Science • Technology • Quality • Regulatory • Community

PDA Letter

Volume XLI • Issue #4

April 2005

In This Issue...

State-Of-The-Art: Three New Technologies Impacting the Community

Keeping up with the latest manufacturing and control technologies is a critical responsibility of any manufacturer in the pharmaceutical and biopharmaceutical industries.

Over the last several years, health authorities in the United States and Europe have turned their attention to the apparent stagnation in manufacturing and control technologies used throughout the industries. They also have taken a hard look at their own regulatory requirements to identify necessary reforms to accommodate a new "innovation revolution" within the industries.

Innovation is occurring in many areas of pharmaceutical/biopharmaceutical manufacturing and control—some involving never before used process analytical technologies, others involving more traditional technologies. Many of these innovations are geared toward improving processes, analytical methods and efficiencies.

In this newly emphasized pursuit to upgrade quality systems, the importance of state-of-the-art laboratory equipment and supporting computer software, like those used at the PDA Training and Research Institute (PDA TRI) and spotlighted through the PDA New Innovative Technology Exhibition™ (NITE™), will only grow.

Below, three innovative and valuable technologies that have great potential to impact our community are reviewed. One, a TOC analyzer is currently being used at PDA TRI. Next, a rapid micro technology and a paperless validation software program were selected as the 2005 PDA NITE™ exhibitors.

New TOC Analyzer at TRI

Total organic carbon analysis is used in a variety of pharmaceutical and biopharmaceutical applications, ranging from cleaning validation to monitoring high purity water systems in a pharmaceutical environment. TOC analysis is considered a nonspecific assay, because the measured TOC cannot be attributed to a specific contaminant.

In 2005, PDA TRI began using a new TOC analyzer that includes an innovative "autorreagent" function and is completely portable. James Wamsley, PDA TRI Coordinator, Laboratory Education, is impressed with the new analyzer for two reasons. He says, "We saw much more accurate TOC measurements during our March Cleaning Validation laboratory course than we did with the previous gen-

continued on page 14

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"Genotypic methods have been shown to be more accurate and precise than traditional biochemical and phenotypic techniques."

FDA Guidance For Pharmaceutical cGMPs
September 2004

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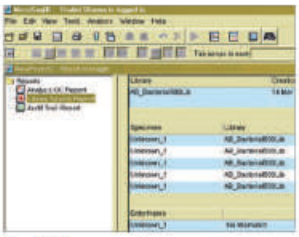

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Applied Biosystems

Neal G. Koller
PDA President

President's Message

PDA's Science & Technology: Off to a Fast Start in '05

2005 is turning into one of PDA's most productive years in fulfilling its commitment to the advancement of pharmaceutical and biopharmaceutical science and technology.

All of the activities I am to highlight below are the direct result of individual member effort. If you would like to contribute in your area of expertise, let us know.

The cover story of this issue highlights three new technologies PDA has already brought to the community in 2005 via the Training and Research Institute (TRI) and the *New Innovative Technologies Exhibition™(NITE™)* program. On behalf of PDA, I want to thank GE Ionics and NovaTeck International for lending TRI equipment and software for use in the Baltimore, Maryland, facility. Also, I want to congratulate Genomic Profiling Systems, Inc., and CaliberSystems LLC for their selection to participate in the 2005 NITE™ program at this year's annual meeting in Chicago.

The PDA conference schedule for 2005 is another example of the commitment our members and staff have to the advancement of science and technology for our community.

For starters, the 2005 International Congress in Rome, March 1-3, was an excellent resource for learning about new and exciting pharmaceutical and biopharmaceutical technologies. The conference featured presentations on disposable manufacturing environments, closed vial filling, rapid microbial methods, and other innovative analytical methods. I was particularly impressed with the quality and variety of presentations featuring technologies for biopharmaceutical manufacturing: a concept facility for biopharmceuticals based on single-use technologies; validation solutions for therapies derived from genetically engineered plants; and controlled freeze-thaw of biopharmaceuticals—to name a few.

The 2005 PDA Annual Meeting in Chicago, the PDA Viral & TSE Safety Conference and the PDA Extractables/Leachables Forum (both in May in Bethesda, Md.) offer great opportunities for our community to engage in the discovery of new science and technology. Also in May, PDA and our France Chapter will cosponsor a meeting on similar biologics medicines. Later in the year, PDA and our Chapters will be holding conferences on contract manufacturing, risk analysis, prefilled syringes, visual inspection, and more.

In addition, PDA is poised to publish a number of Technical Reports in 2005. *Technical Report No. 40, Sterilizing Filtration of Gases,* mailed with the Jan./Feb. *PDA Journal of Pharmaceutical Science and Technology.* TR#41, *Virus Filtration,* is publishing with the March/April *Journal.* TR#42, *Validation of Protein Manufacture,* is pending final PDA approval. Later in the year, TR#38, *Chromatography Post-Approval Changes,* and TR#39, *Cold Chain Management,* are targeted for release. Rewrites of TR#1 and 28 are in the works as well.

It is invigorating to oversee such a wonderful start to 2005. With the hard work and effort of PDA staff and members, this year promises to be one of the most productive at PDA to date!

Member Volunteer Opportunities

Product Quality Research Institute Technical Committees

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

If you are interested in participating in a PQRI Technical Committee representing PDA please contact Vicki Dedrick, Vice President, Quality and Regulatory Affairs, at dedrick@pda.org for more information.

PDA Program Planning Committees

PDA is looking for volunteers to serve on the planning committees for upcoming PDA events. We are currently forming committees for the PDA International Congress, PDA Annual Meeting and PDA/FDA Joint Regulatory Conference through 2007.

If you are interested in participating on a PDA Program Planning Committee, please contact Wanda Neal, Director, Programs and Meetings, at +1 (301) 656-5900, ext. 111 or neal@pda.org.

PDA Regulatory Affairs and Quality Committee (RAQC) Task Forces

RAQC is always looking for Task Force Volunteers. We keep an ongoing list of volunteers in a variety of expert areas to call upon for assistance. Most commitments are ad hoc of 60 - 180 days to prepare regulatory comments. It is necessary to prepare regulatory comments under time constraints so flexibility is required.

If you are interested in participating on an RAQC Task Force, please contact Vicki Dedrick, Vice President, Quality and Regulatory Affairs, at dedrick@pda.org for more information.

PDA Letter Editorial Committee (PLEC)

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

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

The inaugural PLEC meeting has been moved, and will now take place in mid-May via teleconference.

If you would like to volunteer, please forward a brief summary of your professional experience and your contact information to PDA Senior Editor Walter Morris at +1 (301) 656-5900, ext. 148 or morris@pda.org by April 15.

PDA Training and Research Institute Advisory Board (TRIAB)

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

If you would like to volunteer to participate on one of the subcommittees being established to develop training criteria, content and certification programs, e-learning opportunities, and other training and education related programs, please provide a brief summary of your professional experience and your contact information to PDA Training and Research Institute Director Gail Sherman at +1 (410) 455-5981 or sherman@pda.org.

Recent Sci-Tech Discussions

The following unedited remarks are taken from PDA's Pharmaceutical Sci-Tech Discussion Group, an online forum that serve as a platform for exchanging practical, and sometimes theoretical, ideas within the context of some of the most challenging issues confronting the pharmaceutical industry. Join at www.pharmweb.net/pwmirror/pwq/pharmwebq2.html.

OOS Test Results

Will appreciate if you share some thoughts on the FDA draft guidance for investigating OOS test results. On page 7, it states in 4th paragraph: "All test results, both passing and suspect, should be reported and considered in batch release decisions." Does this mean that a suspect (OOS) result should be included in calculating the average for the reportable result? If the answer is "YES", then it contradicts with the guidelines for averaging on page 9, paragraph 2, which states, "To use results for assay reporting, all test results should conform to specifications."

How can one arrive at the decision as to which results to be used? Can you take the average of OOS result and Valid test results and report that as a final result? If not, what would you do with the OOS result for which there is no assignable cause? It can not be thrown away either.

Respondent 1

I have always interpreted the sections cited in the OOS Guidance to mean that all OOS results should be documented in the Investigation Report and considered in the batch disposition decision unless disqualified via the subsequent investigation. But since you are not permitted to average OOS and in-spec. results, they do not have a place in your final numerical result(s) unless confirmed via lab investigation (checklist including method execution, proper sample prep., instrument performance, calibration dates, proper reagents, reference standard, calculations, proper volumes and weights, other samples in the analytical run, etc.). If you have found no assignable or root cause for the one or more OOS result(s) following a comprehensive investigation both in the lab as well as resulting from the formal investigation outside of the lab (i.e., batch record execution review, operator interview, evaluation of in-process samples, possible process and non-process related errors, API/excipient correctness, evaluation of previous batch performance, etc.), then retesting of samples from the original collection delivered to the lab (unless resampled if originals are found to be unsuitable), is usually justified. If, following retesting per the procedure described in your OOS/Deviation SOP, your results are still OOS, or a mix of OOS and within-spec. results, you have confirmed the OOS result (no averaging permitted) and the batch has been deemed to fail. If all retest results pass and are all within a given range (spread), the average of these results is usually reported out usually with an asterisk denoting that it is derived from retesting based on an OOS investigation with ALL original and retesting results documented in the investigation report.

Respondent 2

I think that your questions arise from a confusion of terms. In the OOS terminology, valid and passing results are not synonymous. Passing results are those that comply with the specification. Results are valid when, after investigation, no evidence of analytical error can be demonstrated.

In this respect, I do not find contradictions in the FDA guidance (perhaps only ambiguous writing). When considering the context (first sentence in the same 4th paragraph, page 7), the suspect results have to be reported "If no laboratory or statistical error are identified in the first test..." . In the PDA comments to this draft guidance (11/30/98) it is suggested a change of this paragraph, as follows: "All results should be reported and considered in batch release WHEN NO SCIENTIFIC BASIS IS FOUND TO INVALIDATE THE INITIAL OOS RESULTS." (The capitalizing is mine)

In other words, ALL valid results must be considered when releasing a batch (both passing and OOS). An OOS can only be invalidated if there is an "observation and documentation of a test event that can reasonably be determined to have caused the OOS result" (page 10, 5th paragraph, FDA draft guidance).

Regarding the averaging of results, the FDA guidance is even more ambiguous. But the paragraph that you cite from page 9 only refers to the example in the previous paragraph, where OOS and passing individual results are averaged. The explanation is that "the individual assay results indicate nonconformance because two of the three results are outside of the range", and therefore can not be used to release the lot without further investigation.

And for the question of what to do with OOS with no assignable cause, the guidance states in page 11, first paragraph: "For inconclusive investigations - in cases where an investigation (1) does not reveal a cause for the OOS test result and (2) does not confirm the OOS result – the OOS result should be retained in the record and given full consideration in the batch or lot disposition decision."

A suggestion of change in the PDA comments to the FDA guidance (11/30/98) reads as follows: "In cases where an investigation (1) does not

continued on page 11

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Manic about microbes?

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   By Maik W. Jornitz and Theodore H. Meltzer, Item No. 17208, PDA Member US $185; Nonmember US $229
2. Good Practice and Compliance for Electronic Records and Signatures - Part 2: Complying with 21 CFR Part 11
   Item No. 19001, PDA Member US $95; Nonmember US $190
3. PDA Archive on CD-ROM - PDA Archive Retrieval Index
   Item No. 01101, PDA Member US $395; Nonmember US $590
4. Microbiology in Pharmaceutical Manufacturing
   By Richard Prince, Item No. 17185, PDA Member US $240; Nonmember US $299
5. Good Practice and Compliance for Electronic Records and Signatures - Part 3: Models for Systems Implementation and Evolution
   Item No. 13003, PDA Member US $95; Nonmember US $190
6. Laboratory Validation: A Practitioner's Guide
   Edited by Jeanne Moldenhauer, Item No. 17201, PDA Member US $250; Nonmember US $309
7. Quality Assurance: A Practitioner's Guide
   By U.G. Barad, Item No. 17212, PDA Member US $185; Nonmember US $229
8. Pharmaceutical Quality
   By Richard Prince, Item No. 17207, PDA Member US $240; Nonmember US $299
9. Introduction to Microbiology & GMP in Video CD module
   Item No. 15254, PDA Member US $390; Nonmember US $485
10. Commercial Off-The-Shelf Software Validation for 21 CFR Part 11
    Item No. 17200, PDA Member US $185; Nonmember US $229

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reveal a cause for the OOS test result and (2) does not confirm the OOS result the OOS result should be retained in the record and scientific judgment should be used to determine whether the OOS data point should be included in the averaging."

Respondent 3

First, I do NOT think too much of the FDA's DRAFT guidance on "OOS" because, as I and others have noted, it places the proverbial "cart before the horse."

The first thing that should be done is to critically evaluate the VALIDITY of every result WITHOUT regard to its value [be it "on target," "as expected," "in specification," "unexpected," or "out of specification (OOS)]. Then, if ANY value is NOT PROBABLY valid, the reasons for its non-validity should be investigated and "root cause" corrective actions initiated. For sample or subsample values that are valid and NOT as expected (unexpected or OOS), one needs first needs to establish that the sampling and sample handling that generated the sample is itself valid.

When the sampling is PROBABLY valid, then and only then should you initiate any additional or expanded testing of other parts of the samples or, if your normal sampling plans do not take truly "Batch Representative" samples as required by cGMP (a common failing in many of the plans that I see), perform a representative sampling on the batch or batches in question.

IF your PROVEN valid OOS is outside of the USP's lifetime limits or, if the product is NOT listed in the USP, your filed lifetime limits, THEN you should REJECT the batch, NOT perform any additional testing, and initiate the appropriate investigation directed at finding and eliminating the "Root cause(s)" of the manufacturing failure (remembering to start with a study of the critical physical properties of each component used in the batch or batches that have failed and proceed from there through the process).

IF your PROVEN OOS is inside of the USP's or your lifetime limits, THEN you should TEST a subsample from the representative sample sampled that is sufficient in size (number of units or amounts) and appropriately spans the batch so that the test results are sufficient to provide a 95% or higher confidence level in the acceptability or non-acceptability of the batch — as required by 21 CFR 211.165(d). [NOTE: For the typical batch of discrete dosage units, this means testing NOT LESS THAN (NLT) 200 UNITS. Testing the typical 30 discrete units (even if they somehow span the batch) provides a confidence level of LESS THAN (LT) 20% as to the nature of the BATCH and CLEARLY DOES NOT meet the requirements set forth in 21 CFR 211.165(d).

After testing NLT 200 batch-representative samples and establishing their validity, you should then use the appropriate statistical treatments contained in the recognized ISO Standard (ISO 3951) or its American equivalent (ANSI/ASQC Z1.9) to decide the releasability of the batch.

For the case where one cannot PROVE that the OOS was caused by an analyst error, instrumentation "glitch," or environmental upset, you should proceed as if the result found is valid.

If you truly proceed in the manner outlined above, then your decisions will be based on a body of evidence that is both scientifically sound and appropriate (as required in 21 CFR 211.160) for discrete materials (tablets, capsules, patches, lozenges, unit-dose syringes, suppositories, filled metered-dose containers, bottled liquids, tubed ointments and creams, etc.) where variable factors are tested.

Hopefully, the preceding will help you understand what the required CGMP minimums are so that you can comply therewith as required by law (21 USC Title 9 [commonly referred to as the Food, Drug, and Cosmetic Act]) when your drug product falls within the jurisdiction of the US FDA.

Filtration Handbook – Air and Gases

Maik Jornitz, Sartorious

The complexity of biopharmaceutical filtrations, the large variety of filter types that are available, and the many different purposes for which they may be employed make necessary the careful training of those who would engage in filtration operations. Appropriate explanations of filter properties, of causes and effects in their management, and instructions in their manipulations, gained from experience, would be an ideal first step in such training. The regulatory authorities endorse training as being necessary for individuals working in filtration. Indeed, there is an obligation, so stated by the FDA, to train those who are assigned such work.

A printed presentation of illustrations and textual elaborations can repeatedly be reexamined for guidance, and as often as necessary. *Filtration Handbook – Air and Gases* allows the reader unlimited time to review and digest the lessons presented. Topics like regulations, separation mechanisms, choices of filter types and materials, integrity testing, validation and troubleshooting are practically discussed in a presentation format.

Unlike in an oral presentation, the headline-style limitations of the slides are compensated by the unlimited time available for the reader's comprehension of the ever available text. No new material is presented, to be missed, while the reader reflects on what was last stated. The advantage of asking questions is absent. However, the text is layered in its information. Simple, core answers deliver the basic information considered essential to the training. However, where considered useful, the text is expanded to impart details to those whose background is sufficient to utilize them. The training, then, is tailored to the collective audience, whatever its level of technical sophistication.

A list of reference readings is included. It is based primarily upon technical papers forthcoming from peer-reviewed journals. It reflects the scientific principles relevant to validated air and gas filtrations.

This effort emphasizes the resolve of the authors to present a handbook dedicated to the training of those engaged in the important field of biopharmaceutical air and gas filtrations.

Note: *Filtration Handbook – Air and Gases* is the third installment of an illustrated lecture series created by PDA authors **Maik Jornitz,** PhD, Sartorius, and **Theordore Meltzer,** PhD, Capitola Consulting. *Filtration Handbook – Air and Gases* will be released by PDA and Davis Healthcare International Publishing later this month. The other books in the series so far are: *Filtration Handbook – Integrity Testing* (2003) and *Filtration Handbook – Liquids* (2004). Go to www.pda.org/estore to order a complete set!

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State-Of-The-Art: Technologies Impacting the Community, continued from cover

eration of this equipment. The new 'autoreagents' feature is very valuable because it automatically selects the optimum reagent flow rates for TOC measurements." And, he notes, "the analyzer is truly portable, allowing us to transfer it quickly between learning areas."

The instrument is GE Ionics' latest model, the Seivers 900 Series TOC Analyzer. With this analyzer, TOC samples can be collected in multiple ways, including swabbing and rinse analysis. It utilizes persulfate oxidation to make TOC measurement, and achieves extremely accurate measurements of TOC in a sample at less than 1 ppb [1].

To measure TOC in a sample, the analyzer utilizes two reagents, an acid and persulfate. The acidification of the sample is performed to dissolve inorganic carbon (IC) present in the sample. From that point, persulfate (a powerful oxidizer in the presence of UV radiation) is added to completely oxidize all organic carbon present in the sample to form carbon dioxide (CO_2). The amount of CO_2 can be measured by the conductivity across a membrane and then correlated to the amount of TOC present in the original sample.

The measured TOC in a sample depends on several factors, including the flow rate of the acid and persulfate being added to the sample. Adding too much or too little of either reagent can create significant variations in the measured TOC. With the "autoreagents" feature developed by GE Ionics, the analyzer is able to automatically determine the optimum flow rates for both the acid and the persulfate, to achieve complete oxidation of the organic carbon in the sample.

The effect of persulfate flow rate on the measured TOC in a sample is demonstrated in **Figure 1.** With a flow rate that is either lower or higher than optimum there is insufficient oxidation in the sample which leads to a lower TOC measurement.

The flow rate of acid, can also have a significant effect on the TOC measured within a sample for two reasons. As shown in **Figure 2,** at a pH of less than four, nearly all of the carbon will be in the form of CO_2, but at a pH higher than that, the carbon may not completely oxidize and a lower TOC measurement will be recorded.

The autoreagents feature will also compensate for decomposition of persulfate within the reservoir, and the syringe used to inject it. This feature does however, take more time (~14 minutes), due to the optimum flow rate determinations.

The TOC analyzer is used in two PDA TRI laboratory courses, "Cleaning Validation" and the Aseptic Processing Training Program." In the Cleaning Validation course, participants have an opportunity to use the TOC Analyzer for swab recovery studies. In the Aseptic Processing Training Program, the analyzer is used to supplement the laboratory segment on CIP design and validation.

Members of our community can experience the analyzer firsthand at the PDA TRI Baltimore facility. The "Cleaning Validation" laboratory course will be offered May 25-27 and November 7-9. The next Aseptic Processing Training Program begins April 18.

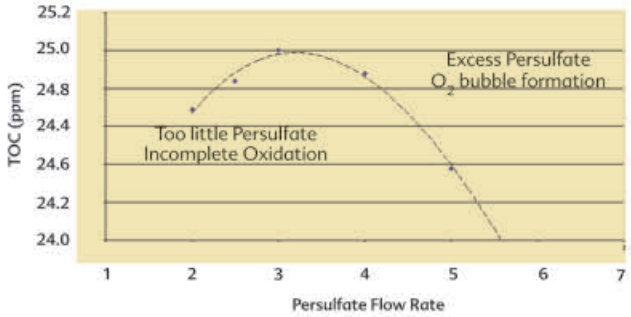

Figure 1. Effect of Persulfate Flow Rate on TOC Measurement

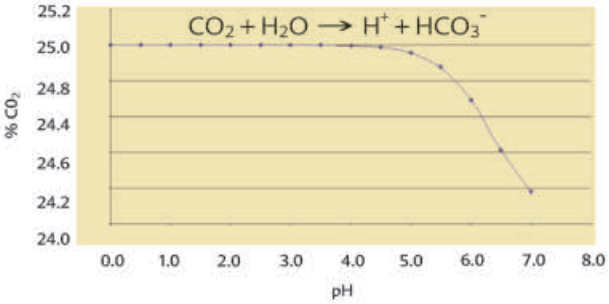

Figure 2. Dissociation of Carbonic Acid versus pH

NovaTek Loans Software to PDA TRI

Many companies have contributed to PDA TRI through loans or donations since the Institute opened in 1997. Each year, approximately 50 companies lend or donate supplies and equipment to help PDA TRI provide state-of-the-art educational experiences in the laboratory and lecture settings. See the sidebar on page 16 for a complete list of PDA TRI supporters in 2004.

In February, PDA TRI received Environmental Monitoring software from NovaTek International. This donation represents a new relationship between PDA TRI and Novatek. The system complements the environmental monitoring (EM) program established by PDA TRI for the Aseptic Processing Training Program.

PDA's Wamsley described Novatek's software as a "very valuable tool to track and trend environ-

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mental monitoring date acquired during courses from year to year."

The software includes two modules: one to manage environmental monitoring data collected, such as viable and nonviable air samples, contact plates , personnel monitoring and other supplemental environmental monitoring samples; the other to monitor utilities such as compressed gas, clean steam, water, etc. NovaTek states that he program is fully compliant with 21 CFR Part 11 requirements, including the implementation of audit trails, a user log and other means of securing data.

NITE™ Winners Spotlighted in Chicago

Exhibitions at PDA's large flagship meetings (Annual, PDA/FDA and the International Congress) and at select focus meetings offer the pharmaceutical and biopharmaceutical community an excellent opportunity to learn about new technologies directly from their creators. To better spotlight the latest and most valuable technologies for our community, PDA launched the New Innovative Technologies Exhibition™ (NITE™) program in 2004 for the Annual Meeting. Now in its second year, this program is already established as an excellent learning tool.

In 2005, two exciting technologies were selected from among 12 competitive applicants: Genomic Profiling Systems, Inc.'s Growth Direct System™ and CaliberSystems LLC's ValGenesis software. These technologies were fully vetted through the NITE™ selection process, which involves two peer-review systems—the NITE™ peer-review board and PDA Interest Groups.

Pioneering Rapid Microbial/Molecular Analysis

Genomic Profiling Systems (GPS) is developing pioneering products to address the significant need for rapid microbial and molecular analysis in industrial microbiology and health care [2]. GPS's suite of technologies for detecting microbes and molecules provides tests that are rapid, quantitative and ultra-sensitive while being simple, user-friendly, and cost-effective to implement.

GPS' Growth Direct System is an advanced imaging technology that delivers microbial enumeration results days sooner than current culture test. The nondestructive test is compatible with all microbial identification systems.

To enumerate microcolonies more quickly than traditional visual plate counting methods, the system employs proprietary digital imaging technology that captures the native fluorescence (autofluorescence) that is emitted by all living cells. By detecting microcolonies that contain as few as 50 cells, the Growth Direct test can automatically count the number of microbes in a sample days before they become visible to the eye.

The sensitivity and efficiency of the test result from imaging microscopic colonies without magnification using large area charged-couple device (CCD) imaging. GPS' test is accurate and efficient even when the manufacturing sample to be tested contains only a single microbial cell. This nondestructive detection simplifies validation and allows for eventual microbe identification.

In 2004, the company completed numerous case studies with pharmaceutical and biologic facilities that demonstrated Growth Direct's capability for rapid enumeration as demonstrated with samples including water, biofermenter material, products, anerobes, slow growers and environmental samples from air and surfaces.

GPS purports that savings derived from faster test turnaround include: reduced product losses, more rapid identification of process contaminants and earlier release of quarantined inventory. The Growth Direct system also reduces labor cost through auto-

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mating sample processing, analysis and report generation.

Moreover, by not harming the microbes it detects, the Growth Direct test simplifies the demonstration of equivalence to the "gold standard" visual plate count. Demonstration of equivalence is the cornerstone of the regulatory validation process that manufacturers must execute before implementing a new test. Users can easily demonstrate equivalence to the current test by imaging microcolonies at an early time with the Growth Direct test then incubating the sample further, until visible colonies appear at which time they can be "picked" and applied to any current microbe identification system for analysis. It is easy to see that a major benefit of the Growth Direct test is that it provides results are equivalent to visual plate count, since the pattern of the microcolonies from the Growth Direct test matches the pattern of the colonies in the traditional visual test.

ValGenesis: Completely Paperless Validation

CaliberSystems' ValGenesis is the first software product in the industry capable of conducting Validation test script execution electronically equating to a completely paperless validation process [3].

During the execution of validation document, the user ID with date and time stamps are captured for each test case and updated in the database automatically through XML. Any exceptional conditions that occur during the execution are routed for through a controlled approval workflow for the appropriate remedial action to rectify the instance.

ValGenesis can be utilized for online execution of approved test scripts, with handling of deviations, online reviews and approvals of test cases handled through configurable workflow. The system generates barcode for the validated entities for the identification and tracking.

ValGenesis System can be used to generate the validation number, track the validation status of all GxP systems/instruments/equipment corporate-wide in all sites. ValGenesis keeps the validation methodology consistent across all departments and company sites—something the FDA recommends for any multi-site rollout. It provides the controls and auditing for compliance with regulatory requirements such as 21 CFR Part 11.

CaliberSystems developed ValGenesis to fill a void in the pharmaceutical and biopharmaceutical industries for a validated inventory tracking system with built in e-signatures capability. The system permits users to set security controls, includes a built in memo/reminder system, complete audit trail and change control, and is Web-based. There is no need for a large support staff after implementation.

Fulfilling the PDA Mission

PDA has many programs to advance science and technology. Through our conferences, the pharmaceutical and biopharmaceutical community can learn about evolving technologies. The 2005 PDA Annual Meeting, for example, featured a number of presentations on pharmaceutical and biopharmaceutical technology, including process analytical technology, rapid microbiological methods, and new filling technologies to name a few. Complementing these presentations are the NITE™ program and all of the technologies on display at the exhibits hall.

The ability of PDA TRI to access the latest innovations for its laboratory and lecture courses is another example of PDA helping the community keep up with technological change.

Notes:

1. Taken from literature supplied by GE Ionics.

2. Taken from information available at Genomic Profiling Systems' Web site, www.genprosys.com.

3. Taken from literature supplied by CaliberSystems.

Gail Sherman, James Wamsley and Walter Morris, PDA

PDA Calendar of Events for North America

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

Conferences

May 16-18, 2005
PDA Viral and TSE Safety Conference
Bethesda, Maryland

May 23-25, 2005
PDA Extractables/Leachables Forum
Bethesda, Maryland

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

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

Training

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

Laboratory Courses

April 18-22, 2005
Aseptic Processing Training Program (Week 1)
Week 2: May 16-20

May 25-27, 2005
Cleaning Validation

June 2-3, 2005
Environmental Mycology Identification Workshop

June 13-17
Aseptic Processing Training Program (Week 1)
Week 2: July 11-15

July 26-29, 2005
Pharmaceutical and Biopharmaceutical Microbiology 101

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

Lecture Courses

May 2-3, 2005
Computer Products Supplier Auditing Process Model: Auditor Qualification

May 23-24, 2005
Sterile Pharmaceutical Dosage Forms: Basic Principles

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

August 8–12, 2005
Career-long Learning™
Training and GMPs

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

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

Course Series

May 2-4, 2005
Pharmaceutical Course Series
Princeton, New Jersey

Chapters

April 11, 2005
PDA Canada Chapter
Annual Meeting
Toronto, Ontario, Canada

April 12, 2005
PDA Delaware Valley Chapter
Sterile Components/Containers: New Technologies in the Filling of Pharmaceutical Final Dosage Units
Malvern, Pennsylvania

April 13, 2005
PDA Southern California Chapter
Dinner Meeting
Focus Resources Where It Really Matters, A Risk-Based Approach to Computer Compliance
Irvine, California

April 19, 2005
PDA Southeast Chapter
Maintaining Control of Your Environment and Your Documentation
Research Triangle Park, North Carolina

April 20, 2005
PDA New England Chapter
Genzyme Tour and Networking Dinner
Boston, MA

May12, 2005
PDA Metro Chapter
Real Quality
Clark, New Jersey

June 10 , 2005
PDA Mountain States Chapter
Golf Tournament
TBD

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

PDA Calendar of Events for Europe/India/Asia Pacific

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

EUROPE

May 9-10, 2005
PDA and the PDA France Chapter present
Similar Medicinal Biological Products
Lyon, France

May 19, 2005
PDA and the PDA Central Europe Chapter present
Conference and Exhibition Outsourcing
Basel, Switzerland

June 1-3, 2005
PDA Training & Research Institute Laboratory Course
Practical Aspects of Aseptic Processing
Basel, Switzerland

June 2, 2005
PDA EuroForum
PDA and the PDA Prague Chapter present
PAT - Industry, Regulator and Academic
Budapest, Hungary

June 2, 2005
PDA EuroForum
PDA and the PDA Prague Chapter present
Technology Transfer and Contract Manufacturing
Prague, Czech Republic

June 6, 2005
PDA EuroForum,
PDA and the PDA Spain Chapter present
IVIVC (In Vivo in Vitro Correlation) and
BPC (Biopharmaceutical Classification System)
Barcelona, Spain

June 13, 2005
PDA EuroForum,
PDA and the and the PDA UK/Ireland Chapter present
Risk Analysis
London, England

June 16, 2005
PDA EuroForum
PDA and the PDA Italy Chapter present
Rapid Micro TM 33
Milan, Italy

June 20, 2005
PDA EuroForum
PDA and the PDA Italy Chapter present
Rapid Micro TM 33
Milan, Italy

October 17-18, 2005
PDA Conference on the Universe of Pre-filled Syringes
Munich, Germany

INDIA

May 20-21
PDA IndiaForum
PDA and the PDA India Chapter present
Risk-based Validation
Goa, India

July 19-20, 2005
PDA IndiaForum
PDA and the PDA India Chapter present
Q7A Update
TBD

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

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

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

ASIA/PACIFIC

May 2005
PDA Korea Chapter

June 2005
PDA Japan Chapter
Training Course: Aseptic Processing

June 2005
PDA Taiwan Chapter
Annual Meeting

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

November 2005
PDA Japan Chapter
Annual Meeting

December 2005
PDA Korea Chapter

Victoria Ann Dedrick
Vice President, Quality and Regulatory Affairs

Vice President's Message

The ABCs of PDA

Every once in a while, I think it is fun to take a "stroll" through the alphabet to find my favorite words for each letter that describes something that is important and meaningful. These are my picks for PDA; please enjoy. Some letters were hard with many great words to choose from; others had one word that stood out as a strong descriptor for PDA. I do admit, I had a hard time with finding an "X" word. I would enjoy hearing your choices to describe PDA as well.

Advancing pharmaceutical and biopharmaceutical technology globally by promoting scientifically sound and practical technical information and education for industry and regulatory agencies to promote the public health.

Benefits—PDA members have access to the latest industry information through educational programs, meetings, interest groups, task forces and publications. PDA provides a forum for interchange between regulatory agencies and the pharmaceutical industry. PDA members also contribute to the regulatory process through joint activities with the U.S. FDA, USP and international standard-setting bodies. Increase your scientific knowledge; PDA is internationally recognized for providing unprecedented education, training and research in pharmaceutical science and associated technologies.

C*areer-long Learning*™ is a big part of the PDA experience. PDA's education courses are managed and conducted by its Training and Research Institute (PDA TRI) in Baltimore, Maryland. The mission of PDA TRI is to establish unprecedented worldwide education, training and applied research in pharmaceutical sciences and associated technologies.

Dedication—The PDA staff and volunteer governance is dedicated to providing you with the best experience possible as part of PDA's mission. When you join PDA, you join a community dedicated to advancing the industry, sharing knowledge and innovation, and developing better products for patients.

Excellence—With a focus on technology, industry and community, PDA will develop Centers of Excellence to draw upon the expertise of the membership involved to showcase groundbreaking activities and to promote excellence in pharmaceutical and biopharmaceutical applications.

Fun is important in your career and your life. We should all like what we do and gain a measure of enjoyment and pleasure from it. Meeting with your colleagues at PDA events, courses and training events and participating in committees, task forces and interest groups provide an excellent opportunity to have fun and learn with your colleagues at the same time.

Guidance comments are an integral part of PDA's process and value. Relevant guidelines address, among others, quality systems, risk management, process analytical technologies, dispute resolution, manufacturing, chemistry and manufacturing controls, and cGMPs. The PDA Quality and Regulatory Affairs Department also publishes news to help PDA members understand and comply with the complex regulatory expectations of our global environment.

Harmonization is important for the future of our industry. PDA works with global leaders from industry, health and other authoritative bodies (e.g., EMEA, ICH, WHO) as well as sister associations through the Product Quality Research Institute (PQRI) and European groups such as ESPIA. Working together helps us to encourage convergence in regulatory practices related to ensuring the safety, effectiveness / performance and quality of pharmaceutical and biopharmaceutical health-care products, promoting technological innovation and facilitating international trade.

Interest Groups were formed at PDA in 1995 and have stimulated member involvement ever since. PDA Interest Groups provide a vehicle, for people with common interests, to interact with one another, exchange information, network, and directly impact the science, technology and regulation of bio/pharmaceutical

manufacturing. Any PDA member can join one or more Interest Groups, and many reasons have been advanced for joining. Most members join PDA Interest Groups not only because they are an excellent source of specialized information, but also because they serve as a springboard for involvement in leading-edge activities, such as the drafting and final publication of PDA Technical Reports and Technical Bulletins.

Join—For more than 55 years, members have turned to PDA for the latest scientific, technical and regulatory information on pharmaceutical/biopharmaceutical manufacturing and quality. PDA members also have access to a wide variety of technical information online, including abstracts to PDA documents and the association's latest comments to regulators. PDA provides numerous forums for the exchange of ideas and information necessary to keep up with the fast-paced and evolving pharmaceutical industry. PDA is pleased to announce the introduction of three new membership types: Developing Economy, Academic and Student. All PDA memberships are individual memberships and include full PDA member benefits and privileges. These membership categories were created to allow greater contribution and participation from professionals of the worldwide pharmaceutical industry.

Knowledge is acquired through experience. PDA is the recognized authoritative voice and leading technical organization in the field of parenteral science and technology. Through our Technical Reports, Technical Bulletins, regulatory comments and conferences, PDA and its members influence the future course of pharmaceutical products technology. What better place to expand your experience.

Learn—PDA is internationally respected for providing unprecedented education, training and research in pharmaceutical science and associated technologies. PDA offers short courses, symposia, workshops and certificate programs in key areas of concern to its members. At PDA TRI, members receive hands-on training in current laboratory methods and techniques. Accredited by the Accreditation Council for Pharmacy Education and taught by the industry's leading experts, PDA's educational programs ensure that members stay on top of the latest developments in the pharmaceutical industry.

Mentor—All of us need advice and guidance in our careers and our lives. You bring a wide range of life experiences to your mentoring relationship. As a result, you can be a wonderful source of advice and information. Regardless of your background, the greatest gift you have to offer or receive is your genuine interest in your mentee's career and life and your willingness to listen attentively to them. Leaders with solid character are consistently admired. Mentoring is a potent strategy for developing character in mentees *and* mentors.

Networking opportunities abound with PDA membership including industry representatives from large and small companies worldwide, biotech companies, medical device manufacturers, equipment vendors, government agencies, academic institutions and consulting firms. In 2004, your peers from more than 750 companies globally attended PDA meetings to exchange ideas and share experiences.

Opportunity—a chance for advancement. PDA's Career Center offers an international online marketplace where job seekers can find the right positions and employers can find the right candidates.

Promote the growth of the pharmaceutical science and technology industry and your career.

Quality is based on customers' perceptions of a product's design and how well the design matches the original specifications. Quality is the ability of a product and service to satisfy stated or implied needs achieved by conforming to established requirements within an organization. PDA strives to provide:

- High-level, long-term business and management strategies
- Processes for developing new products and services
- Quality improvement initiatives
- Core competencies
- Strategies for responding to external changes
- Critical processes and procedures for performing day-to-day work

Regulatory—The PDA Quality and Regulatory Affairs Department monitors the regulatory landscape

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worldwide for relevant new guidances and policies and uses the PDA Web site, PDA e-mails and the *PDA Letter* to keep members informed. The department helps build relationships with health authorities around the globe. Moreover, PDA's all-volunteer Regulatory Affairs and Quality Committee drafts comments to guidances and submits original proposals to regulatory bodies to promote science-based regulations and harmonization.

Science is the foundation upon which PDA was founded. Good science is the basis for all the work that we do and contribute to the betterment of society. One way that you can get involved in science at PDA is to join the Pharmaceutical Sci-Tech Discussion Group. It is designed to provide a vehicle for the free exchange of information in the areas of international pharmaceutical manufacturing, quality control, process validation and regulatory affairs, emphasizing, but not limited to, sterile products technology. The discussion group is open to anybody with an interest in pharmaceutical science and technology. It is a great way to ask questions and stay on the leading edge.

Technical Reports cover a wide variety of subjects relating to pharmaceutical production, validation and quality assurance. These reports are prepared by Task Groups comprised of experts in the areas directly related to the subject of the particular report. The experts are industry scientists and engineers and often include regulators, such as FDA representatives. This level of expertise ensures the completed report will reflect the best thinking and practice currently available.

Understanding your needs as a member is key to PDA's future and your success. By continually interacting and communicating with its members through surveys, forums, interest groups, committees, conferences and training activities, PDA maintains a key sense of what its members need and want. Please continue to communicate with us about your ideas, needs and any opportunities where we can serve you better.

Volunteers worldwide carry out PDAs mission of promoting the exchange of rapidly evolving information on the latest technology and regulations concerning high-quality pharmaceutical production.

Willingness—PDA is your organization, and it is your ideas, invention, participation, dedication and professional power that have driven PDA for 58 years and continue to make it strong. Hundreds of PDA members willingly contribute their time, expertise, skills and ideas every year to create and develop good science, educational opportunities and resources to help further your success.

X—Wow, this is a hard one, but personally I have to go with xenophile—one who is attracted to foreign culture and people. With more than 10,000 members in 64 countries PDA is certainly an organization that could be described as a "xenophile". For me, being Belgian, living in the U.S. and having traveled most of my life, I am definitely a xenophile. We work in a global environment, and understanding and embracing cultural differences is now an integral part of our lives and our success.

You are the reason PDA exists. Our membership is comprised of over 10,000 scientists working in manufacturing, development, quality assurance, quality control and regulatory affairs. When you join PDA, you join a community dedicated to advancing the industry, sharing knowledge and innovation, and developing better products for our patients.

Zealous is defined as filled with, marked by or motivated with enthusiastic and intensive interest. This is how all of us at PDA feel about you.

Post Script: It is never easy to say goodbye, but on April 15, 2005, I will bid a fond farewell to all my colleagues, our wonderful committees, and numerous members and volunteers I have worked with at PDA. I am off to Florida to semi-retire and spend much needed time with my family. Your contributions, knowledge and kindness will not soon be forgotten. My very warmest wishes to all of you for continued good health and success.

Vicki

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The Case For Q10: A Harmonized Quality System Approach

Victoria Dedrick, PDA

In September 2004, the U.S. FDA published the draft guidance *Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations,* which ties into the 1978 final cGMP regulation. This linkage is intended to provide industry with an approach to manage improvements and changes effectively based on product and process knowledge and risk. The guidance is heavily based on ISO 9000 and the Quality Systems Regulation (QSR) for medical devices (21 CFR 820). FDA is currently reviewing and analyzing over 200 pages of comments to the draft as it works to produce the final guidance.

In July 2003, the International Conference on Harmonisation (ICH) agreed to produce a set of three quality guidances to support and encourage innovation and improvement of the pharmaceutical industry through utilization of science and risk-based systems. The third of these guidances, Q10, is intended to harmonize quality systems to stimulate continuous improvement in the pharmaceutical industry. Partnering with Q8, *Pharmaceutical Development,* and Q9, *Risk Management,* the three guidances will work in concert to complete ICH's agreed vision: "A harmonized pharmaceutical quality system applicable throughout the life cycle of the product, emphasizing an integrated approach to risk management and science."

If there was agreement in 2003 through the ICH process to produce a harmonized quality system guidance, why did the FDA issue a draft guidance last September? The answer is easy: Guidance and changes are needed now to support innovation in the pharmaceutical sector. A Q10 working party has not yet been constituted due to resource restrictions. Q10 will follow the completion of both the Q8 and Q9 documents. At the time of publication, only Q8 had advanced to the public comment stage (Step 2).

The FDA draft guidance document on quality systems was developed as part of the guidance package resulting from the agency's "21st Century" risk-based cGMP, implemented to stimulate innovation and enhance product safety and quality. The document will be submitted to the Q10 working party as a potential starting point, but in the interim, it will provide U.S. industry with needed direction. As mentioned earlier, the FDA QS guidance is heavily grounded in ISO 9000 and the medical device QSR. The United States, the European Union and Japan have already successfully harmonized a risk- and science-based quality system approach for medical devices via the Global Harmonization Task Force. This experience should make it easier for the three bodies to harmonize the quality systems approach for pharmaceuticals through ICH.

Why Do We Need Q10?

It has been recognized that the pharmaceutical industry suffers from a lack of innovation and improvement culture. In general, pharmaceutical manufacturing processes are static and inefficient, are not optimized and are based on an end-product testing scheme. The current GMPs do not include the quality improvement concepts or continuous improvement concepts required to optimize processes and product knowledge to ensure quality by design. The low process capability in pharmaceutical manufacturing manifests itself in low utilization levels of 15% or less, scrap and/or rework rates of 5-10%, long time periods (sometimes years) required to demonstrate effectiveness and a "cost of quality" in excess of twenty percent (20%)[1].

Additionally, regulatory authorities and industry are burdened by excessive review and inspection of post-approval changes many of which present little to no risk or provide process improvements (e.g. reduced impurities) that are delayed in implementation and result in multiple parallel processes pending approval. Change often cannot be effected due to a lack of knowledge regarding process robustness and/or a design space that is not clearly established.

Quality by design (Q8) and continuous improvement (Q10) will provide regulatory authorities with the confidence that the industry is and can manage quality, can implement improvements and changes effectively, and reduce process variability. The resulting increased process robustness and efficiency is a win-win-win situation for public health, regulators and industry.

The objectives of Q10 include:

- Harmonize a quality system approach for continuous improvement and change management.
- Provide a structured approach to process and product monitoring and improvement.
- Encourage a climate for continuous improvement.
- Facilitate and encourage the introduction of new technologies, e.g., PAT
- Stimulate the move from a "corrective action" culture to a "preventive action" culture.
- Ensure process improvements can be implemented easily and quickly.

(continued on bottom of page 26)

Regulatory Briefs

Europe

EMEA Publishes Guidance on Grounds for API Inspections for Consultation

In March, EMEA published a draft of the new guidance on the occasions when it is appropriate for competent authorities to conduct inspections at the premises of manufacturers of active substances used as starting materials. EMEA's GMP Inspection Services Ad Hoc Working Group developed this guidance as a harmonized approach for inspections under the amended EC legislation. After finalization, the document will be published under the *Compilation of Community Procedures*. The public consultation period closes in early April. For a link to the document, go to www.pda.org/regulatory/RegNewsArchive-2005.html.

EMEA Publishes Detailed GMP Guidelines for Active Substances Used As Starting Materials for Comment

The Commission published in March a draft of the detailed guidelines on the principles of good manufacturing practice for active substances used as starting materials. The draft revision affects only the introductory text (Section 1) of the GMP Annex 18, which has been published on the Commission´s Web site since 2001, implementing the Q7A guideline developed between the ICH partners, the European Community, the United States and Japan. No changes to the remaining sections 2-20 of the Annex are currently envisaged.

Changes refer to:

- The structural implementation in the GMP guide as Part II of the "Basic Requirements" instead of Annex 18. The current "Basic Requirements" of the GMP guide will become Part I in the future. The remaining annexes will supplement both Part I and Part II as appropriate, and a program to review the guidance already given on active substances in Annexes 2-7 is being undertaken. EMEA will publish a concept paper on this shortly.
- Section I "Introduction" to the existing Annex 18 (the future Part II of the basic requirements).
- Specific exclusion of veterinary ectoparaciticides

The Commission intends to publish the final version before October 30, 2005. The comment period closes in early April. For a link to the document, go to www.pda.org/regulatory/RegNewsArchive-2005.html.

EMEA Publishes Drafts of Authorizations for Manufacturing & Import and GMP Certificates Guidances

The Commission publishes a draft format for the authorizations for manufacturing and import for public consultation. EMEA's GMP Inspection Services Ad Hoc Working Group developed the draft based on a format developed and published previously within the Compilation of Community Procedures. The second draft document for public consultation refers to the GMP certificate for manufacturers. Within 90 days of an inspection, the competent authorities shall issue such a certificate, if compliance with GMP requirements can be confirmed. Member States will have to

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The Case for Q10, continued from page 29

- Ensure that regulatory authorities are confident that industry is managing quality and can manage improvements and changes effectively based on product and process knowledge and risk assessment.
- Reduce process variability, increase process robustness and increase efficiency.
- Create a guideline defining the components a manufacturer should have in place to demonstrate a robust quality system.

The Ultimate Goal of Q10

The ultimate goal of Q10 is for industry to be able to effect continuous process improvements, make low-risk changes without the requirement for prior regulatory approval and stimulate innovation through improved process knowledge. Q10 should also encourage the holistic use of data collected during development and manufacturing to provide "real-time" assurance of quality based on science and risk-management principles.

Regulators and industry need to embrace the ICH process and ensure that Q8, Q9 and, in particular, Q10 are brought to fruition for the benefit of public health, regulators and industry as early as possible.

Author's Note: I would like to thank Joyce Ramsbotham, Solvay Pharmaceuticals, for an excellent presentation given at the PDA International Congress in Rome, March 2005. Her presentation on Q10 was used as a basis for this article.

References

1 Dean, Price Waterhouse, November 2001.

implement these provisions by October 30, 2005. The format is based on that used in connection with the Mutual Recognition Agreements and has been adapted for application in all circumstances in which a GMP certificate is issued.

The comment period on the two proposals closes in early April. For a link to the document, go to www.pda.org/regulatory/RegNewsArchive-2005.html.

EMEA Releases Concept Paper on Dedicated Facilities

This concept paper proposes to update the section of the GMP guide on occasions when dedicated self-contained manufacturing facilities are required. It is foreseen that the guidance will take full account of the quality risk management principles described in the ICH Q9, which is expected to reach ICH Step 2 this year. The comment period for the document concludes in May. For a link to the document, go to www.pda.org/regulatory/regnewsarchive-2005.htm.

EMEA Concept Paper on a Proposal to Revise Annex 14 of the GMP Guide Published

This concept paper provides supplementary GMP guidance on the manufacture of medicinal products derived from human blood or plasma. The revision is necessary to take account of the regulatory changes brought about by Directive 2001/98/EC and its supporting technical directives, which cover the collection and testing of blood and plasma, whether for transfusion or for further processing to produce medicinal products. This work will be carried out in parallel with the development of good practice guidelines for blood and blood establishments which are expected to be developed by the Commission. The comment period for the document ends in May. For a link to the document, go to www.pda.org/regulatory/regnewsarchive-2005.htm.

EMEA Publishes *Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products* for Consultation

This guideline applies to human medicinal products intended for delivery of the drug substance into the lungs or to the nasal mucosa with the purpose of evoking a local or systemic effect. It includes current technologies for administration of the drug substance to the lungs, such as pressurized metered dose inhalers, dry powder inhalers, products for nebulization, and metered dose nebulizers, as well as pressurized metered dose nasal sprays, nasal powders and nasal liquids. Nasal ointments, creams and gels are excluded.

This document covers expected quality aspects of products to be marketed, but the general principles described here should also be considered for products used in clinical trials. It is not expected that all described testing would be conducted on all clinical trial batches. Comments are due by July 30, 2005. For a link to the document, go to www.pda.org/regulatory/regnewsarchive-2005.htm.

EMEA Issues Revised *Compilation of Community Procedures and Exchange of Information*

EMEA revised the section of the *Compilation* on the procedure for coordinating the verification of the GMP status of manufacturers in third countries. The *Compilation* document outlines the quality system requirements for GMP Pharmaceutical Inspectorates. It is intended that each GMP Pharmaceutical Inspectorate use the document as the basis for developing and implementing its own quality system and for preparing its own quality manual. In addition to providing a basis for self-assessment and a reference document for use by external assessors, establishing and maintaining an effective quality system will generate confidence within and between GMP National Pharmaceutical Inspectorates in the assessment of compliance with good manufacturing practice and/or good wholesale distribution practice. For a link to the document, go to www.pda.org/regulatory/regnewsarchive-2005.htm.

United States

PQRI Approves PAC-S Work Plan

PQRI has devised a work plan for the development of a "Post Approval Change Guidance for Sterile Products." The Working Group PAC-S of the Manufacturing Technical Committee of PQRI approved the work plan in March. The draft project proposal was drafted by former PDA Director Glenn Wright, Eli Lilly and Company, who represents PDA in the Working Group. FDA is supportive of this initiative.

FDA to Provide Guidance on "Exploratory" IND Process

FDA is preparing to release a draft guidance that will contain details about a new investigational new drug (IND) application process that might enhance postdiscovery drug development. The guidance will propose the use of an "exploratory" IND application specifically designed for early drug development activities. The new IND process will enable drugmakers to conduct various exploratory studies, referred to as "Phase 0" studies, without being limited by the Phase I trial restrictions that include limiting sponsors to focusing on one research path.

[Note: Briefs are complied from health authority releases.]

Chapter Focus: PDA Israel Chapter

Sigalit Portnoy, Taro Pharmaceuticals

The goal of the PDA Israel Chapter is to promote the pharmaceutical, biopharmaceutical and accompanying industries in Israel by enhancing the scientific and technological knowledge of Chapter members.

In 2005, the Israel Chapter plans to accomplish this goal in several ways:

1. Arranging seminars, revision days and discussion groups to expand the knowledge of industry participants and to enable information exchange.

2. Cooperating with the Ministry of Health (MOH) to improve members' understanding of the expectations and demands of the authority in Israel.

3. Creating encounters between the authorities abroad, the MOH and the Israel PDA Chapter in order to promote our membership in the Pharmaceutical Inspection Cooperation Scheme to facilitate the acceptance of MOH inspections by foreign authorities.

4. Organizing an international conference at the end of 2005 or at the beginning of 2006 to introduce knowledge from abroad and to exchange information with colleagues.

The following activities are planned for this year:

Seminars

1. Microbiological Validation, April 12, 2005, Tel Aviv
2. SCM & IE in the Pharmaceutical & Biopharmaceutical Industries, April 2005
3. From R&D to Market, May 2005
4. API Regulations, June 2005
5. Registration and Approval Changes, September 2005
6. Critical Systems, October 2005

Discussion Groups

1. Cleaning Validation, date to be determined
2. Implementation of LIMS, November, 2005
3. Bio & Imunoassay, September, 2005

International conference

1. Pharmaceutical Quality Tools for the 21st Century

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

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

Production Staff
Peter Marinovich, Manager, Web & Production
Scarlett Anderson, Print and Web Production Assistant

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

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

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

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

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Call for Papers

2005 PDA Visual Inspection Forum

October 20-21, 2005
Bethesda, MD

Abstracts are being sought for a special forum on all aspects of visual inspection processes as applied to injectable pharmaceutical products and production. This event is being planned in cooperation with the PDA Visual Inspection of Parenterals Interest Group. The forum will be held **October 20-21, 2005 at the Bethesda Holiday Inn Select in Bethesda, Maryland.**

The Planning Committee is soliciting abstracts in such areas as fundamental investigations into the inspection process, development and control of manual inspection processes, selection and training of human inspectors, statistical considerations for sampling, new developments in automated inspection technology and validation of automated inspection systems. Papers discussing particulate identification, sources in the manufacturing environment and their control are also welcome. Practical applications and experience in the form of case studies are of particular interest. Papers with commercial content promoting specific products or services will not be considered.

DEADLINE: MAY 20, 2005
Abstracts must be received by this date for consideration.

Send a copy of your abstract and supporting information via e-mail PDA Headquarters: Jason Brown at brown@pda.org. Please include the following information:

- Presenter
- Title
- Company
- Full address
- Phone, fax and e-mail address of presenter
- Presenter's biography (<100 words)
- Co-presenters
- Title
- Company
- Full address
- Phone, fax and email address of presenter
- Co-presenter's biography (<100 words)
- Proposal title
- Target audience (by job titles, department and specialty areas)
- Session description
- Objective for the session
- Rationale: An explanation of how the participant and the organization will benefit from this session (<100 words)

PDA will provide one complimentary meeting registration. Additional co-presenters will be required to pay appropriate conference registration fees. With the exception of regulatory speakers, all presenters are responsible for their own travel and lodging.

Upon review by the Program Committee, submitters will be advised in writing of the status of their abstracts by July 15, 2005.

Noble Laureate to Speak at 2005 PDA Viral & TSE Safety Conference

Christopher Flores, PDA

In 1896, a young Russian from Moscow emigrated to the United States to start a new life free from the religious intolerance that sprang up in Russia after the fall of Czar Alexander II in 1881. A century later, his grandson, **Stanley Prusiner,** MD, became a Nobel Prize winning scientist.

PDA is honored to have this world-renowned scholar as our keynote speaker for the 2005 PDA Viral & TSE Safety Conference, May 16–18, in Bethesda, Md. Dr. Prusiner's research on "prions," a term he coined, earned him acclaim as the world was learning about and struggling with the human variant of Creutzfeldt-Jakob disease (CJD). His study of prions came unexpectedly and not only changed his life, but had a major impact on the world of science.

Dr. Pusiner began his illustrious academic career at the University of Pennsylvania (Penn), which served as an intellectual banquet for this eager student from Ohio. The emerging scientist also studied philosophy, history of architecture, economics and Russian history.

In the last year of his undergraduate education, Prusiner was introduced to major medical research Penn's Department of Surgery while studying hypothermia. His positive experience working in this field enticed him to continue his education at Penn's medical school, during which he studied surface fluorescence of brown adipose tissue in Syrian hamsters as they emerged from hibernation.

During his fourth year of medical school, Prusiner returned to Europe where he conducted research at the prestigious Wenner-Gren Institute in Stockholm, Sweden. His work centered on the metabolism of isolated brown adipocytes. This work inspired him to seriously consider a career in biomedical research.

After returning to Pennsylvania and completing his medical degree, the young doctor moved to the U.S. west coast to complete an internship at the University of California at San Francisco (UCSF). He performed work for the National Institutes of Health (NIH) researching glataminases in E. coli which helped Dr. Prusiner hone critical research skills that would be essential to the progress of his career and later success.

Following his work with NIH, Dr. Prusiner began a residency in Neurology at the UCSF. During his advanced medical training, he would care for a patient that would transform his life and the medical world. The patient was dying of CJD, but the cause was unclear. Dr. Prusiner's intellectual curiosity led to the development of a research project that examined the molecular structure of the disease—a endeavor he has been dedicated to ever since.

After accepting a position as Assistant Professor in the Department of Neurology at UCSF, Dr. Prusiner began, unsuccessfully at first, applying for grants from NIH to study scrapie. Despite some stumbling blocks along the way, Dr. Prusiner was able to make some major breakthroughs in his research and gain a solid funding basis for his work.

When Dr. Prusiner presented his findings in 1982, his results were met with much skepticism from virologists and investigators working on scrapie and CJD. Even though he received much criticism and little support for his findings, Dr. Prusiner persisted. By the early 1990s, thanks to collaboration with other scientists, advances in his research gained him much respect within the scientific community and his theory was becoming generally accepted.

Dr. Prusiner's perseverance eventually earned his the Nobel Prize in medicine among several other accolades. It is his dedication and commitment to the advancement of neuroscience that has had such a profound impact on many areas of science, and for which we are pleased and proud to name Dr. Prusiner as our keynote speaker.

2005 PDA Extractables and Leachables Forum: Toxicology and Regulatory Perspectives

Christopher Flores, PDA

As new drugs are developed and new technology is designed and implemented to create these drugs, understanding of extractables and leacheables is essential to the creation of new drugs, new production methods and storage devices. In this constantly evolving field, the purity of drugs and container systems is a crucial part of regulatory assessment, considering the potential impact of extractables on public health.

With the above in mind, the role of the toxicologist is crucial in determining the consequence of extractables and leachables. Therefore, it is paramount that toxicologist are continuing their education and understanding of the science and new technological developments related to the field. That is why the 2005 PDA Extractables and Leachables Forum is so important to the field of biopharmaceuticals.

At this two-and-a-half day conference, toxicology will be one of four main subjects discussed by experts in the industry and regulators for the United States, Canada and Europe. To complement podium presentations, scientists also will present their work during our poster presentation sessions.

During the toxicology session, presenters will shed light on many uncertainties that remain about toxicology studies and safety risk assessments for qualifying extractables and leachables. To provide greater clarity on the issue, an impressive panel has been formed that will provide information and insight from many different perspectives. **David Porter,** Director of General Policies and Requirements, USP, will open the session with a discussion of the utility of USP <87> and <88>.

Following the presentation from USP, regulators from the Medicines and Healthcare Products Regulatory Agency in United Kingdom and **Timothy McGovern,** PhD, Supervisory Pharmacologist, Center for Drug Evaluation and Research, FDA, will both discuss safety qualification issues from the viewpoint of their respective agencies.

The toxicology session will close with presentations from **David Alexander,** Director, DA Non Clinical Safety Ltd., and **Jon Cammack,** PhD, Senior Director, Baxter. Mr.Alexander will survey current qualitative and quantitative assays of extractables and leachables as well as discuss storage conditions and toxicological qualifications. Dr. Cammack will explore ideal safety qualification processes for extractables and leachables. He will consider the impact of early screening to eliminate raw materials with potential problems and to generate early profile information to direct future studies and final safety testing intended to concentrate on the clinical application of the product.

As a cap to a series of impressive presentations, new insights and provocative discussions, the 2005 PDA Extractables and Leachables Forum will close with the regulatory session. During this session, attendees will have the unique opportunity to hear American, Canadian and European regulatory expectations regarding extractables and leachables in drug and biologic development programs.

The session will end with a comprehensive presentation by **Daniel Norwood,** PhD, Senior Principal Scientist, Boehringer-Ingelheim Pharmaceuticals. Dr. Norwood will describe the Pharmaceutical Quality Research Institute Leacheables and Extractables Project. This project is a joint undertaking by industry scientists, FDA and academia to develop an integrative approach to analysis and safety qualification of extractables and leachables in orally inhaled and nasal drug products.

This will be the first conference of its kind offered by PDA since 2001. So, do not miss this valuable opportunity to learn about and discuss these imperative issues with industry experts and regulatory officials.

PDA Training and Research Institute Lecture Courses Update

Strother Dixon, PDA

PDA Training and Research Institute (PDA TRI) began a successful 2005 by offering six interactive lecture courses in conjunction with the 2005 PDA International Congress in Rome, Italy, and followed by 11 courses in the Biopharmaceutical and Pharmaceutical Course Series in San Francisco, California . Additionly, the Computer Products Supplier Auditing Process Model: Auditor Qualification course was offered at the TRI facility.

This spring PDA-TRI has two lecture course series scheduled. The first is being held in conjunction with the PDA Annual Meeting in Chicago, Illinois, in April. The second is the Pharmaceutical and Biopharmaceutical Course Series in Princeton, New Jersey, May 2-4. The Chicago Series will feature seven courses and the Pharmaceutical and Biopharmaceutical Series will feature 10 interactive courses including a lecture/laboratory course first presented in Rome. TRI's lecture courses provide training for quality, regulatory, manufacturing and validation professionals.

PDA TRI will be presenting the following lecture courses at the TRI facility in Baltimore, Maryland:

- Sterile Pharmaceutical Dosage Forms: Basic Principles
  Faculty: **Michael J. Akers,** PhD and **John D. Ludwig,** PhD
  May 23-24, 2005
- Maximizing SOPs – An Untapped Resource of Training Solutions
  Faculty: **Elaine Lehecka Pratt**
  August 8, 2005
- Ensuring Measurement Integrity in the Validation of Thermal Processes
  Faculty: **Goran Bringert**
  August 9, 2005
- Biotechnology: Overview of Principles, Tools, Processes, and Products
  Faculty: **Antonio Moriera,** PhD
  August 9-11, 2005

Look for future PDA-TRI courses later in 2005 at the: 2005 PDA/FDA Joint Regulatory Conference in Washington, D.C. on September 15-16, 2005 Medical Device Series in Denver, Colorado on October 24 – 26, 2005, and the *Career-long Learning*™ Series in New Orleans, Louisiana on November 29 – December 1, 2005.

PDA Gives It's Members an Opportunity to Play and Learn!

James Wamsley, PDA TRI

It's probably not news to anyone that PAT has been a fairly hot topic around the industry in recent years. Because of this fact, rapid microbiological methods have become commonplace in many companies across the world. If you do not already have a system, one may be coming down the pipeline. It is also probably common knowledge that these systems are expensive, and it can be difficult (or practically impossible) to effectively judge how well each of the various systems available will suit your needs.

To help those who might not have the time or the resources to properly evaluate each system to their specific application, PDA TRI has developed a course to address this very need.

In October 2004, PDA ran its first *Rapid Microbiological Methods* course at its Training and Research Institute in Baltimore. **Jeanne Moldenhauer,** PhD, Vectech Pharmaceutical Consultants, Inc. and the Rapid Micro Users Group™, provided her expertise and experience in this area to get the course up and running.

Seven vendors participated. What made this so exciting, was that the students were actually able to use each piece of equipment and go through the procedure (albeit an abridged version) step-by-step. Technologies featured were: ***Millipore's*** Milliflex Rapid Microbiology Detection System; ***MIDI's*** Sherlock Microbial Identification System; ***AES-Chemunex's*** ScanRDI; ***Dupont Qualicon's*** Riboprinter; ***Advanced Analytical's*** RBD3000; ***Biolog's*** Rapid Identification System; and ***PALL's*** Pallcheck Luminometer.

It was exciting for everyone to see so much technology all in one place, and to see how each piece approached solving the problem for which it was designed. The class was divided into three groups. Each group worked with a technology in two-hour intervals before rotating to a new piece of equipment. In almost every case, the results for each group's tests were available by week's end.

To make sure that the students didn't only have *fun* playing with equipment while they were here, they spent two days attending a lectures on validation, acceptance criteria and comparability protocols. In addition to these lectures, students heard presentations directly from two U.S. FDA representatives regarding the topic of rapid microbial methods. On hand to present were **Bryan Riley,** PhD, and **Brenda Uratani,** PhD, both from the Center for Drug Evaluation and Research.

At the end of the week, following the lectures from instructors, presentations by the FDA and three days trying out new equipment, students broke into three discussion groups to talk about the pros and cons of each system related to its intended use and setting. The groups then shared their ideas with each other. This setting promoted open discussion and allowed people to hear opinions and facts they may not have heard before.

Overall, the first session of *Rapid Microbiological Methods* was a success, and should be again this October 31 through November 4, 2005.

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PDA Training and Research Institute *presents:*

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Overview

This is an introductory two-day course on sterile dosage forms. It is designed to provide a broad overview for individuals working in sterile manufacturing, QA/QC, microbiology, formulation development, package engineering, and compliance training. One hour each day will be devoted to a participatory problem solving exercise and discussion.

Who Should Attend

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

Quality Assurance/Quality Control
- ✓ Manager/Leader/Supervisor
- ✓ Scientist/Auditor

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

Regulatory
- ✓ Manager/Leader/Supervisor
- ✓ Reviewer/Inspector

Benefits of Attending

Gain knowledge of the basic principles of sterile pharmaceutical dosage forms required to:

- Improve processes by utilizing efficient approaches to process validation and sterility assurance
- Prepare for regulatory inspections based on current inspection trends for parenteral manufacturing

Key Topics

- Cleanroom facilities
- Environmental monitoring and control
- Sterilization principles
- Manufacturing unit operations
- Aseptic filling
- Dosage form development, packaging & stability requirements
- Validation of aseptic processing & product specific validation
- QA/QC for parenterals
- Regulatory trends

Baltimore, Md.

May 23-24, 2005

Venue

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

Faculty

Michael J. Akers, PhD
John Ludwig, PhD

Registration Fees

Member	**$1,470**
Nonmember	**$1,665**
Government	**$590**
Health Authority	**$590**
Academic*	**$590**
Student*	**$225**

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

For more information and to register:

Visit www.pda.org/basicprinciples05

Or, complete the attached registration form and fax or mail to:
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