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PDA Letter

August 2004

A Monthly Communication for the Members of PDA—
An International Association for Pharmaceutical and
Biopharmaceutical Science and Technology

Jordanian Health Authority Officials visit PDA, page 7

EM Standards for Sterility Testing Isolator Systems

A Case Study from the 2004 PDA SciTech Summit

Editor's Note: Environmental monitoring, whether in a cleanroom or in an isolator, represents a source of uncertainty in the industry. Changing regulatory expectations over the years only exasperates the problem.

Thomas Burns, Sterility Testing Laboratory Leader, Eli Lilly and Company, is doing his part to help clarify the issue, at least in the realm of sterility testing isolator systems. At the 2004 PDA SciTech Summit in March, Mr. Burns provided a comprehensive review of the environmental monitoring standards available from the United States Pharmacopeia (USP) and the International Organization for Standardization (ISO).

The following is an article by Mr. Burns based on that presentation.

Introduction

The use of isolators for sterility testing of parenteral products is common industry practice throughout much of the world. However, while there are clear industry and compendial requirements for environmental monitoring of parenteral manufacturing and filling areas, including filling isolators, there is little guidance on environmental

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2004 PDA/FDA Joint Regulatory Conference: *The New Guidances*

Don't Miss Your Chance to Meet With Over 20 FDA Officials

Washington, D.C. is *the* networking capital of the world, and in September, *the* place for pharmaceutical and biopharmaceutical manufacturers to network with U.S. FDA officials! This year's PDA/FDA Joint Regulatory Conference features over 20 senior FDA experts speaking about the implementation of newly released guidances and policy changes resulting from the "21st Century" cGMP initiative.

FDA's David Horowitz, Director, CDER Office of Compliance, announced at an FDA-industry forum in Parsipanny, New Jersey, on July 12 that there will be a "major announcement" regarding the 21st Century initiative in September and that the initiative "is not over"—making the 2004 PDA/FDA Joint Conference the ideal setting for interacting with agency experts to learn all about the implementation process.

Monday night, PDA is offering an hour-and-a-half reception in the Exhibit Hall. This event is the perfect conclusion to the first full-day of sessions and will allow conference participants a chance to mingle and relax.

On Tuesday night, the real fun starts with PDA's Evening on the Town. First, join PDA to see the very popular Washington D.C. show, Capitol Steps, and in this election year, the political satire promises to be funnier than ever. Next, PDA is going to "an extraordinary world—a world were something else is possible," also known as Cirque du Soleil's Varekai. Take advantage of special conference pricing for tickets and transportation to the show and join PDA for a great time on the town!

Throughout the conference, optional breakfast and luncheon working sessions are offered to facilitate even more interaction among meeting participants. And finally, PDA has scheduled 45 minute refreshment breaks throughout the two-and-a-half day event to maximize the time participants can interact in between conference sessions. ■

For more information on all these networking events and the general sessions, visit www.pda.org/pdafda2004. For the latest list of product and service providers appearing in the Exhibit Hall, turn to page 28.

Vist us at PDA/FDA Joint Regulatory Conference – Booth #48

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Looking to make a career change or take your career to the next level? Look no further. The PDA Career Center is here! Top employers are posting new positions to find qualified candidates across all segments and levels of the pharmaceutical and biopharmaceutical communities. Log on today to enjoy these features:

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PDA Letter

Important Dates...

- **August 31**—EMEA API Master File guideline becomes effective
- **September 7-8**—PDA/BFS Inter'l. Operators Association Joint Workshop on Blow/Fill/Seal Processing Holopack Verpackungstechnick GmbH, Germany
- **September 20-24**—2004 PDA/FDA Joint Reg. Conf., Courses & Tabletop Exhibits: The New Guidances, Omni Shoreham Hotel, Washington, D.C.

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PDA Audio Conferences

PDA offers audio conferences facilitated by world-class instructors to help expand your knowledge on a variety of important topics. And, since they are audio conferences, you can "attend" and participate right from your office or home. The savings are significant — no travel time or hassle and no travel expense. The tuition investment is per dial-in, so encourage staff members to listen and participate too — all for one fee!

If you miss an audio conference, or would like to refer back to a topic, you can also purchase the conference CD and transcript to get the entire audio presentation, including the question-and-answer portion, speaker handout materials, and a full written transcript. The CD and transcript are generally available three to four weeks after the live event.

Here are a few of our upcoming audio conferences:

ISO 14971: Implementing a Global Risk Standard
Transcript and CD Available

How to Justify ROI and Obtain Management Buy-In for Rapid Microbial Methods
Transcript and CD Available

5 Steps to Establishing Computer System Validation
Wednesday, August 4, 2004
10:30 a.m. – 11:30 a.m., EDT

Failure Investigation: Objective and Effective Analysis of Root Cause
Thursday, August 12, 2004
1:30 p.m. – 2:30 p.m., EDT

Understanding GERM3 Models Document
Thursday, September 9, 2004
1:30 p.m. – 2:30 p.m., EDT

Update to TR#32: Auditing of Suppliers Providing Computer Products and Services for Regulated Pharmaceutical Operations
Wednesday, September 15, 2004
1:30 PM-2:30 PM, EDT

To register for an upcoming audio conference, purchase a CD and transcript of a previous audio conference or for more information, visit www.pda.org or call +1 (301) 656-5900, ext. 158.

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Neal G. Koller
PDA President

President's Message

FDA Implements GMP Overhaul in September

PDA/FDA Joint Regulatory Conference Coincides Perfectly with Two-Year Milestone

Before I discuss the topic of this month's column, I'd like to thank the U.S. FDA for its dedication to the PDA/FDA Joint Regulatory Conference. This meeting—first held 15 years ago—has grown into one of the most important forums for FDA and industry to meet and discuss the important regulatory issues of the day.

Over the years, the joint conference has done much to bring FDA and industry closer together and has helped both sides look at issues through the same lens, which has certainly not always been the case. I refer you to past PDA President Edmund Fry's review of the fifth PDA/FDA Joint Regulatory Conference in the November 1994 *PDA Letter*. In describing the event, Ed noted a significant disparity between FDA presentations and industry presentations. "As I listened to the alternating FDA and industry speakers, it occurred to me that there was little overlap in their presentations," Ed wrote. He went on to point out the different perspectives of FDA and industry speakers as they prepare to address each other at a conference like PDA/FDA. Finally, Ed wisely recommended that "industry representatives might do well to closely consider the overwhelming bureaucratic tasks facing FDA, and FDA representatives might want to listen closer to the problems faced by industry scientists who are doing their best to distribute good products in an ever more perplexing regulatory environment."

Most of us will agree that things have changed. Nothing more clearly illustrates how the relationship between FDA and the manufacturers it regulates has evolved than the "Pharmaceutical cGMPs for the 21st Century: A Risked-Based Approach" initiative. Embodied in this two-year program to revise the approach to quality regulations are many of the issues that at one time or another have caused friction between the agency and industry.

Take, for instance, dispute resolution. A common refrain heard from industry representatives at the PDA/FDA conferences throughout the years has been the inability to convince FDA investigators that new and better ways of doing things are acceptable. Often, companies found themselves perplexed in their attempts to navigate the system in order to find an objective voice to solve disputes. Through the 21st Century quality initiative, the agency has built a new dispute resolution program, the draft guidance for which was published right before the 2003 PDA/FDA Joint Regulatory Conference. FDA launched a pilot program this year to test the draft guidance, and industry will have an opportunity to hear how the guidance is working at the PDA/FDA conference. I'm sure everyone in industry is looking forward to hearing the update on this component of the initiative by the Center for Drug Evaluation and Research (CDER) Office of Compliance.

Other aspects of inspection policy often have become a topic of discussion during the question and answer sessions at each PDA/FDA conference. When the 21st Century quality initiative was unveiled in 2002, FDA showed it had been listening. The program included work on the formation of a "pharmaceutical inspectorate" and the development of procedures to include "product specialists" from CDER in preapproval inspection activities. CDER's Karen Hirshfield, Senior Regulatory Operations, and Frederick Blumenschein, Supervisory Compliance Officer, will provide the 2004 conference updates on both of these activities.

Most interesting to a majority of PDA's members is FDA's updated guidance on aseptic processing. For sure, this topic represented one of the "hot" issues discussed at the PDA/FDA conference since its inception. In fact, the original FDA "guideline" (they were called guidelines back then) on aseptic processing was published in 1987—two years before the very first PDA/FDA Joint Regulatory Conference. Over the years, most aspects of that guideline were addressed at the joint conferences, and FDA learned from industry that changing technologies and practices rendered the 1987 guideline practically obsolete within only a few years of its publication.

At the 2004 conference, CDER's Richard Friedman will discuss what should be the *final* version of the agency's update to that 1987 guideline, entitled, *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*. At the 2003 joint conference, Mr. Friedman spoke about the draft guidance to a packed room. This year, PDA has scheduled his talk for the closing plenary

Jordanian Health Officials Visit PDA HQ

PDA Discusses Ways to Help Jordan's Industry and Health Authorities

On June 1, PDA was honored to receive three distinguished guests from the government of Jordan: Said Darwazah, Jordan Minister of Health, Dr. Salah Mawajdeh, Director General, Jordan Food and Drug Administration, Dr. Samir Khlief, U.S. NIH and Medical Director, King Hussein Cancer Center, and Maher S. Matalka, Director, Economic & Commerce Bureau, Embassy of the Hashemite Kingdom of Jordan.

The meeting was suggested by U.S. Secretary of the Department of Health and Human Services, Tommy G. Thompson, JD. The government of Jordan contacted the Secretary to explore options for bringing its pharmaceutical industry and regulatory controls in line with international standards. Secretary Thompson recommended that a delegation from Jordan visit with several U.S.-based pharmaceutical associations, PDA, in particular, because of the strong reputation of its training programs offered worldwide.

PDA President Neal Koller, VP of Science and Technology George Robertson and VP of Quality and Regulatory Affairs Victoria Dedrick met with the delegation for a lunchtime discussion of PDA's core educational offerings. Some of the Jordanian officials had previously visited the PDA Training and Research Institute and expressed great interest in the career-long learning opportunities PDA provides to the pharmaceutical and biopharmaceutical communities.

In the months ahead, PDA will build on this meeting with the goal of establishing a strong and productive relationship with the Jordan's government and industry. ■

Maher S. Matalka, George Robertson, Dr. Salah Mawajdeh, Dr. Samir Khlief, Vicki Dedrick, Said Darwazah and Neal Koller

Lance Hoboy, CAE
Vice President, Finance
& Strategic Planning

PDA Congratulates Lance Hoboy, PDA VP of Finance & Strategic Planning, for earning the Certified Association Executive (CAE) Credential.

Mr. Hoboy is the first PDA staff executive to receive this certification. The CAE credential is widely recognized as an indication of demonstrated skill in leadership, activity in community affairs and expertise in association management. To earn the credential, Lance achieved a minimum number of years of required experience in non-profit management, completed multiple hours of specialized professional development, passed a stringent examination in all areas of association management, and pledged to uphold a code of ethics. Lance joins an exclusive group of approximately 3,000, association executives who currently hold the CAE credential.

President's Message, *continued*

session of the conference to ensure that all attendees have a chance to hear him and, more importantly, ask questions about the final document.

All other aspects of the 21st Century initiative are on the agenda for this year's conference, and the presentations and Q&A sessions promise to be informative and thought-provoking. By using the 2004 PDA/FDA Joint Regulatory Conference as its a platform to roll out the new guidances and regulatory procedures that have been developed under the initiative over the last two years, it is clear that FDA heard and responded to Ed's message in 1994. It has "listened closely to the problems faced by industry scientists" and responded.

Now industry needs to do its part and work hard to adopt new quality techniques and technologies to ensure only the highest quality medicines are produced. The 21st Century initiative is an open door for industry to upgrade its manufacturing and control capabilities, eliminate process mistakes and improve the overall quality of their products and processes.

Once again, I thank FDA for supporting the PDA/FDA Joint Regulatory Conference and look forward to seeing all of you in Washington, D.C., in September. ■

George A. Robertson
VP, Science & Technology

Vice President's Message

Rapid Micro—Identification Methods

In this article, I would like to expand on the use of Rapid Microbial Methods for identification purposes in the bio/pharmaceutical industry. The most time consuming aspect of conventional microbiological identification methods is the need to have a sufficient sample to analyze. Conventionally, the process used is enrichment, where the organism is grown in sufficient quantity for analysis.

This article will detail polymerase chain reaction (PCR) with reference to current methods, a simple overview of the technique, the availability of rapid and automated PCR methods, and the future and benefits to the pharmaceutical industry.

An "Ideal" Test?

For those interested in detecting and identifying microorganisms, it will come as no surprise that an ideal rapid microbiology test does not yet exist. Such an ideal test would provide an "instant" result, would be easy to use and require minimal operator skills, be applicable to all samples, provide totally accurate data with no false positives or false negatives, and be easy to validate. It would also offer a full range of organisms in one instrument at a low cost per test.

Significant progress has been made in the development of rapid tests in many of these areas. There have been great improvements in many of the traditional methods used to detect microbes, but mostly in the food and clinical fields. Although no single method is suitable for every application, the molecular methods, such as PCR, offer a lot of promise, primarily because these techniques offer advantages in better speed and specificity.

The polymerase chain reaction was first described in 1985, but in the last few years, the method has begun to be considered as a useful tool for the quality assurance (QA) laboratory. The current PCR method entails the

(1) Separation of the DNA molecule into its two strands,

(2) The annealing of short DNA fragments, or primers, on their specific sequences,

(3) Elongation of these short fragments by Taq-Polymerase,

(4) Cycling or repetition of steps 1 through 3, and

(5) Detection by specific probes

Following cycling, low quantities of DNA may be replicated to 60 billion copies in the space of one to three hours. *This resulting specificity is only as good as the primer-probe combination developed for the test, and this is one of the key unspoken issues in the use of PCR.*

Detection

The need for gels in the "old" polymerase chain reaction to detect the actual DNAproduct formed by PCR has been replaced by the use of fluorescence resonance energy transfer (FRET). FRET uses an integral Fluorimeter in the instrument to provide a result. The "online" PCR detection systems was developed to achieve real-time pathogen detection in the food industry utilize FRET.

System Considerations

The common features among real-time PCR systems (instruments, reagents and methods) include sample preparation in 30 to 60 minutes, reagents supplied in kit form, PC-controlled systems, internal positive/negative controls, with reagents and instruments for combined amplification and detection. Selecting the right PCR method for a particular application, i.e., raw material screening or environmental isolate identification, is very difficult. All systems may yield a result and may do so more quickly and easily than five years ago. However, understanding the differences among the current real-time PCR systems becomes an important decision-making factor. Such differences might include:

Sensitivity and accuracy: Sensitivity is closely tied to sample preparation and enrichment procedures, for example, and a potential user should consider carefully the types of sample prep and enrichment the system requires to aid in any PCR decision. Assay times vary from one to three hours.

Software: Ease of use of software also is important to the selection process. Part 11 compliance and or LIMS compatibility are also key decision factors.

Reagent composition: One needs to consider whether lyophilization benefits the user or the manufacturer. Assuming adequate shelf life, use of a liquid product can mean one less preparation step.

Level of system dedication: Is this a dedicated system, or is it better applied as a research and development (R&D) tool? Some of the real-time PCR systems, like the Icycler, LightCycler and PRISM have uses beyond those of the QA application. If R&D is part of the user's capabilities and goals, these systems serve double duty and give added value for the investment made. Alternatively, the same capability for double duty may be wasteful if never used.

Costs of systems and tests: Costs per test can vary from as low as US$2 to as high as US$15, depending on test volume and the manufacturer.

Recent Sci-Tech Discussions

The following, unedited remarks are taken from the Pharmaceutical Sci-Tech Discussion Group, a PDA-sponsored Online Forum at www.pda.org. PDA Online Forums are free of charge and open to the public. They 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. If you are not currently a member of a discussion group, we encourage you to visit our Web site and join. Visit **www.pda.org** to sign up via the Web or send an e-mail to **requests@www2.pharmweb.net.**

Question 1: Blow-Fill-Seal Technology

Can I have some clarification on the below mentioned aspects: How are the plastic bottles depyrogenated in Blow-Fill-Seal Technology? Is the filled and sealed bottle is terminally sterilized? How? Any information on the above subject will be highly appreciated. Also please mention some Guidelines on the above technology.

Response 1

The extrusion process, where the polymer beads are heated so that they become molten and able to form the bottle/vial shape depyrogenates the polymer. You may have to demonstrate this for your process (coat polymer resin in endotoxin, fill, test product for endotoxin levels), but work with the company you use for your LAL testing needs - they have the expertise.

The filled bottles may be terminally sterilized by transferring them to an autoclave and processing them through a validated autoclave sterilization cycle. It's a separate process from filling.

While filling using BFS technology can and does result in sterile product, unless the product is detrimentally affected by the process it must be subjected to terminal sterilization in order to be able to call it sterile (as opposed to aseptically filled).

When I was more closely involved in BFS manufacture, I remember there was quite a bit of supporting documentation available. I'm afraid I am unable to provide you with any references, other than the PDA journal around 1993/94 and follow the references in the articles (search under the names D. Jones, P. Topping or J. Sharp. I think another worker in the field was C. Sinclair).

Response 2

Blow-Fill-Seal technology combines blow molding, sterile filling and hermatic sealing into a single process to produce sterile packages, polyethylene, ranging from low to high densities, polypropylene are the standard resins used for BSF. PP and HDPE can withstand autoclaving at 121 where as LDPE cannot be autoclaved at 121 and a lower temperature is required.

No it need not be depyrogenated since the formation of the bottle bag at high temperature would destroy the endotoxine.

Response 3

There are different materials used in blow-fill-seal technology, the most common is Polyethylene of density 0.93 g/cc.

The Plastic is extruded at a temp of about 180°C to form the bottles which are pyrogen

VP's Message, *continued*

Application support and system support: This is especially true in working with "cutting edge" technologies such as PCR. The best instrument/reagents with weak support, and vice versa, is not the optimal system. Speaking with a company representative in a meeting, trade show or workshop can be one sign of the future in working with that company.

Summary

The advantages of PCR technology QA laboratory are four-fold.

- The speed to result is the reality of an "on line" or "at line" microbial detection and identification test, consisting of sample preparation step then an hour or two later having a result.
- PCR technology offers flexibility in terms of the detection of different pathogens within a run, as well as the detection of multiple organisms within a test (depending on the test).
- It offers security of result in that PCR is a confirmatory test. Indeed, the accuracy of a DNA-based method is a strong point.
- The automation of PCR systems has made the method an analysis that the quality assurance/control laboratory can now do readily. ■

free. These bottles are heat treated to a temp of approx 108°C for 60 minutes (Approx F0 of 3). This is not exactly Terminal sterilization in the classical sense, but due to the built in Sterility assurance in the upstream process (CIP, SIP of the equipment, completely closed system etc.) the combination of BFS and 108°C heat treatment produces reliable results.

Response 4

Right now I am reading a book related with BFS technology, regarding to your questions:

How are the plastic bottles depyrogenated in Blow-Fill-Seal technology? BFS technology melt plastics around 170-230 °C and 350 Bar, this conditions assure sterility of the melted plastic and there are challenge tests with resin contaminated with endotoxines and no endotoxine was proven to be in the filled containers, foreign substances are surrounded by the melted plastic and can not migrate form the plastic to the product.

Is the filled and sealed bottle terminally sterilized? How? Yes, containers are sterilized in sterilization chambers, the parameters used depends on the container plastic (polyethylene, polypropylene).

Response 5

I would like to add to your comment regulating pyrogens — I would have thought that the pyrogens would/should have been eliminated during the distillation process.

Response 6

The bottles are not pretreated - they are formed in situ. I believe that there are some data available in the literature to show that depyrogenation does occur (at least to some extent) during the formation of the polymer parison.

The filled containers are not terminally sterilized as part of the BFS operation but this could be done as a separate process later. Of course, the choice of polymer and/or terminal processing conditions would be very important to avoid problems with softening of the plastic.

Question 2: Autoclave Loading Patterns

I am looking to get feedback from industry on industry norm/current practice for routine use loading patterns in production autoclaves for porous cycles versus what was validated at PQ. At PQ maximum and minimum porous loads to HTM2010 are qualified in triplicate with a specified loading configuration of position and quantity of items of equipment, e.g. 10 plugs on the first shelf left hand side, 4 filters on the second shelf right hand side, etc. These validated maximum and minimum loading patterns are then depicted in the SOP for autoclave use for autoclave operators to comply with.

What I need to know as it isn't written in black and white in any guidelines so we QA can use it as 'ammunition' for procedures...The procedures should state that:

ONLY the load configuration which is validated - position and quantity - can be used routinely or you can deviate from this configuration by quantity of items less than what was validated as long as the items are in the validated position, e.g., 8 plugs instead of 6 on the first shelf left hand side

I would appreciate to hear any comments you have on this topic as usual it stems from what we've "heard" authorities are requiring.

Response 1

It would be best to refer you to the latest draft of the PDA's Technical Monograph #1 revision at www.pda.org which provides coverage of this subject in greater detail than an E-mail permit. In a nutshell, it's quite different from what the regulators believe.

Response 2

I am of the opinion that you can deviate within your minimum and maximum bracket.

For example if your validated configuration is:

Max: 10 plugs on the first shelf left hand side, 4 filters on the second shelf right hand side

Min: 3 plugs on the first shelf left hand side, 1 filters on the second shelf right hand side

It is first essential to establish that the minimum is a variant of the maximum (3 plugs have been kept in the same positions as 10 with space for 7 plugs missing and 1 filter have been kept in the same position as one of the 4 filters with spaces missing).

You would then be justified in allowing 4 to 9 plugs on the first shelf left hand side or / and 2 to 3 filters on the second shelf right hand side, provided the positions of the plugs existing are the same and the spaces are left vacant.

Response 3

You can use anything less than the validated load configuration. Typically you would also have a validated minimum load along with your maximum load; the min. load is generally a single item considered the most difficult to penetrate.

As far as item locations in a load, I'm interested to hear how strict people are. While we have specified load configurations, we also have data showing that a particular item or two are the slowest to heat wherever they are placed in the load (verified by moving the items or having multiple identical items in different locations). ■

Conference
April 4–6

Exhibition
April 4–6

PDA-TRI
Courses
April 7–8

Call for Papers

2005 PDA Annual Meeting

Chicago, Illinois

Scientific abstracts of papers not previously published or presented at scientific meetings are being sought for presentation at **2005 PDA Annual Meeting, which will be held April 4–8, 2005 in Chicago, Illinois.**

This conference offers many opportunities for academicians, practitioners, consultants, and other subject-matter experts to present in a variety of forums—breakfast, luncheon and presentation sessions, keynote addresses, and panels.

Abstracts Must Be Received By August 30, 2004 For Consideration.

PDA is seeking presentations 30-35 minutes in length, that present major challenges and practical approaches to resolution in the following areas:

- Aseptic processing of medicinal products
- International regulatory and harmonization initiatives
- Industry manufacturing/product trends
- New technology
- Combination products
- Risk management and risk-based GMP
- Process analytical technologies (PAT)
- Quality management systems for pharmaceuticals
- Industry case studies—compliance and quality issues
- Microbiology initiatives and trends

Commercial abstracts promoting of products and/or services will not be considered.

Send via e-mail an electronic copy of the abstract and the presenter's biography (approximately 100 words in length) by August 30, 2004 to: Deborah Stokes at Stokes@pda.org.

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

Title ✧ Presenter's biography ✧ Additional authors ✧ Full mailing address ✧ Phone number ✧ Fax number ✧ E-mail address of the presenter ✧ 2-3 paragraph abstract, summarizing your topic ✧ The type of forum you can present your topic in (traditional, case study, discussion/debate, panel) ✧ Target audience (by job title or function) ✧ Explanation of specific take home benefits to target audience for attending this presentation ✧ Key objectives of your topic and the benefits of someone hearing what you have to say.

Upon review by the program committee, submitters will be advised in writing of the status of their abstract after August 30, 2004. PDA will provide one complimentary meeting registration per presentation. Additional presenters will be required to pay appropriate conference registration fees. With the exception of health authority speakers, all presenters are responsible for their own travel and lodgings.

EM for Sterility Testing Isolators, *from cover*

monitoring of sterility testing isolators. This article will describe the current requirements and expectations, and will make recommendations for setting up an environmental monitoring program for a sterility laboratory containing isolators.

Why Monitor?

Why should we perform environmental monitoring in sterility test isolators? When there is a sterility test failure, regulatory expectations are that retesting is only permitted if there is substantial evidence that the testing environment was the root cause of the failure. Given the current state of identification techniques, this evidence may include a DNA level match of the test sample isolate with a viable microbe monitored from the isolator during that same test session. Secondly, monitoring of the interior of the isolator is good practice to show the interior of the isolator is in a state of control. If contamination is observed in the isolator, the body of environmental data available is critical for an investigation into the root cause, and ultimately determining appropriate preventive measures.

When there is a sterility test failure, regulatory expectations are that retesting is only permitted if there is substantial evidence that the testing environment was the root cause of the failure.

Room Classification

Before addressing environmental monitoring of the interior of the isolator, a discussion of room classification is in order. A few years ago, the European Pharmacopeia (EP) proposed a Class D requirement for rooms containing sterility testing isolators, but this requirement was never approved. USP <1208> states that classification is not required for sterility laboratory isolators, but suggests limited access to nonessential staff. It may be good practice, however, to set up a monitoring program to determine the level and type of microorganisms present in the general laboratory areas surrounding the isolator. This data would not be used to classify the room, but simply to assist as supporting information for cleaning frequency, cleaning agents and sterility failure investigations (i.e., existence of that particular microbe type in the laboratory area). These isolates can also be used for growth promotion of the environmental monitoring media. It is recommended that this room monitoring be performed at various times of the year to determine potential seasonal changes.

Monitoring Methods

The four types of monitoring in sterility testing isolators to be discussed are viable surface monitoring, viable active air monitoring, viable passive air monitoring, and nonviable air monitoring.

Viable Surface Monitoring

The standardization of surface sampling methods has not been as widely addressed as the standardization of air sampling. Common methods of surface monitoring are contact plates, swabs and glove monitoring.

Contact plates are usually used for monitoring of flat surfaces, such as the isolator base and sides, and shelving units. Contact plates will leave a residue of agar on the sampled surface, so care must be taken to remove this residue after sampling. Allowing agar to remain may provide an area for future microbes to propagate.

Swabs are usually used for sampling irregular surfaces such as sample vials, half-suits, gaskets, and equipment. A wetting solution should be used that is not inhibitory to the target microorganisms. When using swabs, an appropriate sampling size must be defined, usually 24-30 cm^2. Once sampling is complete, there are various ways to incubate swabs. The swabs can be immediately placed into liquid media, or the swabs can be placed into a non-inhibitory diluent. This diluent can be filtered, and this filter placed onto agar or liquid media, or an aliquot of the diluent can be placed onto solid media.

Gloves are a crucial monitoring location since they are the primary means of spreading contamination throughout the isolator. Gloves can be monitored by:

(1) Finger dabs on contact plates. As mentioned above, care must be taken to remove the residual agar.

(2) Swabs.

(3) Submerging the gloves in diluent. As mentioned in the Swab section above, this diluent can be placed into media or onto agar in various ways.

(4) Wiping the gloves with diluent wetted sterile wipes. This wipe can be placed directly into liquid media, or the wipe can be placed back into the diluent container, and handled as mentioned above for swabs.

Viable surface monitoring: Items to Consider

(1) Locations to monitor

It is suggested to monitor the critical at-risk locations: Half-suit gloves, half-suit armpits, alpha-beta gaskets, areas where two surfaces meet (e.g., where sample racks contact a shelving unit), items transferred into the isolator (if a transfer isolator is used).

(2) When to monitor (which days)

It is suggested to monitor the first day of operation after an isolator biodecontamination. If the isolator will remain in an aseptic state for a certain period of time, also monitor the last day before the next biodecontamination. It is also prudent to perform intermediate sampling between these two dates to demonstrate the maintenance of asepsis in the isolator.

(3) When to monitor during the testing session

Viable surface monitoring is usually performed at the end of a test session, but some sampling may be performed at an earlier time based on a risk assessment (when is the most likely time for contamination?). Alpha-Beta gaskets should be sampled as soon as a transfer isolator door is opened. It might be best to monitor sample vials at the beginning of the test session, since they are frequently not easily available at the end of the test session.

(4) Which media should be used for viable surface monitoring. USP <1116> mentions:

Liquid Media	Solid Media
Tryptone saline	Soybean-casein digest agar
Peptone water	Nutrient agar
Buffered saline	Tryptone glucose extract
Buffered gelatin	agar
Enriched buffered	Lecithin agar
gelatin	Brain heart infusion agar
Brain heart infusion	Contact plate agar
Soybean-casein	
medium	

Specialized agar can be used for specific monitoring of fungi, spores, etc.

(5) How long the media should be incubated

There are generally two schools of thought: Incubate the media for the same length of time as the Environmental Monitoring samples in the Production area (3-5 days), or incubate the media for the same length of time as the sterility test samples (14 days).

Viable Active Air Monitoring

The purpose of active air monitoring is to collect volumetric air samples inside the isolator and pass this air across suitable media. USP <1116> mentions several types of samplers, including Slit-to-Agar (STA), centrifugal samplers, and Sterilizable Microbiological Atrium (SMA).

Viable active air monitoring: Items to Consider.

(1) Which media to use

USP <1116> (see Viable Active Air Monitoring)

(2) Which locations to monitor

Qualify based on worst-case locations, usually near the locations of sterility testing.

(3) How much air should be sampled

USP <1116> says, *"Where the microbial level in the air of a controlled environment is expected to contain not more than three cfu per cubic meter, several cubic meters of air should be tested if results are to be assigned a reasonable level of precision and accuracy."*

Viable surface monitoring is usually performed at the end of a test session, but some sampling may be performed at an earlier time based on a risk assessment.

It may not be practical to sample large volumes of air across one agar plate, so multiple samples may be obtained. Caution: Do not sample so quickly that it affects air flow or isolator pressure!

Viable Passive Air Monitoring

Viable passive air monitoring utilizes agar and/or broth to monitor the air in the isolator during a testing session. Settling plates/bottles are simple, inexpensive, and qualitative (not quantitative). They are beneficial as a supplement to viable active air sampling.

All Viable Sampling: Items to Consider

(1) Must qualify the lengths of time.

(a) How long can swabs be in diluent before going into media?

(b) How long can agar plates (active and passive sampling) be exposed before incubation?

(c) How long can all media be incubated and still support growth?

(2) Which growth promotion microbes should be used for each media type (qualification of the media)?

(a) Can use the Bacteriostasis/Fungistasis organisms for sterility testing from USP<71>, EP 2.6.1.

(b) Can use local flora from the laboratory.

(3) What do you do if you get a 'hit'?

Proceduralize!

(a) Will you genus/speciate the contaminant?

(b) How in-depth will you investigate?

(c) Will you invalidate testing from that testing session?

(d) If the isolator remains aseptic from a certain period of time, how far back (and forward do you question operations?

Non-Viable Air Monitoring

USP <1208> says, *"At rest, the isolator meets the particulate air-quality requirements for Class 100 area as defined in U.S. Federal Standard 209E."* Federal Standard 209E has been replaced with ISO 14644-1 and 14644-2. "Class 100" is now "ISO Class 5". ISO 14644-1 defines calculations for the number of sampling locations in an isolator, the calculations for the volume of air that must be sampled at each location, and the maximum concentration limits for each particle size.

Example: For a two half-suit workstation, the approximate surface area of the isolator deck is 41.9 ft^2 (3.89 m^2). ISO uses this number to calculate 2 sampling points locations. For ISO Class 5, the maximum concentration limits are 3520 for 0.5¼m and 29 for 5.0¼m. (Note that the May 2003 revision to the EU's Annex 1 states that these limits are 3500 and 1, respectively). The volume of air to sample at each location is 687.7L (24.3 ft^3). If the particle monitoring device can only monitor a 1 cubic foot per minute sample, then 1-25 minute sample (or 25-1 minute samples) will be required at each location.

The total particles measured during this sampling cannot exceed the maximum concentration limits. ISO 14644-1 also describes computing averages and confidence limits at each location, in addition to handling of outliers.

Take Home Message

(1) Justify and proceduralize all isolator environmental monitoring. If you elect to perform or not perform a certain type of monitoring, justify and proceduralize it! Since there are very few direct compendial requirements, following your procedures is the major step of compliance in this area.

(2) Justify and proceduralize how to handle contamination or failed non-viable tests (action/alert levels).

(3) Document the training of sterility testing analysts on these procedures.

(4) Track the results to identify potential trends. Hopefully there isn't anything to trend!

References

USP <1116> Microbiological Evaluation of Clean Rooms and Other Controlled Environments

USP <1208> Sterility Testing – Validation of Isolator Systems

ISO 14644-1 Cleanrooms and associated controlled environments, Part 1: Classification of air cleanliness

ISO 14644-2 Cleanrooms and associated controlled environments, Part 2: Specifications for testing and monitoring to prove compliance with ISO 14644-1

EC GUIDE TO GOOD MANUFACTURING PRACTICE REVISION TO ANNEX 1

About the Author

Thomas P. Burns is the Leader of the Sterility Laboratory for Eli Lilly and Company. In more than 19 years at Lilly, he has been involved with various areas of parenteral product testing, including the chemical and biological laboratories, technical services, and sterilization validation. Mr. Burns is a graduate of the University of Pittsburgh at Johnstown with a B.S. in Chemistry. He can be contacted at +1 (317) 276-9207 or BURNS_THOMAS_P@Lilly.com. ■

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PDA Interest Groups & Leaders

The following is a list of PDA Interest Groups (IGs). Starting in 2004, PDA began establishing "Branches" of each IG in the various regions of the world that we serve. The list below includes the names of the Leaders for each Branch of the IG, the Leader's affiliation and his or her e-mail address. More detailed information on PDA's Interest Groups and contact information is available on the PDA Web site at: www.pda.org/science/IGs.html.

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Vice President's Message

PDA Taiwan Chapter Expanding Scope

Victoria Ann Dedrick
VP, Quality and Regulatory Affairs

Naruw'an—"Welcome to Taiwan." That is exactly how I felt during my visit with the PDA Taiwan Chapter from June 22-25, very welcome. Tuan-Tuan Su, the chapter secretary-general, was an exceptional host during my entire visit.

While in Taiwan, I was honored to attend the PDA Taiwan Chapter's Annual Meeting, present an overview of the European Union's medical device regulations at a one-day symposium for local industry, and meet with several officials from the Taiwan Department of Health.

V.A. Dedrick, PDA and Tuan-Tuan Su, Secretary-General, Taiwan PDA

The Taiwan Chapter is privileged to have exceptionally good relations with the Taiwan health officials and has been officially recognized and sanctioned by the Taiwan government to execute projects on their behalf. The Taiwan Chapter has offered numerous training programs for the government on such topics as cGMPs and inspections, including the symposium I attended on this trip.

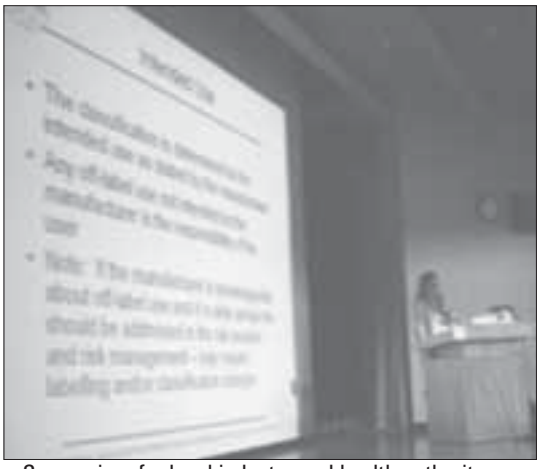
Thanks to arrangements made by the Taiwan Chapter, I had the opportunity to meet with and provide presentations to officials from the pharmaceutical, medical device and in-vitro diagnostic sections of the Taiwan health authority. Our first official visit was with the Department of Health Director General Bureau of Pharmaceutical Affairs, Dr. Hui-Po Wang. Dr. Wang greeted us warmly and thanked PDA for serving as a sponsor for the free symposium for industry on behalf of the government. Dr. Wang expressed Taiwan's desire to develop its medical device and IVD products for export and noted they were working closely with EU and U.S. officials to develop relationships, obtain training for their industry and begin structuring their regulations to be compatible with the global market. My discussion at the symposium represented the first formal training on the EU regulatory process for medical devices and IVDs. The Taiwanese Department of Health will be visited by the EU Commission and Notified Bodies in August to continue building relations in these areas.

The Department of Health's offices are located directly across the street from the impressive Chiang Kai Shek Memorial Hall; the view from their 15th floor conference room of the memorial is impressive. I was afforded the opportunity to take a short stroll through the gardens and also view the beautiful national music hall.

Chiang Kai Shek Memorial Hall

Next, I visited the Taiwan Chapter office, met with their staff and prepared for the following day's program. The Taiwan Chapter has a very nice office that includes a very useful library. The Chapter presented me with a Taiwan Chapter bag and a medical news article (in Chinese) announcing the symposium. Unfortunately, the only thing I could recognize in the article was my name!

The June 24th symposium was a great success, drawing approximately 147 delegates from the industry and health authority. Dr. Hsiau-Wen Huang, Senior Researcher, Bureau of Pharmaceutical Affairs and Head of Medical Devices for the Department of Health, assisted me throughout the day by providing expert summaries of the presentations and translating



Symposium for local industry and health authority

questions. The audience was very lively, resulting in excellent question and answer sessions.

The PDA Taiwan Chapter Annual Meeting and Exhibition on Friday, June 25, was another well-attended event with more than 100 professinals in attendance. Presentations were made by a

distinguished group of experts, including Taiwan Chapter President Shinyi Hsu (Otsuka Pharmaceutical Co.) and Taiwan Chapter Relations Representative James Tu (Eli Lilly/Lilly Suzhou Plant). Mr. Hsu outlined the Taiwan

Taiwan Chapter President Shinyi Hsu, Otsuka Pharmaceutical Co.

Chapter's goal to expand its scope beyond pharmaceutical and biopharmaceutical products to include medical devices, IVDs, medical gasses, dietary supplements and herbal products. These medical product industry sectors are on the rise in Taiwan and offer great potential for future industry growth.

Besides chapter business, three excellent technical presentations were made at the Taiwan Chapter Annual Meeting:

- Pharmaceutical Particle Monitoring Regulation, Mark Hallworth, Particle Measuring Systems and frequent lecturer for the PDA Training and Research Institute;
- Isolator Technology, Karl Kaliebe, E2Joy; and
- Latest Techniques in High Level Disinfection Using Hydrogen Peroxide Vapour, Don Bissell, BIOQUELL UK Ltd.

Following my morning at the Annual Meeting, Mr. Hsu and Mr. Tu accompanied me to the Department of Health for an afternoon session with about 25 health officials to discuss EU medical device regulation. In attendance were: Pei-Weng Tu, Section Chief of Medical Devices, Division of Chemistry; Shiow Jane Lin, Chief of Section, Bureau of Pharmaceutical Affairs; Hsiu-Chiung Yen, Senior Officer, Bureau of Pharmaceutical Affairs; and Li-Ling Liu, Senior Scientist, Bureau of Pharmaceutical Affairs, and a PDA Taiwan Chapter board member.

The final enjoyment of my trip was the Taiwan Chapter board dinner held at the beautiful Grand Taipei Palace Hotel. The meal was exceptional, composed of many Chinese delicacies, many of which I had never tried. While it was the first time I have ever had the opportunity to eat duck tongues, I doubt it will be my last!

Entrance to Grand Taipei Palace Hotel

My trip to Taiwan and meetings with the Department of Health were a great success. It is wonderful to see how well PDA and its Chapters cooperate around the globe and the contribution they make to the industry and the health authorities. I look forward to further opportunities to work with the PDA Taiwan Chapter to increase PDA's level of service to this important health care market. I will remember this trip fondly and look forward to my next visit to Taiwan. ■

Tawain PDA Board of Directors

USP Update

New Supplement New Meeting New Submission Guidelines

The *USP 27-NF 22, Supplement 2* was released June 1, 2004 and will become official August 1, 2004 (unless otherwise indicated). Supplement 2 contains 20 new monographs and one new general chapter. The new USP monographs are Clopidogrel Bisulfate; Gadoversetamide and Gadoversetamide Injection; Irbersartan; Ivermectin, Metronidazole Benzoate; Milrinone; Morphine Sulfate Extended Release Capsules; Oxaprozin and Oxaprozin Tablets; Paricalcitol and Paricalcitol Injection; Paroxetine Hydrochloride and Paroxetine Tablets; Camphorated Phenol Topical Gel; Propofol; Quinapril Tablets; and Terazosin Hydrochloride. The new NF monographs are Ammonio Methacrylate Copolymer Dispersion and Maltose. A new general information chapter on Near-Infrared Spectrophotometry, <1119>, was also published in this supplement.

Coming Sept. 27-29, 2004, USP will host its first annual scientific meeting with educational courses in Iselin, New Jersey. The event will focus on products and process standards and represents an ideal opportunity for interested parties to participate in USP standard setting activities. For further information and registration material visit the USP website at: www.usp.org/conferences.

To facilitate the submission of new monographs and chapters, the USP Council of Experts, expert committees, project teams and staff have developed guidelines that define the information required to submit proposals. These guidelines are available at www.usp.org/standards/revisionguideline/index.html.

The May-June 2004 *Pharmacopeial Forum* (PF) has been published. The "In-Process" section contains 27 newly proposed USP monographs and 7 proposed NF monographs. The target is to publish these monographs in *USP 28-NF 24, 1st Supplement*. In addition, one General Chapter, <730> "Inductively Coupled Plasma," and one general information chapter, <1265> "Written Prescription Drug Information—Guidelines," are also proposed and are targeted for the first supplement, as well. Two "Stimuli" articles were also published in the May-June PF: One, "Pepsin and Pancreatin Performance in the Dissolution of Crosslinked Gelatin Capsules from pH 1 to 8" by Jean Gallery et. al., and one by Lynn Torbeck on " Significant Digits and Rounding."

Lastly, USP wants to remind stakeholders that the 2005-2010 revision cycle is rapidly approaching, and that candidates for the various expert committees are encouraged to apply. Information on the expert committees and online applications can be found at www.usp.org. ■

by Roger Dabbah, PhD, USP

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Regulatory Briefs

Important Dates

Aug. 23 Deadline for public comment on **U.S. HHS** program to expedited approval of new drug and biologic products

Aug. 31 **EMEA** API Master File guideline becomes effective

U.S. FDA

FDA Revies Drug Shortage Questionnaire/Web

FDA officials in the Office of Compliance are reviewing the questionnaire and Web site developed by PDA as part of the FDA/PDA Drug Shortage Initiative. The initiative aims to help FDA mitigate the supply disruptions that occur as the result of manufacturing stoppages and suspensions resulting from enforcement actions and other factors.

FDA Issues Guidances on Medical Imaging Drugs

FDA has released three final guidances to help firms prepare and submit applications for medical imaging drugs and biological products (defined as agents used solely to diagnose and monitor diseases or conditions rather than to treat them. Medical imaging agents are generally governed by the same regulations as other drug and biological products. The agents can be classified into at least two categories: contrast agents and diagnostic radiopharmaceuticals, according to the guidances. Links to the guidances are available at www.pda.org/regulatory/RegNewsArchive.html.

Follow-On Biologics Making News

The Biotechnology Industry Organization (BIO) is urging FDA to give all interested parties the chance to participate in a public process before developing a follow-on biologics initiative. In comments posted on the FDA website, BIO requests that FDA engage in an inclusive public process before issuing a scientific draft guidance on approving follow-on biologics. BIO points out that FDA rarely circumvents the public participation phase in guidance development when guidances change or affect long-standing policy positions. The group asserts that a draft guidance is not the appropriate vehicle for changing FDA policy on the approval of follow-on biologics. "The agency should make such a change only after engaging in a public participatory process designed to fully vet the myriad issues presented by this complex subject," BIO said.

Some in the U.S. Senat have other ideas. For example, Sen. Charles Schumer (D-N.Y.) urged FDA to proceed with the draft guidance as expeditiously as possible. "We've got to get the process rolling," he said, noting that the process already has slowed down following the departure of former FDA Commissioner Mark McClellan for a post as head of the Centers for Medicare & Medicaid Services.

FDA is planning a public workshop by early fall to address the scientific issues surrounding follow-on biologics, after which the agency will release its long-awaited guidance on the issue.

As a scientific matter, the FDA believes that for some relatively simple biologic products, the science has progressed sufficiently to where the agency is able to assess the degree of similarity between the innovator and a follow-on product, FDA acting Commissioner Lester Crawford said during a Senate Judiciary Committee hearing.

Prior to publishing a draft guidance document, the FDA intends to hold a major scientific workshop on the issue, Crawford said. The workshop will seek to develop a common understanding about what is needed in order to regulate "follow-on proteins," he said, referring to the FDA-preferred term for the products. ■

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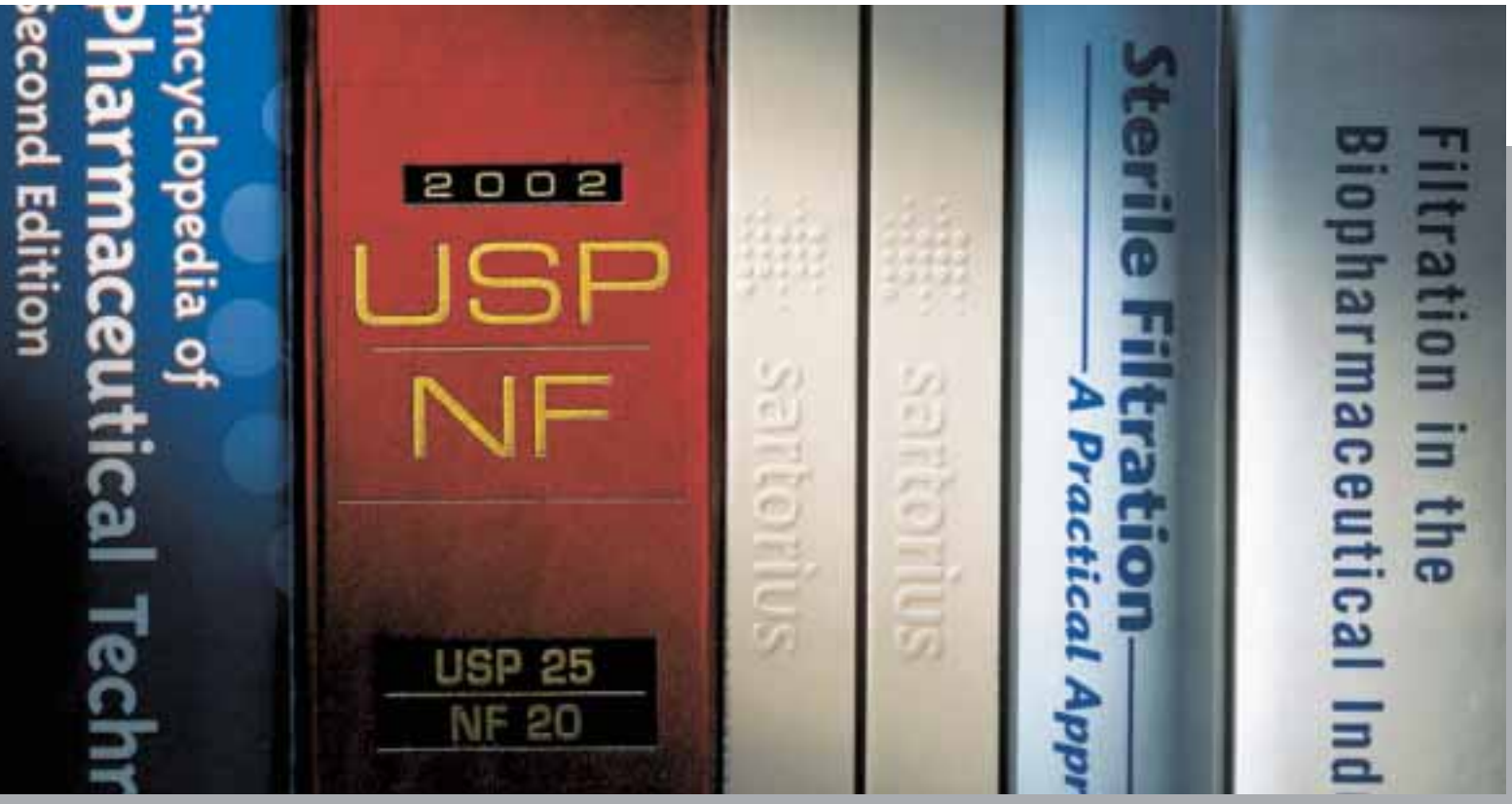

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PDA Chapter Focus: Southern California

Philosopher Marcus T. Cicero said "Before beginning, plan carefully," and the PDA Southern California Chapter plans meticulously.

The Chapter's planning process is ongoing and involves every officer. Chapter officers hold monthly meetings to discuss seminar dates, subjects and guest speakers. The basic planning goal is to host three well-founded events annually. Usually, each event is one day long, save for its annual year-ending dinner seminar held near the holidays every December.

For the holiday dinner, "we try to create a special atmosphere to add holiday spirit with addition of some personal incentives such as raffle prizes," said Chapter Event Coordinator Tarra Roshan (B. Braun Medical).

Guest speakers for the Southern California Chapter events are recruited through many channels, including personal invitations by the Chapter officers and PDA headquarters. The Chapter and prospective guest speakers often mutually agree upon the event, date and subject. Upon establishing the location of the event, flyers are sent out eight weeks in advance with two reminders prior to the day of the event. Typically, speakers provide the chapter with a detailed biography for promotional purposes.

> "This is the first event for us for 2004, but certainly not the last," said Chapter Public Relations Chair Robert Mitchell (B. Braun Medical).

While Chapter officers believe that smaller is better, in some cases the Chapter permits larger audiences. "The Southern California Chapter is not in competition with the larger-scale training institutes," said Roshan. "Therefore, by intentionally trying to keep the cost of the events as low as possible, to the break-even point, we feel that we can encourage more people to come to the events."

The Chapter will hold a dinner seminar September 9, 2004, featuring presentations on the following hot topics: compliance with FDA change control requirements; validation management, and preapproval inspections.

"We're extremely pleased about this meeting," Roshan said.

The Chapter is particular excited about the presentation on preapproval inspections, which will be made by Kenneth Christie, Senior Director, VTS Consultants. "Mr. Christie has over 20 years of experience in QA and Validation Management in the pharmaceutical and biopharmaceutical industries. His responsibilities include quality reviews, training, and execution of validation documentation for aseptic and solid dosage processing equipment, utilities and computer-related systems."

The Southern California Chapter is committed to its three meeting goal for 2004. "This is the first event for us for 2004, but certainly not the last," said Chapter Public Relations Chair Robert Mitchell (B. Braun Medical). "We have an all-day event we are currently scheduling for October 6, 2004. We are also working on another all day event for early November."

Another goal set by the Southern California Chapter for 2004 is to elicit more involvement of PDA members. Plans include increasing the number of Chapter officers (the Chapter currently has seven) so that the duties are more evenly divided, holding elections and improving the Chapter's Web site.

Serving with Roshan and Mitchell as Chapter officers are: President Kikoo Tejwani (B. Braun Medical), President-Elect John Spoden (Allergan), Treasurer and Secretary Maria Wagner (International Medication Systems), Membership Coordinator Juan Cornejo (B. Braun Medical), Site Coordinator Bernice Stein (Independent Consultant) and Public Relations Chair Mike Shahabi (Baxter Healthcare Corporation).

The Southern California Chapter was established to serve the PDA members and the pharmaceutical and biotechnology industry located in Southern California. The Chapter welcomes PDA members in the southern California region who would like to become more involved. Chapter involvement fosters the development of a greater understanding of the industry and expanded professional relationships.

Because the officers continuously plan, they are on a never-ending search for qualified speakers for upcoming events. To suggest a speaker or for more information about the PDA Southern California Chapter, please contact KiKi Coffman, Chapter Coordinator, at coffman@pda.org or visit the Chapter's newly updated Web site at www.pdasc.org. ■

By KiKi Coffman, Chapter Coordinator

2004 CHAPTER EVENTS CALENDAR

Please visit www.pda.org/courses/index.html for lodging, registration, and event description information.

August

19 Midwest
Modern Consideration for Test Method Validation
Northbrook, Illinois

September

2-3 Japan
Education & Training courses: "API GMP & Qualification/Validation," "How to Prepare & Receive FDA Inspection"
Tokyo, Japan

9 Southern California
Compliance with FDA Change Control Regulations & Validation Management
Irvine, Calif.

14 UK & Ireland
Second Open Meeting—The Training Process
Gatwick, England

15 Canada
Free Seminar (topic TBA)
Toronto, Canada

29 Delaware Valley
Aseptic Processing
Malvern, Pennsylvania

29 Capital Area
Topic TBA
Gaithersburg, Maryland

October

1 New England
Workshop on Combination Product Development
Cambridge, MA

6 Southern California
Management Controls/FDA Inspection Planning
Huntington Beach, Calif.

6-7 Central Europe
Visual Inspection Course
Berlin, Germany

18-19 Italy
Biosafety Course
Rome, Italy

October (cont.)

18-19 Central Europe
The Universe of Pre-filled Syringes
Hannover, Germany

19 Israel
Seminar: Process Validation
Tel Aviv, Israel

20 Southeast
Annual Fall Meeting
Research Triangle Park, North Carolina

25 Spain
Science-Based Validation
Barcelona, Spain

27 UK & Ireland
Biotechnology Conference
OSI Pharmaceuticals
Oxford, England

November

9-10 Japan
Japan Chapter Annual Meeting
Tokyo, Japan

17-19 Central Europe
Aseptic Processing Course
Basel, Switzerland

17 Delaware Valley
Environmental Monitoring
Malvern, PA

19 Metro
Current Compliance Trends
Clark, NJ

19 Midwest
Rapid Methods
Northbrook, IL

December

6-7 France
New Success Factors for Bio/Pharmaceutical Manufacturing in Europe
Paris, France

8 New England
Dinner Seminar on PAT
Cambridge, MA

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❑ Individual Membership: ❑ US$195

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Business Environment (check only one)

- ❑ Academic
- ❑ Consultant
- ❑ Engineering and Construction
- ❑ Government Regulatory Agency
- ❑ Industry Supplier
- ❑ Medical Device Manufacturing
- ❑ Pharmaceutical Manufacturing
- ❑ Pharmacy
- ❑ Recruiter
- ❑ Other

Professional Interest (check all that apply)

- ❑ Aerosols
- ❑ Analytical Chemistry
- ❑ Biologicals
- ❑ Biotechnology
- ❑ Computers
- ❑ Engineering
- ❑ Formulation Development
- ❑ GMP Compliance/Inspection Trends
- ❑ Liquids
- ❑ Maintenance
- ❑ Manufacturing/Production
- ❑ Microbiology
- ❑ Ointments
- ❑ Ophthalmics
- ❑ Packaging
- ❑ Parenterals
- ❑ Quality Assurance/Quality Control
- ❑ Regulatory Affairs
- ❑ Research
- ❑ Solid Dosage Forms
- ❑ Sterilization/Aseptic Processing
- ❑ Training
- ❑ Validation

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PDA dues are not tax-deductible as charitable contributions under the Internal Revenue Code of the United States. However, the dues may be deductible as ordinary and necessary business expenses.

3. **Payment Options** (please check one).

❑ A. By **Credit Card** (VISA, MasterCard/EuroCard, American Express, Diners Club), clearly indicating account number and expiration date and billing address. **Proceed to Item 4 below.**

❑ B. By **Bankers' Draft/Check** forwarded together with the application form PAYABLE IN US DOLLARS ONLY to:

PDA, Inc., P.O. Box 79465, Baltimore MD 21279-0465

Please mark here to request a **PROFORMA INVOICE** from PDA to process your company payment. ❑

❑ C. **Wire Transfer Payments**/By bank-to-bank transfer to: (required if paying in foreign currency; prevailing exchange rates at date of submission will apply.)

UBS AG Basel Swift Code: **UBSWCHZH40M**

Account number (please specify correct account number for currency being remitted):

- ❑ CHF: Account No. 292-568-280-01F
- ❑ EUR: Account No. 292-568-280-60Z
- ❑ GBP: Account No. 292-568-280-61W
- ❑ USD: Account No. 292-568-280-62Q
- ❑ YEN: Account No. 292-568-280-63Y

Please reference code: **DUES**

Bank Address:
UBS AG Basel
Postfach
Aeschenplatz 6
4002 Basel, Switzerland

Currency conversions available at: www.forex.com/forex_market_commentary.html

Wire Transfer Confirmation: _____

(insert your confirmation of receipt by UBS Bank here.)

4. **Please check the appropriate box:** Charge: ❑ MasterCard/EuroCard ❑ VISA ❑ AmEx ❑ Diners Club

Account Number: _____ Exp. Date: _____

Name *(exactly as on card)*: _____

Signature: _____ Date: _____

Billing Address: _____

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PDA USE:
Date: _____ Check: _____ Amount: _____ Account: _____

New member contact information is forwarded to Chapters on an ongoing basis. For immediate notification of Chapter events, please contact your local representative and ask to be placed on the Chapter mailing list.

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2005 PDA International Congress, Courses and Tabletop Exhibition

February 28 - March 2, 2005 • Cavalieri Hilton • Rome, Italy

Bringing Practicality to Science?

by program committee co-chairs James Lyda, PAREXEL Consulting, and Claudio Pugliese, S.I.F.I.

Those of you who were PDA members in the late 1980's may remember the PDA coffee cup with the words "Bringing Practicality to Science" emblazoned on it. We don't know who invented that motto, or what they were thinking, but we owe that person a debt of gratitude. Over the years there have been many discussions, sometimes over beer or wine at a PDA reception, about what those words mean. Is science somehow detached from from the practical world? Does practicality somehow suggest a retreat from the rigors of science? Everyday we apply science to real world problems and opportunities in the realms of chemistry, biology and physics. From this we create life-saving, life-enhancing medical products which are distributed around the world to those we know and love, and to those whom we will never see. What a business to be in!

2005 PDA International congress Planning Committee

The world changes fast, and our industry has changed along with it. Today we are all under pressure to produce efficiently and rapidly, while maintaining quality. It is a competitive market where mistakes can be expensive or even life-threatening. Society expects our industry to produce more and better products to improve the quality of life, and to do it with minimal risk to the patient. In a modest, but significant shift, the regulators seem to understand that they share a responsibility in the health and robustness of our industry. Regulatory hurdles continue to increase, and GMP & quality expectations demand zero defects with every possible outcome predicted and planned for. And it all has to be documented! Those of us who see the inside of this business realize how difficult it is to bring a drug to market, and then to make manufacturing changes which capitalize on manufacturing experience.

Today we are seeing innovation initiatives both from FDA and the EMEA. These initiatives seem to reflect the recognition that the system, our system, for drug regulation may have become too stiff, too rigid. We see fewer drugs in the pipeline and companies continuing to battle with the regulators over quality. Both the EMEA and FDA initiatives invite dialogue on this situation. FDA's Risk-Based GMP Initiative is another example of an effort to change the recipe, to offer the industry an opportunity to innovate and grow. In effect, we believe the regulators are inviting us to bring practicality back into science; or should we say science back into practical decision making. It is up to us in the industry to move forward with the opportunity we have.

On behalf of PDA and the volunteer planning committee (see photo), we invite you to join us next March in Rome at the PDA 2005 International Congress. There we will discuss 'Bringing Practicality to Science' together. ■

PROGRAMS AND MEETINGS CALENDAR

Please visit www.pda.org/courses/index.html for lodging, registration, and event description information.

2004

September

7-8 PDA/BFS Inter'l. Operators Association Joint Workshop on Blow/Fill/Seal Processing
Holopack Verpackungstechnick GmbH, Germany

9 PDA Audio Conference: GERM 3: Models Document

15 PDA Audio Conference: Update to PDA TR#32: Auditing of Suppliers Providing Computer Products and Services for Regulated Pharmaceutical Operations

20-24 2004 PDA/FDA Joint Reg. Conf., Courses & Tabletop Exhibits: The New Guidances
Omni Shoreham Hotel, Washington, D.C.

2005

February/March

28-2 PDA International Congress, Courses & Exhibitions
Rome, Italy

April

4-8 PDA Annual Meeting, Courses and Exhibitions
Hyatt Regency, Chicago, Illinois

May

16-18 PDA Viral Safety Conference
Hyatt Regency, Bethesda, Maryland

September

12-16 2005 PDA/FDA Joint Reg. Conf., Courses & Tabletop Exhibits
Washington, D.C.

October

10-11 Taormina Conference
Taormina, Italy

PDA/FDA Joint Regulatory Conference Exhibitors

ACCUGENIX
American Stelmi
Applied Biosystems
BD Diagnostics
bioMerieux, Inc.
BioScience International
Cambrex Bioscience Walkersville, Inc.
Carlisle Life Sciences
Charles River Laboratories
Clarkston Consulting
Document Control Systems
Drumbeat Dimensions, Inc.
General Physics
Genesis Machinery Products
ITW Texwipe
Lloyd's Register Serentec
MDS Pharma Services
Millipore Corporation
NovaTek
Noverant
Pall Life Sciences
Parexel Consulting
PharmaSys, Inc.
Phoenix Imaging
PML Microbiologicals
Prudential Cleanroom Services
PSI
Quality is Learned, Inc.
Qumas
RCM Technologies
Sartorius Corporation
Sparta Systems, Inc.
Stelex
Vectech Pharmaceutical Consultants, Inc.
Veltek Associates, Inc.
Virtis an SP Industry Company
VTS Consultants, Inc.
Working Words

2004 TRAINING AND RESEARCH INSTITUTE CALENDAR

Please visit www.pda.org/courses/index.html for lodging, registration, and course description information.

Laboratory Courses

August

16-20 Aseptic Processing Training Prgm: Week 1

September

1-3 Adv. Environmental Mycology Workshop

13-17 Aseptic Processing Training Prgm: Week 2

October

4-8 Aseptic Processing Training Prgm: Week 1

14-15 Fundamentals of D, F, and z Value Analysis

18-22 Rapid Microbiological Methods

25-27 Designing, Operating, and Controlling High Purity Water Sys for Regulatory Compliance

November

1-5 Aseptic Processing Training Prgm.: Week 2

11-12 Developing and Validating Cleaning & Disinfection Prgms for Controlled Envn.

15-17 Cleaning Validation

17-19 Practical Aspects of Aseptic Processing
University of Basel
Basel, Switzerland

18-19 Remediation of Existing Computer Systems

December

2-3 Environmental Mycology Identification Workshop

6-7 What You Need to Know to Select Adequate Thermal Validation Equipment

Lecture Courses

August

23-27 CGMP Trainer's Qualification Prgm
PDA-TRI, Baltimore, Maryland

September

7-8 PDA-BFS Joint Workshop on Blow/Fill/Seal Processing
Schwabish Hall
Sulzback-Laufen, Germany

October

26-27 21st Century cGMPs: A Risk/Science-Based Approach to Validation
PDA-TRI, Baltimore, Maryland

December

6-7 Computer Products Supplier Auditing Process Model: Auditor Training

Course Series

August-September

30-1 Chicago, Illinois

A Comprehensive Guide to OOS Guidance & Regulations
A Practical Approach to Aseptic Processing & Contamination Control
Assessing Packaging & Processing Extractables/Leachables
Pharmaceutical Water Sys: A Practical Approach
Preparing for an FDA Pre-Approval Inspection
CGMP & Compliance
Application of Clean-In Place to the Pharmaceutical Industry
Environmental Monitoring in Pharmaceutical Manufacturing
Risk Management
Z1.4 Attribute Inspection Sampling in a GMP Environment

September

20-24 2004 PDA/FDA Joint Reg. Conference, Courses and Tabletop Exhibits
Washington, DC

Change Control & Documentation
Auditing Pharmaceutical Microbiology Laboratories
Basic Concepts in Cleaning & Cleaning Validation
Compliance Auditing of Cleanrooms and Controlled Environments
API: Qualificatin and Validation of API Facilities and Processes
Auditing Techniques for CGMP Compliance

October

18-20 Boston, Massachusetts

Analytical Problem Solving for CAPA Sys.
Design and Validation of a Cleaning & Disinfection Prgm
Intro. to Writing and Auditing CGMP Doc.
CGMPs for Bioprocesses
Pharmaceutical Water Sys. Design & Validation
Maximizing SOPs - An Untapped Resource of Trng. Solutions
Everything You Wanted to Know About Environmental Monitoring but Were Afraid to Ask
Qualification and Validation of API Manufacturing Ops.
Achieving CGMP Compliance During Development of a Biotechnology Product
Annual Product Reviews: How to Comply with FDA & ICH Req.

PDA Training and Research Institute Registration Form

R
LTR 08/04

1. **Please type or print your name, address and affiliation.**

Preferred Address: ❑ **Business** ❑ **Home**

❑ Mr. ❑ Ms. ❑ Dr. First Name | Middle Initial | Last Name

Job Title | Membership Number

Company/Organization

Address

City | State/Province | ZIP+4/Postal Code

Business Phone | Fax | E-mail

❑ Substituting for _____
(Check only if you are substituting for a previously enrolled colleague; a nonmember substituting for member must pay the additional fee.)

Were you referred to this event by a PDA Chapter? ❑ Yes ❑ No If so, which Chapter? _____

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✓ Gain access to expert, peer-reviewed information relevant to your career

✓ Become a part of the world's leading international network of pharmaceutical and biopharmaceutical professionals.

Check below to become a PDA member:

❑ **Individual membership fee: US$195** (one year)

❑ **Special discounted government/health authority fee: US$80** (one year)*

* Must be an employee of an official government agency or health authority

For more details on PDA and the benefits of becoming a member, visit www.pda.org today.

2.

Course Title/Course No.	Date	Current Member	Join PDA and Attend Course	Attend Course Only; Do Not Join PDA	Government/Health Authority Employee *

* *You must be an employee of an official government agency or health authority to qualify for this rate.*

TOTAL _____

Deadline: Enrollment is limited for the benefit of all attendees; this necessitates early registration. Paid registrations must be received one week prior to the event. **Confirmation:** Written confirmation will be sent to you once payment is received. You must have this written confirmation to be considered enrolled in a PDA event. Please allow one week for receipt of confirmation letter. **Substitutions:** If a registrant is unable to attend, substitutions are welcome and can be made at any time, even on-site up to the time of the course. If you are pre-registering as a substitute attendee, indicate this on the registration form. **Refunds:** Refund requests must be in writing. If received one month prior to the start of an event (course series, conference, etc.), a full refund, minus a US$55 handling fee, will be made. If received two weeks prior to the event, one-half of the registration fee will be refunded. After that time, no refunds will be made. **Event Cancellation:** PDA reserves the right to modify the material or instructors without notice or to cancel an event. If an event must be canceled, registrants will be notified as soon as possible and will receive a full refund of fees paid. PDA will not be responsible for discount airfare penalties or other costs incurred due to a cancellation. **For more details, call PDA at +1 (301) 656-5900.**

3. **Payment Options** (please check one).

❑ A. By **Credit Card** (VISA, MasterCard/EuroCard, American Express, Diners Club), clearly indicating account number and expiration date and billing address. **Proceed to Item 4 below.**

❑ B. By **Bankers' Draft/Check** forwarded together with the registration form PAYABLE IN US DOLLARS ONLY to:

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Please mark here to request a **PROFORMA INVOICE** from PDA to process your company payment.[1] ❑

[1] You are not considered registered for a PDA course until payment is received and a confirmation letter is issued by PDA. Should you attend a course without a formal confirmation or receipt of payment you will be required to provide a credit card as guarantee of payment at the time of the course.

❑ C. **Wire Transfer Payments**/By bank-to-bank transfer to: (required if paying in foreign currency; prevailing exchange rates at date of submission will apply.)

UBS AG Basel Swift Code: **UBSWCHZH40M**

Account number (please specify correct account number for currency being remitted):

❑ CHF: Account No. 292-568-280-02T
❑ EUR: Account No. 292-568-280-64B
❑ GBP: Account No. 292-568-280-65E
❑ USD: Account No. 292-568-280-66M
❑ YEN: Account No. 292-568-280-67C

Please reference code: **2-2-2000**

Bank Address:
UBS AG Basel
Postfach
Aeschenplatz 6
4002 Basel, Switzerland

Currency conversions available at: www.forex.com/forex_market_commentary.html

Wire Transfer Confirmation: _____
(insert your confirmation of receipt by UBS Bank here.)

4. **Please check the appropriate box:** Charge: ❑ MasterCard/EuroCard ❑ VISA ❑ AmEx ❑ Diners Club

Account Number: _____ Exp. Date: _____

Name *(exactly as on card)*: _____

Signature: _____ Date: _____

Billing Address: _____

Federal Tax I.D. #52-1906152

5. **RETURN COMPLETED FORM WITH CHECK OR BANK DRAFT MADE TO:** PDA, P.O. Box 79465, Baltimore, MD 21279-0465 USA **FAX CREDIT CARD REGISTRATIONS TO:** +1 (301) 986-1093 (credit cards only)

PDA USE:
Date: _____ Check: _____ Amount: _____ Account: _____

ARC Accepts Audits for Aegis Software

By: Mark Johnson, Aegis, and Harvey F. Greenawalt, ARC

The Audit Repository Center (ARC) has informed Aegis Analytical Corporation that a vendor audit report from a top-five global pharmaceutical manufacturer has been submitted to and accepted into the repository for Aegis' Discoverant GlobalVantage software suite. The inspection was conducted earlier by PDA certified auditors at two of the pharmaceutical company's manufacturing sites using the standardized process defined in PDA Technical Report #32. The process is widely recognized as one of the most stringent in the industry.

"Passing this audit, and having it accepted into the ARC is a testament to Aegis' continued commitment to quality," said Mark Johnson, head of quality for Aegis. "We expect that other pharmaceutical manufacturers will want to obtain a copy from ARC, rather than incur the additional cost of performing their own audits of Aegis when they acquire our Discoverant software suite."

PDA developed the concept of a global central repository to maintain audit information based upon its Supplier Audit Process Model, in response to FDA requests to standardize the supplier audit process for computer products and services as well as establish a centralized audit information-sharing venue. The model establishes a standardized framework for conducting supplier audits that reduces costs, inconsistencies and redundancy. ARC is the PDA-licensed service provider for the repository.

Discoverant GlobalVantage is a manufacturing enterprise software suite that helps companies get single point, direct access to all of the data collected in many locations throughout the manufacturing enterprise, in a user environment that allows decision-makers to quickly translate data into useable intelligence. The unbundled product configuration enables manufacturers to reap additional benefits from already implemented data collection systems while implementing a centrally administered enterprise platform architecture that allows for growth and flexibility. The Discoverant GlobalVantage software suite is validation-ready, and it is built to meet or exceed the requirements for Good Automated Manufacturing Practices (GAMP).

About Aegis Analytical Corporation

Aegis Analytical Corporation provides manufacturing software and expertise that helps pharmaceutical and biotech companies improve compliance, increase profits and gain competitive advantage. Discoverant GlobalVantage, an enterprise software application, gathers data from multiple sources and quickly transforms it into useable intelligence. More information about Aegis Analytical Corporation can be found at www.aegiscorp.com. For a streaming video demonstration of Discoverant GlobalVantage, visit www.aegiscorp.com/product/demo.asp.

About ARC

For more information about the audit repository, audits and their availability, visit ARC's Web site at www.auditcenter.com. ■

AVAILABILITY of AUDITS

Currently Sixty-two (62) audits are either under consideration, in process or available for distribution. Thirty audits are available for immediate distribution. The following is a partial list of available audits.

Supplier Name	Supplier Product
Access360, Inc.	enRole 4.0 (provisioning software
Agilent Technologies	**Cerity for Pharmaceutical QA/QC. Network data system for analytical laboratories**
Alacris, Inc.	idNexus
Applied Biosystems, Inc.	**SQL*LIMS™ Software - Laboratory Information Management System**
Automation Tooling Systems, Inc.	Custom programming services for process control software
Axalto, Inc	**Cyberflex Palmer Smart Card and Cyberflex Access Intergration Kit**
Decision Management International, Inc. (DMI)	Regulus(tm) Document Authoring (DA) a member of the Regulus(tm) off-the-shelf solution set

Docent	**Docent Learning Management Server** **Docent Content Delivery Server**
Documentum, Inc.	Administrator Application Builder Content Authentication Services (CAS) Control Manager (DCM) DeskTop Desktop for Macintosh Digital Asset Manager DocApp Installer eContent Server GXPharma Media Services Records Manager (RM) Release 3.1 and 3.1.1 Web Development Kit WebDAV Server Website Manager WebTop Workflow Manager
Epicentric, Inc.	**Foundation Enterprise Server 4.0, which is a tool for coordinating information from disparate sources and for disparate uses.**
First Consulting Group, Inc.	Custom information based strategy software, operations improvements, management and integration services
Fisher-Rosemount Systems, Inc.	**Distributed factory automation, Delta V product line**
GE Kaye Instruments, Inc.	Thermal validation systems, monitoring systems, thermocouple references and turbine temperature monitoring equipment–LabWatch™, ValProbe™ and the Validator®2000 systems
IBM	**Content Manager (CM) v8.2**
Inktomi Corporation	Inktomi Enterprise Search.
Innovatum, Inc.	**DataThread™ - Data audit, workflow, 21 CFR Part 11 and E-signature solution for AS/400 applications, without programming changes**
Lexign Corporation	Lexign Flow™ EPR Software
Merant	**PVCS Dimensions & PVCS Replicator Software Configuration Management Tool**

New Technical Publications Available!

PDA is your source for technical publications produced jointly with industry experts and regulatory bodies, providing the most current scientific, technical and regulatory information you need for success.

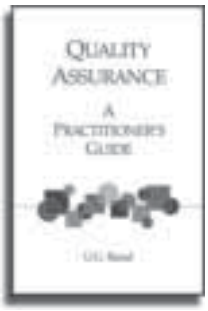
"Quality Assurance: A Practitioner's Guide"

U. G. Barad

"It is for the workforces who are responsible for the make-or-break decisions in a pharmaceutical company – both quality and quantity – that this book is written. **This book...provides the keys to quality**."

Professor Hamad A. Al-Khamees, M.S. (USA), Ph.D. (England)

Professor of Medicinal Chemistry
King Saud University, College of Pharmacy
Saudi Arabia



Item No. 17212
US$185 Member
US$229 Nonmember

In ***Quality Assurance: A Practitioner's Guide***, Dr. U.G. Barad offers a compilation of more than 20 years of practical experience gained by working with leading multinational pharmaceutical companies and with various regulatory agency requirements. Dr. Barad approaches this important topic with great detail, covering most of the regulatory requirements and expectations prevailing worldwide.

This book is ***an indispensable tool*** for students and beginners and experienced professionals working in large and small pharmaceutical companies.

About the author

U.G. Barad, M.Pharm, Ph.D., has been associated with multinational and leading edge pharmaceutical companies for over 20 years in quality assurance, quality control, direction of validation activities, and management of regulatory compliance, documentation, and operations. He has also been responsible for framing and approving quality policies, guidelines, procedures and SOPs. He is the recipient of PDA's Distinguished Author 2004 award for his two previous books: The Essence of GMPs and Excellence Through Validation.

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The descriptive models presented are a collection of enhanced activities for systems engineering that stress a focus on informational objects when describing and managing system context, architecture/design, and system implementation and remediation. Implementation activities are applicable for custom software products and implementations based on configuring commercial-off-the-shelf (COTS) technology. Remediation activities are applicable to bringing existing operational environments to the level of current expectations for good electronic record management.

The models described have two approaches:

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This document includes a glossary and list of references.

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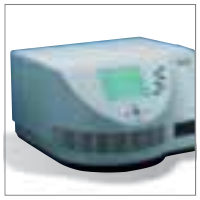

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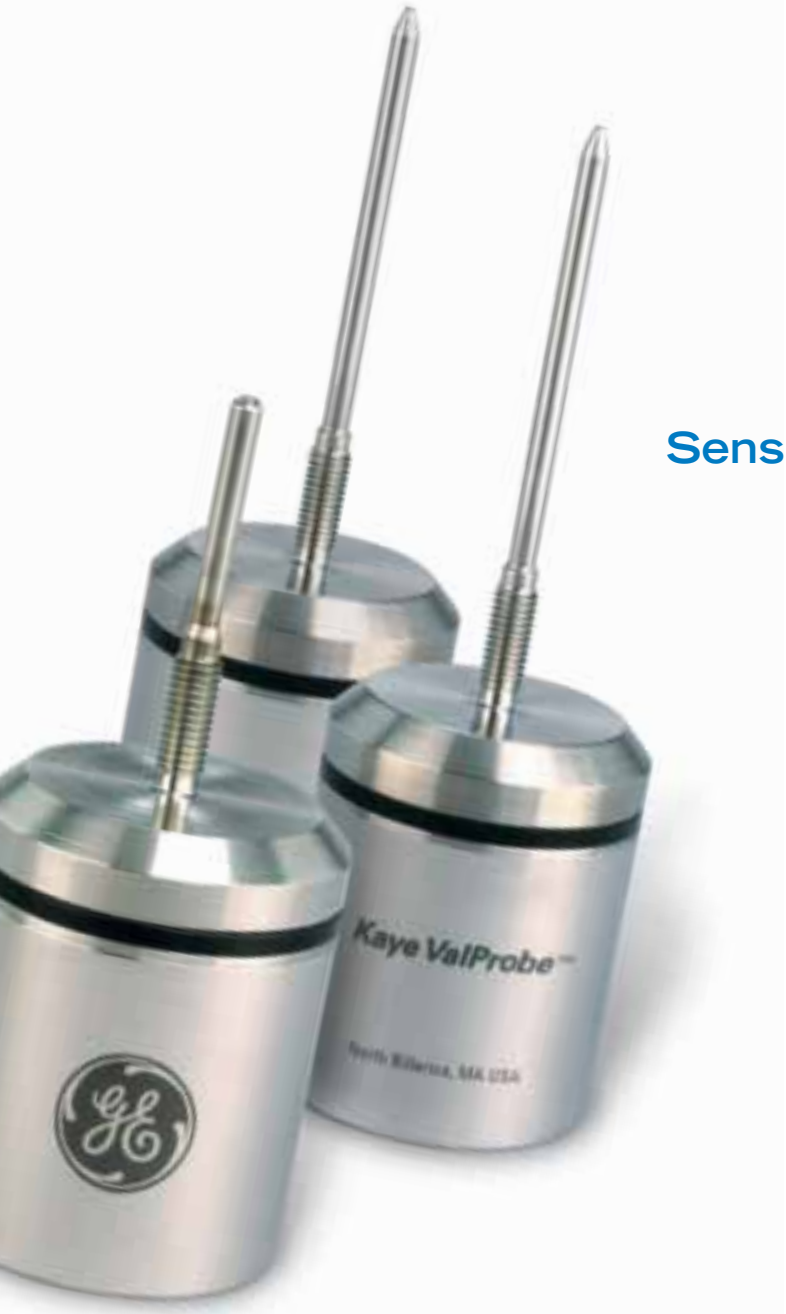

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