Volume XXXVII, No.2

PDA Letter

February 2001

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

FDA Proposes New Rules for Good Tissue Practice, see page 11

TSE Risk for Medicinal Products Marketed in Europe

Strasbourg Conference Outlines Status and Limitations of the System
March 1, 2001 is Certification Deadline!

by James C. Lyda, PDA Europe

Note: On January 11, 2001 a capacity crowd attended a conference in Strasbourg, France entitled, "Certification for TSE Risk Products." The event was organized on short notice by the European Directorate for the Quality of Medicines (EDQM), publisher of the European Pharmacopoeia (Pharm. Eur.), at the request of the EMEA (The European Agency for the Evaluation of Medicinal Products) and the national drug regulatory authorities in Europe. The purpose of the conference was to discuss the status of the European certification system for drug products from animal origin, issues surrounding the implementation of the program and related topics.

The following report is based on notes taken during the conference. While every attempt has been made to maintain accuracy, readers should rely on the official transcript, to be published by EDQM, as the definitive report on the conference. Additional information may be obtained from the EDQM Web site at www.pheur.org and EMEA's new Web site at www.emea.eu.int. For specific information regarding the certification procedure, contact EDQM at certification@pheur.org. For information regarding the European Federation of Pharmaceutical Industries and Associations' (EFPIA) TSE survey, visit www.efpia.org. Thanks are in order to Brian Matthews, Alcon Laboratories, London, for technical assistance.

continued on page 4

Spring Conference 2001

Modern Pharmaceutical Microbiology: Advancing the Science

March 11–16, 2001
Aladdin Hotel
Las Vegas, Nevada

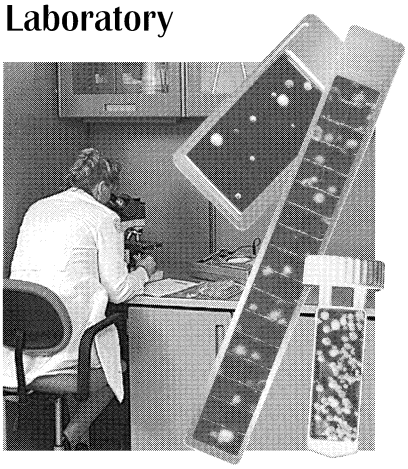
FDA CBER Briefing Added March 11 See page 28

Register today to be with PDA for this exciting conference which will be hosted at the new Aladdin Hotel in Las Vegas, Nevada this coming March. Plan on discovering the latest advances in modern pharmaceutical microbiology as you dramatically expand your international scientific networks.

Sessions will focus on a broad range of important pharmaceutical and scientific topics including aseptic processing, cleaning validation, environmental monitoring, GMPs, 21 CFR Part 11, and changes to the USP, isolator technology, quality auditing, rapid methods in microbiology, stability, sterilization, and sterility and LAL testing. Plenary sessions are designed to include 20-minute presentations by industry experts with opportunities for interactive question-and-answer periods.

continued on page 28

Contract Microbiology Laboratory



Biotest Diagnostics Corporation has a certified microbiology laboratory available providing quantitative and qualitative analysis of your environmental samples.

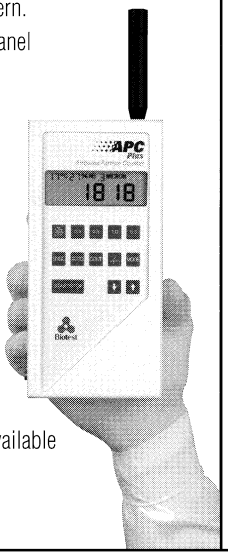
- Microbial identifications of bacteria, yeast and mold to genus/species
- 10 day turnaround time
- "Perfect Score" participant in the EMPAT Program
- Confidential reports for total plate/strip counts and cfu/volume of air
- Consultation with expert Microbiologists on staff
- Free shipping when using Biotest test slides and strips

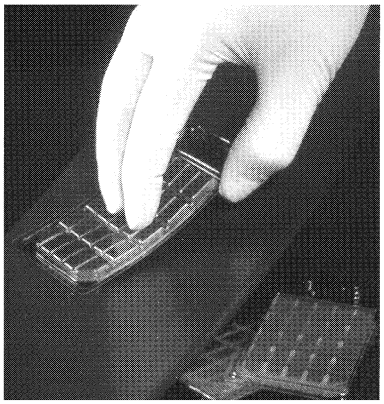
APC Plus

Airborne Particle Counter

Convenient, economical and entirely portable particle counter detects the presence of airborne contaminants. Accurately and simultaneously measures four particle size ranges: 0.3, 0.5, 1.0 and 5 µm. Can be used to monitor controlled environments where particulate contamination is of concern.

- User friendly control panel
- Programmable count and hold times
- Meets JIS for counting efficiency
- Two concentration modes– particles/ft^3 and particles/liter
- Temperature and RH sensors built-in
- Easy to use software included
- Remote and facility monitoring software available





HYCON® Contact Slides

Monitoring liquids and ambient air is not sufficient for most products and processes. Surface monitoring is a must and is recommended in HACCP, ISO and USP guidelines. HYCON® Contact Slides detect surface viable contamination that may adversely affect your product or process.

- Flexible self-contained culture-medium-coated slides ensure surface contact
- Excellent for irregular surfaces
- Provides a 25 cm^2 contact surface
- Various agar media available

Biotest HYCON® RCS High Flow Microbial Air Sampler

The RCS High Flow Microbial Air Sampler allows you to monitor contaminants in any area where reproducible results are necessary. The RCS High Flow monitors air quality—

Faster—the RCS High Flow has an air flow rate of 100 liters per minute, reducing sampling time to 10 minutes for 1 m^3.

Easier—the upgraded infrared remote control with a newly designed keyboard panel and integrated display transmits and receives data from the instrument up to a distance of 10 m.

Better—the rotor, protection cap, and air direction ring are all detachable, easy to clean and autoclavable, allowing less margin for contamination when sampling in any environment.

The instrument is portable and precise and with the use of Biotest HYCON® agar media strips, results are always reproducible. Whether you are monitoring the microbiological quality of ambient air, testing your air handling equipment, or checking on the results of decontamination efforts, you'll find the RCS High Flow to be an effective, reliable sampling device.

Call us at 800-522-0090 for more information.

CE Biotest DIN EN ISO 9001 HYCON

Biotest

BIOTEST DIAGNOSTICS CORPORATION
66 Ford Road, Suite 131, Denville, New Jersey 07834
Phone: (973) 625-1300 • (800) 522-0090 • Fax: (973) 625-9454
www.BiotestUSA.com

PDA
7500 Old Georgetown Road, Suite 620
Bethesda, MD 20814 USA
Tel: (301) 986-0293 Fax: (301) 986-0296
E-mail: *info@pda.org*
www.pda.org

PDA Training & Research Institute
c/o UMBC Technology Center
1450 S. Rolling Road
Baltimore, MD 21227 USA
Tel: (410) 455-5800 Fax: (410) 455-5802

PDA Europe Office
Postfach 620
CH-4144 Arlesheim, Switzerland
Tel: +41 61 703 1688 Fax: +41 61 703 1689
E-mail: *lyda@pda.org*

The ***PDA Letter*** is published monthly by PDA, exclusively for PDA members. Subscriptions are not available.

PDA President
Edmund M. Fry

Director, Communications & Marketing
Linda M. Williams

Editor/Web Editor
Joseph G. Bury

Manager, Publications & Production
Janet Raysick

PDA Letter

Important Deadlines...

- **March 5, 2001—written comments on Draft Guidance for Industry on Recommendations for Complying with the Pediatric Rule, see page 10**
- **Finalize your plans to attend the 2001 PDA Spring Conference in Las Vegas, Registration Form on page 32**

IN THIS ISSUE...

TSE Risk from cover

Copies of the EDQM conference materials are available from PDA pending the issuance of the final conference proceedings. (See "Technical and Regulatory Resources Available," referenced in the Table of Contents elsewhere in this Newsletter, for a list of available documents.) In addition, copies of PDA technical information on cleaning and cleaning validation, discussed later in this article, are also available from PDA. (Refer again to the "Technical and Regulatory Resources Available" section of this Newsletter.)

Below is a summary of the Strasbourg Conference highlights, arranged by major topic.

I. Legal aspects and guidance development

M. Robert, DG III, *European Commission, Brussels*
Dr. John Purves, *EMEA, London*
Prof. D. H. Calam, *European Pharmacopoeia, Strasbourg*
Dr. W. F. van der Giesen, *Medicines Evaluation Board, Netherlands*

"...by March 1, the Medicines Evaluation Board of the Netherlands will have to apply the terms of the TSE directive to 10,000 nationally authorized products registered by 350 companies..."

Industry requirements on Transmissible Spongiform Encephalopathy (TSE) for pharma products started with European Commission Decision 97/534/EC, July 1997. This decision was hence recognized to be too strict and would have adversely affected the majority of the medicinal products sold in Europe. The original decision was subsequently repealed and replaced by Commission Decision 2000/418/EC, June 2000, which specifically excludes cosmetics, medicinal products and medical devices.

Medicinal products came under specific coverage with EC Directive 1999/82/EEC September 1999, and EC Directive 1999/104/EEC, December 1999, covering requirements for human use and veterinary use products, respectively. The effect was to modify directive 75/311/EEC by adding paragraph C.a. which requires that "the applicant must demonstrate that the medicinal product is manufactured in accordance with the Note for Guidance (NfG) on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products." In addition, the directives require that all Members States (1) assure that marketing applications received after July 1, 2000 comply with the directive, and (2) all existing marketing authorizations for medicinal products comply with the directive by March 1, 2001.

Manufacturers may choose to use the EDQM certification procedure. If successful, it would be treated as a Type I variation. This is the preferred method, as it lessens the review time. As an alternative, manufacturers can submit separate scientific data, in which case it would be treated as a Type II variation. A number of Type II variations have been submitted and industry participants offered a number of explanations for these results (see questions and comments below). For products under the centralized procedure, the first variations were received by the EMEA in late 2000 and a large number have been received in November and December.

The following products for human use are currently exempt from the TSE procedures: milk and milk products derived only from milk; and derivatives of wool and hair (lanolin, wool fat, etc.) providing they are taken from live animals. (There is a concern about cross-contamination from dead animal sources.)

In June 1999, The European Pharmacopoeia proposed a new general monograph and general chapter 5.2.8 on TSE risks and expanded the scope of the existing certification scheme which had been implemented in 1994 for regular compendial certifications. In January 2000, the general monograph and general chapter became effective. Chapter 5.2.8 reproduces verbatim the CPMP Note for Guidance on minimizing TSE risk. Under existing treaty, the European Pharmacopoeia and the new monographs and chapters apply to all 27 member countries of the convention, not just the 15 Member States of the European Union (EU).

The implementation of the TSE directive not only places tremendous burden on the pharmaceutical and supplier industry, but places a similar burden on the national authorities of each Member State of the EU. For example, by March 1, 2001, the Medicines Evaluation Board (MEB) of the Netherlands will have to apply the terms of the directive to 10,000 nationally authorized products registered by 350 different companies, or Market Application Holders (MAH). To do this, each MAH will have to check the origin of all of their starting materials and provide proof of compliance with the new TSE requirements by either the EDQM certificate or submission of detailed information to the MEB as a Type II variation. The MEB currently has received about 50 such variations.

The regulatory problem is that there is no approval system for 'starting materials' in the EU (only for 'finished products'). Therefore, for each medicinal product, the MAH has to provide proof of compliance with the TSE requirements. This could result in multiple repetitions of providing authorities with the same information. The EU Commission agreed in March 2000 that multiple submissions of the same information should be avoided where possible and the use of EDQM TSE certificates should be encouraged.

To comply with the directive, the MEB of the Netherlands issued a letter to all MAHs in May 2000 requesting that all medicinal products be listed as follows: (1) products with starting materials with TSE risk and for which EDQM certificates are available; (2) products with starting materials with TSE risk for which a certificate is not available; and (3) products with no starting materials with TSE risk (as defined in section 2 of the NfG). Each MAH was asked to submit the listing by December 1, 2000, along with a signed declaration that all registered products were included in the lists. The MEB is archiving all of the certifications in their database of registered products. In addition, all assessment reports by MEB on TSE will be made available to the other EU Member States electronically, in English, via Eudratrack mail box. Similar actions are being conducted in the other EU member states.

II. Scientific issues and implementation of the directives

Prof. J.H. Trouvin, *Biotechnology Working Party (BWP), EMEA, London*
Prof. P.P. Pastoret, *Immunology Working Party (IWP - Veterinary), EMEA, London*
Dr. A. Artige, *EDQM, Strasbourg*
Dr. C. Pouget, *EDQM, Strasbourg*
Dr. Harold Tietz, *Lilly (Deutschland), representing EFPIA*
Dr. Sol Ruiz, *Agencia Espanola del Medicamento, Madrid*

The TSE directive provides the pharmaceutical manufacturer some guidance in how to approach the TSE risk assessment of materials used in production. The safest choice is to choose non-ruminant animal source materi-

als, or avoid animal materials altogether. Where this is not possible there are several parameters which the manufacturer can use:

A. Geographical origin—by category, based on Scientific Steering Committee (SSC) criteria.
   1. Source country with no-BSE/TSE cases—e.g Argentina;
   2. Countries with no case reports, for which there is a higher possibility—e.g. Finland, Sweden, USA, Canada;
   3. Countries with average to high cases—e.g. most other countries in Europe; and
   4. Countries with high frequency of cases—e.g. UK and Portugal.

B. Age of animal—Younger animals are encouraged for use whenever possible.

C. Animal parts used—four categories based on WHO.
   1. High risk—e.g. brain;
   2. Medium risk—e.g. spleen, proximal ileum;
   3. Low risk; and
   4. Not detectable—e.g. milk products from milk only.

D. Manufacturing process—The choice and design of the manufacturing process can have a bearing on the TSE risk. This may particularly be valuable to avoid cross-contamination and to possibly reduce or eliminate the TSE agent. The impact of the manufacturing process is difficult to determine as the TSE agent can't be readily destroyed and there is incomplete evidence that it can be reliably removed. Process validation studies are required only if the manufacturer claims the process removes or inactivates the TSE agent.

It is the responsibility of the pharmaceutical manufacturer to select adequate measures. There appears to be a consensus that the careful selection of the source of animal and animal products, particularly by geographic basis, is the most reliable method to assure TSE suitability. It is important to have a system for the traceability of the animal source materials used in manufacturing and it is the responsibility of the drug manufacturer to audit the supplier.

There are currently two classification systems for countries with BSE cases: The Scientific Steering Committee (SSC) of the EU Commission, which may be found at http://europa.eu.int/comm/food/fs/sc/ssc/outcome_en.html and the Office of International des Epizooties (OIE), France, which can be found at www.oie.int/eng/info/en_esb.htm.

EFPIA has conducted a survey of its members on experiences with TSE certification. The results will be posted on the EFPIA home page (www.efpia.org). Industry concerns on TSE risk procedures include:

1. Most producers of products requiring certification are not normally regulated and are not used to preparing the type of information needed in a dossier;
2. Will pending certs be available form EDQM by March 1?;
3. The certification procedure will be undermined if EMEA asks for additional TSE safety information for centralized products, not fully accepting the EDQM certs;
4. The EMEA and some of the national authorities have slightly different tables to be completed by the MAH; and
5. A retrospective certification may not be possible—i.e. a finished product, now in stock, which was made from uncertifiable material.

- **Veterinary Issues**

The CVMP note for guidance on veterinary products differs slightly from the CPMP counterpart, the main reason being the absence of species barrier (i.e. sheep have been shown to contract BSE) and the fact that many animal drugs are administered via the parenteral route. Therefore the risk may be greatest when bovine or ovine materials are used in products intended for either ovine or bovine animals. In the CVMP guidance there is no exemption for milk and milk products, but wool and hair are excluded.

Veterinary vaccines are a large part of the veterinary medicinal products (estimated at 25%) and the status of old master seeds need to be addressed. The CVMP will be issuing a position paper very soon which addresses the issue of master seed materials used in production of vaccines.

The development of rapid immunological detection tests for use in the field is an important area of development. Current tests are from: Prionics (Western blotting), Enfer (Elisa) and Biorad (Elisa). The Biorad test shows a detection sensitivity significantly higher than the other tests. Using such tests a Swiss survey demonstrates that preclinical cases of BSE can be detected. A French survey of 15,000 animals showed detection in 2.1 of 1000 animals tested. While these tests are very useful for detecting TSE in animal tissues, they cannot be interpreted as certification that the animal is not contaminated. Similarly, there is no data or suggestion that they would be of use for raw material testing in the pharma manufacturing environment.

"The only industry wide technical guidance on cleaning relating to the pharmaceutical industry are the Technical Reports issued by PDA. The starting material manufacturers and suppliers who need this information most may not be aware of the PDA publications..."

- **Implementation of the EDQM certification system**

Originally applicable only to organic and inorganic active substances, excipients and certain fermentation products, the EDQM certification system was set up in 1994 to facilitate and simplify information exchange on the quality of substances which need to comply with the European Pharmacopoeia. In 1999, the certification procedure was broadened to cover TSE suitability. Less than 20 certificates were granted in 1994. In 2000 the total will be almost 140, of which almost 40 relate to TSE.

Certificates are currently required for the materials used in the medicine, not for the finished medicinal product (though there reportedly has been some discussion of this). Under the procedure, suppliers of any product (raw material, ingredient, etc.) with TSE risk and used in the production or preparation of medicinal products, can apply for a certificate concerning evaluation of the risk under new general monograph (1483) 'Products with risk of transmission of agents of animal spongiform encephalopathies' and the associated general chapter 5.2.8. The certificate can then be used by manufacturers of medicinal products in the marketing authorizations for demonstration of compliance with the EU Directives.

TSE certificates are initiated by the submission of a dossier or file to EDQM which includes the information in the note for guidance on minimizing TSE risk.

EDQM has four months to designate two rapporteurs for the review of the file, and one month to implement the review outcome (total of five months maximum to process the request). If additional information is requested, there is an additional three months for review once it is received. Manufacturers can apply for a combined certificate covering both TSE evaluation and chemical/microbiology purity.

Information in the dossier is divided in to five areas:

1. General information;
2. Origin of raw material and type of tissue used;
3. Manufacturing process;
4. Traceability; and
5. Auditing system.

Certificates are granted for five years and specify the country of origin of the source material, the nature of animal tissues used in manufacture, and when appropriate, the manufacturing process applied.

As of January 5, 2001, EDQM has approved 37 certificates in the following categories:

1. 22 gelatins;
2. 14 for FBS; and
3. 1 aprotinin.

More than 120 dossiers are under evaluation, 20 have been returned as out of scope (e.g. milk derivatives, poultry, etc.). Dossiers can be submitted in English or French. The cost is EUR 3000 for TSE, EUR 5000 for combined chemical and TSE.

"Process validation studies are required only if the manufacturer claims the process removes or inactivates the TSE agent."

III. Gelatin, Tallow, Serum and other media

Dr. M. Ruffing, *BfArM, Germany*
Dr. Alexandrine Maes, *Scientific Institute of Public Health, Belgium*

Gelatin for pharmaceutical use is mainly produced by acid or alkali treatment of bovine hides or bones. It is used in the manufacturing of capsules, microencapsulation and tableting, or chemically modified as a blood plasma substitute. Appropriate selection of the source animals is crucial to the safety of the gelatin. Skulls and spinal cords must be removed from processing. Gelatin made from bovine hides from any country is considered safe, providing cross-contamination from infectious material is avoided.

The validation of the alkaline manufacturing process has shown higher potential to inactivate TSE agents than acid treatment and is currently preferred. Gelatin manufacturers should implement Hazard Analysis and Critical Control Point Procedures (HACCP) to ensure quality.

Tallow is generally used as a starting material for production of derivatives, e.g. magnesium stearate, glycerol and polysorbate. For TSE purposes, all of the same precautions prevail, e.g. sourcing of materials, use of animal parts, etc. Commission Decision 92/562/EC lists the critical parameters that have to be monitored during different rendering processes for the production of tallow. It is generally accepted that tallow derivatives are unlikely to be infectious provided that tallow is produced according to a system which complies with this decision and processes as mentioned in 5.2.8 of the Pharmacopoeia.

Bovine serum is used during production of medicines such as vaccines, monoclonal antibodies and recombinant proteins. It can be sourced from the foetal, calf or adult animal. In general, animals from countries with a high incidence of BSE should not be used for sourcing of the raw materials. For serum, the method of slaughter is the critical point. Other media components such as blood derivatives, peptones and brain extract are mainly used during production of biological/biotechnological medicinal products. The risk assessment for certification is based on the same parameters as for serum and the safety is best assured by controlling the animal source.

In general, adequate cleaning of manufacturing equipment, including removal of protein residues, should be helpful in the reduction of any TSE materials and in avoiding cross contamination of co-processed materials.

IV. Comments from Conference Participants:

- **On Medical Devices**: Many health care product manufactures make products classed as both drugs and medical devices. Many of these incorporate the same materials and are the subject of the pharmaceutical directives (e.g. heparin, gelatin, tallow, etc.) The European Commission is reportedly working on a separate, mandatory guidance for medical devices which does not seem to recognize the EDQM certification system. Rather, the guidance will require the use of 'notified bodies' and other approaches more characteristic of medical devices and the ISO 9000 approach (which will cover one product at a time). There has been poor transparency on this guidance with very little public input. If published as drafted (and this reportedly is very close to happening) it will be a tremendous burden on many companies. There should be one way to handle the TSE risk process for a manufacturer of health care products, be they classed as drug or device.
- **On Proportional Risk**: While the pharmaceutical industry is being required to commit tremendous resources to eliminating almost any conceivable risk of TSE contamination, what is being done about the food industry? Most of the gelatin produced worldwide ends up in food products with no certification. For example, less than 1% of the world gelatin production is used in pharmaceuticals. There needs to be a measure of proportionality in the response to this problem. (Note: a round of applause followed this comment.)
- **On why there are fewer certificates than the EMEA or the national authorities would prefer**: While the TSE rules apply to the MAH, it is the supplier of the starting material who must take the lead in preparing a dossier and securing EDQM approval. Many of these products, e.g. wool fat, have minimal economic value to the producers. Also, producers do not have the expertise to prepare an acceptable dossier. Finally, there are sometimes trade secret issues which companies refuse to divulge. For these reasons many suppliers simply do not want to deal with the certification system. As a result, the number of certification applications hoped for will simply not materialize.
- **On technical information for cleaning validation**: It has been stressed that suppliers of TSE risk materials must perform adequate cleaning to prevent cross-contamination of materials. However, the only industry-wide guidance on cleaning relating to the pharmaceutical industry are the Technical Reports issued by PDA. The starting material manufacturers and suppliers who need this information most may not be aware of the PDA publications [Ref: PDA Technical Report No. 29, *Points to Consider in Cleaning Validation*, 1998, and *Cleaning and Cleaning Validation: A Biotechnology Perspective* (PDA 2), 1996. Both available from PDA, see page 40.]
- **On revoked or rejected certifications**: When an EDQM Certificate is revoked or refused on scientific

grounds, this information needs to be shared in a public fashion so other users of the material will be made aware of the TSE risk.

V. Questions from Conference Participants:

Q. Some materials can be from animal origin or from synthetic process. How much information must a manufacturer provide to prove that such a material is of non-animal origin?

A. A clear statement to that effect will normally be adequate.

Q. How far back in the production system for a TSE risk material must a pharmaceutical manufacturer conduct traceability and supplier audit?

A. There can be no single answer and it will depend on the material and it's source. In general, it is the responsibility of the user to do whatever they believe is appropriate to reduce the TSE risk to acceptable levels.

Q. In coming months and years, inspectors from all the national authorities will be dealing with the TSE control steps taken by manufacturers. The directives are very fluid and generally give manufacturers much latitude in how to handle this problem. Has any thought been given to the guidance which should be given to Inspectorates and how they should audit a company's performance?

A. For both Type I variation (EDQM certification) and Type II (data in the dossier) the inspector should only review conformance with the approved dossier submission. They should not do more.

Q. On March 1 what is the status of 'pending' certifications which have been supplied to EDQM but which are not yet approved?

A. Small delays (a few days or weeks) will not be a problem. It should be remembered that there is a common interest by all parties (regulators, drug producers, and the material suppliers) to get the problem under control and to assure the public confidence in the medicines supply.

> "There should be one way to handle the TSE risk process for a manufacturer of health care products, be they classed as drug or device."

Q. If a country's BSE status changes from BSE-free to BSE cases, how will that impact any certificate already issued?

A. If certifications are shown to no longer be reliable they can be revoked.

Q. Are clinical trial materials subject to the TSE directives?

A. Probably yes.

Q. Should a medicines manufacturer audit a supplier who holds a TSE certificate?

A. Periodic audits are a normal aspect of GMP. ■

See page 24 for Program Details and page 42 for a Registration Form

TR-32 UPDATE

by Harvey Greenawalt, Audit Repository Center

For Auditor Training Schedule, see page 33

Industry participation in the PDA Process for Auditing of Suppliers Providing Computer Products and Services for the Regulated Pharmaceutical Operations, defined in PDA Technical Report No. 32, continues to increase.

The inventory of available audits and membership to PDA's licensed audit repository, administered by Audit Repository Center (ARC), continues to grow.

Membership

Three major Pharmaceutical and Chemical Companies and three Suppliers of computer products to the industry have become members of the Audit Repository since June of 2000.

In January of 2001 ARC entered into subscription agreements with two major suppliers to voluntarily place their audit data in the repository for distribution to the pharmaceutical industry.

Availability of Audits

Currently, thirty-one audits are either available for distribution, in process or planned to be completed within the next six months.

Table 1.0 provides a summary of the audits that are currently available for distribution from the repository.

Auditor Resources

Eighty auditors have been trained and qualified by the PDA during the year 2000. Forty-two percent of these auditors are from pharmaceutical industry companies, with seven percent coming from the European Union. Nine independent consulting firms have placed agreements in effect to provide qualified auditors to the industry.

New Initiatives

PDA and ARC recognize that the quality of computer products is a function of the processes used to create them. Independent assessments of technology process are an important asset to Suppliers as it helps them in their process improvement initiatives to improve their software products. The PDA Technical Report No. 32 is designed to provide Suppliers with the maximum benefit of audits, which are based on assessment practices while using a global, industry-endorsed program for audit sharing.

Regulatory inspections of how well Health Care industry firms qualify application software and validate computer systems are assessed on a case-by-case basis. Technically sound systems practices for evaluating and implementing computer technologies is a key part of computer validation today. The PDA Process is designed to provide good data to document the technology practices and quality systems involved to bring computer products to the marketplace.

Suppliers now have a vehicle through which they can provide audit data to their Pharmaceutical industry clients. The audit data is generated with a minimum impact to the supplier community and it retained in a secure repository for industry by ARC for the PDA.

In November, ARC introduced a new pricing schedule for Suppliers who wish to have their PDA Technical Report No. 32 audit data on file with the Repository. The new schedule reduces financial risk to the Supplier, eliminates up-front subscription fees, provides the Supplier with credit incentives for use by Subscribers, provides access to the repository and PDA process for all Suppliers and allows Pharmaceutical clients access to Suppliers who are not currently entrenched in the industry.

ARC is pleased to announce that two major suppliers of computer products to the industry have taken advantage of the new pricing schedule in January. Profiles of these suppliers will be published in future issues of the newsletter.

For more information about the audit repository visit either ARC's Web site at www.auditcenter.com or PDA's Web site at www.pda.org. ■

Table 1.0 Audits Currently Available in ARC.

Supplier	Product
Accraply, Inc.	Label Applicators, Automatic Labeling Systems, & Custom Designed and Self Adhesive Material Application Systems
Action Point	Input Accel Document Imaging LIMS
Applied Biosystems	SQL*LIMS—Laboratory Information Management System including the QA Stability & Schedule Modules
Etrails.com, Inc.	Electronic Data Capture—EDC Electronic Patient Diaries—EPD Electronic Trail Management—ETM
Merant Inc.	PVCS Dimensions & PVCS Replicator Configuration Management Systems
Precision Solutions	Custom Development, SLE—Capture of check weight data Custom Software Programming
Qumas, Ltd (Participating Supplier)	Qumas-Doc: Electronic Records Document Management Systems

USP UPDATE

by Roger Dabbah, Ph.D.

The January–February 2001 Pharmacopeial Forum (PF) has been published. It has been redesigned and includes additional section that will facilitate the retrieval of new proposals for public comments. The section "How to use PF" summarizes the various sections and provides the reader with a variety of modes for commenting on proposals. A "Staff Directory" section provides for easy and individual access to appropriate staff with telephone numbers, e-mail, and specific assignments. Another section "The Interim Revision Announcement" provides with a mean to accelerate the implementation of revision items that occur between Supplements, or that are necessary to be implemented immediately. It also includes the list of new Reference Standards that have been established, and the list of Reference Standards that are not available.

In this PF, under the In-process section, there are 11 new USP monographs proposed. They are: 6-Aminopenicillanic Acid; Bromodiphenhydramine Hydrochloride and Codeine Phosphare Syrup; Desogestrel, Desogestrel and Ethinyl Estradiol Tablets; Atracurium Besylate; Felodipine Extended-Release Tablets; Ivermectin; Lamivudine; Paroxetine Hydrochloride; Solatol Hydrochloride Tablets; Theophylline Syrup; and Torsemide. There are also two new NF monographs proposed: Valerian Capsules; and Valerian Tablets.

In the General Information chapter section, a new chapter <1046>, Cell and Gene Therapy Products, is proposed. Revisions to chapter <1> Injections include the revision of Volume in Container to allow for the testing of up to four 1-mL or 2-mL using a 10-mL "to contain" graduated cylinder, in the event a smaller cylinder is not commercially available.

A new section containing monographs or chapters undergoing harmonization has been initiated and starting in the next PF we will include the harmonization proposal in that new section.

In the Pharmacopeial Previews section we have proposed a new monograph on Nimodipine. Finally in the Stimuli for the Revision process section we have published a paper on "An Alternative Methodology for the General Test Chapter Microbial Limit Tests<61>" by Warren M. Casey et al. from GlaxoWellcome Inc. ■

Regulatory Briefs

by William Stoedter, PDA

Drug Re-importation Plan Revisited

A new law aimed at cutting prescription drug prices, by allowing US-made drugs to be re-imported from other countries after distribution, was not implemented by the Clinton Administration. Concerns were cited that the safety of the drugs could not be assured. However, the drug re-importation issue was revived on January 31, 2001, when Senator Jim Jeffords (R-VT) sent a letter, signed by 16 Congressional co-signers, to President George W. Bush requesting that the bill be implemented.

The law attempts to give the elderly, and those on fixed incomes, access to less expensive drugs. The legislation was first introduced when it became widely known that drugs manufactured in the United States can be purchased for much less in Canada than in the USA. The disparity is due to Canadian government price controls.

Address for written comment to FDA unless otherwise indicated:
Dockets Management Branch (HFA-305)
FDA
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Post Inspection Notification Letters

The Food and Drug Administration announced in the January 4, 2001, *Federal Register* (Volume 66, Number 3) certain changes in its standard practices for medical device, drug, food and biologics inspections. Based on the outcome of the medical device industry initiatives pilot program, FDA is discontinuing the practice of post inspection notification letters for all inspections. The agency now provides inspected establishments with a copy of the Establishment Inspection Report (EIR) when the inspection is deemed closed. The FDA has decided to maintain pre-announced inspections and annotations of the inspection observations (FDA 483) as standard practice for medical device inspections. For inspections other than medical devices, these initiatives will be applied at the discretion of the district management.

For further information contact: Denise D. Dion, Office of Regulatory Affairs (HFC-130) Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-5645, FAX 301-443-6919.

Draft Guidance for Industry on Recommendations for Complying With the Pediatric Rule

In the *Federal Register*, December 4, 2000 (Volume 65, Number 233) the FDA announced the availability of a draft guidance for industry entitled "Recommendations for Complying With the Pediatric Rule." The draft guidance provides recommendations for sponsors of New Drug Applications (NDAs) and Biologics Licence Applications (BLAs) on how to meet the requirements of the final rule. Under the Pediatric Rule, applications for new active ingredients, new indications, new dosage forms, new dosing regimens and new routes of administration must contain a pediatric assessment. Applicants may obtain a waiver or deferral of pediatric studies per 21 CFR 314.55(a) and 601.27(a). Submit written comments on this draft guidance by March 5, 2001.

This draft guidance describes how the Pediatric Rule will be implemented. Areas covered include an overview of pediatric assessments, pediatric plans, waivers and deferrals, compliance issues, pediatric exclusivity and the role of FDA's Pediatric Advisory Subcommittee.

This draft guidance is available on the internet at http://www.fda.gov/cder/guidance/index.htm. For further information contact Terrie Crescenzi, CDER, FDA, 5600 Fishers Lane, Rockville, MD 20857. Phone 301-594-7337, FAX 301-827-2520, e-mail crescenzit@cder.fda.gov. or Elaine Esber, CBER, FDA, 1401 Rockville Pike, Rockville, MD 20852. Phone 301-827-0641, FAX 301-827-0644, e-mail esber@cber.fda.gov.

Electronic Filing of Drug Registration and Listing Information, Notice of Pilot Project

In the *Federal Register*, January 9, 2001, (Volume 66, Number 6) the FDA announced that it is seeking volunteers to participate in a pilot project to implement the electronic filing of drug registration and listing information. Manufacturers, repackers and relabelers who engage in the manufacture, preparation, propagation or processing of human or veterinary drugs and human biological products are required under current regulations to submit a listing of every product in commercial distribution. This information is presently submitted in paper format. FDA is developing an electronic system for submitting the required information and is seeking volunteers to test this pilot project.

Eventually the FDA expects that they will require electronic filing under part 207. Participants in this project will provide technical feedback to FDA about the system and gain experience with using the system.

Existing registration requirements will not be waived for those participating in this project. Participants must continue to submit paper documents in accordance with FDA's current requirements.

Written requests to participate in this pilot project should be submitted to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. Include Docket No. 00N-1669, on your request.

For further information contact: James Hunter, FDA, CDER (HFD-9) 5600 Fishers Lane, Rockville, MD 20857. Phone 301-594-6779, e-mail hunterj@cder.fda.gov.

International Conference on Harmonization, Guidance on Q6A Specifications

Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products.

The Food and Drug Administration printed in the December 29, 2000, *Federal Register* (Volume 65, Number 251) a guidance entitled "Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances." The guidance was prepared under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The guidance describes or provides recommendations concerning the selection of test procedures and the setting and justification of acceptance criteria for new chemical drug substances and new drug products produced from them. The guidance is intended to assist in the establishment of a single set of global specifications for new drug substances and new drug products. The guidance can be found in the above mentioned *Federal Register*.

For further information regarding the guidance contact: Neil Goldman, CBER, (HFM-20), FDA, 1401 Rockville Pike, Rockville, MD 20852, 301-827-0377.

For further information regarding ICH, contact Janet Showalter, Office of Health Affairs (HFY-20) FDA 5600 Fishers Lane, Rockville, MD 20857, 301-827-0864 or visit the ICH Web page at www.ifpma.org/ich1.html. ■

FDA Proposes New Rules for "Good Tissue Practice"

by William Stoedter, PDA

On January 5, 2001, FDA proposed a new regulation on current Good Tissue Practice (GTP), which includes the methods, facilities and controls used for the manufacture of human cellular and tissue-based products. This rule is the last of three proposals designed to implement FDA's 1997 "Proposed Approach to the Regulation of Cellular and Tissue-based Products." This comprehensive risk-based regulatory framework was designed to help ensure the safety and quality of products, including new technologies, without imposing unnecessary regulatory requirements.

The purpose of the GTP regulations is to help ensure that donors of human cellular and tissue-based products are free of communicable diseases, and that the cells and tissues are not contaminated during manufacturing and maintain their integrity and function. Key elements of the proposed rule are:

- Establishment of a quality program, which would evaluate all aspects of the firm's operations, to ensure compliance with GTP;
- Maintenance of an adequate organizational structure and sufficient personnel;
- Establishment of standard operating procedures for all significant steps in manufacturing;
- Maintenance of facilities, equipment and the environment;
- Control and validation of manufacturing processes;
- Provisions for adequate and appropriate storage;
- Record-keeping and management;
- Maintenance of a complaint file; and
- Procedures for tracking the product from donor to recipient, and from recipient to donor.

These fundamental, baseline regulations would apply to manufacturers of all human cellular and tissue-based products. In addition, all of these manufacturers would be required to report adverse reactions and certain product deviations, have adequate labeling that is not false or misleading and allow FDA inspections to ensure compliance with regulations. Certain cellular and tissue-based products that require licensing or premarket approval as biological products or medical devices would be subject to more comprehensive requirements based on their risks.

Two other related proposed rules to implement the 1997 regulatory approach to tissues and cells have already been published. The first ("Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products") was published May 14, 1998 and required tissue facilities to register with the FDA and list their products. This proposed rule is currently undergoing review and is expected to be published in final form soon. The second ("Suitability Determination for Donors of Human Cellular and Tissue-Based Products") was issued on Sept 30, 1999 and focuses on donor screening and testing measures to prevent the unwitting use of contaminated tissues with potential to transmit infectious diseases.

FDA's current regulations addressing tissues were promulgated in December 1993 with an interim final rule that required the screening and testing of tissue donors for certain transmissible diseases such as HIV and hepatitis, as well as the screening of donors for behavioral risk factors. The final rule, which was published on July 29, 1997, became effective on January 26, 1998. The new proposed rules are more comprehensive and include provisions for the regulation of innovative products.

For more information contact: Paula McKeever, CBER, (HFM-17), FDA, 1401 Rockville Pike, Suite 200N, Rockville, MD, 20852, 301-827-6210. ■

What Does the Office of the Ombudsman Do?

by William Stoedter, PDA

The functions of the Center for Drug Evaluation and Research (CDER) Ombudsman, James Morrison, parallel that of the Food and Drug Administration (FDA) Ombudsman, Amanda Bryce Norton. The office of the CDER Ombudsman permits those both inside and outside the Center an avenue for getting complaints involving CDER programs resolved at a level closer to the source.

The FDA is committed to the principle that regulated industry has a right to disagree with an agency decision, action, or operation, and that full and open discussion of issues in controversy produces a better decision in the end. Moreover, regulated industry is entitled to receive high quality administrative practices and procedures from all parts of the FDA. The goal of the FDA's Ombudsman is to help ensure that the agency fulfills its regulatory responsibilities well. In the short term, the Office is dedicated to facilitating problem resolution. In the long term, the Office looks at issues systematically in order to make the process work better. Thus, it welcomes more general complaints, comments and suggestions about FDA's regulatory processes.

Some people in the drug industry are reluctant to use the services of the Ombudsman for fear of some type of reprisals from the agency.

Inevitably, a variety of problems arise. When a member of the regulated industry has a concern about an agency action, getting the problem resolved can be confusing, frustrating and time-consuming. The services of the Office of the Ombudsman, which has agency-wide jurisdiction, are available to any company or individual with a dispute with FDA. The Office works in a range of ways, from a confidential consultation, in which options are discussed and practical guidance is offered, to taking an active role in resolving the problem or investigating the situation.

The Office of the Ombudsman has two main functions: (1) to investigate complaints and resolve disputes (http://www.fda.gov/oc/ombudsman/dispute.htm) between companies or individuals and agency offices; and (2) to determine the appropriate classification and regulatory pathway for combination products and for drug, device and biological products when the jurisdiction of a product (http://www.fda.gov/oc/ombudsman/pj.htm) is unclear or in dispute.

In a recent interview, James C. Morrison, CDER Ombudsman, stated that his office deals with cases that range from a quick phone call to cases that take months to close. Some calls are to discuss options and bounce ideas around or the caller might want to determine if they are being treated unfairly. The majority of the calls come from the drug industry while a few calls come from the public and a few calls even come in from the agency itself. In one year it is usual to handle more than 100 substantial cases. The responsibility of the office is not to be a decision-maker, but a facilitator and negotiator.

Some people in the drug industry are reluctant to use the services of the Ombudsman for fear of some type of reprisals from the agency. Mr. Morrison told me that this is not a valid perception in the current climate at the agency. There is a formal process for dispute resolution and all phone calls are kept confidential from the agency and others in the industry. A log is kept of all phone calls to document the conversation but the name of the individual and the company is not entered in the log. If Mr. Morrison is asked to intervene on behalf of a company, then data and facts must be brought to the table and the name of the company must become known. If the office receives several comments on the same issue, the Ombudsman can look into the issue independently.

More than 50% of the cases are issues of miscommunication and interpretation. For example, if a reviewer asks a question, sometimes the company will think there is a new requirement or that it is a request for more or different data. When asked how often the industry prevails versus the agency, Mr. Morrison said that it is difficult to classify results in that manner because most often both groups get some satisfaction and he thought that the industry would be surprised by how many satisfactory resolutions there are. It was also stressed that companies should not wait until an issue is critical before contacting the Ombudsman. Call early to get an assessment of the situation so you can start planning your strategy. Remember, the call is confidential.

As stated above, the second main function of the Ombudsman is to determine the appropriate classification and regulatory pathway for combination products and for drug, device, and biological products when the jurisdiction of a product is unclear or in dispute. There is a formal process for making this decision. Mr. Morrison will work with the Ombudsmen from the Centers for Devices and Biologics, discussing the current thinking at the agency and reviewing past jurisdiction decisions. When a consensus has been reached by the center, the center Ombudsmen will make a formal recommendation to the FDA Ombudsman for a final decision.

To learn more about the role of the Ombudsman, visit http://www.fda.gov/cderombud.htm. James Morrison, can be reached by phone at 301-594-5443, by fax at 301-827-4312, by mail at CDER Ombudsman (HFD-1), 5600 Fishers Lane, Rockville, MD 20857, or by e-mail at morrisonj@cder.fda.gov. ■

PDA
An International Association For Pharmaceutical Science And Technology

We Don't Want to Lose Touch with You!

Keep your PDA mailings coming and ensure that your friends and colleagues in PDA know how to reach you. Send us your updated address, phone, fax or e-mail today! Remember, PDA's Online Directory is updated weekly—you'll want your most current information available.

Simply fill out the form below and fax it to PDA at (301) 986-0296. If you would prefer, e-mail your updated information to info@pda.org.

Member Info

Please type or print clearly

Last Name _____

First Name _____ Middle Initial _____

Member Number (if known) _____

Degree/Credential _____

Job Title _____

Company _____

Address _____

City _____ State/Province _____ Zip+4/Postal Code _____

Country _____

Business Phone# _____ Fax# _____

E-mail _____

Fax completed form to PDA at (301) 986-0296 or e-mail to info@pda.org.

Interest Groups Update

by Russell E. Madsen, PDA

Many of the PDA Interest Groups (IGs) met at the Annual Meeting in Philadelphia in December 2000. This article summarizes several of those IG sessions. Summaries of other IG sessions will be published in future issues of the PDA Letter. More information about PDA Interest Groups can be found on the PDA Web site at www.pda.org.

Validation Interest Group

Bohdan Ferenc

The Validation Interest Group session focused on key areas and issues with a validation protocol. The group also discussed validation master plans. Additional discussions centered on the need for industry to address Quality System Elements for their operations. The definition of these elements goes beyond the Validation Master Plan. It is likely that regulatory bodies will be looking for companies to develop, define and implement the Quality System Elements for their respective processes.

Lyophilization Interest Group

Edward Trappler
Lyophilization Technology

Six discussion topics were proposed during a survey of the participants:

1) Setting and the basis for residual moisture specifications;
2) Are processes implemented in systems using mechanical systems and liquid nitrogen the same? Are they validated the same way?;
3) Concerns of product on the stopper;
4) Cycle deviations;
5) Media Fills; and
6) Scale-up and moisture control.

A number of considerations in residual moisture testing were discussed. The use of Near-IR is a method that lends itself well to testing large numbers of samples, as in demonstrating batch uniformity in the lyophilizer. The results from this method need to be correlated to those achieved by Karl Fischer titration. In such comparison, one attendee noted that their company assesses the range and uniformity by testing the outliers measured by N-IR using a Karl Fischer method.

For setting specifications, three overtones were noted:

- How the specified moisture level is correlated to stability;
- What level the process can achieve; and
- How the specification is related to the method of analysis.

Since the achievable moisture level may change when progressing from development through scale-up to manufacturing, the specification should be well established when producing Phase III clinical trial material.

The group discussed whether the specification should be based upon the average value or results for any individual sample. Overwhelming consensus was for basing the criteria on any individual result. Part of the discussions encompassed the variability. Circumstances of an increasing range in measured moisture content were suggested to be associated with lower water content and larger lyophilizer. There was strong agreement that some type of statistical analysis is warranted, with methods including use of a statistical software package, standard deviation, or % confidence interval.

Extensive discussions on residual moisture left little time to consider the question of different processes and any additional validation that would be necessary for different refrigeration systems. The group quickly arrived at the conclusion that the process is the same. Perhaps due to industry's limited experience with the use of liquid nitrogen, additional validation may be necessary to convenience oneself if indeed there are any differences. Perhaps this question could be addressed during the next session scheduled for the spring meeting.

On a personal note, a heartfelt thanks to Dr. Duncan McVean for moderating numerous sessions over many years. Duncan retired from Ben Venue Laboratories where he held the position of Vice President of Marketing and New Business Development. Those of us who have had the pleasure of knowing Duncan will not only miss his dedication to the PDA but also his contributions to the PDA and industry. My best wishes to Duncan for success and enjoyment in all of his endeavors.

Production and Engineering Interest Group

David Maynard
Maynard & Associates, LLC

The discussions were set in an open forum without having a "focus" presentation. Comments from the attendees indicated they appreciated the opportunity to "air a problem" knowing it would not get back to their company versus having a "focus" presentation. They would accept a "focus" presentation as a point of discussion as a springboard for open discussion.

Topics that were listed for discussion were:

1) Critical Process Parameters (what are they and how do we establish them);
2) Non Viable Particle Classification (differences between Europe, WHO and USA and how to address them);
3) Tools Used in Aseptic Areas (types, how to bring them in);

4) 21 CFR Part 11 Compliant Equipment (how, why and validation);
5) Bowie Dick Test (use, implication);
6) Steam Quality (what is it, how to do it, why do we need to do it);
7) HEPA Testing (what does finding a leak mean in an aseptic area);
8) Pharmaceutical Engineering (do we lead or lag other industries, do we adopt or adapt from them); and
9) Chemical Sanitization (where is it being used).

The topics chosen by the group were 1, 2, 3, 7 and 8.

Most of the session was spent discussing Critical Process Parameters, with several viewpoints expressed on the desirability for a "guide" to enable the "standardization" of how to develop and choose the Critical Process Parameters that are used during production. This topic will be expanded in future meetings of the interest group.

The second most discussed topic was the utilization of Chemical Sanitization and the application of a trend in bulk production to use strict regimes, similar to those followed by those used in the aseptic area.

The topic outlining some of the differences found between the various standards for particulate evaluation will lead to a more in-depth discussion during future sessions. Several of those attending the session were international companies trying to "standardize" the testing between locations.

QA/QC Interest Group

Robert Dana
Bristol-Myers Squibb Co.

The highlight of the IG meeting was a presentation by FDA's Fred Blumenschein, who spoke about the upcoming pilot program focusing on a systems approach to the conduct of drug product inspections. This program will be implemented for a 6-month trial, beginning January 2001, in the Dallas, Los Angeles, Newark, New York, Philadelphia and San Juan districts. Systems slated for coverage include the quality system, and those governing facilities and equipment, materials, production, packaging and labeling, and laboratory operations.

Blumenschein described the goals and anticipated outcomes for the pilot program, and provided some examples of the anticipated coverage for each system. There will be three inspection options under the pilot: full inspection (will include the quality system and three other systems), abbreviated inspection (quality system and one other system) and compliance inspections (follow-up to verify corrective actions and for cause inspections). A key point of the pilot is that one biennial inspection will result in determination of acceptability/non-acceptability for all the firm's profile classes. In addition, that biennial inspection will cover a few representative profile classes, the findings for which will be extrapolated to cover all the firm's profile classes. So, finding a system adequate (or inadequate) will impact all product profiles. Revised Compliance Program 7356.002 describing the pilot is anticipated to be published shortly. Blumenschein provided a Web site where this program will be available (www.fda.gov/cder/dmpq/index.htm). A copy of his presentation, with additional details, is available elsewhere on the PDA Web site. We thank him for his presentation.

Other significant topics discussed during the IG included:

- Investigating OOS results in the micro lab;
- OOS investigations – how much is enough?;
- A methods validation and resolving investigator concerns; and
- Quality standards for incoming cleaning agents.

Input from the attendees was requested for the Interest Group meeting at the PDA Spring 2001 Conference. Attendees were requested to contact Don Elinski with any ideas/suggestions.

Inspection Trends/Regulatory Affairs Interest Group

Robert Dana
Bristol-Myers Squibb Co.

This was the first Interest Group attended for several persons, and a large number indicated it was their first time attending this particular IG. All in attendance were there to focus on inspection issues. A number of topics were addressed with input provided by several of those in attendance.

Quality Systems Drug Product Inspections

An overview of the upcoming FDA program to pilot a quality systems approach for inspections of drug product manufacturers was provided. This program will be implemented for a six-month trial, beginning January 2001, in the Dallas, Los Angeles, Newark, New York, Philadelphia and San Juan districts. Systems slated for coverage include the quality system, and those governing facilities and equipment, materials, production, packaging and labeling and laboratory operations. Differences between top down quality systems inspections and bottom up "compliance-based" inspections were discussed and participants shared their experiences and lessons-learned in other systems-based inspections. Several participants observed that the systems approach could result in broadening the scope of inspections to functions not normally treated extensively, such as purchasing and human resources. The need to provide training for these functions was discussed and Fred Blumenschein of FDA went into more detail during the QC/QA Interest Group meeting and copies of his slides are posted elsewhere on the PDA Web site.

QSIT Inspections (Medical Devices)

As an extension of the previous topic, some of the outcomes of FDA's Quality System Inspection Technique (QSIT) for medical devices were reviewed. QSIT inspections also adopt a quality system approach, although not necessarily the same one to be used in the conduct of the drug pilot. It was not-

ed that, under QSIT, there are four major subsystems:

- Management Controls;
- Design Controls;
- Corrective and Preventive Action (CAPA); and
- Production and Process Controls.

A summary of Warning Letters issued to device firms from April–November 2000 revealed the following incidence of citations:

- Production/Process Controls—40%;
- CAPA—24%;
- Management Controls—22%; and
- Design Controls—14%

Current inspection activities and findings, as reported at the recent PDA/FDA Conference

- Most frequently visited countries in FY 1999: Italy (26), Canada and Japan (21 each), Germany (17) and Switzerland and the United Kingdom (14 each)
- EIR Final Classifications FY 1999: Voluntary Action Indicated (59%), No Action Indicated (33%) and Official Action Indicated (8%).
- Most common API GMP deficiencies Fiscal Year 1999: Laboratory Controls (16%), Equipment Cleaning and Records and Reports (13% each), Raw Materials and Intermediates (8%), Water Systems (7%), Process Validation, Reprocessing and Reworking and QA Systems (4% each), Stability Programs (3%) and Written Procedures (2%).

ERS Inspections

While there is not a great deal of hard information available, attendees felt that inspections were focusing more on ERS issues than in the past. Examples of a few FDA 483 observations and Warning Letter citations were noted. The need to provide training for IT groups was discussed.

Volunteers to serve on a steering committee to plan the agenda for upcoming Interest Group meetings were solicited. Anyone not able to attend this meeting, but interested in serving on this steering committee, is asked to contact Bob Dana at robert.dana@bms.com. Ideas and suggestions for future meeting agenda items and programs are also solicited from the membership at large. Please respond to the same address.

Drug/Device Delivery Interest Group

Michael Gross, Aventis

Steven Borchert, Pharmacia Corp.

The discussion at the DDIG focused on the planning of a one-day special forum focused on packaging extractables. A similar meeting on the same topic is was held in 1996. There is significant interest in organizing a follow-up forum in late spring 2001. A planning committee is being organized. The first planning meeting will be held in late January 2001. Michael Gross, Aventis (Leader DDIG) and Ed Smith, Packaging Science Resources (Leader PSIG) are the co-chairs of the planning committee. Additional members will be drawn from pharmaceutical companies, contract testing laboratories, pharmaceutical packaging and component manufacturers, device companies, filter manufacturers, USP, and other appropriate groups.

There is a variety of topics that could be covered in the program. Most attendees should be familiar with FDA's Guidance on Container Closure Systems for Packaging Human Drugs and Biologics. It would be desirable to discuss blinded real-life examples to illustrate the practical aspects of addressing extractable issues according to the guidance. For instance, a speaker from a contract testing laboratory may be able to provide the practical details without divulging proprietary information. A second topic would be to illustrate the information gathering process. In particular, how a pharmaceutical manufacturer works with manufacturers of the packaging components and their material suppliers before attempting to address the analytical, pharmacological, and toxicological issues associated with extractables. Extractable issues involving materials other than packaging will probably be included, in particular, extractables from filter components, tubing materials, and other polymeric materials used in pharmaceutical processing. Extractables from glass containers, especially siliconized glass vials, could also be covered. In addition, extractables from labels, adhesives, and printing inks will probably be covered in the presentations pertaining to the extractables from plastic-containing packaging materials.

From the analytical perspective, it will be desirable to address the practicalities of which extractables need to be identified, since it is not practical to attempt to identify all potential extractables. The role of pharmacopoeia tests and other standardized tests will also be discussed since most do not provide specifications for specific extractables. Since changes to packaging materials are inevitable, it would be desirable to discuss what needs to be done on a lot-to-lot basis and when changes in materials occur [e.g., resin change]. It will be important to have the symposium maintain a balance coverage of the analytical, pharmacological, and toxicological issues.

The conference may rely heavily on input from USA-based personnel (USA-based pharmaceutical company personnel, USA-based contract testing laboratories, USP representatives, FDA personnel, etc.), it would be valuable to utilize expertise from personnel outside the USA. For example, ISO and EP testing (e.g., ISO 10993, EP 3.1.4., EP 3.1.5., EP 3.1.6., EP 3.1.7.,EP 3.1.12., etc.) often provide useful extractable information.

Training Interest Group

Thomas Wilkin, Ed.D.

Schering-Plough Corp.

Prior to the main IG discussion session, two training-related presentations were delivered by Rick Rogers, PDA, and Dave Gallup, Training and Communications, Inc.

The topics identified at the outset of the Interest Group discussion session to be of importance were:

- Developing Competency-Based Training;
- Return on Investment;
- Evaluation the Effectiveness of Training;
- Top Management Support;
- Guidelines;
- Small Company Training Issues;
- Appropriate Training for Technical People;
- SOP Training; and
- Web-Based Training.

Interactive discussion was held on each of these topics with the attendees contributing to the development of helpful responses. A number of individuals have volunteered to form a subgroup to examine the notion of Training Guidelines. Rick Rogers, PDA, and Tom Wilkin, Interest Group Leader, will also participate.

Feedback on the session was very positive. The next Interest Group meeting will be held during the PDA 2001 Annual Meeting.

Filtration Interest Group

James D. Wilson

Experts from four different filter manufacturers representing Cuno, Millipore, Pall, and Sartorius gave presentations. The Cuno presentation(Robert Conway) was on materials and filter development. Presentations by Millipore (Randy Wilkins) and Sartorius (Mark Trotter) were on physical integrity testing. The Pall presentation(Sri Sundarum) centered around the influence of microbial size; he discussed the implications of SEM studies that show size exclusion is not the sole mechanism for removal of microorganisms. He reported recovery of larger and smaller cells as compared to the standard challenge organism downstream of the test filters.

Visual Inspection of Parenterals Interest Group

John G. Shabushnig
Pharmacia Corp.

A summary of recent regulatory activity was presented. Excerpted text from inspection related FDA483 observations from 1998–2000 can be found on the interest group Web page.

Time did not permit a presentation on foreign material in sterile powders prepared by Eduardo Cabas of Vitropharma. This presentation is available on the interest group Web page. Our interest group is not scheduled to meet at the Spring Meeting, but sessions are planned in conjunction with the PDA/FDA Joint Meeting and at the Annual Meeting. A follow-up to the one-day Special Scientific Forum on Visual Inspection, held September 2000, is also being developed for 2001.

Packaging Science Interest Group

Edward J. Smith, Ph.D.
Packaging Science Resources

The meeting included several reports from members and presentations by two guest speakers.

Dr. Allen Vaida, Executive Director of the Institute for Safe Medical Practices (ISMP), spoke to the interest group about the importance of labeling and packaging in medical error reduction. His full presentation can be found at http://www.ismp.org/pdapackaging.ppt.

Dr. Robert Hamilton, Johns Hopkins University School of Medicine, reported the results of his study on the latex sensitivity of rubber closures. He reported that some latex-sensitive subjects did elicit a positive response to certain extracts of closures made from dry natural rubber. The full report will submitted for publication in an upcoming issue of the *Journal of the American Medical Association* (JAMA).

Dr. Dana Guazzo, RxPax, L.L.C., summarized the important aspects of PACPAC for the group, and Diane Paskiet, from Monarch Analytical Laboratories, presented the latest information and issues on Phthalate plasticizers.

USP <381> on rubber closures is being revised and Karl Weimann of Wheaton Pharmatech summarized the differences between a proposal presented by PDA and one published by USP in *Pharmacopeial Forum*. The PSIG will submit a written response to USP's proposal based on comments and issues discussed at the PDA meeting.

Edward Smith, Ph.D., Packaging Science Resources, reported on some evolving changes in EP and ISO test methods on rubber closures as well as a proposal by Nancy Sager of FDA regarding "CDER Approved Packaging."

Mike Gross, Ph.D., Aventis, addressed the group on the formation of a planning committee for a Special Forum on Extractables. (See Drug/Device Delivery System IG section, above.)

Finally, Roger Asselta of Comar is looking for more user-members interested in joining the Task Force on the Standardization of Glass Tubing-Vial Measurements. Please contact Roger at 856-507-5715 if you have an interests in vial specifications. ■

QA/QC Interest Group Is Now Online

by Don Elinski
Geneva Pharmaceuticals, Inc.

In response to increasing interest in QA/QC issues an online forum has been established on the PDA Web site. The forum is intended for QA/QC Interest Group Members to share insights and to request information on Quality Systems, QA/QC Organization, Compliance concerns, Technical inquiries, and other topics. To participate, either go directly to the forum at http://forum.infosrc.com:8080/~PDA or to www.pda.org (select 'Online Forums' then register for the forum or enter as a guest).

Interactions will be monitored and topics of interest can serve to develop future Interest Group meetings, technical reports, training, and seminars. We look forward to what we expect to be a high-level discussion forum. ■

2001 Spring Interest Group Meetings

As of the date of publication, the following Interest Groups will meet at the upcoming PDA 2001 Spring Conference in Las Vegas, March 11–14, 2001:

Monday, March 12
4:15 p.m.–5:30 p.m.

Contract Manufacturing
Leader: Michael R. Porter,
Eli Lilly & Company

Ophthalmics
Leader: Richard M. Johnson,
Alcon Laboratories, Inc.

Stability
Leader: Rafik H. Bishara, Ph.D.,
Eli Lilly & Company

Vaccines
Leader: Frank S. Kohn, Ph.D.,
Wyeth-Lederle Vaccines & Pediatrics

Tuesday, March 13
4:15 p.m.–5:30 p.m.

Computer Systems
Leader: Michael L. Wyrick,
KMI/Parexel

Inspection Trends/Regulatory Affairs
Leader: Robert L. Dana,
Bristol-Myers Squibb

Lyophilization
Leader: Edward H. Trappler,
Lyophilization Technology

Quality Assurance/Quality Control
Leader: Don E. Elinski,
Geneva Pharmaceuticals, Inc.

Wednesday, March 14
10:30 a.m.–12:00 p.m.

Biotechnology
Leader: Frank Matarrese,
Chiron Corporation

Filtration
Leader: James D. Wilson

Microbiology/Environmental Monitoring
Leader: Jeanne E. Moldenhauer, Ph.D.,
Vectech Pharmaceutical Consulting, Inc.

Return your completed PDA membership application, with payment made to: **PDA, Inc., P.O. Box 79465, Baltimore, MD 21279-0465 USA** or fax it to: (301) 986-1093. *(If form is faxed, it must include necessary credit card information.)*

Member Info

Please type or print clearly

Last Name _____

Mr.❍ Ms.❍ Dr.❍ First Name _____ MI_____

Job Title _____

Company _____

Address _____

City _____ State/Province _____

Country _____ Zip+4/Postal Code _____

Business Phone# _____ Fax# _____

E-mail _____

Member Profile

Business Environment (check one)

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

Professional Interest (check all that apply)

- ❑ Aerosols
- ❑ Analytical Chemistry
- ❑ Blow-Fill-Seal
- ❑ Biologicals
- ❑ Biotechnology
- ❑ Calibration
- ❑ Contract Manufacturing
- ❑ Computer Validation
- ❑ Drug/Device Delivery Systems
- ❑ Formulation Development
- ❑ Filtration
- ❑ GMP Compliance/Inspection Trends
- ❑ Inspection Trends/Regulatory Affairs
- ❑ Isolation Technology
- ❑ Liquids
- ❑ Lyophilization
- ❑ Manufacturing/Production
- ❑ Microbiology/Environmental Monitoring
- ❑ Maintenance
- ❑ Ointments
- ❑ Ophthalmics
- ❑ Packaging Science
- ❑ Parenterals
- ❑ Production & Engineering
- ❑ Quality Assurance/Quality Control
- ❑ Research
- ❑ Solid Dosage Forms
- ❑ Stability
- ❑ Sterilization/Aseptic Processing
- ❑ Training
- ❑ Vaccines
- ❑ Validation
- ❑ Visual Inspection of Parenterals

Payment (US Dollars Only)

Please note: *Contributions or gifts to PDA are not tax-deductible as charitable contributions. However, they may be deductible as ordinary and necessary business expenses.*

Individual Membership $150. Please check the appropriate box:

❑ **Check** enclosed ***Charge:*** ❑ MC/EuroCard ❑ VISA ❑ AMEX ❑ **Wire Transfer:**

(must be net of all bank charges; include member name) Instructions: SunTrust Bank, ABA #051000020, PDA Account #209364254, Swift#UVBIUS33

Account Number _____ Exp. Date _____

Name _____
(exactly as on card)

Signature _____ Date _____

Federal Tax I.D. #52-1906152

LTR 02/01

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

Use of Microsoft Access in FDA-Regulated Databases (Part 1)

compiled by Russell E. Madsen, PDA

The following exchange, taken from the Pharmaceutical Sci-Tech Discussion Group on the Internet, provides interesting and current perspectives on practical—and sometimes theoretical—issues affecting the pharmaceutical industry on a day-to-day basis.

This month's posting explores the use of Microsoft Access in FDA-regulated databases in the pharmaceutical industry. Because of the length of the discussion, the article will be concluded in next month's issue of the *PDA Letter*.

For information about becoming a member of the discussion group see the PDA Web site at www.pda.org. As always, the opinions expressed are those of the writers.

Question

We heard from two different consultants that the FDA is not approving computerized systems based on Microsoft Access. The main two reasons were:

1. Lack of security means; and
2. No audit trail.

Now for the questions:

1. Is this true? If yes, where was it published?
2. If a system is based on Access but programmed in a way that solves the security and audit trail problems, is this enough?

Response 1

To the best of my knowledge, the FDA does not "approve" computerized systems (OK, I suppose if the system were a medical device it would be a different story). They do, however, cite companies for deficiencies found in those systems during inspections.

The lack of security and lack of audit trail in Access is a serious problem because of 21 CFR Part 11 - the agency would view records maintained in such a system as noncompliant.

If you provide solutions to those issues, then Access should be acceptable (assuming, of course, you are in compliance with the rest of Part 11).

Response 2

I believe that your consultants are right. The information you seek is published in the *Federal Register*, which you can access via the internet.

Security and traceability are primary concerns for any computer system. As you must know from experience, computer firms are notoriously lax in admitting their problems, closing backdoors in programs, etc. This has led to a lot of mistrust. Regulatory agencies must be assured that data, once entered, cannot be altered, and if it is that a full and complete record is maintained of the original as well as the corrected entry, a feature I do not believe Access has.

The easiest solution is to limit program acceptances to a few well established and maintained programs. While this is a blow to the ego of some people who enjoy doing their own program, it really is the only easy, safe and secure way for an international organization like FDA to act, or any international company. Proprietary software may make you feel good but it is a nightmare for large organizations faced with reviewing thousands of submissions. Remember, regulatory agencies must think globally.

My advice is to always talk to FDA, especially the Divisions doing your review, before making far reaching decisions for your company. That way you avoid conflicts and delays. Up until about two years ago, some Divisions required data submissions in Apple not Windows format. A big difference.

Response 3

I don't know which crazy consultant told you such…, but sad to say it's true.

Response 4

Even though I've never heard of a FDA investigator explicitly naming a computer software package and stating it is not acceptable, it would probably be warranted in this instance. But I seriously doubt you will find a 483 or warning letter that says MS Access is not acceptable. If I'm wrong, I'd also be VERY interested in seeing the official FDA transmittal stating such.

As for your second question, let me flip this around. If you contacted Microsoft, told them what you were trying to do with MS Access (i.e., building a Part 11 compliant system), explained to them the regulatory requirements for audit trails and security, I guarantee you they will NOT recommend Access as a solution. They will instead direct you to their SQL Server Database product. MS Access was never designed to be a robust, large scale, secure environment—MS created SQL Server to fill that niche instead. Its kind of like getting mad at Ford because your new Escort won't pull a 30 foot camper trailer properly!

You can place as many programming front ends on top of Access as you want to try and fulfill these requirements, but they will not be fully successful—there are too many limitations, back doors and hacks against Access to ever prove it was secure or capable. The level of security and integrity required to be Part 11 compliant require these features to be built into the database as core functionality, not kluged together as an afterthought. Look to SQL Server, Oracle, or DB2 for solutions, not Access.

Response 5

So here is a follow-up question.

My company was planning to design an inventory database using Access (since we had staff members familiar with the program). Apparently,

this is not wise, so, is SQL the way to go? Or are there other inventory programs out there currently available that may be acceptable? We are wanting to have something that will both handle our raw material and final product inventories.

Response 6

I think it depends on what you want to use Access for. If you want it to fulfil a requirement for GMP records, the lack of Part 11 compliance is certainly a problem. However, if it is merely an aid to control hard copy documents and records, such as an indexing system for SOPs or training records, I doubt if FDA could object.

Response 7

Your best bet is to first determine what your exact needs are, then find a tool to fit those needs, rather than the other way around. SQL Server, Oracle, DB2 (to name a few) are all good databases, but they each have peculiarities that lend themselves better to different applications. Also, even though SQL Server looks similar to Access on the surface, only a properly trained DB developer will know how to develop and configure the system to support Part 11.

What you should do is develop your user requirements—independent of platforms or applications. Detail your work flows, what data you need to collect, what the business rules are surrounding that data, what other systems need to integrate to your inventory system, and put it together in a formal document. Both PDA Technical Report No. 18 and GAMP have good appendices that detail what should be in a user requirement document.

Then, contact vendors, developers, and/or integrators, show them your requirements (which should include Part 11 information), and have them propose platforms and applications to fulfill your needs. If there is an off the shelf package that meets all your needs, great! If not, then you will need to follow the lifecycles detailed in both TR No. 18 and GAMP to develop a robust and validatable system that meets your needs.

Like I stated in my earlier post, Part 11 compliance can not be cobbled together as an afterthought, it must be designed in from the beginning. Any vendor or integrator that tells you they can massage Access and/or Windows 9X to be Part 11 compliant should probably be removed from your bid list.

Response 8

Like you said, Access isn't a software compliant with 21 CFR Part11 for several reasons such as lack of security, no audit trails, etc. You should be looking for products for Windows NT, SQL, and Oracle environments. You can visit the Web site http://www.dmius.com and search information about Regulus Equipment Tracking. This product is developed for "FDA regulated industries" and could be the right choice for you.

Response 9

In implementing 21 CFR Part 11, FDA laid out for us their concern about the integrity of data stored in computer systems. They laid out a series of specifications that, when met, produce a compliant system. They DO NOT require that a security system be totally unbreakable! FDA is looking at accidental or intentional misuse of a system containing manufacturing or quality system records.

As pointed out earlier, you should not get mad at Ford because your Escort has a hard time pulling your trailer. Likewise, the FDA will not issue a ruling saying that you cannot use an Escort after you put in a customized transmission to handle the load.

Clearly, if you're designing a new system from scratch, regulatory pressures will probably lead you into an ultimately simpler path of using a 'Big' database system: SQL Server, Oracle, etc.

But—many, many companies are already using Microsoft Access database systems to maintain quality system records; whether they are manufacturing batch records, personnel training files, or inventory control systems. These users will often not have the ability to design a new system and migrate all of their existing records to that new system. These users can and must consider implementing front-end changes that accomplish, by code, what Access does not natively provide: Improved password security with aging and intrusion detection; an audit trail with prevention and/or detection of tampering; electronic signature authority with issuance, application, verification, and revocation functions; and other Part 11-specific functions.

I am aware of development activities to produce a 'retrofit' module for users to install into existing Access databases, to assist in implementing Part 11 functionality. And it can't be soon enough!

Response 10

A post by the commenter states "Any vendor or integrator that tells you they can massage Microsoft Access and/or Windows 9X to be Part 11 compliant should probably be removed from your bid list." He also states "Microsoft Access was never

Join this lively online discussion group, where more than 2,000 of your colleagues from around the globe meet and find solutions to complex issues. Access is open to both PDA members and nonmembers, and discussions may be accessed via e-mail or the web.

See the PDA Web site at **www.pda.org** to sign up via the web. Send an e-mail to *requests@www2. pharmweb.net* if you don't have web access, with one of the following commands placed in the body of the message: "subscribe PharmTech" (to receive individual messages daily), or "subscribe digest PharmTech" (to receive one daily digest). Replace "subscribe" with "unsubscribe" to leave the list. For help topics, type "help PharmTech" in the body of the message and send.

designed to be a robust, large scale, secure environment—MS created SQL Server to fill that niche instead. It's kind of like getting mad at Ford because your new Escort won't pull a 30 foot camper trailer properly!"

I disagree.

a) The choice is not between Access and SQL Server. Microsoft Access is a front end—the back end may be Jet, SQL Server, or any other SQL/ODBC Compliant database. While Jet may not be the database of choice for all automated systems, it has served admirably as a back end for the very popular, and very validatible Calibration Manager from Blue Mountain software (which incidentally runs on Windows 9x) albeit with a Visual Basic front end.
b) Speaking of Visual Basic, of course you would not use Microsoft Access out of the box for a 21 CFR Part 11 compliant system.
You would not utilize Microsoft Access macros to build a 21 CFR Part 11 compliant system.
You could however use the built-in Visual Basic platform coupled with a well defined development methodology (as specified in your Software Quality Assurance documents) and build a 21 CFR Part 11 compliant system that meets your user's documented requirements. If those requirements call for the robustness of an enterprise wide system with many, many concurrent users, you may incorporate SQL server—for many department level systems, Jet will suffice. If these requirements call for electronic signatures/submissions, you may incorporate an ActiveX components with this functionality (if Silanis Approve It is good enough for Kemper Masterson's GMPware software, it may be good enough for you).
c) Finally, there are many good sources of 21 CFR Part 11 compliance information—my advice is to seek them out and develop an informed opinion. The industry faces a challenge to meet the very rigorous (and very appropriate) requirements of 21 CFR Part 11 in a way that enhances, not hinders pharmaceutical product development.

Response 11

Well, then I guess we will have to agree to disagree on some points (but not most).

I will go back to my earlier post and reiterate that if you contact Microsoft and explain to them what you are trying to do with a database to make it Part 11 compliant, they will refer you away from Access and Jet. Jet was never designed to fill the "mission critical" database niche—SQL, Oracle, and DB2 were. What software vendors, suppliers, integrators, and sales reps need to understand that for the pharmaceutical industry, Part 11 *is* "mission critical" because it is codified law. If the database engine manufacturer doesn't support using Jet/Access for a particular application, how can third party vendors say differently?

We can spend weeks going back and forth where Jet has shortcomings and how you can program a VB/VBA/C++/etc front end to work around or address these shortcomings, but it misses my main point—your database engine should have Part 11 compliant features as part of its core functionality, not as an afterthought, or an add on by a third party. That is the fundamental reason why an Access proponent will be immediately crossed off my bid list.

When third party vendors continue to choose Jet over other more appropriate engines, it is mainly for several reasons: license costs, lack of experience working with more advanced database engines, and not wanting to expend the costs to rework their product to a new engine. The cost of a SQL license over Jet is peanuts compared to the cost of validation, integration, or worse yet a 483 or Warning Letter, so why should we accept lack of developer experience or effort as an answer to Part 11 non-compliance?

The agency used Part 11 to raise the bar on the pharmaceutical industry, now it is our turn to raise the bar on our software vendors. What was validatable and acceptable three years ago, is no longer the case. If you have legacy Jet/Access based systems, using front end upgrades to supply an interim solution to address Part 11 is probably acceptable: the agency has made it clear they don't expect overnight full compliance. However, as a long term solution, the vendor had better be coming up with a migration path to a more suitable engine. We don't need something that will just suffice, we need something that is designed to be robust, stable, and compliant, from the engine out.

Response 12

I disagree. This is from a white paper on the Microsoft site:

Microsoft Access 2000 is a powerful relational database application that a desktop user can use to efficiently create and manipulate database systems.

The combination of ease-of-use and power in Access makes it the top choice among developers who frequently use Access as a front-end to SQL.

Access has two major components. The first contains an application development environment for Visual Basic for Applications programmers that include forms technology, reports and database administration. In addition, as mentioned earlier, there is also the User Interface (UI) common to both Access and the other Office applications.

The second component in Access, and the main topic of this paper, is the data engine. Before Access 2000, users and developers were using the Jet data engine, whether they knew it or not. In the next version, users and developers will be given a choice of data engines. They can continue with an improved version of the default Access data engine Jet 4.0, or MSDE, a new data engine

option in Access 2000.

Jet works best if you want the highest compatibility with Access 97 or earlier versions; MSDE works best for new applications if you want to develop from a single code base that scales from a single user to thousands of users or if you ever anticipate a future need to scale up to SQL Server. By the end of reading this short paper, you will be able to determine which data engine.

So, what Microsoft does say is that Access is a viable front end to develop a system that could scale from a single user's desktop with the Jet database engine as the back end, to an enterprise-wide system using SQL Server as a back end. They say that Access is robust enough to support thousands of users. The choice therefore is not between Access and SQL Server but instead how to structure a system that fits the user's requirements.

Response 13

A commenter stated, "When third party vendors continue to choose Jet over other more appropriate engines, it is mainly for several reasons: license costs, lack of experience working with more advanced database engines, and not wanting to expend the costs to rework their product to a new engine. The cost of a SQL license over Jet is peanuts compared to the cost of validation, integration, or worse yet a 483 or warning letter, so why should we accept lack of developer experience or effort as an answer to Part 11 non-compliance?"

Now we are getting somewhere. He correctly now points out that the real choice is between database engines—not between front-ends. Why then does he state that "…an Access proponent will be immediately crossed off my bid list."?

I am an Access proponent. In a given system I will use Jet, MSDE, or SQL server as my back-end. I will use a well developed design methodology incorporating risk analysis to decide which is most appropriate to my client's need. I am sorry that the commenter would cross me off his bid list.

Response 14

Has anyone determined how much it cost to be Part 11 "compliant"?

Does anyone really expect FDA to go into Microsoft Headquarters to perform an audit?

Has any NDA or ANDA not been approved due to lack of computer qualification or software validation?

Response 15

The agency felt that when it finalized Part 11 that the costs would be minimal. In fact, page 13462 of the preamble says "Thus, the industry will incur no net costs as a result of this rule." In reality, that has not been the case. Some Industry pundits have projected that the cost of Part 11 compliance will exceed the costs we incurred for Y2K compliance. I suspect they aren't too far off base.

As for auditing Microsoft, IBM, or even Intel for that matter, I doubt it will ever happen. Their resources are spread pretty thin as is, why would they go delving off into areas that are really outside their scope of expertise.

I couldn't tell you about NDAs or ANDAs not being approved, but, there is a fairly substantial list of FDA 483s and Warning Letters that have been issued citing computer and software validation (or lack thereof).

Just to name a couple: http://www.fda.gov/foi/warning_letters/m671n.pdf and http://www.fda.gov/foi/warning_letters/m2811n.pdf.

Response 16

As we all know from the newspaper, literature, regulatory actions, etc., computers are far from secure. Even the big boys like Microsoft have been hit by hackers. Few companies will ever admit their security has been breached.

Having examined many hard copies of records, both in government and industry, I personally have seen records that were altered without proper documentation or authorization, not all documented. That's why the FDA is so hard-nosed about this issue. It all boils down to one word—ACCOUNTABILITY. I'm willing to bet that some firms might have trouble documenting what documents they have on file with FDA.

If everyone out there develops their own program, will they be willing to train every FDA inspector to use and understand the program and subject it to numerous attacks? That surely doesn't sound like a cost effective approach to me.

To my simple mind it is easier to use an approved vendor's system rather than try and reinvent the wheel. How much beta testing of your special program will be done? Can you equal or surpass the beta testing of the vendor?

Do you know all of the back-doors into the programs that you use to develop yours? What about the ones the companies who wrote them put in?

If industry continues to make demands for faster inspections and reviews, it is in their own best interest to standardize wherever possible. Getting faster results from FDA is a common goal for industry and the Agency, not FDA's job alone.

I suggest that everyone think of how to standardize as many items as possible and do so by working with the Agency and one another. Not lip service but real action based on scientific facts.

Having been on both sides of the fence I can tell you that both sides could use improvement. They are both guilty of the same sins.

[To be continued next month.] ■

PDA's International Opportunity of the Year

Global Pharmaceutical Manufacturing and Quality Strategies

by James C. Lyda, PDA

April 5–6, 2001
Hotel Grand Timeo
Taormina, Italy

English Only

Join fellow PDA members for this special opportunity sponsored by PDA and the PDA Italy Chapter. Not likely to be repeated, this special two-day conference will feature industry leaders and experts from across PDA who will address international quality and manufacturing issues. Situated in the breathtaking venue of Taormina, with a view of the Mediterranean and Mt. Etna, the largest active volcano in Europe, this conference will equip you with information today that will ensure you are efficient, competitive and quality-safe tomorrow.

For more information visit the PDA Web site, www.pda.org, or contact PDA at info@pda.org. In Europe, contact lyda@pda.org.

Chairs: **Robert B. Myers**, Schering-Plough, USA and **Antonino Giannetto**, S.I.F.I, Italy

Thursday, April 5

Welcome & Opening Remarks
Antonino Giannetto, Technical Director, S.I.F.I, Italy

Pharmaceutical Manufacturing in Today's International Market
- Opening Address—"The Global Business Environment and Strategic Manufacturing Issues"
  James R. Kamienski, VP Manufacturing, Baxter Healthcare Corporation, USA
- "Global Manufacturing and Sourcing Today"
  Robert Myers, VP Operations, Schering-Plough, USA, PDA Chair

Quality Challenges in International Business Growth
- "Building a Multinational-Culture, Quality and Costs"
  Mary Pendergast, Executive VP Government Affairs, Elan Pharmaceuticals, (former Deputy and Senior Advisor to the Commissioner, FDA), USA
- "Risk Assessment in Mergers & Acquisitions"
  Joyce Aydlett, Aydlett and Associates, Immediate Past Chair, PDA, USA

Lunch Provided

International Technology Issues
- "Supply Chain Management"
  Jim McKiernan, Partner and Leader of Pharma SCM Practice, Pricewaterhouse Coopers, Switzerland
- "International Technical Transfer"
  Antonino Giannetto, Technical Director, S.I.F.I., Italy

Information Management—Strategies for Optimizing What You Know
- "Ensuring Quality Through Knowledge Management: Establishing a Culture of Exchange"
  Michael Vivion, Professor, Director Special Communications, F. Hoffmann-La Roche, Switzerland
- "PDA's Role in Facilitating Pharmaceutical Quality and Manufacturing"
  Edmund M. Fry, PDA President, U.S.A.

Adjourn for the day

Dinner in Catania—*Offered by S.I.F.I. President, Dr. Giuseppe Benanti*

Friday, April 6

Manufacturing of Biologics and Biotechnological Drug Products—International Issues
Chairman: Prof. Guiseppe Vicari, Ministero della Sanità, Italy, & past member CPMP, past Chair EMEA Biotechnology Working Party (BWP)
- "Perspectives on Biotechnology Regulatory Issues in Europe"
  Dr. Carlo Pini, Chief, Department of Immunology, Instituto Superiore di Sanità, Italy, & member, EMEA BWP
- "Overview of Global Biologics Production"
  Coleman Casey, General Manager, Schering-Plough, Ireland

International Sourcing of Active Pharmaceutical Ingredients and Starting Materials—Risks and Issues Today
- "BSE/TSE Risks Associated with APIs and Starting Materials—The Situation in Europe and the Global Implications for Manufacturing"
  Brian R. Matthews, Superintending Pharmacist, Alcon Laboratories Ltd., UK
- "International Sourcing of APIs A Producer/User Perspective"
  Georg Roessling, Head CMC Ultrasound, Schering AG, Germany

Lunch Provided

Regulatory Environment and International Compliance Issues Affecting Global Manufacturing
- "Current EMEA Developments Affecting Pharmaceutical Manufacturing"
  Frank Hallinan, Chairman, Irish Medicines Board
- "Industry Perspective on US FDA"
  Stephanie Gray, VP Worldwide Quality Strategy and Policy, GlaxoWellcome (former Director, Office of Compliance, CDER,FDA), USA
- "Managing International Compliance in a Global Business"
  Tim R. Marten, Vice President International Compliance, AstraZeneca, UK

Closing Remarks

Registration Form on page 42

International Calendar

March 26–28, 2001
IV European Parenteral Conference
Supported by the European Sterile Products Confederation (ESPC)
Barcelona, Spain
Contact:
Organization Secretary, International Meetings
Capitan Arenas, 3-5 bajos
08034 Barcelona
TEL: +34 93 2039293
FAX: +34 93 2804643

March 29–30, 2001
Pestivirus Contaminations of Bovine Sera and Other Bovine Virus Contaminations
Home Plazza Hotel
Paris, France
Contact:
http://www.pheur.org or
European Directorate for the Quality of Medicines (EDQM)
at info@pheur.org.

April 5–6, 2001
PDA & PDA Italy Chapter Conference on
Global Pharmaceutical Manufacturing and Quality Strategies
Grand Hotel Timeo
Taormina, Italy

May 13–16, 2001
R^3 Nordic Annual Symposium
Stockholm, Sweden
Contact: Leif Mansson
Kamrersvagen 63
SE-23734 Bjared, Sweden
E-mail: contam@minpost.nu
TEL: +46 (0) 46-29 2581

May 17–18, 2001
Computer Products Supplier Auditing Process Model: Auditor Training
Stockholm, Sweden
Grand Hotel

Contact PDA or go to www.pda.org for additional details on PDA events

Contact Information for PDA Europe

Mailing Address:
PDA
Postfach 620
CH-4144 Arlesheim
Switzerland

Reminder: the following numbers should be used to contact Jim Lyda and the PDA Europe Office:
phone +41 61 703 1688,
fax (analog) +41 61 703 1689.

Layered Ad

4th PDA European Forum Tracks Latest in Environmental Monitoring

Environmental Monitoring for Aseptic Processing of Medicinal Products

by James C. Lyda, PDA

6–7 November 2000

The 4th annual PDA European Forum 2000, "Environmental Monitoring for Aseptic Processing of Medicinal Products," was held November 6–7, 2000 in Basel, Switzerland. Over 130 people attended the conference, which is the primary annual event of the PDA European Chapter. The forum featured lectures, case studies and group discussions including presentations by Dr. David Hussong, CDER, FDA, who described the latest FDA initiatives for sterile products.

Discussing the European PDA 2000 European Forum: Bernard Kronenberg, Bakrona Basel AG, Switzerland and President of the PDA European Chapter; and Carlo Voellmy, Novartis Pharma AG, Switzerland and Program Chair.

The following speakers made presentations at the conference:

Klaus Haberer, Compliance-ASIM, Germany
Julia Mottishaw, Aventis, UK
Doris Kattner, Novartis Pharma, Switzerland
Jeff Price, Pharmacia, USA
Iain Baxter, GlaxoWellcome, UK
Robert Johnson, SmithKline Beecham, UK
Eric Dewhurst, Norton Steripak, UK
Nigel Halls, GlaxoWellcome, UK
Kenneth Muhvich, The Validation Group, USA
Bernd Sessler, F. Hoffmann La Roche, Switzerland
Fabrice Greutert, Ares Serono, Switzerland
Russell E. Madsen, PDA, USA

Environmental monitoring continues to be a hot topic. And while the forum brought a clearer understanding of the issues which must be considered, there is still a high degree of variation from region to region in the world.

PDA again thanks the Program Committee which gave their time and expertise to develop the forum:

Clive Blatchford, Aventis Pharma, France
Klaus Haberer, Compliance-ASIM, Germany
Nigel Halls, GlaxoWellcome, UK
Bernard Kronenberg, Bakrona Basel, Switzerland
James Lyda, PDA Europe
Russell E. Madsen, PDA USA
Georg Roessling, Schering AG, Germany
Fulvio Tavellini, Lilly Italia
Carlo Voellmy, Novartis Pharma, Switzerland
Keith Wickert, Pall Biopharmaceuticals, UK ■

Environmental Monitoring Today: Fulvio Tavellini, Lilly Italia, (moderator); Andrea Raso, Lilly Italia; David Hussong, CDER, FDA, USA; Klaus Haberer, Compliance-ASIM, GmbH, Germany; and Russell Madsen, PDA, USA.

Microbiological Aspects of Environmental Monitoring I: Doris Kattner, Novartis Pharma AG, Switzerland; Keith Wickert, Pall Biopharmaceuticals, UK, Moderator; and Julia Mottishaw, Aventis, UK.

Microbiological Aspects of Environmental Monitoring II: Iain Baxter, GlaxoWellcome International Product Supply, UK; Clive Blatchford, Aventis, France, (moderator); and Jeff Price, Pharmacia, USA.

Advances in Microbiological Monitoring: Bob Johnson, SmithKline Beecham, UK; Nigel Halls, GlaxoWellcome, UK, (moderator); and Eric Dewhurst, Norton Steripak, UK.

Data Evaluation for Microbiological Monitoring: Nigel Halls; Kenneth H. Muhvich, The Validation Group, USA; and James Lyda, PDA Europe (moderator).

Physical Monitoring: Fabrice Greutert, Laboratories Serono, Switzerland; Bernd Sessler, F. Hoffmann La Roche, Switzerland; and Bernard Kronenberg (moderator).

Spring Conference 2001 from cover

The conference will offer two days of interactive *Interest Group* discussions and roundtable breakfast discussions to provide additional forums for information exchange and to expand your networking opportunities.

Education courses being offered in conjunction with this conference include:

- ✓ Cleanroom Management
- ✓ Environmental Surveillance and Control
- ✓ Introduction to Validation
- ✓ Identification of Microorganisms Using Comparative DNA Sequencing
- ✓ PDA Computer Products Supplier Audit Management: Overview Training
- ✓ How to Design an Effective Regulatory Training Program
- ✓ Writing and Auditing CGMP Documentation
- ✓ Environmental Mycology

Registration Form on page 32!

Benefit from the informative and educational exhibit hall, which includes the latest displays in science and technology. All registrants receive access to the full exhibition, providing the opportunity to interact with over 75 exhibiting companies. Exhibitors will host r*oundtable lunch discussion groups*, providing a unique forum for information exchange on the industry's latest technologies and products.

PDA's meetings and conferences provide a forum for the most current regulatory information, scientific discoveries, research and technology in the industry. Those interested in pharmaceutical science and technology in the research and generic pharmaceutical, biotechnology, bulk chemical, medical device and related industries will benefit from participation in this cutting-edge conference. Register today. ■

FDA Briefing JUST ADDED

Reporting of Biological Product Deviations in Manufacturing

Sunday, March 11, 2001

1:00 p.m.–5:00 p.m.

Arrive early on Sunday, March 11 so you can participate in the newly added session featuring an FDA briefing on the *Reporting of Biological Product Deviations in Manufacturing.* **Sharon O'Callaghan**, Center for Biologics Evaluation and Research, Food and Drug Administration, will provide an informative briefing from the FDA on the amended regulation requiring licensed manufacturers of biological products to report errors and accidents in manufacturing that may affect the safety, purity or potency of a product. The final rule requires licensed manufacturers, unlicensed registered blood establishments and transfusion services who had control over the product when a deviation occurred to report to FDA the biological product deviation if the product has been distributed. The final rule also establishes a 45-day reporting period. This rule will become effective May 7, 2001.

PDA Good Electronic Records Management (GERM) Conference, Courses and Exhibition

April 2–6, 2001
Hyatt Tampa Hotel
Tampa, Florida

Hotel Information
Hyatt Regency Tampa
Two Tampa City Center
Tampa, Florida

Be sure to request the PDA Conference Rate:
$164.00 single and $189.00 double

Reservations:
813-225-1234 *or*
800-233-1234
Fax: 813-273-0234

Make your reservation by March 9, 2001 to guarantee the discounted PDA rate. After the March 12, 2001 reservation deadline, rooms will be released for sale to the general public.

PDA's GERM conference is designed to go beyond the traditional Part 11 conference format, with a comprehensive overview of the entire life cycle of an electronic record being addressed from pre-record to post-record. The sessions will focus on pragmatic approaches to dealing with all aspects of electronic records and electronic signatures, with an emphasis on the end-user perspective.

Many attendees at the PDA/FDA Public Conference on Technical Implementation of Part 11 in June 2000 in Philadelphia expressed a desire for more substantive presentations on creative Part 11 solutions, especially for Legacy systems, and to hear more from end-users rather than vendors. PDA has developed the GERM conference to address those needs and to promote good electronic records management practices. The principle goal of this conference is to provide a forum for information exchange based on practical experiences and to build on lessons learned from real-life Part 11-compliance work.

The conference will feature presentations and case studies by leading pharmaceutical industry companies including: Abbott Laboratories, Amgen, Inc., Bristol-Myers Squibb, Centocor, Convatech, Dupont Pharmaceuticals, Pharmacia, Jansen Research Foundation, Pfizer and Pharmacia Corp. The FDA has been invited to present the latest information on the development of Part 11 guidance documents.

PDA will feature the nation's leading thought leaders on managing electronic records including:

Charles Dollar, Ph.D., Senior Consultant with Cohasset Associates, Inc. has extensive experience in dealing with the impact of digital technology issues on archives and records management. From 1974 to 1994 he was on the staff of the National Archives and Records Administration where he specialized in electronic storage media issues.

Randolph Kahn, Esq., Senior Consultant, Co-

hasset Associates, Inc. With an extensive background as a trial attorney, Mr. Kahn advises major clients in complex document-based litigation.

Jeff Rothenberg, Ph.D., Senior Computer Scientist in the Social Policy Department of the RAND Corporation. Dr. Rothenberg is the author of the landmark *Scientific American* article, "Ensuring the Longevity of Digital Documents," in which he called for immediate action to prevent future loss of today's electronic documents.

Hon. Kathie Blackman Dudley, Esq. Along with her experience as a criminal prosecutor and a private practitioner, Ms. Dudley was also elected as State Court Judge in Missouri for 12 years. She recently spent five years in Corporate Law at State Farm Insurance Companies as legal counsel for issues relating to records management.

A multi-track format is being offered to address the following topics:

- **Concepts and Practices in GERM**

Before an organization can implement an effective Part 11 strategy, it must first understand and interpret the regulations, and translate this understanding into specific guidance for the company. The focus of this track will be on characterizing current and desired states for e-records and e-signatures. Also included will be the establishment of e-record policies and practices for information trustworthiness that support business needs and conform to emerging laws and regulations. Papers covering concepts for secure computing frameworks based on sound organizational, operational and computer controls will be presented. The session will also address challenges in establishing a knowledge base among users and business management relative to electronic records and signature concepts.

- **Diagnosing and Assessing**

The early stages of a comprehensive Part 11 strategy include identifying affected systems and conducting gap analyses to uncover deficiencies. The focus of this track will be on methods and techniques used for inventorying and assessing existing record assets and installed computing bases. Papers will present case situations and experiences associated with determining e-record and e-signature exposures and sensitivities relative to existing and planned computing environments. Papers will also present examples of project team performance and operation methods in assessing installed computing bases.

- **Strategies and Approaches**

After the systems and gaps are categorized, the next steps include determining appropriate solutions (e.g., remediation, replacement or retirement). This track will focus on examples of strategies to evolve legacy environments with the goal of minimizing exposures and threats to operating environments and informational assets.

- **Hybrid Arrangements**

Perhaps 90% or more of systems today exist in a hybrid arrangement, whereby paper records and/or handwritten signatures are maintained in addition to e-records. This track will highlight creative solutions for linking handwritten signatures on paper to the corresponding e-records.

- **Record Archival and Retention**

The focus of this track will be record utility and processability issues associated with record migration and long term retention. Papers will present case studies in designing and implementing e-record retention environments using current technologies and hybrid arrangements.

- **Project Execution**

With system solutions identified, the next phase includes establishing prioritization criteria, project planning, developing and implementing plans for execution. The focus of this track will be on executing strategies for legacy remediation and engineering new computing environments. Papers will present case studies of project management experiences, cost estimating, prioritization techniques and business process change management in fulfilling remediation plans.

- **e-Signatures and e-Records: Global Issues and Legal Considerations**

The focus of this track will be the legal and global implications of e-records and e-signatures executed in the computing environment. Papers will present studies and analysis of emerging global laws and court judgments impacting the use of e-records and e-signature practices in FDA-regulated businesses.

- **Authentication**

Section 11.10 of 21 CFR Part 11 calls for the use of "procedures and controls designed to ensure the authenticity, integrity, and where appropriate, the confidentiality of electronic records and to ensure that the signer of such records cannot readily repudiate the signed record as not genuine." The focus of this track will be to examine controls that can be applied to authenticate both the identity of users of systems and the records they create as genuine and trustworthy. Papers will address the technologies and processes that can be used to provide evidence that the users are who they claim to be and that electronic records remain reliable throughout their life cycle.

- **Outsourcing**

The focus of this track will be the expectations for trustworthy e-records and e-signatures created in service-oriented environments such as contract manufacturing services and contract clinical organizations. Papers will be presented that present case situations and examples for specifying, evaluating and assessing outsourced services performing regulated activities. ■

Included as part of each full registration is a complimentary training course on **Introduction to 21 CFR Part 11** by John McKenney, SEC Associates.

Pre-and post-conference PDA-TRI education courses will be offered, including:

Awareness Training
Supplier Auditing Training
Training and Education: The Overlooked Tool for MER Success
Key Practices for Computer Validation
Information Access and Security

Make your plans to be in Tampa April 2–6 for this important technology-focused conference. Visit PDA's Web site at www.pda.org for additional information.

Interactive exhibits and vendor demonstrations will be offered, giving attendees the hands-on opportunity to experience the latest tools and technologies. For *exhibiting opportunities*, contact Nahid Kiani at PDA, 301-986-0293 ext. 128

Discounted Airfares Information

Receive a 5% discount off published rates when you or your travel agent make your airline reservations through:

US Airways (877) 874-7687
GOLD FILE #35131668
or
United Airlines (800) 521-4041
Meeting ID # 552TW

If you use a travel agent, please ask your agent to reference the PDA meeting code.

Company, Colleague & Product Announcements

Michael Gross, Ph.D. has joined Aventis Behring as Vice President of World Wide Compliance for the blood products and therapeutic proteins business. Michael was previously Director Corporate Regulatory Affairs, Becton Dickinson and prior to that worked at Schering Plough and Triton Biosciences-Shell Oil. He began his career in regulatory affairs at the Bureau of Biologics, FDA as a review chemist for blood products. He and his family are relocating from Northern New Jersey to the Philadelphia area.

Destin A. LeBlanc recently announced the formation of a new consulting company, Cleaning Validation Technologies. The firm provides cleaning and cleaning validation services for pharmaceutical manufacturers. LeBlanc, now retired from STERIS Corporation, has more than 20 years of technical service and product development experience in cleaning and antimicrobial applications in regulated industries. He is a member of PDA, serves on the faculty of the PDA Training and Research Institute (PDA-TRI), and has lectured and is published widely on the subject of cleaning technologies and cleaning validation for pharmaceutical manufacturers. Each month, his company's Web site, www.cleaningvalidation.com, features a new "cleaning memo" on a relevant cleaning validation topic. You may contact LeBlanc at 210-481-7865 or destin@cleaningvalidation.com.

The **United States Pharmacopeia (USP)** announced a five-year cooperative agreement with the US Agency for International Development (USAID) to develop international programs in the area of drug quality and drug information. USP's activities will support the objectives of the USAID's Bureau of Global Programs, Center for Population, Health and Nutrition. The USP/USAID cooperative agreement will also support the efforts to build a Global Network for Drug Quality with the goals of reducing counterfeits, improving bioavailability/bioequivalence and improving safety. The grant activities will be implemented in Latin America, Asia, Africa and the former Soviet states. For further information, contact Nancy Blum, Program Director, Global Assistance Initiatives at 301-816-8161 or USPDQI@usp.org.

The USP also announced that the official drug standards publication, United States Pharmacopeia and the National Formulary (**USP-NF**) would soon be released as an Intranet version, on a CD-ROM. The new format is designed to provide wider, easier access to essential USP-NF information, especially for multiple users within a single organization. The Intranet version of USP-NF allows users to access standards information through a Web browser's interface and can be easily installed on a company's Intranet Web server (no activation keys are required). Details and pricing may be obtained by contacting Chris Colburn at 800-227-8772, ext. 8308, or 301-816-8308, or at cwc@usp.org.

BioWhittaker Inc., a subsidiary of Cambrex Corporation, announced the introduction of ProMEDIA Select™, the first commercially available, custom-formulated media package for media optimization. The innovative media toolbox, combined with BioWhittaker's Media Optimization Consultation Service, accelerates cell culture process development timelines by transcending traditional media selection methods. Each ProMEDIA Select™ formulation is developed to support high cell density, high and extended cell viability, and high protein production, and is certified for non-animal origin raw materials. The media contains only one recombinant human protein to simplify downstream purification processes.

Drug Delivery Systems (DDS), a division of 3M, and Purdue Pharma L.P., announced an agreement to jointly develop a new, transdermally delivered pain medication product. The novel 3M/Purdue Pharma product will deliver the potent opioid analgesic, fentanyl, via a unique transdermal drug delivery system. This prescription product, currently in Phase I evolution, is designed to provide up to seven days of continuous pain relief for patients with moderate-to-severe pain resulting from cancer, arthritis, trauma, back and disc diseases. For more information visit either the 3M Drug Delivery System's Web site at www.mmm.com/dds or the Purdue Pharma Web site at www.purduepharma.com.

Sigma-Aldrich Fine Chemicals, a division of **Sigma-Aldrich Corporation**, announced the availability of commercial quantities of a unique and broad range of high-purity inorganic materials. These items are manufactured using proprietary technologies by Aldrich-APL, LLC (AAPL), a joint venture between Aldrich Chemical Company, Inc. and APL Engineered Materials. AAPL's proprietary technology portfolio includes synthesis, sublimation, distillation and recrystallization techniques that are applied to produce high-purity inorganics and metals, in gram to metric ton quantities, to demanding purity standards in the range of 99.99%to 99.9999+% trace element basis. Sigma-Aldrich Fine Chemicals provides raw materials process development, scale-up and complex, multi-step custom synthesis services to the pharmaceutical, biopharmaceutical and industrial marketplace. These products are available in large-scale quantities for the development and manufacture of pharmaceutical, biopharmaceutical, and high-technology chemical and life science products. For more information contact Susan Lapke at 800-336-9719 ext. 5600 or slapke@sial.com. For technical inquiries contact Dr. Prashant Savle at 414-298-7924 or psavle@sial.com. ■

REGISTRATION FORM

2001 PDA Spring Conference • March 12-16, 2001 • Aladdin Resort & Casino • Las Vegas, Nevada

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

❑ Dr. ❑ Mr. ❑ Ms.

First Name | Middle Initial | Last Name

Job Title | Membership Number if known

Company (indicate full company name)

Business Address

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

Business Phone | Fax | E-mail

❑ Substituting for _____

(Check only if you are substituting for a previously enrolled colleague. If you are a nonmember substituting for a member, the additional nonmember fee must be paid.)

2. Fees

Individuals registering at the nonmember rate receive one full year of PDA membership. *(If you DO NOT want to become a PDA member, please check this box ❑).* Nonmembers registering for multiple events need only pay the nonmember fee once.

Spring Conference Registration	PDA Member	Nonmember
❑ Full Annual Meeting: *(does not include courses)*	$995	$1145
❑ Monday, March 12 Only:*	$595	$745
❑ Tuesday, March 13 Only:*	$595	$745
❑ Wednesday, March 14 Only:*	$295	$445
Optional Event Registration (included in Full Registration)		
❑ Viva Las Vegas Reception, Monday, March 12*	$75	$75
❑ Exhibit Hall Lunch, Monday, March 12*	$30	$30
PDA-TRI Courses Registration		
❑ PDA Computer Products Supplier Audit Management: Overview Training (PDA #499)	$380	$530
❑ How to Design an Effective Regulatory Training Program (PDA #414)	$350	$500
❑ Identification of Microorganisms Using Comparative DNA Sequencing (PDA #234)	$680	$830
❑ Cleanroom Management (PDA #361)	$1010	$1160
❑ Environmental Surveillance and Control (PDA #247)	$1010	$1160
❑ Introduction to Validation (PDA #375)	$1010	$1160
❑ Environmental Mycology (PDA #203)	$680	$830
❑ Writing and Auditing CGMP Documentation (PDA #755)	$680	$830
TOTAL FEES	$_____	$_____

**Additional Conference Event Registration (these events are included in full registration)*

Business Environment (check one)

❑ Pharmaceutical Manufacturing
❑ Engineering and Construction
❑ Industry Supplier
❑ Consultant
❑ Employee of Government Regulatory Agency
❑ Academic
❑ Medical Device Manufacturer
❑ Recruiter
❑ Pharmacy
❑ Laboratory
❑ Contract Manufacturing
❑ Other

Areas of Interest (check one or more)

❑ Aerosols
❑ Analytical Chemistry
❑ Biotechnology
❑ Blow-Fill-Seal
❑ Computer Validation
❑ Contract Manufacturing
❑ Drug/Device Delivery Systems
❑ Production and Engineering
❑ Filtration
❑ Formulation Development
❑ Inspection Trends/Regulatory Affairs
❑ Isolation Technology
❑ Lyophilization
❑ Microbiology/Environmental Monitoring
❑ Ointments
❑ Ophthalmic
❑ Packaging Science
❑ Parenterals
❑ Quality Assurance/Quality Control
❑ Research
❑ Solid Dosage Forms
❑ Stability
❑ Sterilization/Aseptic Processing
❑ Training
❑ Vaccines
❑ Validation
❑ Visual Inspection of Parenterals

3. Please check the appropriate box:

❑ Check enclosed ❑ Wire Transfer Charge to: ❑ MasterCard ❑ VISA ❑ AMEX

Account Number | Exp. Date | Name exactly as on card

Signature | Date

4. Return completed form with payment made to:

PDA, Inc.
P.O. Box 79465
Baltimore, MD 21279-0465 USA
Fax: (301) 986-1093 (credit cards only)

Payments must be made to PDA in U.S. dollars by check drawn on a U.S. bank, by electronic money transfer (SunTrust Bank ABA #051000020, PDA Account #209364254, Swift #UVBIUS33), net of all bank charges; by MasterCard, VISA, or American Express.

LTR 02/01

Federal Tax ID #52-1906152

Confirmation: Written confirmation will be sent to you once payment is received. You must have written confirmation to be considered enrolled in a PDA event. Substitutions: If a registrant is unable to attend, substitutions are welcome and can be made at any time. If you are preregistering as a substitute attendee, indicate this on the registration form. A nonmember substituting for a member must pay the additional fee. Refunds: Refund requests must be made in writing. Registrants whose written requests for refunds are received at PDA on or before February 12, 2001 will receive a full refund less a $35 processing fee. Registrants whose written requests for refunds are received after February 12 and on or before February 26 will receive 50% of the registration fee. After February 26, no refunds can be made. Event Cancellation: PDA reserves the right to modify the material or instructors without notice or to cancel an event. If the event must be cancelled, registrants will be notified as soon as possible and will receive a full refund of fees paid. PDA cannot be responsible for discount airfare penalties or other costs incurred due to a cancellation.

PDA USE: Date: | Check: | Amount: | Account:

Upcoming PDA-TRI Education Courses

These courses will be held at PDA-TRI in Baltimore, Maryland. For course content information, call PDA-TRI directly at 410-455-5800. To register, call PDA headquarters in Bethesda, Maryland at 301-986-0293. See page 34 for PDA-TRI Location/Hotel Information.

Assay Validation (**PDA #469**), March 5, 2001—*taught by Lynn D. Torbeck, President, Torbeck and Associates*; $550 PDA members/$700 nonmembers.

Assay Validation Using Excel Software (**PDA #751**), March 6, 2001—*taught by Lynn D. Torbeck, President, Torbeck and Associates*; $750 PDA members/$900 nonmembers.

Students must bring an IBM compatible laptop or notebook computer equipped with Windows 95, 98, NT, ME, or 2000 and Microsoft Excel (with "Data Analysis Toolpack" installed.

Contamination Control Basics (**PDA #213**), *Five dates scheduled*: March 9, 2001; April 30, 2001; June 29, 2001; September 7, 2001; November 30, 2001—*taught by Sandra A. Lowery, President of Quality Systems Consulting*; $750 PDA members/$900 nonmembers.

Computer Products Supplier Auditing Process Model: Auditor Training, April 5–6, 2001 in Tampa, Florida; May 10–11 and October 11–12, 2001 in Baltimore, Maryland; **May 17–18, 2001 in Stockholm, Sweden**; $950 PDA members/$1100 nonmembers. *For more information, vist our Web site,* www.pda.org. ■

to sign up for these PDA-TRI courses see the Registration Form on page 35.

Aseptic Processing Courses at PDA-TRI

A Comprehensive Program in Manufacturing Sterile Products

Presented by the PDA Training and Research Institute in two 1-week segments.
Week 1: *Principles and Practices in the Aseptic Processing of Small-Volume Parenterals*;
Week 2: *Practical Experience in the Manufacturing of an Aseptically Processed Parenteral Product*.
(Registrants must attend both Week 1 and Week 2 as listed in the pairings below.)

- March 26–30 & April 23–27, 2001
- May 14–18 & June 18–22, 2001
- July 23–27 & August 20–24, 2001
- October 1–5 & November 5–9, 2001

For more information on the Aseptic Processing Courses, visit our Web site at ww.pda.org. ■

PDA-TRI Education Courses at the 2001 PDA Spring Conference

Las Vegas, Nevada

PDA Supplier Auditing Process Model: Overview Training (**PDA #499**), March 15, 2001—*taught by Harvey Greenawalt, President of Audit Repository Center*; $380 PDA members/$530 nonmembers.

How to Design an Effective Regulatory Training Program (**PDA #414**), March 15, 2001—*taught by Rick H. Rogers, Vice President, Education, PDA*; $350 PDA members/$500 nonmembers.

Identification of Microorganisms Using Comparative DNA Sequencing (**PDA #234**), March 15, 2001—*taught by Michael G. Waddington, Accugenix, a new division of Acculab, Inc.*;$680 PDA members/$830 nonmembers.

Cleanroom Management (**PDA #361**), March 15–16, 2001—*taught by Anne Marie Dixon, Managing Partner, Cleanroom Management Associates, Inc.*; $1010 PDA members/$1160 nonmembers.

Environmental Surveillance and Control (**PDA #247**), March 15–16, 2001—*taught by James D. Wilson, The Validation Group and Elizabeth Moy, High Bridge Data Systems, Inc.*; $1010 PDA members/$1160 nonmembers.

Validation: An Introduction (**PDA #375**), March 15–16, 2001—*taught by Robert G. Kieffer, Ph.D., President, RGK Consulting*; $1010 PDA members/$1160 nonmembers.

Environmental Mycology (**PDA #203**), March 16, 2001—*taught by Kenneth Muhvich, Ph.D., The Validation Group*; $680 PDA members/$830 nonmembers.

Writing and Auditing CGMP Documentation (**PDA #755**), March 15, 2001—*taught by Strother D. Dixon, GMP Trainer for PDA-TRI*; $680 PDA members/$830 nonmembers.

These courses will be held during the 2001 PDA Spring Conference at the Aladdin Hotel, Las Vegas, NV. To sign up, see the registration form on page 32.

PDA-TRI Location/Lodging Information

Unless otherwise noted, PDA Institute courses are held at: PDA Training and Research Institute, 1450 South Rolling Road, Baltimore, MD 21227, Tel: (410) 455-5800; Fax: (410) 455-5802. PDA has not secured any specific room blocks for participants attending courses at the Training and Research Institute. There are several hotels in the Inner Harbor (downtown Baltimore) and BWI airport areas. These include, but are not limited to:

■ **Baltimore Hilton & Towers Inner Harbor**—Tel: (410) 539-8400; Fax: (410) 625-1060 ■ **Baltimore Marriott Inner Harbor**—Tel: (410) 962-0202; Fax: (410) 625-7892 ■ **Embassy Suites-BWI**—Tel: (410) 850-0747; Fax: (410) 859-0816 ■ **Holiday Inn-BWI**—Tel: (410) 859-8400; Fax: (410) 684-6778 ■ **Holiday Inn Inner Harbor** —Tel: (410) 685-3500; Fax: (410) 727-6169 ■ **Homewood Suites BWI****—Tel: (410) 684-6100; Fax: (410) 684-6810 ■ **Hyatt Regency Baltimore Inner Harbor**—Tel: (410) 528-1234; Fax: (410) 685-3362 ■ **Sheraton Inner Harbor Hotel**—Tel: (410) 962-8300; Fax: (410) 962-8211. ■ **Marriott Residence Inn-BWI****—Tel: (410) 691-0255; Fax: (410) 691-0254.

***no on-site restaurant*

For additional hotel information, please visit *www.baltconvstr.com*, the Baltimore Convention and Visitors Bureau's website. **Transportation to PDA-TRI:** All listed hotels are no more than a 15–20 minute taxi ride to the Training and Research Institute. All hotels can assist you with taxi arrangements. Registrants may prefer to rent a car for easier access to and from the Institute. ■

PDA-TRI Thanks the Following...

Sponsors

Abbott Laboratories
Allegiance Healthcare Corporation
Alma, Inc.
Becton Dickinson Microbiology Systems
Berkshire Corporation
Biolog, Inc.
bioMerieux Vitek, Inc.
Biotest Diagnostics Corporation
Chemunex, Inc.
Cole-Parmer
Comar, Inc.
Contec, Inc.
Corning, Inc.
Dow Corning, Inc.
DuPont Pharmaceutical Co.
Dycem Ltd.
Eagle Picher
Eisai U.S.A., Inc.
Electrol Specialties Company
Endosafe
Environmental Monitoring Technologies
Genesis Machinery Products, Inc.
GlaxoWellcome Inc.
Helvoet Pharma
IDEXX Laboratories, Inc.
Interpharm
Kimberly Clark, Corp.
KMI/Systems
La Calhene, Inc.
Larson Mardon Wheaton
Micro Diagnostics
MIDI Laboratories, Inc.
Millipore Corporation
Nalge Co.
Pacific Scientific Instruments
Pall Corporation
PML Microbiologicals
Raven Biologicals, Inc.
Research Equipment Services
Rhone-Poulenc Rorer
Sartorius AG
Siemens Building Technologies, Inc.
SGM Biotech, Inc.
STERIS Corporation
Veltek Associates, Inc.
VWR Scientific Products
West Pharmaceutical Services
Wilco AG
Wyeth-Ayerst Laboratories

Contributors

Amgen, Inc.
Automated Liquid Packaging, Inc.
Berkshire Corporation
Chesapeake Biological Laboratories, Inc.
Cotter Corp.
Eli Lilly and Co.
Fedegari
Kaye Instruments, Inc.
Kimberly Clark, Corp.
National Instrument Co., Inc.
Neslo, Inc.
Perfex Corporation
Pharmacia
Sievers Instruments, Inc.
Technovation

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

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

Membership Number

Job Title Company

Business Address

City State/Province ZIP/Postal Code

Tel Fax E-mail

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

2. Indicate the course(s) you'd like to attend (please print). Individuals registering at the nonmember rate receive one full year of PDA membership. Nonmembers registering for multiple events need only pay the nonmember fee once. (If you do **NOT** want to become a PDA member, please check here ❑).

COURSE TITLE	COURSE #	DATE	LOCATION	PRICE (member or nonmember)
			TOTAL :	$

3. Please check the appropriate box:

❑ **Check** enclosed ❑ Wire Transfer ***Charge:*** ❑ MC/EuroCard ❑ VISA ❑ AMEX

Account Number_____ Exp. Date _____

Name _____
(exactly as on card)

Signature_____ Date _____

Payments must be made to PDA in US dollars by check drawn on a US bank, by electronic money transfer **(SunTrust Bank ABA #051000020, PDA Account #209364254, Swift#UVBIUS33), net of all bank charges**; by American Express, MasterCard, or VISA.

4. Return completed form with payment made to:

PDA, Inc.
P.O. Box 79465
Baltimore, MD 21279-0465 USA
USA Fax: (301) 986-1093 (credit cards only)

Payment must be included to be considered registered.

Federal Tax I.D. #52-1906152

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.*
Substitutions: *If a registrant is unable to attend, substitutions are welcome and can be made at any time, even on-site. 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 start of an event (course series, conference, etc.), a full refund, minus a $35.00 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 the 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.*

LTR 02/01

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

Biotechnology
Frank Matarrese
Chiron Corporation
4560 Horton Street
Emeryville, CA 94608
Tel: 510-923-3128
Fax: 510-923-3375
E-mail—
frank_matarrese@cc.chiron.com

Blow-Fill-Seal
Garry W. Schmitt
Pharmtech, Inc.
14048 Petronella Dr. #101
Libertyville, IL 60048
Tel: 847-816-6848
Fax: 847-816-7369
E-mail—
gwschmitt@pharmtechinc.com

Computer Validation
Michael L. Wyrick
KMI/Paraexel
2080 St. Andrew's Court
Franklin, IN 46131
Tel: 317-736-0853
Fax: 317-736-9249
E-mail—
mwyrick@belmont.kminc.com

Contract Manufacturing
Michael R. Porter
Eli Lilly & Company
DC 3814
Eli Lilly Corporate Center
Indianapolis, IN 46285
Tel: 317-277-2595
Fax: 317-277-9693
E-mail—
porter_michael_r@lilly.com

Drug/Device Delivery Systems
Michael A. Gross, Ph.D.
Becton Dickinson & Company
1 Becton Drive
Franklin Lakes, NJ 07417-1886
Tel: 201-847-5930
Fax: 201-847-4854
E-mail—
michael_gross@bdhq.bd.com

Filtration
James D. Wilson
The Validation Group
115 Newell Village Circle
Seymour, TN 37865
Tel: 423-609-1690
Fax: 423-609-1690
E-mail—
wilsojdel@intermediatn.net

GMP Purchasing
Nancy M. Kochevar
Amgen, Inc.
MS 9-1-E
One Amgen Center
Thousand Oaks, CA 91320-1799
Tel: 805-447-4813
Fax: 805-447-1904
E-mail—
nancyk@amgen.com

Inspection Trends/ Regulatory Affairs
Robert L. Dana
Bristol-Myers Squibb Company
P.O. Box 182
East Syracuse, NY 13057
Tel: 315-432-2894
Fax: 315-432-2995
E-mail—
robert.dana@bms.com

Isolation Technology
Dimitri P. Wirchansky
Jacobs Engineering Group, Inc.
Three Tower Bridge
Two Ash Street, Ste. 3000
Conshohocken, PA 19428
Tel: 610-567-4452
Fax: 610-238-1100
E-mail—
dimitri.wirchansky@jacobs.com

Lyophilization
Edward H. Trappler
Lyophilization Techology
30 Indian Drive
Ivyland, PA 18974
Tel: 215-396-8373
Fax: 215-396-8375
E-mail—
etrappler@lyo-t.com

Microbiology/Environmental Monitoring
Jeanne E. Moldenhauer, Ph.D.
16100 W. Port Clinton Rd.
Lincolnshire, IL 60069
Tel: 847-977-4580
E-mail—
jeannemoldenhauer@yahoo.com

Ophthalmics
Richard M. Johnson
Alcon Laboratories, Inc.
Mail Code Q-146
6201 South Freeway
Fort Worth, TX 76134
Tel: 817-568-6085
Fax: 817-568-7004
E-mail—
richard.johnson@alconlabs.com

Packaging Science
Edward J. Smith, Ph.D.
Packaging Science Resources
237 Chapel Lane
King of Prussia, PA 19406
Tel: 610-265-9029
Fax: 610-265-2307
E-mail—
esmithpkg@aol.com

Production and Engineering
David W. Maynard
Maynard & Associates, LLC
226 Renfrew Ave.
Trenton, NJ 08618
Tel: 609-392-6462
Fax: 609-392-8623
E-mail—
davmaynard@aol.com

Quality Assurance/ Quality Control
Don E. Elinski
Geneva Pharmaceuticals, Inc.
2655 W. Midway Blvd.
Broomfield, CO 80038
Tel: 303-438-4532
Fax: 303-438-4590
E-mail—
don.elinski@gx.novartis.com

Solid Dosage Forms
Pedro J. Jimenez, Ph.D.
Eli Lilly & Co.
Eli Lilly Corporate Center
Indianapolis, IN 46285
Tel: 317-277-3618
Fax: 317-276-4669
E-mail—
jimenez_pedro_j@lilly.com

Stability
Rafik H. Bishara, Ph.D
Eli Lilly & Co.
DC 2623 Eli Lilly Corporate Center
Indianapolis, IN 46285
Tel: 317-276-4116
Fax: 317-276-1838
E-mail—
rhb@lilly.com

Sterilization/Aseptic Processing
James P. Agalloco
Agalloco & Associates
2162 US Highway 206
Belle Mead, NJ 08502
Tel: 908-874-7558
Fax: 908-874-8161
E-mail—
jagalloco@aol.com

Training
Thomas W. Wilkin, Ph.D.
Schering-Plough
Building K-1-2 F41
2000 Galloping Hill Road
Kenilworth, NJ 07033
Tel: 908-298-5213
Fax: 908-298-2720
E-mail—
thomas.wilkin@spcorp.com

Vaccines
Frank S. Kohn, Ph.D.
Wyeth-Lederle Vaccines & Pediatrics
4300 Oak Park
Sanford, NC 27330
Tel: 919-775-7100 ext. 4304
Fax: 919-774-1142
E-mail—
kohnf@labs.wyeth.com

Validation
Bohdan M. Ferenc
1 Brandywine Ct.
Succasunna, NJ 07876
E-mail—
biferenc@aol.com

Visual Inspection of Parenterals
John G. Shabushnig, Ph.D.
Pharmacia & Upjohn, Inc.
7171 Portage Road
M/S 4951-259-175
Kalamazoo, MI 49001-0199
Tel: 616-833-8906
Fax: 616-833-5195
E-mail—
john.g.shabushnig@am.pnu.com

PRELIMINARY REGISTRATION FORM

Hyatt Regency Tampa, Tampa, Florida

Good Electronic Records Management Conference (April 2-6, 2001) and PDA-TRI Course: PDA Computer Products Supplier Auditor Process Model: Auditor Training (April 5-6, 2001)

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

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

Membership Number

Job Title Company

Business Address

City State/Province Zip + 4/Postal Code Country

Business Phone Fax E-mail

☐ Substituting for

(check here only if you are substituting for a previously enrolled colleague. If you are a nonmember substituting for a member, the additional nonmember fee must be paid.)

2. Fees. Please check the appropriate box (exclusive of education and training courses). Individuals registering at the nonmember rate receive one full year of PDA membership. (If you DO NOT want to become a PDA member, please check this box ☐). **Nonmembers registering for multiple events need only pay the nonmember fee once.**

GOOD ELECTRONIC RECORDS MANAGEMENT CONFERENCE	PDA Member	Nonmember
Full Conference Registration (Includes all sessions, meal tickets and bonus session. DOES NOT include fee for PDA-TRI Course. See below for Course Registration.) * Full registration includes this bonus session: Monday, April 2, 2001: Introduction to 21 CFR Part 11– *John McKenney, SEC Associates*	☐ $ 995	☐ $ 1,145
Monday, April 2 Only	☐ $ 225	☐ $ 375
Tuesday, April 3 Only	☐ $ 499	☐ $ 649
Wednesday, April 4 Only	☐ $ 499	☐ $ 649
ADDITIONAL/GUEST TICKETS		
☐ **Lunch Ticket, Tuesday, April 3. _____ @ $35 each**	$	
☐ **Lunch Ticket, Wednesday, April 4. _____ @ $35 each**	$	
☐ **Reception Ticket, Tuesday, April 3. _____ @ $75 each**	$	
PDA COMPUTER PRODUCTS SUPPLIER AUDITOR PROCESS MODEL: AUDITOR TRAINING PLEASE NOTE: Attendees must submit an application and qualify to take this course. The fee includes a $100 nonrefundable application fee. Course registration fees for those applicants who do not meet the prerequisites as specified in the application will be returned, less the application fee. Application can be found at www.pda.org/PDF/Auditor/Training020501.PDF ☐ **PDA #474, April 5-6**	$ 950	$ 1,100
Total	$	$

3. Please check the appropriate box

☐ Check Enclosed ☐ Wire Transfer* Charge to: ☐ MC/EuroCard ☐ VISA ☐ AMEX

Account Number_____ Exp. Date _____

Name Exactly as on Card _____

Signature_____ Date _____

* Payments must be made to PDA in US dollars by check drawn on a US bank, by electronic money transfer (SunTrust Bank ABA #051000020, PDA Account #209364254, Swift #UVBIUS33), net of all bank charges; by MasterCard, VISA or American Express.

4. Return completed form with payment (payment must be included to be considered registered) made to:

PDA, Inc.
P.O. Box 79465
Baltimore, MD 21279-0465 USA
Fax: (301) 986-1093 (Credit Cards Only)

Federal Tax I.D. #52-1906152

Confirmation: Written confirmation will be sent to you once payment is received. You must have written confirmation to be considered enrolled in a PDA event. **Substitutions:** If a registrant is unable to attend, substitutions are welcome and can be made at any time. If you are preregistering as a substitute attendee, indicate this on the registration form. A nonmember substituting for a member must pay the additional fee. **Event Cancellation:** PDA reserves the right to modify the material or instructors without notice or to cancel an event. If the event must be cancelled, registrants will be notified as soon as possible and will receive a full refund of fees paid. PDA cannot be responsible for discount airfare penalties or other costs incurred due to a cancellation. Course enrollment is limited for the benefit of all attendees; this necessitates early registration. **Refunds:** Registrants whose written requests for refunds are received at PDA on or before March 16, 2001 will receive a full refund less a $35 processing fee. Registrants whose written requests for refunds are received after March 16, 2001 and on or before March 23, 2001 will receive 50% of the registration fee. No refunds will be issued for cancellations received after March 23, 2001. Substitutions may be made at any time.

Business Environment (check one)

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

Professional Interest
(check all that apply)

- ☐ Aerosols
- ☐ Analytical Chemistry
- ☐ Blow-Fill-Seal
- ☐ Biologicals
- ☐ Biotechnology
- ☐ Calibration
- ☐ Contract Manufacturing
- ☐ Computer Validation
- ☐ Drug/Device Delivery Systems
- ☐ Formulation Development
- ☐ Filtration
- ☐ GMP Compliance/ Inspection Trends
- ☐ Inspection Trends/ Regulatory Affairs
- ☐ Isolation Technology
- ☐ Liquids
- ☐ Lyophilization
- ☐ Manufacturing/Production
- ☐ Microbiology/ Environmental Monitoring
- ☐ Maintenance
- ☐ Ointments
- ☐ Ophthalmics
- ☐ Packaging Science
- ☐ Parenterals
- ☐ Production & Engineering
- ☐ Quality Assurance/ Quality Control
- ☐ Research
- ☐ Solid Dosage Forms
- ☐ Stability
- ☐ Sterilization/Aseptic Processing
- ☐ Training
- ☐ Vaccines
- ☐ Validation
- ☐ Visual Inspection of Parenterals

LTR 02/01

PDA Use: Date:_____ Check #:_____ Amount:_____ Account:_____

New dimensions in aseptic processing with disposable MaxiCaps

Scale up. Get BIG RESULTS with 30" capsules.

Get up to 20 sq.ft. of filter surface area in a convenient, disposable filter capsule. Now there's no reason to settle for anything less than exactly what you need for convenient, high-flow aseptic processing.

At Sartorius, we're always looking for ways to improve our products and your processes. Our newest innovation is a big step up in capsule design -- up to 30", based on our standard cartridge format. There's no need to revalidate because there's no need for any new hardware. And our disposable design reduces cleaning validation.

Maintain maximum flow and throughput as you scale up!

Available in 10", 20" and 30" formats, these high-flow capsules utilize what we call "circumventional flow." This technology, combined with our smart design of the inlet/outlet ports, provides superior flow and higher throughput. As your process demand continues to increase, we meet that challenge. By using the same filter materials and type of construction throughout the complete product range, you can flexibly scale up and down, always relying on the highest level of reproducibility.

Focus on *Scale-up*

sartorius

In USA: +1 800 368 7178 • In Germany: +49 551 308 0 • In France:+33 1 69 19 21 00
In the UK: +44 1 372 737100 • In Italy: +39 055 505671 • In Japan: +81 3 3329 5533

New members are forwarded to chapter mailing lists on an ongoing basis. For immediate notification of chapter events, please contact your local representative below and ask to be placed on the chapter mailing list.

Australia Chapter
Contact: **Mary Sontrop**
ZLB Bioplasma AG
Tel: +41-31-344-4305
Fax: +41-31-344-5555
E-mail: *mary.sontrop@zib.com*

Canadian Chapter
Contact: **Grace Chin**
Pellemon, Inc.
Tel: (416) 422-4056 x230
Fax: (416) 422-4638
E-mail: *ching2@snc-lavalincom*
Web site: ***www.pdacanada.org***

Capital Area Chapter
Areas Served: Maryland, District of Columbia, Virginia, West Virginia
Contact: **Allen Burgenson**
Life Technologies, Inc.
Tel: (301) 610-8567
Fax: (301) 610-8768
E-mail: *aburgens@lifetech.com*

Delaware Valley Chapter
Areas Served: Delaware, New Jersey, Pennsylvania
Contact: **Mark Kaiser**
Lancaster Laboratories
Tel: (717) 656-2300 x1263
Fax: (717) 656-2681
E-mail: *Mwkaiser@lancasterlabs.com*
Web site: ***www.pdadv.org***

European Chapter
Contact: **James Lyda**
PDA Europe Office
Switzerland
Tel: +41-61-703-1688
Fax: +41-61-703-1689
E-mail: *lyda@pda.org*

Israel Chapter
Contact: **Karen S. Ginsbury**
PCI–Pharmaceutical Consulting Israel Ltd.
Tel: +972-3-9214261
Fax: +972-3-9215127
E-mail: *kstaylor@netvision.net.il*

Italy Chapter
Contact: **Vincenzo Baselli**
Pall Italia
Tel: +39-02-477-961
Fax: +39-02-4122-985
E-mail: *vincenzo_baselli@pall.com*

Japan Chapter
Contact: **Hiroshi Harada**
Tel: +81-3-3815-1681
Fax: +81-3-3815-1691
E-mail: *van@bcasj.or.jp*

Korea Chapter
Contact: **Jong Hwa A. Park**
Tel: +82-2-538-9712
Fax: +82-2-569-9092
E-mail: *Jong_Hwa_Park@pall.com*

Metro Chapter
Areas Served: New Jersey, New York
Contact: **Felicia Manganiello**
Tel: (732) 521-8274
Fax: (732) 521-5933
E-mail: *fmanganiello@aol.com*

Midwest Chapter
Areas Served: Illinois, Indiana, Ohio, Wisconsin, Iowa, Minnesota
Contact: **Robert S. Murphy**
Searle
Tel: (847) 581-6118
Fax: (847) 581-6553
E-mail: *robert.s.murphy@monsanto.com*

Mountain States Chapter
Areas Served: Colorado, Wyoming, Utah, Idaho, Nebraska, Kansas, Oklahoma, Montana
Contact: **Jeff Beste**
Pendleton Resources
Tel: (303) 832-8100
Fax: (303) 832-9346
E-mail: *cmdjeff@aol.com*
Web site: ***www.boulder.net/~rmpda/***

New England Chapter
Areas Served: Massachusetts, Connecticut, Rhode Island, New Hampshire, Vermont, Maine
Contact: **Robert A. Pazzano, P.D.**
Validation and Training Services
Tel: (508) 870-0007 x140
Fax: (508) 870-0224
E-mail: *robert_pazzano@vtsinc.net*

Southeast Chapter
Areas Served: North Carolina, South Carolina, Tennessee, Virginia, Florida, Georgia
Contact: **Mary Carver**
Eisai, Inc.
Tel: (919) 474-2149
Fax: (919) 941-6934
E-mail: *carver@eisai.com*
Web site: ***www.pdase.org***

Southern California Chapter
Areas Served: Southern California
Contact: **Beth Bertelsen**
BB Consulting Services
Tel: (858) 487-1022
Fax: (619) 253-4322
E-mail: *bbcs@gateway.net*

Taiwan Chapter
Contact: **Tuan-Tuan Su**
Tel: +8862-2550-9301
Fax: +8862-2555-4707
E-mail: *pdatc@ms17.hinet.net*

United Kingdom and Ireland Chapter
Contact: **Colin Booth**
Glaxo Wellcome
Tel: +44-1-920-883-637
Fax: +44-1-920-882-295
E-mail: *cb3883@glaxowellcome.co.uk*

West Coast Chapter
Areas Served: Northern California
Contact: **Michele Livesey**
Genentech, Inc.
Tel: (650) 225-3536
Fax: (650) 225-5402
E-mail: *Livesey@gene.com*

PDA
An International Association For Pharmaceutical Science And Technology

FDA Documents Available

For a full listing of documents available, please contact PDA or visit our Web site, www.pda.org.

Guide to Inspections of Pharmaceutical Quality Control Laboratories; July 1993; Office of Regulatory Affairs; 15 pp; $15 members/$30 nonmembers. FDA 28

Guide to Inspections of Validation of Cleaning Processes; July 1993; Office of Regulatory Affairs; 9 pp; $15 members/$30 nonmembers. FDA 29

Guide to Inspections of High Purity Water Systems; July 1993; Office of Regulatory Affairs; 13 pp; $15 members/$30 nonmembers. FDA 31

Guide to Inspections of Microbiological Pharmaceutical Quality Control Laboratories; July 1993; Office of Regulatory Affairs; 8 pp; $15 members/$30 nonmembers. FDA 32

Guideline on Sterile Drug Products Produced by Aseptic Processing; June 1987; CDER, CBER, Office of Regulatory Affairs; 43 pp; $15 members/$30 nonmembers. FDA 33

Guideline on Validation of Analytical Methods: Definitions & Terminology (Q2A); March 1, 1994; CDER; 4 pp; ICH Step 5 Final Guideline. $15 members/$30 nonmembers. FDA 53

Review Guidance, Validation of Chromatographic Methods; November 1994; CDER; 33 pp; $25 members/$40 nonmembers FDA 108

Validation Documentation Inspection Guide; 1993; ORA; 27 pp; ***Not available on the Internet.*** $25 members/$40 nonmembers. FDA 110

Guideline on the Validation of Analytical Procedures: Methodology; May 19, 1997; ICH; 5 pp; ICH Step 5 Final Guideline. $15 members/$30 nonmembers. FDA 125 (revised)

Draft Guidance for Industry: Manufacturing, Processing or Holding of Active Pharmaceutical Ingredients; April 17, 1998; CDER/CBER/CVM; 57 pp; Revised draft of FDA GMP guidance for APIs originally released in September 1996. $35 members/$50 nonmembers. FDA 158

General Principles of Software Validation Guidance for Industry; June 1, 1997; CDRH; 20 pp; $25 members/$40 nonmembers. FDA 187

Stability Testing of Drug Substances and Drug Products; June 1998; CDER/CBER; 114 pp; FDA's revised draft guidance for industry on stability testing. $35 members/$50 nonmembers. FDA 220

Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production; Draft Guidance; September 1998; CDER; 11 pp; $15 members/$30 nonmembers. FDA 229

PDA Books Available

Cleaning & Cleaning Validation: A Biotechnology Perspective; *R. Brunkow* et al.; 1995; 190 pp; $125 members/$145 nonmembers. Item No. 13002

PDA Technical Reports Available

Evaluation, Validation and Implementation of New Microbiological Testing Methods; This report is intended to provide a general approach to the introduction of new microbiology methods in a government-regulated environment. It is also intended to provide guidance for the successful evaluation, validation and implementation of new microbiological methods needed by the pharmaceutical, biotechnology and medical device industries to assure product quality. These new methodologies offer significant improvements in terms of the speed, accuracy, precision and specificity with which testing can be performed. 2000; 37 pp; $75 members/$125 nonmembers. TR 33

Auditing of Suppliers Providing Computer Products and Services for Regulated Pharmaceutical Operations; Developed in response to an FDA challenge to develop a standard way to assess the structural integrity of acquired software, TR 32 was written by the PDA Supplier Auditing and Qualification Task Group (SA&Q), which included pharmaceutical companies, suppliers, auditors and FDA members who used their experiences with supplier audits and performed research to draft a common practice to satisfy industry needs. The scope of the project included audits of computer products and services and describes how the SA&Q Task Group, led by George J. Grigonis, Jr., Merck and Co., Inc., developed and tested a Process Model and Data Collection Tool. Use of these tools will provide consistent audit information that can be shared within the industry. December 1999; $90 members/$140 nonmembers (paper copy)**; TR 32**. $50 members/$75 nonmenbers (CD-ROM format) TR 32 CD.

Validation and Qualification of Computerized Laboratory Data Acquisition Systems; Prepared by the PhRMA CSVWG and the PDA Computer Related Systems-Laboratory Systems Task Group, TR 31 provides guidance to lab scientists, technicians and managers responsible for the implementation, testing, control and usage of Laboratory Data Acquisition Systems (LDAS) used within a GMP-, GLP- or GCP-regulated environment. Addresses computerized LDAS within a regulated environment; also applicable to systems critical to the operation of a company, department or function, regardless of the system's regulatory impact. 1999; 12 pp; $50 members/$75 nonmembers. TR 31

Points to Consider for Cleaning Validation; This document provides guidance relative to the validation of cleaning for a broad range of processing systems and product types within the pharmaceutical industry. The report includes perspectives on the application of cleaning validation guidance in the areas of finished pharmaceuticals, bulk pharmaceutical chemicals, biopharmaceuticals and clinical products. It is the pharmaceutical companion to "Cleaning and Cleaning Validation: A Biotechnology Perspective" published by PDA in 1996. 1998; 23 pp; $75 members/$125 nonmembers. TR 29

Ordering Documents and Publications from PDA

Use this form to order any of the documents mentioned in the *PDA Letter*. If ordering by mail, include a check payable to PDA to the address below. Be sure to include shipping and handling charges in the total. If ordering by fax, please include all credit card information. All orders must include payment.

Name _____ Member No. _____

Company _____

Address _____

City _____ State _____ Country _____ Zip/Postal Code _____

Tel: _____ Fax: _____ E-mail: _____

Payment type: ☐ Check drawn on a US bank ☐ MC ☐ VISA ☐ AMEX

☐ Wire Transfer

Credit Card # _____ Exp. _____

Mail to: PDA, P.O. Box 79465
Baltimore, MD 21279-0465 USA
Fax: (301) 986-1093

Name as it appears on credit card (please print clearly) _____

Questions? (301) 986-0293 x133 or *info@pda.org* Signature _____

Document No.	Title	Qty.	Price	Total

Shipping
Domestic US orders are shipped via UPS Ground. Second-day and Next-day Air service is available. Call or e-mail for prices.

Domestic US Shipping & Handling Rates

If your order totals:	*Add:*
$ 15.00 and under	$ 5.95
$ 15.01–$ 75.00	$ 7.95
$ 75.01–$150.00	$ 9.95
$150.01–$250.00	$11.95
$250.01 or more	$13.95

International orders (including Puerto Rico & Canada): Please add 20%, minimum $18.00, maximum $150.00. Items are sent priority air, but 2-day service is available for some countries; please call for details.

Payment
Payments must be made in US dollars by check drawn on a US bank, **by electronic money transfer (SunTrust Bank ABA #051000020, PDA Account #209364254, Swift #UVBIUS33), net of all bank charges**; or credit card.

Federal Tax I.D. #52-1906152

Please allow 4-6 weeks for delivery on some items.

Subtotal	
Shipping & Handling	
5% Tax *(MD Residents Only)*	
TOTAL	

LTR 02/01

PDA USE:
Date: _____ **Check:** _____ **Amount:** _____ **Acct:** _____

Global Pharmaceutical Manufacturing and Quality Strategies

April 5–6, 2001

1. Please type or print your name, address and affiliation. ❍ Mr. ❍ Ms. ❍ Dr.

First Name/MI _____ Last Name _____

Job Title _____ Membership Number (if known) _____

Company _____

Business Address _____

Postal Code/City/Country _____

Phone: _____ Fax: _____

E-mail: _____

❍ Substituting for: _____

(Check here only if you are substituting for a previously enrolled colleague. If you are a nonmember substituting for a member, the additional nonmember fee must be paid.)

2. Participation Fees:

Individuals registering at the nonmember rate receive one full year of PDA membership. Persons registering for multiple events need only pay the full nonmember fee once. If you do **not** want to become a PDA member, please check here ❍

- Conference Fee (Members) ..... US$845 ❍
- Conference Fee (Nonmembers) ..... US$995 ❍
- Conference Fee (Government) ..... US$495 ❍

Total Amount: US$ _____

3. Payment Instructions: Make check payable to PDA in US Dollars by check drawn on a US bank, or indicate your credit card number, expiration date and authorization below.

Credit Card: ❍ Amex ❍ MasterCard ❍ Visa

Cardholder Name: _____

Card Number: _____ Expiration: _____

Cardholder's Signature: _____

Confirmation: Written confirmation/invoice will be sent to you once registration is received.

Substitutions: If a registrant is unable to attend, substitutions are welcomed and may be made at any time. If you are a nonmember substituting for a member, the additional nonmember fee must be paid.

Refunds: Refund requests must be in writing. If received at PDA Headquarters by March 5, 2001, a full refund, less a processing fee, will be made. If received by March 19, 2001, 50% 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 the 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. Course enrollment is limited for the benefit of all attendees; this necessitates early registration.

4. Return completed form via Fax to 301-986-1093 or mail to:

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

Payment must be made to PDA in US Dollars by check drawn on a US Bank; by electronic money transfer (SunTrustBank ABA #051000020, PDA Account #209364254, Swift #UVBIUS33), net of all bank charges; or by MasterCard, VISA, or American Express (Amex).

PDA Use: Date:_____ Check: _____ Amount:_____ Account:_____

PDA
An International Association For Pharmaceutical Science And Technology

Business Environment
(check one)

- ❍ Pharmaceutical Manufacturing
- ❍ Engineering and Construction
- ❍ Industry Supplier
- ❍ Consultant
- ❍ Employee of Government Regulatory Agency
- ❍ Academic
- ❍ Medical Device Manufacturer
- ❍ Pharmacy
- ❍ Recruiter
- ❍ Contract Manufacturing
- ❍ Other

Professional Interest
(check all that apply)

- ❍ Aerosols
- ❍ Analytical Chemistry
- ❍ Biotechnology
- ❍ Biologicals
- ❍ Blow-Fill-Seal
- ❍ Calibration
- ❍ Computer Validation
- ❍ Contract Manufacturing
- ❍ Drug/Device Delivery Systems
- ❍ Filtration
- ❍ Formulation Development
- ❍ GMP Compliance/ Inspection Trends
- ❍ Isolation Technology
- ❍ Liquids
- ❍ Lyophilization
- ❍ Maintenance
- ❍ Manufacturing/ Production
- ❍ Microbiology/Environmental Monitoring
- ❍ Ointments
- ❍ Ophthalmics
- ❍ Packaging Science
- ❍ Parenterals
- ❍ Production & Engineering
- ❍ Quality Assurance/ Quality Control
- ❍ Regulatory Affairs
- ❍ Research
- ❍ Solid Dosage Forms
- ❍ Stability
- ❍ Sterilization/Aseptic Processing
- ❍ Training
- ❍ Vaccines
- ❍ Validation
- ❍ Visual Inspection of Parenterals

LTR 02/01

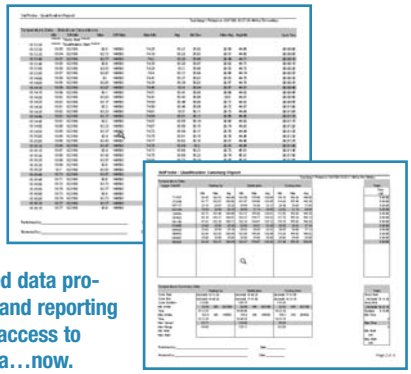
Introducing

ValProbe™

Another innovation from the leader in process validation.

Process monitoring has never been easier.

Wireless design. Advanced data processing. Wide operational ranges. FDA compliant. Customized reporting. It all adds up to a revolutionary wireless process monitoring and validation system with unprecedented ease-of-use benefits.



Advanced data processing and reporting provide access to your data…now.

Accuracy and flexibility you can count on…because it's from Kaye.

The ValProbe system employs a wireless probe design which eliminates the need for hard-wired sensors, simplifying access to hostile, remote, and hard-to-reach environments. Operating from –60° C to 360° C and 0–75 psi, it's suitable for a wide range of applications including steam and Et0 sterilization, tunnels, ovens, incubators, rotating machinery, and conveyors.

Innovation from the leader.

ValProbe's ability to rapidly process data from up to 99 sensors saves time and provides quick access to critical temperature, humidity, and pressure data. Of course, the ValProbe system complies with FDA Regulation 21 CFR Part 11, ensuring that the most stringent requirements for electronic signatures and records are met.

To request more information or a demonstration of this breakthrough process validation system, call us at

1-800-964-5293

or visit us at www.kayeinc.com

- **ACCURACY**
- **COMPLIANCE**
- **EASE OF USE**
- **SERVICE**

KAYE®

PDA Conferences and Meetings

MARCH

March 11–16, 2001

PDA Spring Conference, Courses and Tabletop Exhibit

Modern Pharmaceutical Microbiology: Advancing the Science

Aladdin Resort & Casino
Las Vegas, NV

PDA-TRI Education Courses

March 15 *(half-day courses)*

- *PDA Computer Products Supplier Audit Management Overview Training*
- *How to Design an Effective Regulatory Training Program*

March 15 *(one-day course)*

- *Identification of Microorganisms Using Comparative DNA Sequencing*

March 16 *(one-day courses)*

- *Environmental Mycology*
- *Writing and Auditing CGMP Documentation*

March 15–16 *(two-day courses)*

- *Cleanroom Management*
- *Environmental Surveillance and Control*
- *Introduction to Validation*

APRIL

April 2–6, 2001

PDA Good Electronic Records Management (GERM) Conference, Courses and Exhibition

Hyatt Regency Tampa
Tampa, Florida

April 5–6, 2001

PDA & PDA Italy Chapter Conference on ***Global Pharmaceutical Manufacturing and Quality Strategies***

Grand Hotel Timeo
Taormina, Italy

SEPTEMBER

September 10–13, 2001

PDA/FDA Joint Conference, Courses and Tabletop Exhibit

Hyatt Regency Washington, DC on Capitol Hill
Washington, DC

OCTOBER

October 1–3, 2001

PDA/FDA Viral Clearance Forum and Tabletop Exhibit

Hyatt Bethesda
Bethesda, Maryland

DECEMBER

December 3–7, 2001

PDA Annual Meeting, Courses and Exhibition

Marriott Wardman Park
Washington, DC

See page 33 for additional PDA-TRI education course listings.

Be sure to watch **www.pda.org** for conference and course updates!