations* the employee performs (i.e., SOPs). Notice this is a finer level of detail than "functions"
4) Provide GMP training with sufficient frequency. Sufficient frequency is whatever it takes to ensure staff employ and remain familiar with GMP concepts
5) Offer continuing training; training should not be a one time event
6) Assess training effectiveness
7) Identify training needs
8) Approve training programs by department heads and/or Quality
9) Maintain training records
10) Discuss the concept of quality with all employees

If there are so many things we should be considering, why is the focus so often on getting the documentation instead of all of the other important regulatory expectations mentioned? We've all heard the old industry adage, "If it isn't documented, it didn't happen;" but I'd like to add the corollary, "Just because it's documented, doesn't mean it was effective!" Sure documentation of training is vital, but if that's all you have to show for it, with no real results, than you've not met the compliance goal at all.

### Training Still a Top Investigator Observation

Training is one of the top ten reasons companies get 483s. At the 32nd International GMP Conference in Athens, Georgia (March 12–13), FDA Atlanta District Office Supervisory Safety Officer **Philip Campbell** presented the top 10 CFR section cites for FDA fiscal years 2004 to 2007. Personnel training (21 CFR 211.25(a) was in the top 10 each year, according to Campbell's data. This is consistent with data Campbell shared with PDA in 2006 for the article "Personnel Training: A Growing Compliance Concern" (see the *PDA Letter,* April 2006, cover).

A review of recent FDA 483's demonstrate the various types of problems investigators observe. In one case, FDA investigators found a manufacturer of sterile eye solutions out of compliance with 211.25(a) for not training employees for the particular operations they were performing for product filling. According to the 483:

> *Employees are not given training in the particular operations they perform as part of their function. Specifically…the operators within…operations have not participated in…media fills, as per SOP…"Validation of Aseptic Fill Challenges," to ensure operators remain current with relevant established procedures and cGMPs.*[2]

**"Just because it's documented, doesn't mean it was effective!"**

Another firm was recently cited for a similar infraction:

> *There is no assurance that training/qualification of all operators performing aseptic operations in the flu manufacturing area is complete. Specifically: A…Sterile Filtration training module requires initial Aseptic Technique training and SOP…, Aseptic Process simulation (APS) Validation Requirements for the…Aseptic Processing Area requires…requalification through participation in a process simulation study. Influenza Department Technician SW completed her Aseptic Technique Qualification on…but has not participated in a media fill since her qualification. This technician has participated in sterile filtration operations….B…SOP states that participation of aseptic personnel in process simulation studies should be tracked and maintained in personnel training files. This is not being done for operators involved in the sterile filtration of…*[3]

The 483 listed a number of questionable practices by the firm's personnel:

> *Operators performing level 1 cleaning in between pre-filtration and sterile filtration operations were observed applying disinfectant to the floors of the dirty side of the Class C areas and returning to the Class B areas without re-gowning…*
>
> *Personnel with egg carts containing eggs were observed traveling into room 140 via this hallway during the filtration operations for Lot U08182.*

A contract testing firm was cited recently for allowing an untrained employee to perform analytical methods:

> *An analyst performed an assay for sodium citrate samples before training was complete and there was no record of the training in the analyst's training file.*[4]

In its response to the 483, the firm informed the Agency that the firm was in compliance with its own training procedures, however, the procedure needed revision to make the case clear:

> *It is the practice of the St. Louis facility to allow for the use of concurrent training of analysts with certain samples where the analysts may have the appropriate experience/training from other similar tests… 'Training in the Chemistry Department' will be revised to more clearly highlight this practice.*

While regulators do not always make the link to faulty training when listing inspection observations, there are many examples of observed personnel deficiencies which could be remedied through proper retraining or prevented with adequate initial training. Employee behavior is under heavy scrutiny in sterile product environments. ➤

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# 2008 PDA BIENNIAL TRAINING CONFERENCE

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## Focus on Performance: Partnering For Business Success

Join colleagues and connect with thought leaders at the ***2008 PDA Biennial Training Conference*** and take home the knowledge and skills you need to train your workforce. The conference is designed for anyone with training responsibilities in the bio/pharmaceutical industry and will provide the most current information needed to strengthen your training expertise. **Training and medical device experts and FDA representatives** will provide valuable insight on how to:

- Implement best training practices in a highly regulated environment
- Improve the performance of your employees
- Apply the latest training trends and techniques
- Inform your team of the most current regulatory requirements

Complementing the conference are PDA Training and Research Institute (PDA TRI) training courses and an exhibition featuring vendors who provide excellent services in support of training efforts.

### CONFERENCE
MAY 19–21

### EXHIBITION
MAY 19–20

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MAY 22–23

In a 2006 483 to one firm, FDA investigators cited numerous questionable personnel practices:

- *Production personnel failed to mop all walls and floors of the Vial Fill Suite following the production run*
- *Production personnel failed to remove all debris, such as, broken glass and stoppers, from the Vial Fill Suite floor prior to mopping*
- *Production personnel failed to properly clean the walls of the Vial Wash Room on a regular basis, "which resulted in a build-up of airborne lint on the HVAC return air grills on the lower east and west walls being pressure during the production run*
- *Personnel performing sterility testing were observed with exposed skin*
- *A technician was seen sanitizing hands immediately before touching finger touch plates used for personnel monitoring*
- *A technician was observed adjusting clean room clothing*
- *Sterility testing personnel were required to sanitize their gloves, but on Oct. 3, 2005, technician's gloves were so heavily coated with sanitizing solution, that it was dripping off the gloves*
- *Personnel were observed wiping the surface of the LAF hood after filling final product and prior to performing surface monitoring*[5]

It's suggested that you can examine your company's deviations and uncover training issues which, when corrected, could prevent future occurrences of similar problems. Now that's a novel suggestion—make training a preventive action in lieu of just a corrective action!

A recent article[6] cited an inspector's advice with regards to training compliance. The inspector said it is most important to ensure that employees understand and employ GMP concepts and to observe employees' behavior to see if it is consistent with the training that was provided. Also, training should not be a one-shot deal; continuous training and reinforcement of concepts is crucial to maintaining compliance.

Basically, the goal of training is to ensure that people perform tasks safely, correctly, and effectively—every time. While people and training cannot be validated like machines and processes, there are certainly measures that can be taken to increase your chances of success when it comes to training in your organization:

1) **Assess training needs effectively**

   It's important to ensure that each process has responsible parties clearly identified, and that the right level of training for the various participants in any given process is provided. How do you know what the right combination is of education, training and experience? It's not the same for everyone. You really have to look at "assigned function" and "particular operations" separately. Ensure that you have training standards for each position in your company, and for each operation as well, ideally approved by Quality.

2) **Identify when training IS the answer**

   Training is the answer when you have a knowledge deficit. It is NOT the answer when the problem relates to motivation or the employee's capacity to do the job well. Root cause analysis and identification of training objectives can alleviate training for the sake of training.

3) **Ensure instructors are qualified and that they employ effective adult learning techniques**

   Instructors need to know more than just your systems and procedures—they need to know how to train adult learners.

   Provide trainers with the skills and resources to do the job well. Trainers need to understand educational practices, especially adult learning techniques like educational domains, learning styles, knowledge retention techniques, etc. Invest in your trainer's expertise and your entire organization will benefit.

4) **Practice good instructional design and develop materials which optimize learning and retention**

   Instructional design is a specialized skill. Good design will render better retention of the material in a fraction of the time. A widely recognized standard is the ADDIE method which involves **A**nalyzing a subject/process, **D**esigning training objectives to best suit the type of learning, **D**eveloping materials, **I**mplementing the delivery of the training, and **E**valuating the level of success against the original objectives.

5) **Engage learners in active learning. Don't be passive!**

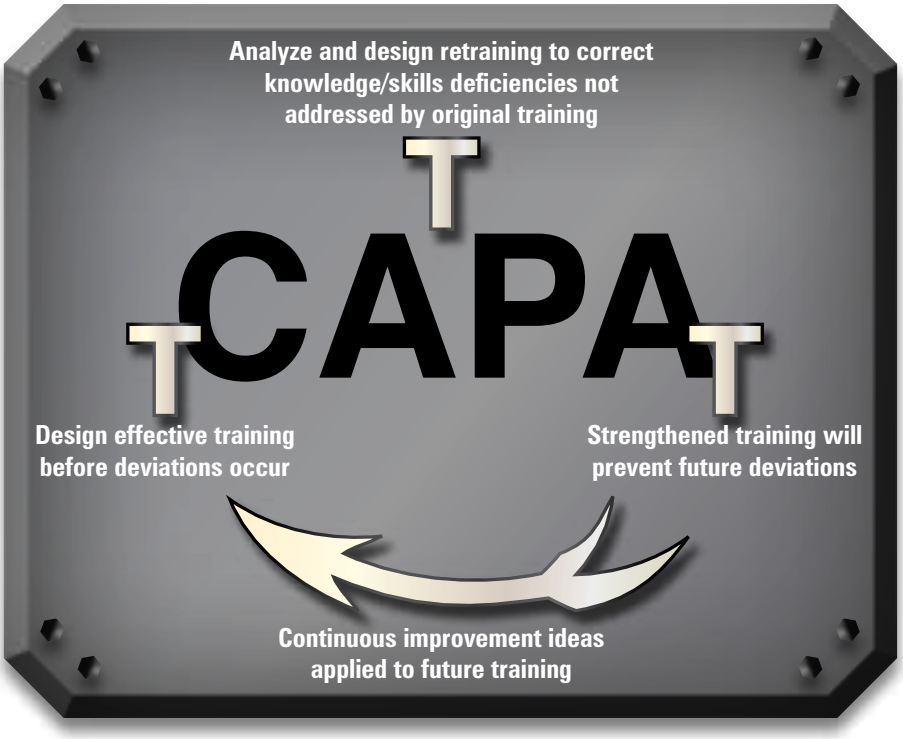
   After an hour or two—we tend to zone out and lose our ability to take in anything new—especially if the learning experience is very passive! When possible, engage the learners! Get them to think about how the topic relates to them and give them ways to apply information so that it is more than just data.

6) **Train with sufficient intensity and frequency**

   Often we're overtraining on the little things and undertraining on the critical things. All training shouldn't be delivered in the same style at the same intensity, and the evaluation methods should vary as well. It goes back to good instructional design. Analyze the task or process to determine the level to which various people need to understand and employ the concepts. Design the training according to the objective and the level needed.

7) **Investigate deviations and determine where training improvements are needed**

   Identify the root cause of deviations to figure out if knowledge or skill deficit is the issue—then find out why. Was it poor training delivery, limited capacity to learn, or poor measurement of competency? Ensure that retraining addresses initial training deficiencies.




8) **Don't underestimate the "human" element to training**

Instructor led training is on the decline for many reasons. It's expensive, difficult to schedule, and involves a commitment in resources; but don't underestimate the "human" element. With the advent of electronic learning management systems (LMS), many companies have taken the attitude that the LMS can not only track the training, but **deliver** the majority of the training too! And it can—but we need to measure how effectively it does so. Learning management systems that are used to shove "read and sign" SOPs through their channels and then render personnel "trained" can be dangerously deceptive tools. Ensure that you only use e-learning and "read and sign" where it is most effective, which is with knowledge/recognition levels of learning vs. application/task levels.

9) **Measure training effectiveness appropriately**

You'll only know if your training is working if you measure training effectiveness. Often, we're so focused on delivery and documentation, that measurement of success is overlooked. If you have competency assessments, ensure that they adequately measure competency. Identify exact skills that you want to see demonstrated and define how they are measured.

10) **Continuously improve training programs so that they become "preventive actions" in lieu of "corrective actions"**

The cycle would not be complete without seeking continuous improvement. Analyze your success measurements and work on ways to improve training.

Effective training systems do more than just satisfy the mandatory compliance criteria; they elevate training programs to the level where they are preventive actions in lieu of corrective actions. Anticipate where processes can go awry and see where training can factor into risk analysis measures to ward off problems before they occur. Training is a powerful tool in quest for compliance. Use it effectively and proactively to replace CAs with PA!

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If you would like to comment on this article, contact Kristina at kristina.spitler@almacgroup.com.

Quality & Regulatory Snapshot

# Six Regulatory Documents and a Trip Make For an Unusually Busy Week

**Bob Dana, PDA**

Welcome to another edition of the Quality and Regulatory Snapshot. As I write this, I'm at 35,000 feet somewhere over the Atlantic Ocean on my way home after a very successful PDA/EMEA Conference in Budapest, Hungary. This Conference was attended by over 400 people, and over 50 regulators from all across Europe were present, either as attendees or presenters. Congratulations to the Program Committee, chaired by **Steve Bellis, David Cockburn** and **Lothar Hartman** for assembling such an outstanding program. Thanks also to all the speakers who took time out from their day jobs to prepare their presentations and share their knowledge and perspectives with the attendees. In next month's issue of the *PDA Letter* you will be able to read more details on the Conference. We hope to be able to bring you the third PDA/EMEA Conference sometime in the future—stay tuned for news on this.

Just before the PDA/EMEA conference, the Regulatory Affairs and Quality Committee (RAQC), the Board of Directors (BoD) and the PDA Quality and Regulatory Staff together worked very hard to complete the Association's comments on Annex 2 and Annex 3 to ICH Q4B, *Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions.* These were due to the U.S. FDA February 15th, and I credit all the volunteers on the RAQC and BoD who worked diligently on these documents, especially those who were also simultaneously preparing to join me the following week in Budapest.

This was the first time we submitted according to the U.S. government's new process for submitting comments on proposed regulatory documents, so there were some new details and wrinkles to sort out. For future use, you may want to make note of the new address for the Federal Dockets Management site, regulations.gov.

As if that wasn't enough, comments on FDA's proposed changes to the drug GMPs were due February 19th. Last month, I wrote about the process PDA uses to develop and approve those comments and noted that sometimes the process goes smoothly, sometimes the decision to comment or not can be controversial, and still sometimes there can be some lengthy discussions about the content of the comments themselves. It would be fair to say that in the case of our comments on the proposed GMPs, the last two parts do a better job of describing the process than the first. There were numerous teleconferences with the Task Force, the Science Advisory Board, the RAQC and the BoD to ensure these comments were finalized prior to everyone's departure for Budapest.

That we were able to pull this off is a tribute to the hard work of everyone involved and ultimately we arrived at scientifically sound comments on a regulatory proposal, focused on issues which have the potential to significantly impact the regulatory arena for years to come. Thanks to everyone involved.

PDA recently submitted comments to the EMEA on Draft Annex 2 of the EU GMP. The cover letter is reproduced on p. 28. All comments mentioned in this message are available at www.pda.org/regulatorycomments.

Just as we were putting all of these comments to rest, more regulatory documents were published. Literally while we were in the air to Budapest, the long awaited revision of Annex 1 to the Europe GMP regulations was published. This document finalizes a number of changes to the EU aseptic processing requirements, including changes affecting: clean room and clean air device classification; process simulation testing; bioburden monitoring; and capping of freeze dried vials.

Annex 1 was originally published as a draft in September 2005. A PDA task force developed comments on this draft and they were submitted to EMEA for consideration on April 24, 2006. Task Force chair **Steve Bellis** provides an overview of Annex 1 and looks at the potential impact PDA's comments in the article.

As if that wasn't enough, also on February 15th, additional updates to the European GMP Guidelines were published. Newly published Annex 20, "Quality Risk Management," incorporates the ICH Q9 guideline and provides guidance on a systematic approach to quality risk management which facilitates compliance with GMP and other quality requirements. In addition, for consistency, Chapter 1 "Quality Management" of the EU Guidelines to GMP for Human and Veterinary Products was also revised to include aspects of quality risk management within the quality system framework.

Don't forget—we welcome your input, feedback and suggestions on the Quality and Regulatory Snapshot at any time. Just submit them to snapshot@pda.org. Until next month.

# PQRI *Update*

## Establishing the Science for Regulations

Since 1999, the Product Quality Research Institute (PQRI) has established itself as the premier organization for providing a neutral environment where industry, academia and the FDA collaborate on pharmaceutical product quality research and development in support of policy relating to the regulation of drug products.

The Institute is guided by a board of directors that is responsible for fiduciary matters and a steering committee that oversees technical and scientific operations. The committee is comprised of representatives from member organizations, which currently include the American Association of Pharmaceutical Scientists; Consumer Healthcare Products Association; International Pharmaceutical Aerosol Consortium on Regulation & Science; International Pharmaceutical Excipients Council of the Americas; Parenteral Drug Association; Pharmaceutical Research and Manufacturers of America; U.S. FDA's Center for Drug Evaluation and Research; and U.S. Pharmacopeia.

PQRI's collaborations are growing. The Institute is proud to announce the recent addition of Health Canada as a member organization. In addition, a Memorandum of Agreement has been signed with the National Institute for Pharmaceutical Technology and Education for future collaboration on work projects.

Key focus areas for PQRI currently include advancing the science of Quality by Design, addressing regulatory and scientific issues associated with pharmacokinetics, and developing science and risk-based approaches to pharmaceutical manufacturing.

The following are examples of recent accomplishments and ongoing projects:

**Leachables and Extractables Management in Orally Inhaled and Nasal Drug Products (OINDP)**

A working group composed of chemists and toxicologists from FDA, industry and academia developed recommendations for:

- safety thresholds
- approaches for establishing analytical thresholds
- best practices for qualification and management of leachables and extractables in OINDP

*continued on page 29*

# PDA Comments *Analysis*

## Annex 1 Comments

**Stephen Bellis, CMC Biopharmaceuticals**

In April 2006, PDA submitted comments to EMEA regarding proposed changes to the May 2003 version of Annex 1, "Manufacture of Sterile Medicinal Products." The purpose of this article is to compare the original key comment points submitted by the PDA versus the final EMEA document published on Feb. 14, 2008 and effective March 1, 2009.

**PDA Point 1:** We offer clearer text associated with the environmental classification table in Clause 4. We have revised the table to be more aligned with EN ISO 14644-1, which is the internationally accepted standard for non-viable particle classification.

**Annex 1 2008 Version:** EMEA accepted the use of EN ISO 14644-1 as the basis for the classification of Grade A, B, C and D clean rooms and clean air devices. See section 4, Table 1.

**PDA Point 2:** We agree with the intent of revised Clause 47 to harmonize process simulation tests (media fills) with the equivalent FDA guidance document. We have slightly modified the section to more closely align it with the FDA guidance document. We have suggested removing the requirement for performing media fills per shift and replaced it with the requirement that each person involved in aseptic processing should participate in at least one media fill per year. This is to address the need for each person, as part of their ongoing training/qualification requirements, to participate in at least one media fill, and to address the point that with modern manufacturing practices it is becoming increasingly difficult to define a shift.

**Annex 1 2008 Version:** EMEA modified the new section 69 on the number of containers used for process simulation tests (media fills) to harmonize with the FDA guidance document entitled, *Sterile Drug Products Produced by Aseptic Processing.* EMEA did not remove the requirement for performing process simulation tests per shift. The new section 68 retains this requirement.

**PDA Point 3:** We have suggested an adjustment to new Clause 57 to take account of the improved sterility assurance provided by the practice of using duplicate in-line sterilizing grade filters for solution filling operations. When using duplicate in-line filters, we believe it appropriate that the bioburden might be monitored only at suitable scheduled intervals.

*continued on page 31*

# Regulators Focus on Cold Chain Practices

**Emily Hough, PDA**

Transportation, storage and distribution of temperature-sensitive pharmaceutical and biopharmaceutical products continue to be scrutinized by regulatory agencies around the world. On March 13–14, PDA held the *2008 PDA Pharmaceutical Cold Chain Management Conference: Temperature Controlled Pharmaceutical Supply Chain Life Cycle,* where regulators and industry experts discussed their latest plans for ensuring that products in the supply chain are handled in compliance.

Representatives of the U.S. FDA and the German inspectorate discussed recent regulatory concerns of their respective agencies. **Rosa Motta**, Compliance Officer, CDER, said that cold chain is becoming an important topic because a growing number of drugs are labeled with temperature-specific storage requirements. **Rico Schulze**, GMP Inspector, Regierungspraesidium Dresden, in his presentation on the global regulatory environment, pointed out deficiencies that were found during recent inspections.

Schulze mentioned an inspection he conducted of a wholesaler's warehouse during which he found that the firm was using consumer refrigerators as opposed to models suitable for industrial pharmaceutical storage. He also cited the firm for blocking a refrigerator with boxes. About the conditions uncovered at this facility, Schulze observed, "Maybe this is a symbol of the importance attached to cold chain practice by some companies in Europe or in Germany."

Motta said FDA expects manufacturers to know and take into consideration the effects temperature and temperature regulations have on drug products. "For example, manufacturers are expected to know the [effects of] temperature excursions on the drug. This is an important element of stability testing. Also we expect manufacturers to gather knowledge regarding the stability characteristics of the drugs they manufacture as part of drug development and also as part of cGMP requirements. This knowledge of this particular characterization of drugs will help manufacturers in selecting adequate containment closure systems and shipping methods. Information about the stability characteristics of drugs can be useful in developing plans for procedures for disposition of drugs exposed to adverse conditions and to conduct those investigations related to these events."

Schulze said one of the challenges associated with cold chain is that many stakeholders in the supply chain do not know about the regulations; lack of knowledge leads to transportation and storage errors. "It is a problem that there is a lot of people involved in supply chain that do not know these documents. In the manufacturing site often we find state-of-the-art storage conditions, but when you look further at the transportation or during storage at the wholesaler site, we find a situation that is sometimes unacceptable, and that is no joke."

**Table 14.0-6: Example of a Transportation Control Strategy Document Based On Product-Specific Stability Data To Determine the Effect of Temperature Excursions [from PDA TR-39]**

| Storage Condition: Refrigerated Condition (2 to 8°C) | |
|---|---|
| **Temperature Range** | **Time** |
| <-20°C (<-4°F) | Do Not Use |
| -20 to 2°C (-4 to 36°F) | 2 days |
| 2 to 8°C (36 to 46°F) | Until Expiry |
| 8 to 25°C (46 to 77°F) | 6 days |
| 25 to 40°C (77 to 104°F) | 2 days |
| >40°C (104°F) | Do Not Use |
| This table needs to be designed for every product and transportation route/method used. | |

**Mary Foster**, PharmD, Vice President, Regulatory Compliance, Catalent Pharama Solutions, outlined good storage and shipping practices. Her presentation derived from her work on the U.S. Pharmacopeia committee to revise General Chapter <1079> called "Good Storage and Shipping Practices." Foster noted that temperature mapping, according to the USP, must occur for "a minimum of 24 hours for three consecutive days." Foster said there is no science behind those numbers and she is aware of one company that uses seven days as a mapping standard. **[Editor's Note:** PDA TR-39 includes information on product differentiation. Table 14.0-6 from TR-39 shows a range of temperatures and times best for the transportation of a product.**]**

Schulze said frequent storage miscues include failure to conduct temperature mapping, no or inadequate temperature monitoring records, uncalibrated temperature monitoring devices and/or alarm systems, lack of or inadequate written procedures, and insufficient handing of deviations. Schulze advised, "First of all you must be able to detect a deviation and second of all you must assess them. This is a real big problem in practice."

Indeed, Motta reviewed various FDA 483 observation specific to shipping and storage and highlighted a case where a firm failed to have written procedures for both drug product storage and monitoring the temperature and humidity at the warehouse.

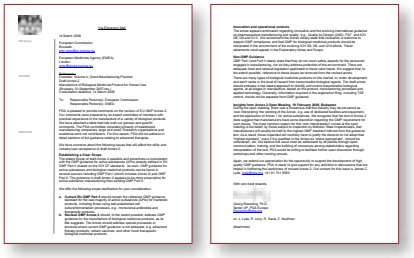
### FDA Mapping Need for Additional Guidance

Motta said FDA is "still considering" whether or not to write a guidance specifically for cold chain control issues. "We need to gather data. We need to perhaps test sensitive products to see what the state of compliance and the risks are. We need to decide

*continued on page 29*

# Scope of Annex 2 Inconsistent with GMP API Guide

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



14 March 2008

European Commission • Brussels • entr-gmp@ec.europa.eu

European Medicines Agency (EMEA) • London • gmp@emea.europa.eu

Reference: Eudralex, Volume 4, GMP, Draft Annex 2,
Manufacture of Biological Medicinal Product for Human Use (Brussels, 03 September 2007/rev.)

To: Responsible Person(s): European Commission and EMEA

PDA is pleased to provide comments on the revision of EU GMP Annex 2. Our comments were prepared by an expert committee of members with practical experience in the manufacture of a variety of biological products. We have attached a table that lists both our general and specific comments. The PDA committee consisted primarily of established manufacturing companies, large and small. Research organisations and academia were not contributors. For this reason, PDA did not address in detail sections of the guidance relating to advanced therapies.

We have concerns about the following issues that will affect the utility and industry/user acceptance of draft Annex 2.

**Establishing a Clear Scope**

The stated Scope of draft Annex 2 parallels and sometimes is inconsistent with the GMP guidance for active substances (APIs) already defined in EU GMP Part II (based on the ICH Q7 standard)**.** As such, GMP guidance for active substances and biological medicinal products can be found in several sources including GMP Part I (which includes Annex 2) and GMP Part II. The guidance in draft Annex 2 appears to be more prescriptive for active substance manufacturing than existing GMP Part II.

We offer the following scope clarification for your consideration:

**a. Current EU GMP Part II** should remain the reference GMP guidance standard for the vast majority of active substances (APIs) for marketed products, including those using well-established cell culture/fermentation processes, e.g., monoclonal antibodies and therapeutic products.

**b. Revised GMP Annex 2** should, to the extent possible, address GMP guidance for the manufacture of biological medicinal products, as its title suggests. The Annex should address special processes or products where current GMP guidance is not adequate, e.g. advanced therapy products, certain vaccines, and other novel therapeutic biological medicinal products.

**Innovation and operational controls**

The annex appears ambivalent regarding innovation and the evolving international guidance on pharmaceutical manufacturing and quality, e.g., Quality by Design (QbD), PAT, and ICH Q8, Q9 and Q10. We recommend the Annex clearly state that innovation is welcome to support GMP compliance, and that GMP for biological medicinal products should be interpreted in the environment of the evolving ICH Q8, Q9, and Q10 efforts. These statements could appear in the Explanatory Notes and Scope.

**Non-GMP Guidance**

GMP Part I and Part II clearly state that they do not cover safety aspects for the personnel engaged in manufacturing, nor do they address protection of the environment. There are adequate local and national legislation applicable to these valid needs. We suggest that, to the extent possible, reference to these issues be removed from the revised annex.

There are many types of biological medicinal products on the market, or under development, and each varies in the level of hazard from transmissible biological agents. The draft annex should embrace a risk-based approach to identify and control transmissible biological agents, at all stages in manufacture, based on the product, manufacturing processes and applied technology. Generally, information required in the registration filing, including TSE control, should not be separate from GMP guidance.

**Insights from Annex 2 Open Meeting, 19 February 2008, Budapest**

During the open meeting, there was a consensus that the industry may be perceived as 'over interpreting' the wording of the Annex, e.g. use of dedicated facilities and equipment, and the application of Annex 1 for active substances. We recognize that the text of Annex 2 does suggest that manufacturers have some discretion regarding the GMP requirement for such issues. The most common reason for this 'over interpretation' voiced at the open meeting is the belief, by those subject to inspection by Member State Inspectorates, that manufacturers will usually be held to the highest GMP standard inferred from the guidance text. As a result, those inspected will routinely have to justify the decision to not adopt that "highest standard," even if it is qualified in the Annex as 'where appropriate', 'should be considered', etc. We believe this issue must be addressed by all parties through open communication, training, and the building of consensus among stakeholders regarding interpretation of the text. PDA would be willing to facilitate further open discussion through workshops and other training venues.

Again, we extend our appreciation for the opportunity to support the development of high quality GMP guidance. PDA is ready to give support for any activities or discussions that are helpful in furthering the usefulness of revised Annex 2. Our contact for this issue is James C. Lyda, lyda@pda.org, +41 61 701 9550.

With very best regards,

Georg Roessling, Ph.D.
Senior VP, PDA Europe

*PQRI Update, continued from page 25*

This was accomplished by assessing safety data found through extensive literature and database searches and generating data by extraction studies and placebo leachable studies. This work has resulted in multiple public presentations, a publication in a major toxicology journal and numerous training sessions for interested stakeholders from both industry and regulatory agencies. The working group is drafting further publications, including a book addressing development of safety thresholds.

**Biopharmaceutics Classification System (BCS) Waiver for Class III Drugs**

The objective of this ongoing project is to determine the feasibility of allowing BCS-based waivers for Class III drugs in immediate release (IR) solid oral dosage forms. The hypothesis of the work is that many common excipients do not influence intestinal drug permeability and that in-vitro and physicochemical product tests can be developed to assure equivalent rate and extent of drug absorption of many pharmaceutical dosage forms. The project will measure the influence of many excipients commonly used in IR oral solid dosage forms on the intestinal permeability of BCS Class III drugs. Results are expected in 2008.

**Quality by Design**

PQRI has several initiatives ongoing related to the science of Quality by Design. The goals of these efforts include:

To define a systematic approach to drug development through the identification of potential critical process parameters (CPPs) and critical quality attributes (CQAs). The team will deliver a high-level decision tree that can be followed to determine what the potential CPPs and CQAs might be for a given manufacturing process with examples of how to use the decision tree.

To develop a clinical protocol for assessing the impact of multiple manufacturing variables on plasma profiles. These pharmacokinetic studies would determine if potential CPPs and CQAs, identified as such based on the manufacturing process and existing knowledge, have any impact on bioavailability. If successful, such an analysis may result in true correlation of the manufacturing process with in-vivo performance.

**Potential Genotoxic Impurities**

The goal of this project is to understand the kinetics of formation and decomposition of these esters so that science-based decisions can be made about the appropriateness of use of sulphonic acids during API manufacturing. Sulphonic acids (in the presence of alcohols) can form sulphonate esters, which are potential genotoxic impurities in drug substances. Reactions using sulphonic acids are not uncommon in active pharmaceutical ingredient (API) manufacturing, resulting in the need to develop a better understanding of the conditions under which this reaction will result in the formation of sulphonate esters. Results are expected in 2008.

**Get Involved**

PQRI relies on the efforts of our member organizations and volunteers. If you are interested in more information about PQRI or its current projects, please go to www.pqri.org or contact PQRI by email at pennv@pqri.org.

*Regulators Focus on Cold Chain Practices, continued from page 27*

if we need to emphasize this issue in our compliance program." Part of the decision making process will involve dialogue with field investigators. And as always, she said, FDA "appreciates any input from industry regarding this issue."

She also said that if industry was comfortable with the currently available best practice documents like TR-39, FDA would prefer not to write a guidance. "We get input from industry about too much guidance or too little guidance, this is why it is important for [FDA] to try and make a determination in the office as if it is really needed and if what is currently out there is sufficient. Unless I get feedback or [there are] increased observations of violations in this regard, I don't think that FDA will be writing a guidance specifically for cold chain."

Schulze concluded with, "We should keep in mind the importance of [the] conference subject. We should keep in mind the massive problems that can occur to the patient when things go wrong. We should keep in mind that the importance of good cold chain management will increase in the future."

# Regulatory Briefs

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

## North America

### Container/Closure Guide Released by U.S. FDA

The U.S. FDA has released the final version of the guidance entitled, *Container and Closure System Integrity Testing in Lieu of Sterility testing as a Component of the Stability Protocol for Sterile Products*.

The guidance document provides recommendations to sponsors for using methods other than sterility testing to confirm the integrity of container and closure systems as part of stability testing for sterile biological products, human and veterinary drugs and medical devices. The guidance document does not apply to sterility testing methods for product sterility testing prior to release, as container and closure system integrity tests cannot demonstrate a product's initial sterility.

For sterile product NDAs, FDA recommends that container and closure system integrity tests are included in the stability protocol. Pending new marketing applications may be amended prior to approval.

## Europe

### EC Launches a Study to Solve Counterfeit Medicines

The European Commission (EC) has launched a study that will look at various policy options to prevent counterfeiting of medicinal products in the European Union.

The Directorate-General for Enterprise and Industry is using the study to consult interested parties on key ideas for amending the regulatory framework for medicinal products in an effort to combat counterfeiting.

Tightening the requirements for the manufacturing, trading and distribution of medicines for human use and active substances may include amendments to Directive 2001/83/EC, which relates to medicinal products for human use, and to the Commission Directive 2003/94/EC, which relates to the pharmaceutical legislation in regards to medicinal products for human use.

Changes to these amendments ultimately might have implications on technical guidelines within the EC, such as the Good Manufacturing Practice guidelines, the Good Distribution Practice guidelines and the Compilation of Community Procedures on Inspections and Exchange of Information.

Comments should be sent by May 9 to entr-pharmaceuticals-counterfeit@ec.europa.eu. All contributions will be analyzed and a summary of the outcome of the consultation will be published on the pharmaceuticals website of the Directorate-General Enterprise and Industry.

### MHRA Signs an MOU with a Non-Governmental Organization

To help achieve core objectives and strengthen working relationships, the Royal Pharmaceutical Society of Great Britain and the Medicines and Healthcare products Regulatory Agency (MHRA) on March 3, 2008, signed a Memorandum of Understanding (MOU).

According to the MHRA, the memorandum outlines the basis of cooperation between the two organizations and clarifies the boundaries and areas of joint collaboration, such as ensuring the safe public use of medicines and devices.

The organizations will share relevant information, as well as organize joint training for inspectors and possibly undertake joint investigations.

### EU revises Manufacture of Sterile Medicinal Products

The revision of Annex 1, Volume 4, *Manufacture of Sterile Medicinal Products* has now been released to the public.

According to the European Union, the revision to the annex was necessary to align the clean room classification table with ISO standards.

The revised Annex 1 provides supplementary guidance on the application of the principals and guidelines of GMP to sterile medicinal products.

The guidance has been updated in four main areas: classification table for environmental cleanliness of clean rooms and associated text, media simulations, bioburden monitoring and capping of freeze-dried vials.

The new annex should be implemented by March 1, 2009, except for the provisions on capping freeze-dried vials, which will take place in March 1, 2010.

### European Commission Revises GMP Guidelines

The European Commission is reviewing existing GMP provisions, as an implementation measure related to the International Conference on Harmonisation (ICH) Q9 guideline on quality risk management.

The ICH Q9 guideline has been implemented with the new Annex 20. It should be noted that the new annex is not intended to create any new regulatory expectations, but rather provides an inventory of internationally acknowledged risk management methods and tools together with a list of potential applications at the discretion of manufacturers.

*PDA Comments Analysis, continued from page 25*

**Annex 1 2008 Version:** EMEA did not remove the requirement for bioburden testing when solutions are processed through duplicate in-line filters. EMEA has agreed to subsequent comments agreeing with PDA that where overkill sterilization parameters are set for terminally sterilized products the bioburden assay might be monitored only at suitable scheduled intervals. See new section 80.

**PDA Point 4:** We have provided a revised guidance on appropriate environmental conditions for the handling of lyophilization vials between partial stoppering and final sealing. The new Clause 93 received the largest number of comments with all disagreeing with the requirement that: "Partially stoppered freeze dried vials should be maintained under Grade A conditions at all times, from the time of partial stoppering to capping." We offer a revised Clause 93 that represents proven good aseptic practice that is harmonized with other internationally accepted cGMP guidance documents.

**Annex 1 2008 Version:** EMEA revised its original position. New section 116 states "Partially stoppered freeze drying vials should be maintained under Grade A conditions at all times until the stopper is fully inserted." This is a significant advance as noted in Point 4 this section received the largest number of adverse comments, and PDA is pleased that EMEA has carefully considered PDA's position. Please note that provisions on capping of freeze-dried vials should be implemented by March 1, 2010.

**PDA Point 5:** In general, we offer comments to more align Annex 1 with EN ISO 14644 and internationally accepted aseptic practice and GMP.

**Annex 1 2008 Version:** EMEA aligned Annex 1 to EN ISO 1644-1. Please refer to section 4, table 1.

The development of Annex 1 has been a long process with considerable input from PDA and other industry groups. The time the process has taken demonstrates that EMEA has carefully considered our comments and PDA and its members should be pleased with the number of comments successfully implemented by EMEA.

**[Editor's Message:** The author provides a detailed point-by-point analysis of the PDA comments in a table included with the online version of this article at www.pda.org/pdaletter.**]**

# Volunteer Spotlight

*I developed several mathematical models based on key success indicators to provide information on the essential types of players required to build a winning basketball team. My analyses of the homecourt advantage were used by one National Basketball Association head coach to provide team insight.*

## Kimberly Brown

**Company:** Amethyst Technologies, LLC

**Title:** CEO

**Education:**

BS, Chemical Engineering, University of Delaware

PhD, Chemical Engineering, University of Maryland

**PDA Join Date:** 2006

**PDA Member Type:** Standard

**Areas of PDA Volunteerism:**

Task Force to revise TR-3, *Validation of Dry Heat Processes Used for Sterilization and Depyrogenation*

Task Force to revise TR-1, *Validation of Moist Heat Sterilization Process: Cycle Design, Development, Qualification, and Ongoing Control*

**Interesting Fact about Yourself:**

I developed several mathematical models based on key success indicators to provide information on the essential types of players required to build a winning basketball team. My analyses of the homecourt advantage were used by one National Basketball Association head coach to provide team insight.

**Why did you join PDA and start to volunteer?**

I joined the PDA after reading my first PDA technical report on sterile filtration. The balance between the science, regulatory guidance, and practical industry standards in the technical reports indicates the commitment and dedication of the staff and members. I knew that joining and volunteering with the PDA would enable me to stay current in industry standards and contribute some of my experiences.

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

Attending the face-to-face meetings for the two Task Forces that I currently serve on was memorable. The meetings were well organized with a clear focus on developing meaningful, accurate, current, and comprehensive guidance documents.

**How has volunteering through PDA benefited you professionally?**

Volunteering with the PDA has allowed me to interact with subject-matter experts in numerous areas which helps ensure that I provide my clients with sound industry practices and solutions.

**Which member benefit do you most look forward to?**

The PDA Technical Reports.

**Which PDA event/training course is your favorite?**

The PDA/FDA Joint Regulatory Conference is my favorite.

**What would you say to someone considering PDA membership?**

Joining the PDA is essential for professional development in the pharmaceutical industry.

# Volunteer Spotlight

## Hannelore Willkommen

**Company**: Regulatory Affairs & Biological Safety Consulting

**Title**: CEO, Founder

**Education:** PhD Pharmacy, Humboldt University of Berlin

**PDA Join Date**: 2001

**Areas of PDA Volunteerism:**

Member of the Program Committee for PDA Virus & TSE Safety conferences in 2001, 2003, 2005 and Chair of the committee in 2008

Member of the Virus Filtration Task Force

Co-Chair of the Virus Preparation Task Force

Member of BioAB

Chair of the Interest Group Biotech in Europe

**Professional Awards Won:**

Max von Pettenkofer Award of the German Society of Hygiene and Microbiology

**Interesting Fact about Yourself:**

My family is very important to me; I have two adult sons and two grandchildren. I am very proud of them. In my free time, I like to take long cycle tours with my husband. The most exciting tour was though Norway and Sweden—over 1800 km (1118 miles).

**Why did you join PDA and start to volunteer?**

When I contacted PDA, I had worked already for more then 20 years in different capacities; finally as the Head of the Virus Safety Section in the Paul-Ehrlich Institute. I was involved in the development of European guidance documents regulating different aspects of quality and safety of biologics. Membership in PDA provided me a broader perspective and a better understanding of the problems and the needs of the industry.

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

I enjoy the networking opportunities provided by PDA, because they allow me to meet and interact with colleagues in the industry. During my time as a member of the Paul-Ehrlich Institute, I networked frequently with colleagues in other European regulatory agencies, especially through my involvement with the EMEA and its Biologics Working Party of the Committee for Medicinal Products for Human Use. I also routinely interacted with colleagues in other agencies, like the U.S. FDA and the Therapeutic Goods Administration in Australia, and partly also others, like the Ministry of Health Labor and Welfare in Japan and the Korean FDA.

When I left the agency and started consulting, the interaction with colleagues in the industry became even more important for me, so I intensified my activities with PDA. One recent exciting experience was the discussion with the EMEA about the virus safety evaluation of investigational medicinal products. This was regulated in a new draft guideline published for consultation, and it was widely discussed in the industry. The development of the consolidated opinion between the industry members of PDA and the presentation of this opinion at the workshop of the EMEA with invited industry associations was an impressive example of the importance of the interactive work that can be done at PDA.

**How has volunteering through PDA benefited you professionally?**

The understanding of the industry views on current regulatory requirements and the science behind is a very important aspect of my professional work. PDA is a good place to develop such skills and experience.

**Which member benefit do you most look forward to?**

I benefit most from the networking that I established through PDA. The task forces, the Biotechnology Interest Group, as well as the work in program committees for the preparation of the different conferences have provided me with the best opportunities for networking. Furthermore PDA's Technical Reports and also the *PDA Journal of Pharmaceutical Science and Technology* are very useful.

**What would you say to someone considering PDA membership?**

Participate in PDA and see what you can take from it for your personal and professional life! There are opportunities.

*The understanding of the industry views on current regulatory requirements and the science behind is a very important aspect of my professional work. PDA is a good place to develop such skills and experience.*

# PDA Chapters Educate Members in San Juan and Montreal

**18° 15′ N 66° 30′ W**

**Hassana Howe, PDA**

My latest travel destination is home to exotic hideaways, miles of sandy white beaches, and natural wonders…and the PDA Puerto Rico Chapter's *Update on Cleaning Validation,* Feb. 20. When I was asked to attend, I jumped at the chance to board the next plane to San Juan, Puerto Rico. Who wouldn't want to escape the dreary winter Washington, D.C. weather for a February trip to the Caribbean!

Having family in Peru, I was excited at the opportunity to practice my Spanish, which some might say more closely resembles "Spanglish"—a mixture of Spanish and English. For sure, the trip put my rusty Spanish skills to the test.

On arrival, I was greeted with nice hot Puerto Rican weather and a warm reception by the local Puerto Rico chapter members. I was also treated to an excellent chapter event, which consisted of two lectures and a cocktail reception sponsored by Pharma-Bio Serv Inc.

**William E. Hall,** PhD, presented "Where Are We Now with Bio. and Pharma. Cleaning and Where Are We Headed," which covered the 4 C's of cleaning: cleaning, contamination, containment and control. William suggested that the pharmaceutical industry look at methods employed by the food industry, and he outlined examples of good contamination detection devices. Next, **Brent Schoeb**, gave a presentation on the applications of quality by design and cleaning validation based on a group study.

The presentations set the stage for a lively cocktail reception where attendees and speakers mingled and discussed the issues at hand.

The speakers and over 50 attendees, including representatives from the U.S. FDA's local District Office, contributed to a successful event.

The resurgence of a successful Puerto Rico Chapter can be attributed to president **Manuel Meléndez** and the other Chapter leaders, along with volunteers and speakers. They are planning to host their next event on PDA Technical Report No. 1 on moist heat sterilization and have invited **Martin Van Trieste,** Amgen and former FDA'er **Kristen Evans,** Amgen to be the featured speakers.

If you would like more information please contact Manuel at manuelm@amgen.com.

As the Puerto Ricans say, *Puerto Rico lo hace mejor!* (Puerto Rico does it better!)

San Juan, Puerto Rico

(l-r): Miguel Montalvo, Expert Validation Consulting; William Hall, Hall and Associates; Johnny Guerra, Guerra Consulting Group; Manuel Meléndez, Amgen Manufacturing Limited

## Risk-Based Airport Inspections

**Trevor Swan, PDA**

I once thought that the global regulatory harmonization was an issue solely for the pharmaceutical industry, but I found this untrue when a certain U.S. federal agency chose to randomly search my luggage. Although I cleared customs with no problems, my bags missed the flight. The harmonization of security regulations at the United States-Canadian border assured that I would attend the *2008 Montreal Annual Conference* conference without my good clothes!


Nevertheless, I arrived at that the Canada Chapter hosted on Monday morning to find a group of nearly 50 attendees and vendors from around Canada and the Northeastern United States.

Lead by Chapter President **Patrick Bronsard**, Treasurer **Vagiha Hussain** and Chapter Committee Member **Sabrina Ullah**, PDA's Canadian volunteers hosted their annual conference on February 18th at the Holiday Inn Montreal Midtown.

There were five industry experts speaking on a variety of exciting topics.

**Anthony Ridgway**, PhD, presented "Regulatory Activities Relevant to Biotech Biologics," in which he gave examples about challenges related to ICH Q8, Q9 and Q10. He also touched on proposed changes to Health Canada's implementation of international regulatory practices.

Next, **Steve Lovell**, PhD, discussed Lonza's microCompass™, in "Detection of Microbial Contamination by Rapid RT-PCR." Lonza's method is based on extraction, amplification and detection of nucleic acids from microorganisms using quantitative RT-PCR technology.

When another speaker had to cancel his trip, **Susan Cleary** filled in and spoke about environmental monitoring. Susan's talk, "Challenges in Implementing an Electronic EM Data Management System," offered a wealth of tips for selecting and implementing complex new systems.

After lunch, Biotechnology Specialist **Robert Horan,** PhD, gave his views on FDA's quality system inspections. Finally, **Michel Comtois**, informed the attendees about qualifying temperatures throughout the supply chain. Michel highlighted important sources of information regarding cold chain maintenance, including PDA's Technical Report No. 39 on cold chain management.

Meanwhile my luggage wended its way through the supply chain, touching down in Montreal just in time for my departure. The other attendees at this year's Canada Chapter Annual Conference will agree when I tell you that the planning and execution of this meeting far surpasses that of our airports these days!

### PDA's Who's Who?

**Patrick Bronsard,** Validation Director, SNC-Lavalin Pharma and Canada Chapter President

**Susan Cleary,** Director, Product Development, Novatek

**Michel Comtois,** President, Micom Laboratories

**Kristen Evans,** Director, Global Quality Compliance, Amgen

**William E. Hall,** PhD, President, Hall and Associates

**Robert Horan,** PhD, Biotechnology Specialist, Pharmaceutical Inspectorate, U.S. FDA

**Vagiha Hussain,** Project Manager, Validation, SNC Lavalin Pharma and Canada Chapter Treasurer

**Steve Lovell,** PhD, Technical Director of Research & Development, Rapid Testing Systems, Lonza Bioscience

**Manuel Meléndez,** Sr. Director, Quality, Amgen Manufacturing and Puerto Rico Chapter President

**Anthony Ridgway,** PhD, Sr. Regulatory Scientist, Biologics & Genetic Therapies Directorate, Health Canada

**Martin Van Trieste,** Vice President, Quality, Amgen

**Brent Schoeb,** Principal Validation Engineer, Amgen

**Sabrina Ullah,** Project Director, Validation, SNC-Lavalin and Canada Chapter Committee Member

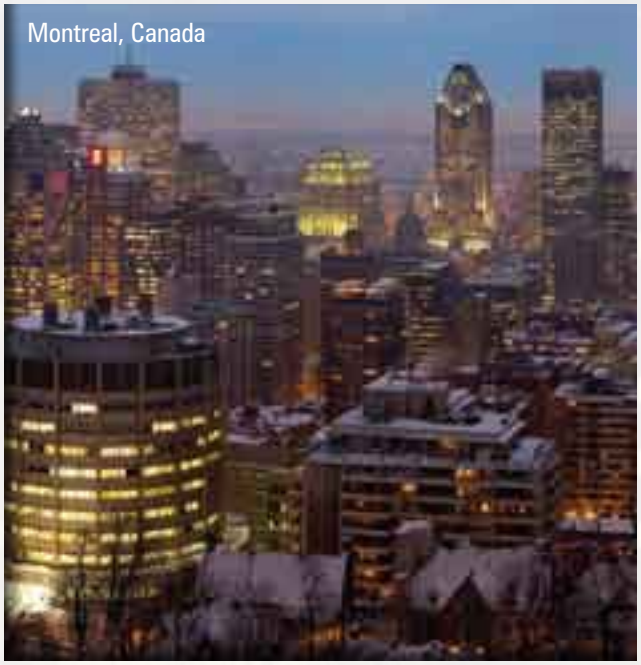



Image of Montreal is by Diliff

# Please Welcome the Following Industry

**Mine Akgöc,** Turkish Ministry of Health

**Jose Alejandro,** Amgen

**Safwa Al-Mousa,** The Jordanian Pharmaceutical Manufacturing

**Pam Applehans,** Sandoz

**Adiel Aslam,** Locum

**Helen Avitabile,** Alexza Pharmaceuticals

**Sharon Barrett,** IT Sligo

**Bernard Bautista,** Bayer Healthcare

**Athena Benjamin-Miller,** NCI SAIC

**W. Burke Bero,** Masy Systems

**Felecia Bishop,** Lonza

**Angela Blume,** Alkermes

**Carl Bock,** BD

**Robert Boehm,** Bristol Myers Squibb

**Anna Bohman,** Wyeth

**Danny Bouwhuis,** Progress-PME

**Brooks Boyd,** Zogenix

**Tammy Brittain,** Schwarz Pharma

**Jamie Brooks,** Amgen

**Sandra Buczolits,** Mycosafe Diagnostics

**Sylvia Bullock,** Bayer

**Chris-Doerthe Buttkus,** Bayer

**Katey Caccavelli,** Pfizer

**Keyesha Charles,** NCI SAIC

**Wendy Chiang,** Charles River Laboratories

**Sun Choi,** Advanced Sterilization Products

**Stuart Coomber,** Laminar Medica

**Meredith Cossano,** Bayer Healthcare

**Mesbah Creitz,** Sandoz

**Alan Cutler,** Three Rivers Pharmaceuticals

**Sophia Czechowicz,** Johnson & Johnson

**Bruce Davis,** Inspiration Biopharmaceuticals

**Tjebbe de Gruijter,** Biogen

**Camille Denoga,** Baxter Bioscience

**Christophe Derrien,** Draximage

**Dave Dezan,** Artes Medical

**Biljana Dimitrova,** Ministry of Health Macedonia

**RJ Doornbos,** Schering-Plough

**Ruth Dotson,** Bayer Healthcare

**Gary du Moulin,** Genzyme Biosurgery

**Jennifer Earp,** Talecris Biotherapeutics

**Carrie Edwards,** Schwarz Pharma

**Stephanie Garcia,** Hospira

**Erin Germino,** Sanofi Pasteur

**David Gerolemom,** Wyeth

**Bruce Girton,** Poniard Pharmaceuticals

**Roberta Gonzaga,** DEY

**Mark Greene,** Bristol Myers Sqibb

**Josh Grieco,** Genentech

**Wendy Haines,** Central Carolina Community College

**Patti Harris,** Abbott Vascular

**Michael Harrison,** Eli Lilly

**Jose Hechavarria,** HechTech Pharma Consult

**Nigel Hernandez,** Northeastern University

**Patricia Hodge,** DPT Laboratories

**Dean Hodgson,** Genentech

**Frieder Hofmann,** ProCon International

**Betty Huqueriza,** DEY

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**Barbara Jentges,** PhACT

**Caroline Jewett,** Amgen

**Lene Juhl,** Novo Nordisk

**Conni Juhl,** Novo Nordisk

**Raju Kanumuri,** Catalent

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**Peter Makowenskyj,** Sartorius Stedim Biotech

**Herve Marcilly,** LFB SA

**Lynne Martin,** Bavarian Nordic

**Bryan Mascioli,** Novartis Diagnostics

**Robert Matthews,** Sanofi-Aventis

**Myriam McCoy,** Baxter Healthcare

**Amy McGhee,** Greiner Bio-One

**Julie Michaud,** Acambis

**Jennifer Morales,** Alcon Laboratories

**John Mosack,** Medarex

**Carlos Motta,** MedImmune

**Christy Nagel,** Genentech

**Ted Nalesnik,** Merck

**Csilla Nemes,** HAS Chemical Research Center

**Paul Newby,** GlaxoSmithKline

**Toan Ngo,** Wyeth

**Beth Nichols,** ThermoSafe Brands

**Renee Nygard,** Biogen Idec

# Leaders to the PDA Community

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**William Okita,** Genzyme

**Ruben Omega,** Bayer Healthcare

**Alexis Papilion,** Baxter

**Michael Parrish,** Schering-Plough

**Kathleen Pinon,** Teva Pharmaceuticals

**Christopher Procyshyn,** VanRx Pharmaceuticals

**Timothy Ramsey,** PPD Development

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**Brian Riley,** Biogen Idec

**Omar Riyal,** Abbott

**Aileen Roberts,** Pfizer Ireland Pharmaceuticals

**Maik Roehl,** Sartorius Stedim Biotech

**Dawn Rubel,** Immunomedics

**Patricia Rustanius,** Agilent Technologies

**Craig Ruth,** MedImmune

**Christopher Scanlon,** Mannkind Corporation

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**Josephine Ysais**

**Tomasz Zawislak,** Homeofarm

**Judy Zdanowciz,** Teva Parenteral Medicines

**Shannon Zelina,** Cook MyoSite

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# Israel Chapter's Annual Meeting Covers Hot Topics

**Karen Ginsbury, PCI Pharmaceutical Consulting Israel Ltd**

The PDA Israel Chapter held its annual meeting on December 16, 2007 at the David Intercontinental Hotel, Tel Aviv. The annual meeting has become something of a tradition among chapter members with many waiting eagerly for this professional and social get-together with colleagues from throughout the country.

The meeting opened with **Raphael Bar**, Israel Chapter President, welcoming guests and was followed by **Karin Baer**, Treasurer, who gave her annual report.

Thereafter proceedings shifted to the presentations with the first talk given by **Yafit Stark**, PhD, entitled,"Roadmap of Drug Development: From the Chemical to the Clinical." Yafit spoke about the critical path to successful development of New Molecular Entities and concluded that innovation in study design is critical to the success of clinical development. Innovation can include randomization techniques, selection of outcomes and statistical analyses. She asserted that for traditional trial designs, innovation will be less applicable and that companies unable to innovate will stagnate

Yafit pointed out that to go forward, the use of biomarkers and surrogate markers must be utilized; because of vast development costs, studies have to be sped up and efficiency increased including new initiatives to translate animal data into early human testing and phase 0 micro-dosing studies. In conclusion, she emphasized that new biomedical science is being used in the pharmaceutical industry and companies planning innovative development need to be at the forefront of these technologies.

The second speaker of the evening, Professor Yoseph Caraco addressed the hot topic of biosimilars in his presentation "How similar are Biosimilars." Discussing the science behind biosimilars, Yoseph presented some interesting facts and problems that have occurred with biosimilars. His thought-provoking presentation left the audience wondering if biosimilars are really generic products at all, and just how similar a biotechnology "generic" really can be. He also raised concerns with issues such as leachables and extractibles where no less work is required in developing a biosimilar than for the original, innovator product. He presented a case study where the work was insufficient with resulting product failure causing immunogenicity in patients.

After a cocktail reception and visits to the vendor exhibits, **Ilan Cohn's,** PhD, lecture on "Patents and the Pharmaceutical Industry: Business Significance and Strategies" explained the concept of extending patents and the period in which an innovator benefits from the patent after registration of a product. Ilan also addressed the matter of generic companies filing patents for their methods of synthesis of known chemical entities.

The professional portion of the evening was closed out by **Karen Ginsbury,** who provided an update in her presentation, "Hot Quality and Regulatory Topics from PDA's Regulatory and Quality Affairs Committee (RAQC)." Karen described to delegates how the RAQC operates using the ballot system and which topics were recently balloted; such as the ICH Q10 Guideline on Pharmaceutical Quality Systems, Content of Clinical Trial Material (CTM) Batch Release, and the EMEA Guideline on Vial Safety of Investigational Medicinal Products(IMPs). This was an opportunity for the Israel Chapter Members to learn about the PDA processes and how as members, they can be active in commenting on guidances in the making through their professional organization. Delegates were invited to indicate their particular areas of interest and to volunteer to participate in future task forces.

A fine dinner capped the meeting, and over 300 participants closed out another successful and active year of the Israel Chapter.

(l-r) Delegates and the Executive Committee: Rina Yamin, CTS; Gilad Bernadsky, Teva Pharmaceutical; Einat Frydman, Teva Kfar-Saba; Eitan Gross, Kamada; Karin Baer, Omrix-Biopharmaceutica; Mordechai Izhar, Ludan; Raphael Bar, Pharmos Ltd

## PDA's Who's Who?

**Karin Baer,** PhD, Quality Assurance Director, Omrix-Biopharmaceuticals LTD and Israel Chapter Treasurer

**Raphael Bar,** PhD, Sr. Director, Analytical Development, Pharmos Ltd and Israel Chapter President

**Yoseph Caraco,** Professor/Head of Clinical Pharmacology Unit, Hadassah University Hospital

**Ilan Cohn,** PhD, Patent Attorney, Reinhold Cohn & Partners

**Karen Ginsbury,** CEO, PCI Pharmaceutical Consulting Israel and Israel Chapter Liaison

**Yafit Stark,** PhD, VP and Chief Clinical Officer, Teva Pharmaceuticals

## Calling All Writers!

The *PDA Letter* staff wants *you* to submit articles!

Not sure if you can write in the PDA style? Don't worry. *PDA Letter* editors, **Emily Hough** and **Walt Morris** will help. For questions or to submit articles, write "PDA Letter Submission" in the subject line to either hough@pda.org or morris@pda.org.

Articles can be on case studies; reviews of science, technology, regulations, books, etc., commentary or summaries of PDA meetings, events training, interest group/task force meetings, etc. These articles should be about 500 to 1,500 words in length.

Feature articles should be relevant to the *PDA Letter* editorial calendar, and anywhere from 1,500 to 2,500 words in length, with references, high resolution images when applicable. In the coming months, we are looking for articles on the following themes:

- **Sterile Products/Aseptic Processing** (submissions due May 15)
- **New Trends in Validations** (submissions due June 23)
- **Risk Management** (submissions due July 28)
- **FDA regulatory trends** (submissions due September 1)

Articles must be submitted as Word attachments, accompanied with the author/authors' biographical information, including company, title, mailing address, phone number and email address.

All articles submitted to the *PDA Letter* will be published at the editor's discretion and will be edited for clarity, grammar and length. Headlines may be rewritten by the editor.

PDA
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## October 20 – 23, 2008
## Chicago, Illinois

Conference | October 20 – 22
Exhibition | October 20 – 22
Courses | October 23

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**www.pda.org/microbiology2008**

# Chapter Contacts

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

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# PDA Staff Make Final Preparations for the Annual Meeting

**Wanda Neal-Ballard, PDA**

With just days until the big conference, **Leslie Edmonds** and **Meaghan Dowd** are making sure that the 2008 PDA Annual Meeting is spectacular.

Leslie Edmonds and Meaghan Dowd

Called *Science Driven Manufacturing: The Application of Emerging Technologies,* this year's Annual Meeting will be the strongest science program PDA has offered in many years. The event includes several engaging and relaxing networking activities and over 50 presentations in just three short days.

Leslie has spent countless hours corresponding with the majority of the speakers to provide them with the information they need to make their speaking experience more enjoyable. She said the speaker list is comprised of leading industry experts in a variety of science and technology fields.

Meaghan helped arrange the various networking activities for this year's event. Members are invited to attend a Gala Reception, a pottery painting extravaganza, the second annual golf tournament, a walk/run event to many other activities. She has also been busy with the logistical work of planning menus for members.

Meaghan said that she and Leslie have enjoyed planning out the details for the conference and they look forward to their efforts coming to fruition. They are confident members and speakers alike will enjoy PDA's Annual Meeting to the fullest.

As of press time, over 800 members have signed up for the conference. Leslie and Meaghan look forward to seeing them, and hopefully you, there!

# Discuss Virus and TSE Safety Issues with Regulators

## 2008 PDA Virus & TSE Safety Forum • Berlin, Germany • June 3–5

**Conference Chair Hannelore Willkommen, PhD, RBS Consulting**

Virus and TSE safety are important quality attributes for biological medicinal products. No regulatory body will approve a product for the market or even for the first clinical trial if the safety profile is not appropriate. Different strategies to demonstrate and assure virus and TSE safety are applied, considering the specific risk of different product categories of biological medicinal products.

The development of a guideline on the virus safety evaluation of clinical trial material has been a long process in Europe. After years of work, the EMEA's Committee for Medicinal Products for Human Use (CHMP) released in 2006 a draft guideline, *Viral Safety Evaluation of Biotechnological Investigational Medicinal Products.* The consultation period continues.

The time needed for the development of this guidance document illustrates the difficulties in developing rules applicable to a category of products that ranges from cutting-edge new or to well-established. Even if established rules for the virus and TSE safety assessment are applied, there are differences in the interpretation of these rules. It is therefore important to provide a platform for discussion between industry and regulatory bodies.

For nearly a decade, PDA has been providing the platform for discussion of virus safety concerns. The first conference was organized in 2001, with follow-ups held in 2003 and 2005. The next conference in this series, the *2008 PDA Virus & TSE Safety Forum,* will take place June 3–5, 2008 in Berlin. In line with the previous conferences, representatives of European agencies, the EMEA and the U.S. FDA will provide their view and concerns related to virus and TSE safety for different categories of medicinal products, including those derived from cells and human plasma and those categorized as *advanced therapies.*

The conference will allow the agencies to discuss regulatory interpretation and further development of regulatory tools. It will also cover scientific issues like virus testing of source materials, virus removal techniques, quality attributes of virus spike preparations, etc.

The conference is supplemented with a workshop on methodologies of risk analysis and risk management for cell derived products, vaccines, plasma derivatives and cell-based medicinal products.

The virus section of the conference will continue a dialogue from the 2005 meeting on the influence of virus spike properties on the outcome of virus reduction studies. Especially if virus removal by filtration is studied, the virus spike can influence the outcome of these studies. PDA formed the Virus Spike Preparation Task Force in September 2005 with the goal to summarize in a technical report the current knowledge about virus spike properties and characterization. Several presentations will focus on virus spike preparation, and an update on the work of the Task Force will be provided.

Another session considers testing of source materials for virus contamination. While polymerase chain reaction (PCR) and other nucleic acid amplification techniques are well established and successfully used for detection of specific virus contaminants, there are other methods under development that may supplement the current technologies in the future. Micro-array-based systems or screening by broad range PCR in combination with mass spectrometry might be helpful in specific cases; they are used already today for the clarification of contamination cases.

How can the in-house data base be used to demonstrate virus safety of clinical material? This topic is covered by the European draft guidance document but it is difficult to use it in practice. This and other topics related to virus removal will be the focus of the virus removal session.

The conference also will cover and summarize current knowledge regarding TSE tissue infectivity, the impact of prion spike preparations on the outcome of prion removal studies, as well as the current development of tests for detection of Variant Creutzfeldt-Jakob disease (vCJD) agent in human plasma. TSE safety of plasma derivatives and current problems with TSE studies will be considered from the regulatory point of view as well.

Such discussion must be seen in close relationship to infectivity in tissues, in human blood and in urine because these materials are used for production of medicinal products. Several TSE spike preparations were used in the past for performing TSE studies, but industry has learned that the nature and preparation of the spike is also important for the outcome of studies—at least if the removal of the TSE agent by filtration processes is investigated. An overview about TSE safety studies to demonstrate safety of plasma derivatives, in-vivo and in-vitro assays for detection of TSE as well as demonstration of equipment sanitization related to TSE will be discussed.

Related to the safety of blood products, especially for cellular components, the tests for detection of the vCJD agent in blood were developed. Test methodologies and materials available for testing will be presented, as well as regulatory and ethical perspectives on introduction of such blood screening assays.

Once again, PDA has stepped forth to help advance the dialogue on these important safety issues. The program planning committee hopes you will participate!

# TR-22 and TR-44 Task Forces to Speak at 2008 PDA Risk Management and Aseptic Processing Conference

**Bethesda, Md. • May 15–16 • www.pda.org/aseptic2008**

**Program Committee Co-Chairs James Agalloco, Agalloco & Associates and Harold Baseman, Valsource**

The pharmaceutical and biopharmaceutical community produces sterile products using aseptic processing on a daily basis. The elimination of contamination risk has always been a major consideration in the design, operation and control of aseptic processing activities, and the decision-making process has long been clouded by a general lack of understanding on how risk in aseptic processing can be properly assessed. The advent of risk-based compliance initiatives on a global basis has brought about fundamental changes in the evaluation of technologies and practice for aseptically filled products, and improved capabilities of the newer technologies have raised awareness that risk to the patient can be reduced through these technical advances.

A number of recent publications on aseptic processing risk assessment, such as *PDA Technical Report No. 22, Process Simulation Testing for Aseptically Filled Products,* and a fundamental shift in regulatory perspective relative to risk-based compliance have fostered an environment where objective discussion for risk mitigation can now take place.

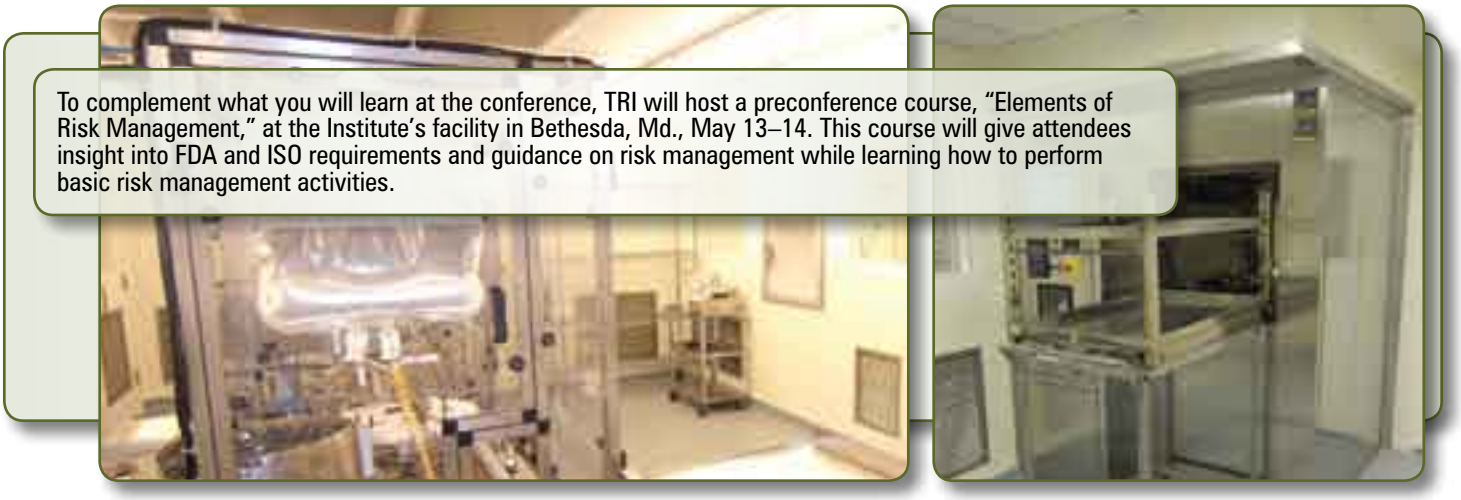
On behalf of the Program Planning Committee, we would like to extend an invitation to the *2008 PDA Risk Management and Aseptic Processing Conference*, May 15–16, in Bethesda, Md. The conference will explore risk management and mitigation as related to aseptic processing. It will bring together subject-matter experts from the industry and regulatory bodies on risk analysis and aseptic processing to discuss the available risk models, relevant regulations and industry guidances. Presentations and panel discussions will explore existing and emerging technologies for aseptic processing with a risk-based focus.

The PDA Risk Management and Aseptic Processing Conference provides a unique opportunity to join colleagues, experts and regulators to explore risk-based aseptic processing in detail. Conference speakers will provide expertise and practical experience in the application of risk assessment tools on aseptic processing technologies to ensure product and patient safety. Members of the PDA TR-22 and *PDA Technical Report No. 44, Quality Risk Management for Aseptic Processing* Task Forces will outline how risk assessment fits within the context of aseptic processing. In addition, regulatory representatives will help interpret current expectations for risk management.

The well-rounded conference program will provide attendees with a wealth of information. The conference will provide a variety of learning opportunities and an environment that stimulates open discussion. Seven plenary and panel sessions will address the following areas:

- Aseptic Risk Assessment modeling alternatives
- Regulatory expectations for Aseptic Processing and Risk Evaluation
- Overview of regulatory and industry guidance documents for Aseptic Processing
- Regulatory initiatives on risk-based compliance
- Case studies of Risk Assessment in Aseptic Processing
- Technology Assessment for Aseptic Processing
- Emerging Technologies for Aseptic Processing Risk Mitigation

We look forward to seeing you in May at the *2008 PDA Risk Management and Aseptic Processing Conference*.



To complement what you will learn at the conference, TRI will host a preconference course, "Elements of Risk Management," at the Institute's facility in Bethesda, Md., May 13–14. This course will give attendees insight into FDA and ISO requirements and guidance on risk management while learning how to perform basic risk management activities.

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# New "Stuff" and New Faces at TRI

**Gail Sherman, PDA**

TRI TALK

We are a quarter of the way through 2008, and we have delivered a lot of new stuff and welcomed new instructors to some of our familiar offerings.

First, we provided a very successful course series at the PDA/EMEA Joint Conference in Budapest in February; three of the courses had never been offered before: "Drug Registration in Europe—An Insightful View," "ICH Q10 and Its Potential Impact on the Pharmaceutical Industry," and "Briefing Meetings, Scientific Advice/Protocol Assistance, and Pre-Submission Meetings with EMEA—When to Do What and How to Prepare." Participation in these courses was high, and we hope to offer them again during the year. Perhaps we will include them in the upcoming course series we are planning to hold in Europe later this year (keep an eye on "TRI Talk" for more details).

In March, TRI visited San Francisco and offered three new courses: "Problem Solving Techniques in Nonconformance Investigations," "Effective Application of a Quality Systems Approach to Pharmaceutical cGMPS in Compliance with the FDA Guidance," and "Auditing for Microbiological Aspects of Pharmaceutical and Biopharmaceutical Manufacturing." With strong interest in the three courses, we have already added one of them to the *2008 PDA/FDA Joint Regulatory Conference* series of courses in September. PDA TRI wishes to thank the PDA Chapters who assisted in making the San Francisco Course Series a success through posting our information on the chapter sites, distributing the course agenda, sharing course information as part of their chapter presentations at events, and writing individual letters of support for TRI to their members. We could not have done it without you!

Also in March, we added training to PDA's Pharmaceutical Cold Chain Conference in Bethesda—a repeating event that PDA has offered since 2006. We first offered training in conjunction with this conference at the 2007 event in Berlin, Germany; based on our success there, we decided to do so as a precursor to the U.S. event. Interest in our cold chain management courses, including a stand-alone course we offered in Cork last year greatly exceeded our expectations, so we've recently added it to the line-up of courses to be offered at the 2008 PDA/FDA conference—"Global Regulations and Standards: Influences on Cold Chain Distribution, Packaging Testing and Transport Systems." Let me thank the PDA's Pharmaceutical Cold Chain Interest Group for helping establish the curriculum.

New in our TRI facility during the first quarter was a course on "Development of Prefilled Syringes" taught by experts on this topic from Europe. The course allowed us to showcase equipment donated to TRI by the German equipment manufacturer, Groninger. We also offered the ever popular "An Introduction to Visual Inspection" course, and for the first time were able to train in the laboratory environment. The last time we offered the course, the training took place in a hotel conference room in Bethesda! The lab facility provided a much more realistic environment for examining vials and learning about the inspection processes.

Our first Aseptic Processing Training Program of 2008 was held in January (session 1) and February (session 2). PDA Board member **Hal Baseman** (ValSource) joined the faculty for this session, and **Carolyn Briguglio** (Genzyme) returned for her second stint. With the next course (April/May), **Matthew Ostrowski** (Pfizer) will join the group, along with representatives from both the U.S. FDA's centers for drugs and biologics—the first time the two organizations will participate together! These new faces are bringing fresh perspectives to PDA's oldest and most successful laboratory course. I would be remiss if I didn't mention lead instructor **Dave Matsuhiro,** who helped create the course eight years ago, **Bob Dana,** who's added his own regulatory insights since 2006, and **James Wamsley,** who keeps this course running efficiently. If you are interested in sharing your knowledge of aseptic processing or other area of expertise, please contact us!

So all in all, I think we've had a pretty exciting first quarter, and we have a lot of new activities in the second quarter as well. Besides offering lecture courses at the 2008 Annual Meeting, we are launching a new TRI booth in the Exhibition Hall where we will conduct training demonstrations and answer member questions. I hope to see many of you there!

Stay tuned for more updates. And please, if you haven't visited us in Bethesda, stop by and see the new laboratories, clean room and lecture halls—better yet, bring your colleagues for some training in this great facility!

And don't forget, the calendar is not full yet for 2008—there are limited openings for new lab and lecture courses. So please send your requests to me at sherman@pda.org!

David Matsuhiro performing a dynamic airflow evaluation with students during the "Aseptic Processing Training Program"

An instructor demonstrating for the students proper visual inspection technique for liquid products

# A Little *Cup* of Heaven at PDA/EBE Conference

## Vaccines and other Immunotherapeutic Products on the Agenda

**Program Chair Frank Hallinan, Wyeth**

There is an Irish ballad that goes, *Dublin can be heaven with coffee at 11 and a stroll round Stephen's Green.* You can validate this for yourself by participating in the second *PDA/EBE Conference on Biopharmaceutical Development and Manufacturing* in Dublin on June 24–25. We can guarantee you the coffee at 10:30, and the location of the meeting is just a short stroll from Stephen's Green, which I assure you is particularly attractive in June. As Chairman of the Planning Committee, I would like to invite you all to come to Dublin and join with us in what I am sure will be an exciting and stimulating occasion.

The Planning Committee has put a lot of work into assembling an exciting agenda for the two day meeting. Each day the morning is devoted to plenary lectures and the afternoon to a series of parallel workshops based on the themes of the plenary lectures. The Committee also has tried to ensure that the agenda is balanced and has recognized the growing importance of biopharmaceutical vaccines and therapeutic proteins. Consequently, there is substantial coverage in the program of vaccines and other immunotherapeutic products such as fragments of antibodies.

We have focused the first day on the development aspects and the second day on approved products. The first plenary session is entitled "Science and Technology Behind Manufacture of Biotechnological Vaccines" and the second plenary session is called "Improving the Efficiency of Bioprocesses." Afternoon workshops will cover these topics for more focused discussion.

On day two, we will cover a regulatory theme around the Annex 2 update, the facility of the future, a case study on a recently approved biopharmaceutical and a session on lean manufacturing. For each of these there are associated parallel workshops.

In Dublin you will experience a vibrant European city that is full of fun places with many young people and a proud history of literary excellence. If you appreciate the writings of Swift, Shaw, Joyce, Beckett or Heaney, to name a few—this is the place for you.

Dublin is also the capital of a country that hosts a lot of the world's leading pharmaceutical companies including major players in biopharmaceuticals like Wyeth Biotech, Elan, Schering-Plough, Allergan, Genzyme, Centocor, Pfizer and Eli Lilly. So there is also a lot of technical excellence to be appreciated on your trip. By the time you are due to leave you may very well be humming *Dublin can be heaven!*

Hope to see you here.

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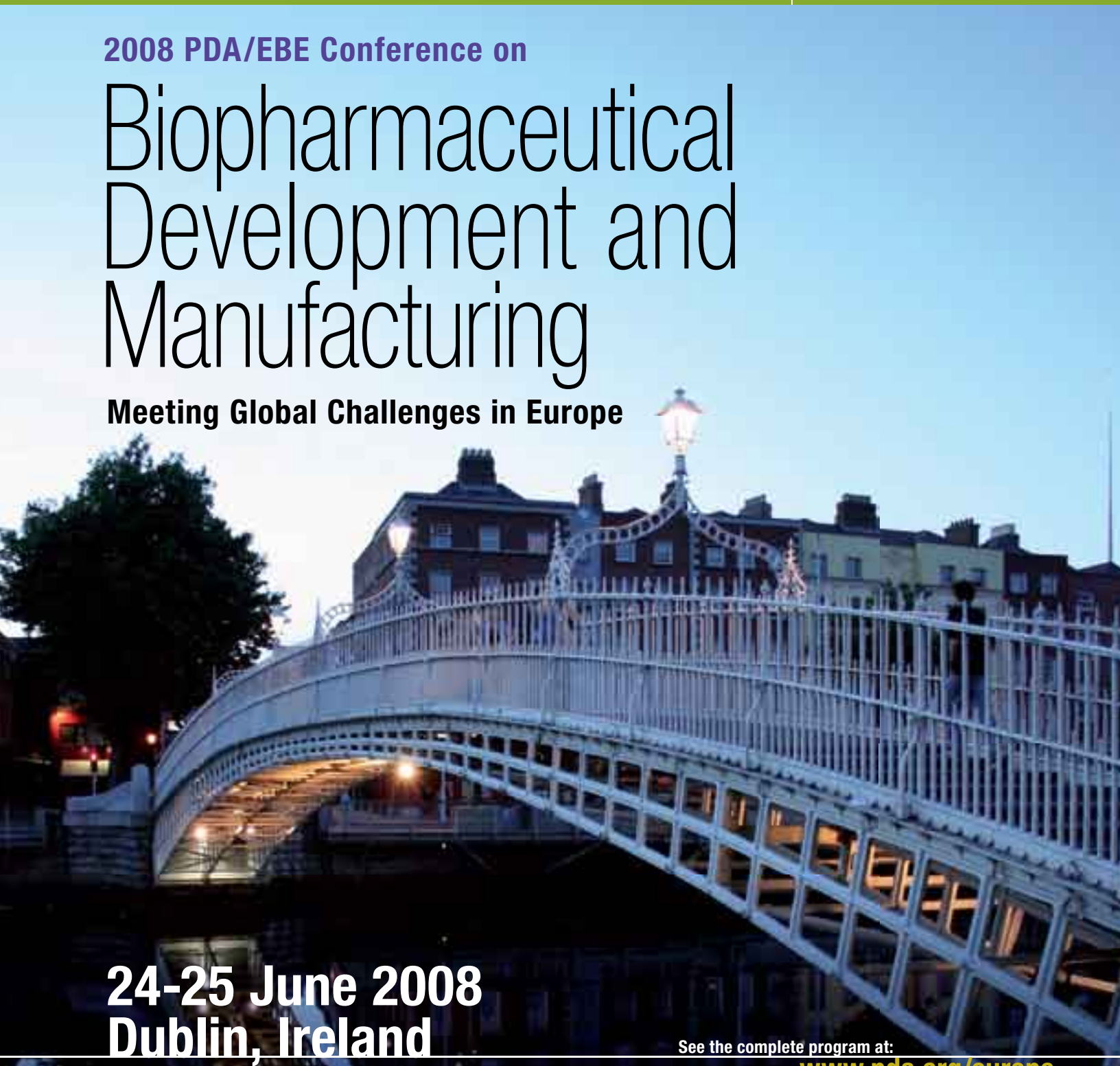

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- Regulatory harmonisation of Quality by Design (QbD)
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- Case studies
- The facility of the future
- Lean manufacturing

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# Scalable laboratory technology

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A partner for research and development in industry and the public sector with advanced and scalable cell cultivation, filtration and purification technologies as well as microbiological analysis and lab water systems.

Fermentation | Filtration | Purification | Fluid Management | Laboratory | Services



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turning science into solutions

# lyoseal™ one step class A freeze drying & capping

- ▲ Increases product quality
- ▲ Eliminates sticking rejects
- ▲ Optimizes operations


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# Now you can have your cake and eat it too!

**The most comprehensive *out-of-the-box* Quality Management Solutions with the *ultimate flexibility* to be tailored to all your current and future needs *without* any *programming changes!***

TRACKWISE®

The Ultimate Quality Management Solution

Leverage Sparta's proven best industry practices and domain expertise implementing Quality Management solutions with more than 300 successful installations worldwide. With hundreds of customers who passed stringent FDA and EMEA regulatory compliance based on TrackWise deployed solutions. Sparta has out-of-the-box solutions ready to deploy for a rapid go-live, including:

- ✓ *Deviations*
- ✓ *Investigations*
- ✓ *CAPA*
- ✓ *Change Control*
- ✓ *Complaint Management*
- ✓ *Regulatory Reporting*
- ✓ *Internal Audit & Observation*
- ✓ *Supplier Audit & Observation*
- ✓ *Effectiveness Check*
- ✓ *More..*

Leverage our best practices and domain expertise to provide you with a system fully tailored to your business needs, eliminating time-consuming and risky custom software development.

No other QMS vendor offers such a wide variety of out-of-the-box solutions **that can be quickly and easily tailored to all your needs!**

Why risk your success with unproven solutions, when going live on time, within budget and having a true globally scalable solution are at stake?

*Visit us at the PDA Annual Meeting*
*Booth # 527*

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