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PDA Letter

December 2001

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

PDA 2001 Board of Directors and Election Results, page 4

Basel 2002: PDA International Congress, Courses and Exhibition

Adding Value to the Pharmaceutical Industry: Leveraging the Future

Convention Center Basel, Switzerland

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Congress Overview

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- Aseptic Processing;

continues on page 31

PDA Responds to FDA on TR 34

FDA provided comments on a preliminary draft of *PDA Technical Report No. 34: Design and Validation of Isolator Systems for the Manufacturing and Testing of Health Care Products* in a July 27 letter to Russell Madsen, PDA's Senior VP Science and Technology. The letter was signed by Joseph C. Famulare and John A. Eltermann, Jr., Directors, Division of Manufacturing and Product Quality, CDER and CBER, respectively.

The letter provides useful information about FDA's response to PDA's position on the use and control of isolators for the production of pharmaceutical products, and it supports, in general, the content of TR 34. However there are two issues, in particular, where the FDA and PDA positions diverge: the operating environment for the isolator; and the use of fraction negative studies to determine the resistance of the biological indicators to the decontaminating agent. FDA believes production isolators should be surrounded by at least a Class 100,000 environment while PDA believes the surrounding environment should be controlled but not formally classified. FDA believes the use of fraction negative studies is inappropriate due to the error introduced to these equations from potential non-uniformity of decontaminating agents within the isolator; PDA's position is that non-uniformity, if it exists, supports the use of the fraction negative approach.

The issues are discussed in the letter PDA sent to FDA on October 26. We intend to schedule a meeting with FDA to resolve these issues. In the interim, the content of both letters should provide useful information to anyone using isolators for pharmaceutical production and control operations. ■

—Russell E. Madsen

The text of both letters appears on pages 18 and 21, and on www.pda.org.

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Important Dates...

- **January 18, 2002**—Poster abstracts for Basel 2002 due—*page 31*
- **March 11–15, 2002**—PDA Spring Conference, Courses and Exhibition, Orlando, Florida—*page 30*
- **May 19–22, 2002**—PDA/USP Joint Conference on Sterile Product Manufacturing—*page 30*

IN THIS ISSUE...

Fry

Results of 2001 Election

Edmund M. Fry

I am pleased to announce the results of the 2001 election for PDA Directors and Officers, whose photos appear here. Thanks to outgoing members Kenneth Seamon and Georg Roessling, whose terms expire at the end of 2001. Their service on the PDA Board is greatly appreciated. The Board is happy that Roessling has agreed to continue to participate in Board meetings as a special representative, in his role as Chair of PDA's European Steering and Development Committee.

This year we used a Web-based election, in which members used their member numbers to cast ballots online rather than mailing a paper ballot. Unfortunately, the participation was much lower than in previous years, and I would appreciate hearing any suggestions from members as to whether Web-based voting should continue, and how it might be modified to increase participation. Send your comments to fry@pda.org or via mail to my attention to PDA, 7500 Old Georgetown Road, Suite 620, Bethesda, MD 20814. The voting process is important to PDA and to the candidates, who put much thought and preparation into running for the PDA Board. ■

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US Regulatory Briefs

International Conference on Harmonization; Guidance on Q1A Stability Testing of New Drug Substances and Products. From the *Federal Register*: November 7, 2001 (Volume 66, Number 216 Page 56332-56333). The FDA is announcing the availability of a revised guidance entitled "Q1A(R) Stability Testing of New Drug Substances and Products." The revised 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 sets forth recommendations on the information to be submitted in the stability data package for a new drug substance or drug product for a registration application within the three ICH regions, the European Union (EU), Japan and the USA. The purpose of the revision is to add information to certain sections and to provide clarification to other sections of the guidance. The following sections are the most important sections that have been revised:

- The section on stress testing of the active substance has been moved from the glossary to the main text;
- The text on test procedures has been brought in line with the ICH Q6A guidance;
- Relevant cross-references to other ICH guidances have been introduced;
- The text on testing frequency has been amended for accelerated testing conditions;
- Storage conditions have been described in more detail;
- Testing at low temperature and testing of aqueous liquids in semipermeable containers have been specifically addressed;
- The post-approval commitment is now clearly described; and
- The guidance has also been revised to remove several editorial inconsistencies, including some revision of the glossary.

Persons with access to the Internet may obtain the document at www.fda.gov/cder/guidance.

ICH was organized to provide an opportunity for tripartite harmonization initiatives to be developed with input from both regulatory and industry representatives. FDA also seeks input from consumer representatives and others. ICH is concerned with harmonization of technical requirements for the registration of pharmaceutical products among three regions: the EU; Japan and the USA. The six ICH sponsors are: European Commission; European Federation of Pharmaceutical Industries Associations; Japanese Ministry of Health, Labor and Welfare; Japanese Pharmaceutical Manufacturers Association; Centers for Drug Evaluation and Research and Biologics Evaluation and Research, FDA; and the Pharmaceutical Research and Manufacturers of America. The ICH Secretariat, which coordinates the preparation of documentation, is provided by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

In accordance with FDA's good guidance practices (GGPs) regulation (21 CFR 10.115), this document is being called a guidance, rather than a guideline.

To facilitate the process of making ICH guidance's available to the public, the Agency has changed its procedures for publishing ICH guidance's. As of April 2000, FDA no longer includes the text of ICH guidance's in the Federal Register. Instead, a notice published in the *Federal Register* announces the availability of an ICH guidance. The ICH guidance is placed in the docket and can be obtained through regular agency sources. Draft ICH guidances are left in the original ICH format. Final guidances are reformatted to conform to the Good Guidance Practices (GGP) style before publication.

Guidance for Industry, M4, The Organization of the Common Technical Document. This is one in a series of guidances that provide recommendations for applicants preparing the Common Technical Document for the Registration of Pharmaceuticals for Human Use (CTD) for submission to the USA FDA. This guidance presents the agreed upon common format for the preparation of a well-structured harmonized application that will be submitted to regulatory authorities. A common format for the technical documentation will significantly reduce the time and resources used to compile applications for registration of human pharmaceuticals and will ease the preparation of electronic submissions. Regulatory reviews and communication with the applicant will be facilitated by a standard document of common elements. In addition, exchange of regulatory information among regulatory authorities will be simplified.

Guidance for industry on preparing the CTD has been divided into four guidance documents on: (1) the organization of the CTD; (2) the quality section, M4Q; (3) the efficacy section, M4E; and (4) the safety section, M4S. For specific information on the quality, efficacy and/or safety sections of the CTD, see the individual guidances for industry that discuss those parts of the CTD. For general information about submitting a marketing application in the CTD format in the USA region, as well as specific information about Module 1 (USA administrative information), see the guidance for industry, *General Considerations for Submitting Marketing Applications According to the ICH/CTD Format*. The CTD guidances are intended to be used together with other ICH and Agency guidances. The M4 guidance can be found at www.fda.gov/cder/guidance/index.htm.

Reopening CBER's Document Control Center. Due to concerns arising from reports of presumptive positive screening tests for Anthrax in FDA mailrooms there have been some disruptions in normal mail handling. On November 5,

2001, FDA issued a statement that the Agency received the results of confirmatory anthrax testing at all its buildings, and those results are negative for anthrax. As a result, CBER has reopened the Document Control Center (DCC). There are several important points to note:

- Express overnight packages sent via common carrier (FedEx, UPS, DHL, etc.), will be processed in the order in which they were received. There is a backlog of packages and submissions from the last several days that will have to be handled before any new submissions are processed. It may take several days to get caught up.
- The receipt date given to a submission is the date that the submission is opened and processing is begun by DCC, not the date that the item was delivered.
- USA Mail that was received in CBER after October 25 has to be returned or forwarded to DCC from the FDA's off-site Central Mail Screening Facility. It is anticipated that this will take several days.
- Priority is being given to the backlog of new submissions.

FDA Bioterrorism Page. A new page with links to bioterror-related information from FDA, as well as from other authoritative sources such as the Centers for Disease Control and Prevention and the National Library of Medicine, is now on FDA's Web site. Also available separately online is related information on labeling for two anthrax treatments and FDA warnings issued to sellers of unapproved foreign Cipro.

Bioterrorism page: http://www.fda.gov/oc/opacom/hottopics/bioterrorism.html

Anthrax treatment labeling: http://www.fda.gov/bbs/topics/ANSWERS/2001/ANS01112.html

Unapproved Cipro: http://www.fda.gov/bbs/topics/ANSWERS/2001/ANS01115.html

Some useful Web sites for more information on bioterrorism:

- HHS: http://www.hhs.gov/hottopics/healing/biological.html.
- FDA: http://www.fda.gov/oc/opacom/hottopics/bioterrorism.html.
- CDC: http://www.bt.cdc.gov/.
- Army surgeon general: http://www.nbc-med.org/.
- CDER: http://www.fda.gov/cder/drugprepare/default.htm.
- The Johns Hopkins University Center for Civilian Biodefense: http://www.hopkins-biodefense.org.
- *The Journal of the American Medical Association* has made available for free its series of articles on five biological agents that might be

used against a civilian population—smallpox, anthrax, plague, botulinum toxin and tularemia: http://www.jama.com.

Guidance for Industry, Sterility Requirements for Aqueous Based Drug Products for Oral Inhalation, Small Entity Compliance Guide. This small entity compliance guide is one of a series of guidance documents prepared in accordance with section 212 of the Small Business Regulatory Fairness Act (Public Law 104-121). The guidances are intended to explain the actions small entities are required to take to comply with rules for which the agency prepared a final regulatory flexibility analysis.

In the final rule, the FDA amended its regulation governing specific classes of drug products by adding new 21 CFR 200.51 to the regulations. Section 200.51 requires that all aqueous based drug products for oral inhalation be manufactured sterile as of the effective date of the rule. Manufacturers must also comply with 21 CFR 211.113(b), which requires them to establish and follow appropriate written procedures designed to prevent microbiological contamination of any product manufactured sterile, including validation of any sterilization process used. Manufacturers must be in compliance with the final rule as of its effective date, May 27, 2002. This guidance, based on a question and answer format can be found at www.fda.gov/cder/guidance.

In November 2001, FDA issued *The Leveraging Handbook* as a Guidance for FDA Staff. Leveraging consists of partnerships, cooperative agreements, or any similar collaborative arrangement that is entered into by FDA and another organization, such as a corporation, educational institution, trade or consumer group, government agency or foreign government. Leveraging is always cooperative and beneficial to all the parties involved, and advances FDA's mission to protect and promote the Nation's public health.

The technology and science used to evaluate the status of the nation's public health and to devise remedies for identified problems is constantly becoming more complex and sophisticated. Often, traditional solutions are no longer adequate to address all the critical dimensions of the problems. At the same time, most government and private organizations world-wide are being pressured by stakeholders and shareholders to deliver better results within tighter budget margins. Leveraging has been identified by FDA's leadership as a critical long-term strategy that can achieve the Agency's goal of protecting and promoting the nation's public health consistent with the need for greater operating efficiencies.

The value of and the need for further leveraging has been underlined by FDA leaders in both internal communiqués and in presentations to external audiences. In a January 2000 memorandum to all Agency staff, Commissioner Henney stated that the leveraging of Agency staff expertise is critical to performing FDA's mission. Among the important leveraging concepts that the Commissioner emphasized in her letter were:

- FDA's mission to protect and promote the public health is not the agency's alone; academia, health providers, other government agencies, regulated industry, and consumers all have roles to play in advancing the public health;
- Leveraging, collaboration, cooperation, or partnering are not new to the Agency;
- Resources from outside organizations and individuals that have shared interests have helped FDA accomplish its vital mission in the past and these efforts are on-going and will expand in the future;
- Cooperative leveraging ventures are a means to maximize the agency's intellect, time, money, and resources; and
- FDA, at all levels of the organization, should think of leveraging and other collaborative opportunities as primary strategies for achieving its mission.

The complete Leveraging Handbook can be found at: http://www.fda.gov/oc/leveraging/handbook.html

International Regulatory Briefs

Priority Review of Drug Submissions in Canada. A revised policy proposal for the Priority Review of Drug Submissions in Canada was made available for comment on November 2, 2001. This proposal is intended to replace the policy, ***Priority Review of Drug Submissions***, dated December 13, 1996.

Also available for comment is ***Guidance for Industry; Priority Review of Drug Submissions***. This guidance is intended to provide assistance to sponsors in the interpretation of the policy, as well as in the preparation and submission of an application for Priority Review status of a New Drug Submission (NDS) or Supplementary New Drug Submission (S/NDS).

A reassessment of the policy was prompted in December 1999 by concerns communicated through industry and stakeholder groups. These groups questioned the criteria used to assign priority review status to submissions and expressed a desire for increased transparency of the drug review process.

In providing additional clarification for both eligibility criteria and the application process, Health Canada aims to increase the consistency of the Priority Review application process while continuing to satisfy the intent of the policy in providing a prioritized review of critical new drugs and allowing access to breakthrough therapies under the identified scope.

The policy proposal and associated guidance

are available on the Therapeutic Products Directorate Web site (http://www.hc-sc.gc.ca/hpb-dgps/therapeut) and can be accessed in the DRAFT section of the POLICIES page, under the name "Priority Review of Drug Submissions."

The deadline to provide comments on the documents is January 4, 2002. Any comments regarding the policy or guidance documents may be forwarded to: Tara Bower, Bureau of Policy and Coordination, 2nd Floor, Tower B Holland Cross, 1600 Scott Street, A.L. 3102C5, Ottawa, Ontario. K1A 1B6
E-mail: tara_bower@hc-sc.gc.ca

Future Directions of the Australian GMPs.

- The International Conference on Harmonization (ICH) Tripartite Guideline *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients (APIs)* will be adopted as a Manufacturing Principle for the auditing and licensing of manufacturers of APIs in Australia. The application of the ICH GMP Guide to overseas manufacturers of APIs used in therapeutic goods supplied to Australia will continue to apply only to prescription medicines evaluated by the Drug Safety and Evaluation Branch of TGA. A 12 month transition period will apply from the time the guide becomes a Manufacturing Principle, which was anticipated to be in place in October 2001.
- The TGA is proposing to adopt the PIC/S GMP Guide for Medicinal Products as a Manufacturing Principle. Industry associations have been consulted on the proposal and it is hoped that the Guide will be adopted early in 2002. The PIC/S GMP Guide will replace the 1990 edition of the Australian Code of GMP for Medicinal Products. As with any new Manufacturing Principle, a 12 month transition period will apply from the commencement date of the Manufacturing Principle.

—William Stoedter

European Regulatory Briefs

US–EU Mutual Recognition Agreement. The EMEA and FDA have released joint procedures relative to the Pharmaceutical Good Manufacturing Practices (GMP) Annex of the MRA: The second draft of a *Joint Procedure for the Exchange of Information Between the USA and EC for Serious or Life-threatening Human/Animal Pharmaceutical Product Quality Defects and Recalls* (May 10, 2001). Article 20 of the USA–EC MRA Pharmaceutical GMP Annex requires that an alert system be developed and maintained so that the appropriate authorities are promptly notified of quality defects, recalls, counterfeiting and any other quality issues which could require additional actions or suspend distribution of product. The purpose of this procedure is to share such product information in a timely and effective manner in order to

minimize the risk to the affected public and to maintain confidence in the system. In addition to protecting consumers, the sharing of information should facilitate recalls as well as promote collaboration between regulatory authorities when there are emerging product quality problems.

This draft outlines the scope, definitions, procedures, and implementation of this agreement. The specific types of information to be exchanged as well as the various methods of communications and responsibilities are defined. Attachment A includes the *Rapid Alert Notification* document to be used in the exchange of information. Attachment B, *Designated Contacts*, lists the various USA FDA contact points for recall notification for human drugs, biologics and veterinary drugs. This SOP is for immediate implementation and will be reevaluated after being in effect for six (6) months.

On September 29, 2001, the EMEA also released *Mutual Recognition Agreements Pharmaceutical Annex Status Report* (EMEA/MRA/21/01, September 29, 2001). This document reviews the implementation status of the Mutual Recognition Agreements (MRA) between the EC and Canada, United States, Australia, New Zealand, Switzerland and Japan. The majority of countries already have an operational two-way alert system in place with the EC and all are moving forward towards completing the requirements for MRA implementation.

The EMEA Released *EMEA Public Statement on BeneFIX (nonacog alfa)* (EMEA/CPMP/2777/01/en/Final, October 4, 2001), which recommends intensive post-marketing surveillance for all new patients treated with this product and the initiation of two new clinical studies. The CPMP made this recommendation based on inspections of two of the three clinical studies on which the Marketing Authorization for BeneFIX is based. The inspections revealed deficiencies which cast doubts on the reliability of the clinical data. BeneFIX has been available in the United States since 1997 and Europe 1999. Though data accumulated since that time from physicians treating haemophilia B patients support the safety and efficacy profile of BeneFIX, this data is insufficient to be certain of the frequency of some adverse drug reactions. There will be enhanced surveillance of new patients receiving BeneFIX through the use of a registry and, at the request of the CPMP, two new clinical trials will be conducted to collect new efficacy and safety data. Patients already treated with BeneFIX may continue with their therapy.

In October, the EMEA published a press release to announce the creation of a new Communications and Networking Unit (Doc. Ref: EMEA/D/27597/01, October 18, 2001). The responsibility of this Unit is to facilitate communications and networks between the Agency's partners and ties in with the Agency's plans to develop and prepare for changes in the European system for authorization and supervision of medicines expected in 2003. This change reinforces the network character of EMEA by focusing on the communication tools and IT systems that will be required in the future. The new Unit will incorporate some function of the former Technical Coordination Unit as well as other new areas of activities.

The EMEA released a report on the outcomes of the October 18 *Good Regulatory Practices/Quality Management Systems, Second Benchmarking Meeting* (EMEA/27827/01/QMS, October 19, 2001). Delegates attended the meeting from 23 countries, the European Commission, and the EDQM to hurry the progress made since the first benchmarking meeting in March 2001. The purpose of the meeting was to benchmark management systems of the competent authorities to assure the quality of the authorization and supervision of medicines for human and veterinary use, and the harmonization of the best regulatory practices. Topics included: practical implementation of QMS with focus on staff and management; identification and documentation of processes in SOPs; establishment of a quality policy/mission statement; and performance measurement. The meeting is part of the EMEA Pan-European Regulatory Forum (PERF II) with the next meeting scheduled for May 7, 2002. ■

—James Lyda

Human Drug CGMP Notes

Volume 9, Number 1
First Quarter, 2001

Questions On:

- Do the CGMPs allow for locating in a non-penicillin production facility a shared laboratory for testing penicillin and non-penicillin products?
- Is it mandatory for a drug product manufacturer to conduct an on-site audit of the manufacturing of a component supplier for CGMP compliance?
- How can a firm demonstrate validation of alternative methods for testing the purity of Oxygen U.S.P. against the official U.S.P. method? What are the requirements for showing specificity for oxygen and range of method?
- What level of documentation is necessary to demonstrate that a lab analyst has the education, training and experience to perform laboratory analysis? Is it necessary to document training on each specific method?

General Comments

Here is another edition of *Human Drug CGMP Notes,* FDA's periodic memo for FDA personnel on CGMP for human pharmaceuticals.

You may notice a change in the editors of the Notes. Russ Rutledge recently ended his long FDA career in favor of what I hope is an even more fulfilling opportunity outside the government. Since Russ contributed to the editing of this edition just before his departure, I thought it would be appropriate to retain his "Ramblings," as he called them, for this, his final edition.

"Looking back upon the last year, I appreciate how lucky I've been to be associated with so many talented individuals. My job is easier when I take a topic of current interest to someone within the Division and ask for an article, and receive a well-written piece. I have received many warm e-mails from you, expressing thanks for the quality and timeliness of the articles published."

Good luck, Russ.

Another change has also been made and which explains in part our delay in publishing this edition of the Notes. As of this edition, we are now only publishing the *Human Drug CGMP Notes* EXCLUSIVELY for FDA personnel. This change was prompted by the recent promulgation of the Good Guidance Practices: Publishing at our INTERnet Web site requires adherence to GGPs and that means each edition would be subject to extensive internal review and approval. Since the intended purpose of the Notes is to provide agency personnel with timely answers to their CGMP questions, we've decided to publish in-house only. So, as of this edition, it will be published *exclusively* in electric format at the CDER INTRAnet Web site.

Thank you,
Brian Hasselbalch

Editor's note: PDA received this copy of *Human Drug CGMP Notes* through the FDA Freedom of Information (FOI) Division and will continue to publish them in the *PDA Letter.*

Questions and Answers

Do the CGMPs allow for locating in a non-penicillin production facility a shared laboratory for testing penicillin and non-penicillin products?

References: 21 CFR Sections: 211.42(d) Design and construction features; 211.46(d) Ventilation, air filtration, air heating and cooling; 211.176 Penicillin contamination

Yes. A shared laboratory can be located within a non-penicillin production facility. Although CGMPs require separate facilities for the production of penicillin and non-penicillin products, they do not require separate laboratories for the testing of penicillin and non-penicillin products. However, CGMPs require that there be adequate controls to prevent penicillin cross-contamination of non-penicillin drugs in production areas of the firm.

The CGMP regulations also require that the air handling system in such a shared laboratory be separate (not connected) to non-penicillin production areas of the facility. The purpose of the references to CGMP regulations is to avoid penicillin cross-contamination of non-penicillin products.

Likewise, it is important that the laboratory exercise good containment controls to ensure that people and equipment entering and exiting the laboratory do not inadvertently contaminate non-penicillin production areas with traces of penicillin. This is especially important for any personnel or equipment coming in contact with penicillin drugs in the laboratory or penicillin production areas. The firm should assess its procedures used to prevent cross-contamination and qualify them under worst case scenarios.

Is it mandatory for a drug product manufacturer to conduct an on-site audit of the manufacturing of a component supplier for CGMP compliance?

Reference: 21 CFR 211 Section 211.84 Testing and approval of rejection of components, drug product containers, and closures

Note: A related article was published in the December 1998 edition of Human Drug CGMP Notes.

No, it is not mandatory for a dosage form manu-

facturer to perform site audits of the component supplier's manufacturing operations. 21 CFR 211.84 does require that all lots of all components (API and excipient) be tested before use to ensure that they meet their predetermined quality attributes. This responsibility of the dosage form manufacturer to ensure component quality prior to use can be abridged but only if certain conditions have been met, i.e. after the supplier has been qualified for that component. Supplier qualification is provided for at 211.84(d)(2), and allows a manufacturer of a drug product to cease complete testing of every lot of component when "…the manufacturer established the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals." It's worth emphasizing that the language of this regulation and the preamble clearly intend that "validation of the supplier's test results" is achieved by testing and/or examination—not audits.

Once a manufacturer has validated a supplier the regulations permit the reliance upon the supplier's acceptable Certificate of Analysis (CoA) if, in addition, they perform at least one specific identity test on each lot received. If all is well, the lot can then be accepted for use in manufacturing. Supplier validation is an exception to the rule of full testing for each component lot received. A manufacturer may choose not to take advantage of this exception and always perform at least one specific test for identity and have and review a CoA showing the lot was tested and found to meet its predetermined specifications and is otherwise fit for its intended use.

We know, of course, that many companies in fact do perform such audits as part of a supplier validation program—though not necessarily just for quality assurance reasons—and we recognize their potential value. Site audits may provide a manufacturer with additional confidence that laboratory testing can not. Controls over air handling systems, cross-contamination, and the adequacy of a water purification system, for example, are perhaps best verified by direct inspection.

Performing an audit does not, conversely, relieve the drug product manufacturer of its absolute obligation to verify by test or examination component quality prior to use. Nonetheless, a supplier validation program incorporating site audits may justify a longer interval between re-validations. In evaluating the firm's frequency for re-validation of a component and supplier, you should verify that the firm has accounted for the past history of the supplier as well as the quality reliability of the component. A manufacturer should give full and prompt attention to any information they receive which calls into question a supplier's reliability or component quality.

How can a firm demonstrate validation of alternative methods for testing the purity of Oxygen U.S.P. against the official U.S.P. method? What are the requirements for showing specificity for oxygen and range of method?

References: 21 CFR Sections: 211.160(b), General Requirements; 211.165, Testing and Release for Distribution; 211.194, Laboratory Records

U.S.P. 24: General Notices section, Tests and Assays: "Foreign Substances and Impurities"; and Article <1225> "Validation of Compendial Methods".

Two requirements in particular seem to account for many of the questions regarding what constitutes acceptable validation data for alternative methods to analyze Oxygen, U.S.P. for purity: 1) Evidence of specificity for oxygen in the presence of other gases; and 2) showing method performance over the proper range.

1. Specificity

Any documentation submitted to show equivalency to the U.S.P. method should be in accordance with Current Good Manufacturing Practice regulations 21 CFR 211.165(e) and 211.194(a)(2). Section 211.165(e) states "the accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented." For purposes of validating an alternative method against official methodology, there should be documentation showing that its performance in each of the above categories is equivalent to or better than that shown by the official method.

Criteria in the current edition of the U.S.P., Article <1225> "Validation of Compendial Methods" offer guidance on how a method may be supported. One of these criteria is evidence of specificity for the analyte in the presence of other compounds that could reasonably be expected as contaminants or interferents. The requirements to show specificity for oxygen in validation data for alternative Oxygen, U.S.P. purity methods has been frequently overlooked because oxygen analyzers based on the paramagnetic principle and some based on spectrophotometric measurement have been assumed to give a specific response for oxygen. Such analyzers are not exempt from this requirement. Documentation of specificity for oxygen is of particular importance for two reasons.

a. Many analyzers of the paramagnetic type are also used to provide a specific identity test for oxygen.

b. The practice in the medical gas industry of filling medical gases and industrial gases in the same facility, and in the same area of the facility, is increasing. Consequently the possibilities for cross-contamination and mix-ups increase.

The data presented should demonstrate that the analyzer used does not give falsely positive results with the gases most likely to be involved

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in such mix-ups. Thus, the data should address specificity for oxygen in the presence of such gases as helium, argon, nitrous oxide, carbon dioxide, etc. The presence of such specificity data in a firm's alternative method validation does not exempt a manufacturer of a U.S.P. product from their responsibility to test for other impurities that might be present due to their specific manufacturing situation as outlined in the General Notices section of the U.S.P.

1. Range of Method/Methods Performance

Another source of questions concerns the range in which the performance characteristics of the alternative method should be documented. To be considered acceptable, the data presented should show performance equivalent or better than that of the U.S.P. method, not only within and at the extremes of the acceptable range (i.e., specification) of results, but outside the acceptable range as well. For Oxygen, U.S.P., the acceptable range of purity if 99.0% to 100.0%. Thus, U.S.P. equivalent method performance would have to be demonstrated at concentrations below the 99.0% limit as well as above. Demonstrating good analytical performance across the limit of acceptability is one way of assuring that the alternative method used will give accurate and reliable results in "borderline" cases where the purity is near or at an extreme of the regulatory limit. To use a test value for release of product there should be adequate support for the validity of the test method for that result. USP General Information Chapter <1225> provides guidance for establishing the linearity of an assay method.

Although specific requirements for range of results are not listed in the CGMPs, section 211.160(b) requires sound test procedures. Demonstrating that the method used can give accurate and reliable results in the vicinity of the limit of acceptability is also a necessary consequence of the CGMP requirement (211.194(a)(2) that the documentation "…establish that the methods used in the testing of the sample meet proper standards of accuracy and reliability as applied to the product tested." Thus, an obvious CGMP violation is where a firm has relied upon a test result falling outside the validated range for linearity.

What level of documentation is necessary to demonstrate that a lab analyst has the education, training and experience to perform laboratory analysis? Is it necessary to document training on each specific method?

References: 21 CFR Sections: 211.25 Personnel qualifications

The CGMPs require adequately trained personnel to perform analyses of drugs (21 CFR 211.25). Consequently, firms should document the specific training an analyst has received. An analyst who is trained in general analytical techniques as evidences by coursework or degree (e.g. chemistry), and has been given in-house training and/or other OJT to show familiarity with the company's specific methods, could satisfy this CGMP requirement. There is no need to document analytical training for each individual product analysis when the analytical method for each of these products follows applicable general principles for which training is done. For example, once the analyst has been trained in the general technique of HPLC they could be considered trained to perform HPLC analysis for a broad range of dosage strengths and types. This applies to any common analytical method used in laboratories, such as HPLC, FTIR, UV-Vis, Karl Fischer, GC, TLC, Dissolution, etc.

Sometimes a firm used a modification to a general technique, for example incorporating a specialized detector. If a firm utilizes a modified technique to their product, we would expect to see documentation that the analyst has been trained to use that technique. ■

—William Stoedter

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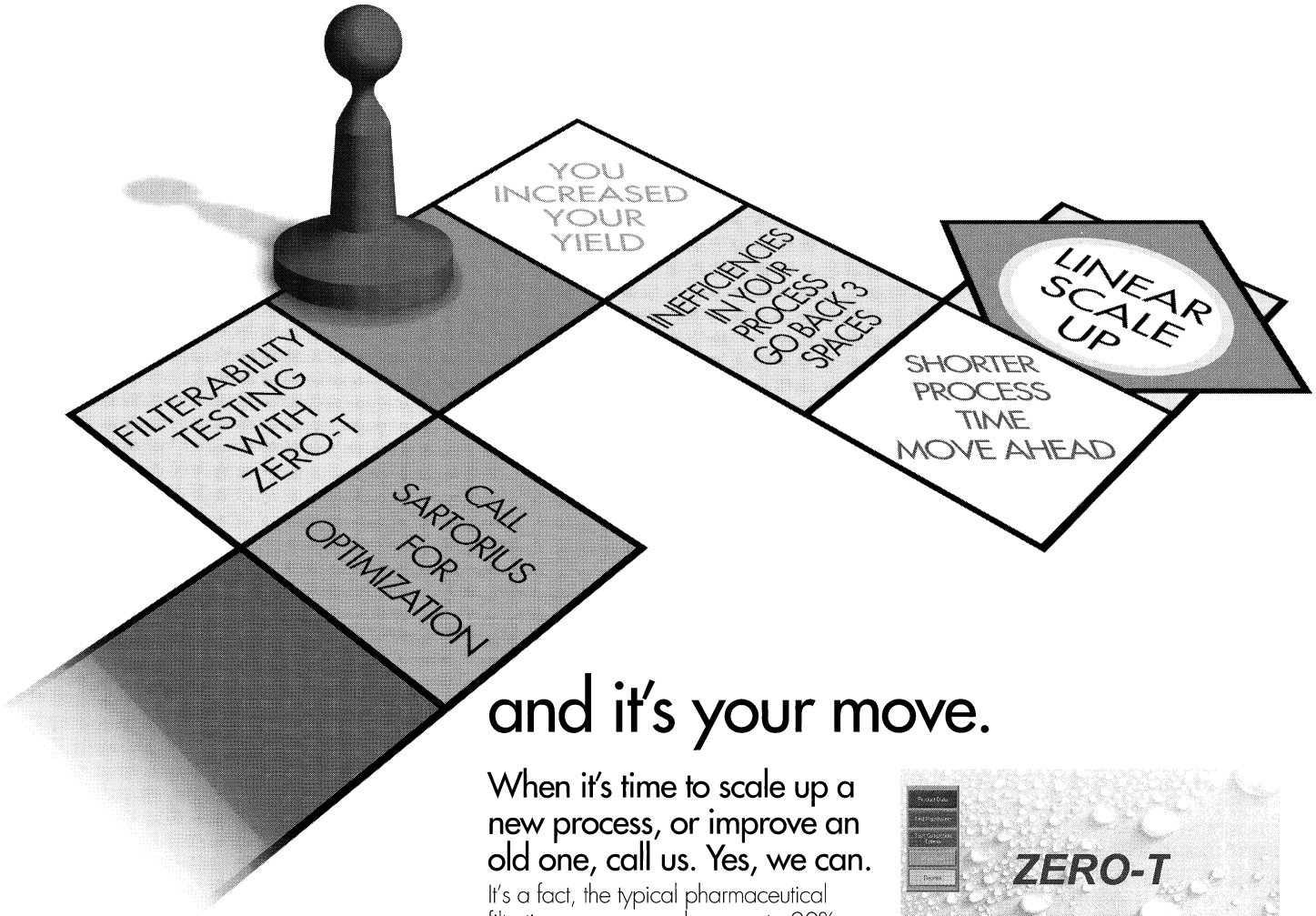

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USP Update

by Roger Dabbah, Ph.D., USP

At its recent meeting, the Pharmacopeial Discussion Group approved a procedure to communicate the interchangeability and harmonization status for monographs and general chapters. USP and EP will use a statement in each of their General Notices on the "Interchangeability of Methods"—an introductory statement at the beginning of each harmonized general chapter and a General Chapter on Harmonization that will be continuously updated. The JP will use a harmonization notification from the Ministry of Health, Labour and Welfare.

Starting in 2002, USP-NF will be published annually and during the year we will publish two Supplements.

In the *Pharmacopeial Forum* of November–December 2001 on p. 3217, USP published a calendar of Pharmacopeial Education Courses for the remainder of 2001 and for 2002.

Note in this PF the 13th Interim Revision Announcement to USP 24 and to NF 19 become official on December 1, 2001. This announcement includes a monograph on Cyclosporine Capsules, and one on Rifampin, Isoniazid, Pyrazinamide and Ethambutol Hydrochloride Tablets.

In the In-Process Revision section of the same PF there are a number of revisions proposed, most of them targeted for the Second Supplement of USP 25-NF 20. In addition, a number of new monographs are also proposed: Benazepril Hydrochloride; Benazepril Hydrochloride Tablets; Ciprofloxacin Opththalmic Ointment; Dinoprostone; Doxazosin Mesylate Tablets; Ferumoxsil Oral suspension; Fluoxetine Tablets; Fosphenytoin Sodium; Fosphenytoin Sodium Injection; Graftskin; Iodixanol; Iodixanol Injection; Megesterol Acetate Oral Suspension; Pseudoephedrine Hydrochloride Extended-Release Capsules; Repaglinide; Taurine; and Zileuton. A number of general chapter revisions are also included. New reagents specifications are also included in this section of PF. The Graftskin monograph is the first of its class to appear in PF. It is used for wound dressing and is a bioengineered skin tissue that is metabolically active.

Under Pharmacopeial Previews in the same PF we proposed either new monographs or revisions to existing monographs that are significant at the earliest possible time to obtain public comments. The new USP monographs proposed are Cyanocobalamin Co 58 Capsules; Sumatriptan; and Sumatriptan Nasal Spray. The new NF monographs proposed are: Horse Chestnut; Powdered Horse Chestnut; Powdered Horse Chestnut Extract; Red Clover; Powdered Red Clover; Powdered Red Clover Extract; Red Clover Tablets; Alpha-Lipoic Acid Capsules; and Alpha-Lipoic Acid Tablets.

In the Stimuli for the Revision Process, an article by Joseph Sherma on "Modern Thin-layer Chromatography in Pharmaceutical and Drug Analysis" is presented. Vivian Gray et al. published a proposal for a general information chapter on Dissolution. ■

PDA/FDA "Lite" Comes to Italy

Italy Chapter Presents Highlights of September Conference in Milan and Rome

In an effort to better serve their increasing membership, the PDA Italy Chapter presented two half-day roundtables covering the highlights of the annual PDA/FDA Joint Conference held in Washington, DC. in September. Since it is frequently difficult for members to travel internationally for such meetings, leaders in the Italy Chapter decided to cover the USA conference with the intent of delivering summaries of key points for local members in Italy.

The roundtables were conducted in Milan on October 22, and in Rome on October 24. The Rome meeting was hosted at Sigma Tau Pharmaceuticals. Vincenzo Baselli, Pall, President of the Italy Chapter, delivered opening remarks at both roundtables. Topic leaders guided the presentations and discussions for each of the following topics:

- Active Pharmaceutical Ingredients (API) and ICH Q7A
  Leader: Stefano Salmieri, Farmabios
- Good Manufacturing Practice (GMP) During Drug Development
  Leader: Pier Giorgio Valeri, CTP
- Validation: Existing Facilities, Process Validation for Drugs and Biologics
  Leader: Claudia Nardini, Bayer
- Current Issues and Hot Topics in Aseptic Processing and Isolators
  Leader: Gabriele Gori, Bausch and Lomb
- Preparation for Inspections, Including Microbiology and Analytical Laboratories
  Leader: Gilberto Dalmaso, Steris
- Compendial Issues and Water for Pharmaceutical Use
  Leader: Jim Lyda, PDA

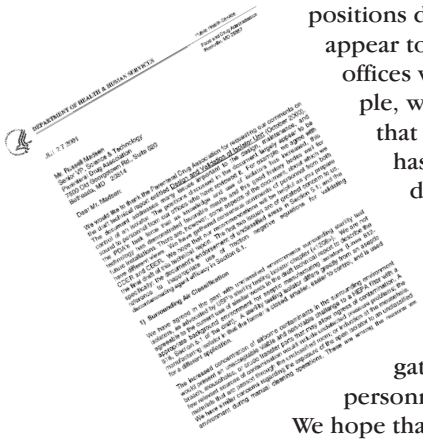
Evaluations were positive and discussion lively. Dinner was served for all following each roundtable. Based on this trial program the chapter has agreed to consider a repeat in 2002. ■

—James Lyda

The roundtable team in Rome (l-r): Jim Lyda, PDA Europe; Vincenzo Baselli, Pall; Claudia Nardini, Bayer Biologicals; Gabriele Gori, Bausch & Lomb.

More of the roundtable team (l-r): Pier Giorgio Valeri, CTP; Giorgio Bersani, Sigman Tau Pharmaceuticals, Stefano Salmieri, Farmabios. (Not shown: Gilberto Dalmaso, Steris.)

Letter from FDA to PDA Regarding TR 34



Dear Mr. Madsen:

We would like to thank the Parenteral Drug Association for requesting our comments on the draft technical report entitled Design and Validation of Isolator Unit (October 2000). The document addresses many issues important to the design, maintenance, and control of an isolator. The positions discussed in the document largely appear to be sound to personnel from our offices who have reviewed it. For example, we agree with the PDA's task force that as knowledge and use of isolators has increased, this technology has demonstrated favorable results and this good history bodes well for future installations. There are, however, some aspects of the document, about which we have different views. We have gathered consensus comments of personnel from both CDER and CBER.

We hope that our recommendations will be helpful as you prepare the final draft of this technical report. The first two issues are of greatest concern to us, specifically: the document's endorsement of unclassified areas in Section 5.1; and the reference to inappropriate use of fraction negative equations for validating decontaminating agent efficacy in Section 6.1.

1) Surrounding Air Classification

We have agreed in the past with unclassified environments surrounding sterility test isolators, as advocated by USP's sterility testing isolator chapter (<1208>). We are not agreeable to the current use of similar words in the draft technical report to describe the appropriate background environment for aseptic manufacturing isolators (Lines 612-618, Section 5.1 of the draft). A sterility testing isolator differs greatly from an aseptic manufacturing isolator in that the former is closed, smaller, easier to control, and is used for a different application.

The increased concentration of airborne contaminants in the surrounding environment would present an unacceptable viable and non-viable challenge to a HEPA filter with a breach, mouseholes, or crude transfer ports that may allow ingress of contamination. A few relevant sources of contamination would include undetected pressure problems; the materials that are passed through the unclassified room; or induction at the mousehole. We have similar concerns regarding the exposure of the open isolator to an unclassified environment during manual cleaning operations. These are among the reasons we would recommend your technical guide state that the environment surrounding an aseptic manufacturing isolator should be classified (e.g., at least Class 100,000).

To further illustrate our concern, Section 1.3 of the draft technical report defines, in part, an Aseptic Processing Isolator as a unit that includes a "retentive filter (HEPA Minimum)." On many occasions, we have seen semi-annual testing HEPA filter certification that revealed leaks in HEPAs. Because isolator systems described in this draft technical report use the same HEPA filters, there is no basis to expect HEPA filters to be any less prone to developing leaks. We regularly see isolator systems using air from the surrounding room as whole or partial makeup air. Industry practice does not include testing HEPA filters everyday or every month, rather, these are normally certified only semi-annually. Moreover, even the best environmental monitoring program would be unlikely to rapidly and readily reveal the existence of a problematic breach.

Section 4.2.2 also acknowledges that isolators leak at some level, and risks associated with that leakage may need to be evaluated. In addition, open isolators directly communicate air with the surrounding environment, permitting the interface of a highly classified isolator with an unclassified room. The choice of an unclassified room in this application would be tantamount to operating on the edge of failure. As a consequence, we recommend changing the proposed wording (e.g., advocating a single HEPA in tandem with an unclassified environment) to be consistent with our above recommendations.

2) Use of the Fraction Negative Approach

The use of fraction-negative, Stumbo Murphy Cochran, or similarly premised equations in calculating efficacy for the chemical agents used to decontaminate an isolator is not recommended. The industry has frequently applied fraction negative analysis of Biological Indicator (BI) data when the BIs were distributed in locations that were subject to unequal process lethality. While this practice is technically incorrect, the error has been generally overlooked for those processes that impart a minimal difference in lethality (e.g., well-controlled steam chambers). For those specific processes, the errors inherent in fraction-negative calculations are likely to be greater than the differences in the heat distribution.

However, the theory behind such calculations is undermined when used to describe the process lethality of chemical agents that are circulated in a large chamber. Because uniform sterilizing conditions are not achieved, BIs placed throughout isolators are exposed to variable chemical treatment. The lack of penetrating characteristics of the chemical agents also factors into this variability. Under these limitations, the equations are of dubious supportive value when used in an isolator decontamination validation. Therefore, we

continues on page 20

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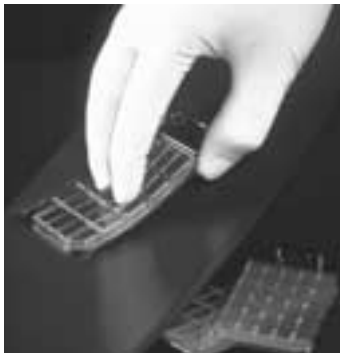

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FDA Letter from page 18

recommend that all references to such equations be removed from this document.

On the other hand, total kill analysis is an example of a validation approach that has been found to be consistent with the nature of chemical decontamination agents. We concur with the document's endorsement of this validation approach.

We recommend one further clarification in this section. When reading the current draft, it appears that decontamination methods with a 3-log reduction are deemed to be "suitable for isolator decontamination" (line 742, Section 6.1.2). We believe it is inappropriate for such a standard to be given an apparent blanket acceptance by this document. Manufacturers have consistently established, and successfully achieved, significantly better log reduction values.

We do agree that a lower value than the minimum standard routinely used (i.e., 6-log reduction) may be applicable to certain transfer isolators or "pass-throughs" used to introduce controlled, very low bioburden materials (an example: wrapped sterile supplies which have been briefly exposed to the surrounding cleanroom environment). But this topic clearly should be differentiated from the other decontamination processes and addressed in a separate subsection of the document.

3) Glove Change

We recommend deletion of the following excerpt: "Some isolator manufacturers suggest that it is possible to change the glove in a two piece glove/sleeve assembly without compromising the aseptic environment within the isolator. The practice of changing gloves during aseptic production operations must be cautiously considered. When glove changes during operations are allowed, data demonstrating that the change does not affect isolator integrity are required." Given the significance of potential problems associated with this practice, we would not recommend its use by firms.

We also note that Section 6.1.8.4 appears to imply that periodic physical testing of gloves should be done in place of regular microbiological testing of gloves. At minimum, we recommend that the isolator's gloves be microbiologically tested as part of each campaign. This frequency represents a reduced testing burden for isolation technology versus conventional aseptic processing operations.

4) Air Supply Specifications

While we agree that reduced velocities may be found to be appropriate for many isolators, the use of a narrow 0.075–0.15 m/s velocity range (See 4.1.2) in this document counters what is used by many firms. Uncharacteristically for a PDA technical report, such a range seems exclusionary and prescriptive for a firm, especially following the earlier statement that "the user need only demonstrate that their particular choice in operating conditions works" (See 4.1, "Air Supply Specifications"). Perhaps a more comprehensive survey of manufacturers, including those not on the committee authoring this document, should be done before too narrow a range is included. We are concerned that this range may be interpreted by the reader as the optimum design requirement before it has been supported by more complete data collection in the industry. (In contrast, we note that section 6.1.4.3 takes a more broad approach to discussing pressure differentials.)

5) Apparent Overstatements

Line 528-529 of 4.2.2 refer to a "seal" formed by air overpressure in "ordinary clean rooms." We recommend use of language that more clearly reflects the major role of overpressure in preventing contamination although certainly not providing a "seal" in the traditional cleanroom context.

We find the same problem with Line 724 of 6.1.1.3, which overstates that it is "impossible" for an organism to reproduce in an isolator. (Also, this section does not address sporeformers, which are of at least equal relevance and concern.)

6) Definitions

The definition proposed for "barrier system" (page 2) does not seem to adequately describe what a barrier system is. The current definition does not distinguish it from other equipment (e.g., laminar flow hood) included in the "Isolation Continuum" on page 5. It may also be useful to provide a definition for certain other terms used in the document. For example, clarification of the differences between terms such as sanitization, sterilization, decontamination, and "bio-decontamination" may be helpful.

In addition, the Isolation Continuum chart on page 5 is not intuitively clear. It not certain whether the lower arrows are meant to indicate increasing positive pressure from right to left, and increasing negative pressure from left to right. Also, on the left margin is an arrow indicating "Increased Reliability of Operation," however, this aspect of the chart does not lend itself to ready interpretation and is not further explained.

7) Monitoring of the Environment

Isolators vary in configuration and use, and it would thus be impractical to provide many generalized monitoring program recommendations. However, it may be useful to mention some additional notes that would help the user make a judgement on the appropriateness of their validation or monitoring plan. For instance, as part of validation and routine operations, we would expect environmental monitoring to extend for as long as the actual use of the isolator (i.e., the time between decontamination cycles). In addition,

some sites provide particularly important data and should be routinely monitored (e.g., such as a non-viable particulate-monitoring site near mouseholes and other isolator ports).

We have previously provided detailed editorial comments to the early 2000 draft of this document and have not prepared further line-by-line comments for this version. We have identified the above issues as of most importance, and we look forward to discussing these topics with PDA. Please feel free to contact Richard Friedman (301-827-7284), Laurie Norwood (301-827-6031) or Robert Sausville (301-827-6205), if we can provide further insight into our CGMP expectations regarding these issues.

Sincerely yours,
Joseph C. Famulare,
Director, Division of Manufacturing
and Product Quality,
Center for Drug Evaluation & Research

John A. Eltermann, Jr.
Director, Division of Manufacturing
and Product Quality,
Center for Biologics Evaluation & Research

PDA Response to FDA Regarding TR 34

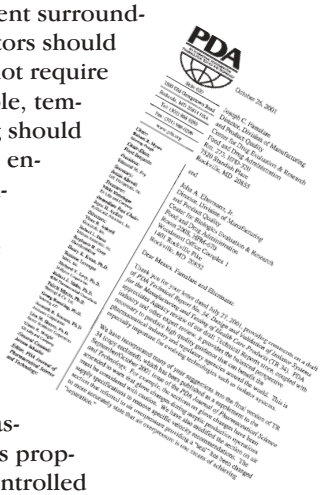
Dear Messrs. Famulare and Eltermann:

Thank you for your letter dated July 27, 2001, providing comments on a draft of *PDA Technical Report No. 34: Design and Validation of Isolator Systems for the Manufacturing and Testing of Health Care Products* (TR 34). PDA appreciates Agency review of our draft Technical Reports since, coupled with industry and other expert review, it provides the balanced perspective necessary to produce high quality guidance that can benefit the pharmaceutical industry and regulatory agencies around the world. This is especially important for evolving technologies such as isolator systems.

We have incorporated many of your suggestions into the final version of TR 34 (copy enclosed), which has been published as a supplement to the September/October 2001 issue of the *PDA Journal of Pharmaceutical Science and Technology*. For example, the sections on glove changes have been amended to warn that glove changes during aseptic production operations must be considered with caution. We have also modified the section on air supply specifications to remove specific velocity recommendations. The section that referred to air overpressure providing a "seal" has been changed to more accurately state that air overpressure is one means of achieving "separation."

However, there are two areas where, based on technical grounds, we must "agree to disagree": these are your positions that the environment surrounding an aseptic manufacturing isolator should be classified to at least Class 100,000 (ISO Class 8) and that the use of the fraction negative approach is not recommended in calculating the efficacy of chemical agents used to decontaminate an isolator.

Surrounding Air Classification



PDA believes that the environment surrounding aseptic manufacturing isolators should be controlled, but that it does not require formal classification. For example, temperature, humidity, and lighting should be maintained at levels that will ensure a satisfactory work environment. Appropriate air filtration systems should be in place. The area should also have controlled access to prevent entry of unauthorized operational and maintenance personnel. We do not believe, however, that the area requires formal classification if the isolator system is properly designed, instrumented, controlled and alarmed.

One of the concerns expressed in your letter is the possibility that the HEPA filters supplying air to the isolator could develop undetected leaks between the semi-annual testing, potentially compromising the environment within the isolator. Given that a Class 100,000 environment is only about one log better in terms of particulate level than a typical unclassified pharmaceutical production or laboratory environment, the added safety margin provided by the Class 100,000 environment seems rather ineffective. Also, consider that in conventional clean rooms the HEPA filters are typically supplied with about 20 percent fresh air, which has only been pre-filtered to perhaps the 90 percent ASHRAE level, making it far "dirtier" than the intake air typically supplied to an isolator HEPA filter. If potential, undetected leaks are such a concern, there is much more of a problem with a conventional clean room than

continues on page 22

PDA Response Letter from page 21

with an isolator in a controlled, but unclassified environment.

We have recently become aware of an FDA concern which was not explicitly stated in your letter: that the need for external classification stems from observations that firms are accessing isolator internals during shutdown periods from an unclassified environment without adequate protection from the workers. The concern is that such access can create a substantial microbial insult to the isolator internals, thereby overwhelming the capabilities of the decontamination process. We believe that the probability of microbial contamination reaching levels that could overwhelm the decontamination capability of the isolator system during a changeover activity is exceedingly low. The technical report requires a three-log reduction of highly resistant spore bearing organisms. Therefore, it is improbable that the bioburden load introduced during changeover would reach a level that could affect decontamination efficacy, since organisms in the normal microbial flora are typically 10–50 times less resistant to the decontaminating chemicals than are biological indicator spores. Finally, all decontamination operations, whether by gas, steam or other method, are preceded by a thorough cleaning of the affected surfaces before exposure to the decontaminating agent. Once an isolator has been opened, it must be thoroughly cleaned in a closed mode prior to decontamination. This precaution is consistent with industry practices in ordinary clean rooms. When managed in a comparable fashion, with closed cleaning and decontamination of isolator internals after any major breach of system integrity, we remain convinced that our position on this subject is scientifically sound.

The final version of TR 34 states, "There need not be a specific particulate clean air classification requirement for the room surrounding isolators or isolator networks. Regardless of their specific usage, properly designed isolators do not allow the exchange of contaminants with the surrounding environment. Therefore, the quality of the surrounding room is a very minor consideration relative to the quality of the internal environment of the isolator or isolator network. The surrounding room should have limited access, and should be clean and well organized."

Use of the Fraction Negative Approach

The final version of TR 34 includes the following passage describing the use of fraction negative studies in the validation of isolator decontamination.

"The three-log reduction can be demonstrated as follows:

Fraction Negative Studies in which a three-log kill or greater spore reduction value is calculated using the Holcomb, Spearman, Karber Procedure, Stumbo Murphy Cochran, Limited Stumbo Murphy Cochran Method, or Limited Spearman Karber Procedure. A suitable number of biological indicators must be used for the method chosen as described in relevant AAMI Standards or ISO/DIS 14161."

Fraction negative (F-N) studies are a widely used methodology for the cycle development of sterilization processes, particularly those which entail the use of a sterilizing gas such as EtO. The demonstration of partial kill at multiple locations within a vessel is used to estimate the resistance of the microorganism to the conditions within the sterilizer or chamber. Multiple replicate runs at the same processing conditions are generally required. The end result of F-N studies is the time in minutes in which the population of the challenge organism can be reduced by 90% at the defined processing conditions. Once the D-value is known the cycle duration can be established to achieve the desired log reduction.

Further support for the use of fraction negative studies comes from reports of significant BI population effects in VHP D-value studies. For example, the same BI preparation in some cases will show D-values that are 2 to 3 times higher at 10^6 than at 10^3. This phenomenon was reported at the PDA Isolator Conference last October and a paper has been submitted to a peer-reviewed journal on this subject. This effect must be considered in isolator decontamination because the challenge level, even at the 10^3 level is 10 to 100 times greater than the actual pre-decontamination bioburden.

The F-N method also is useful in establishing the resistance of the biological indicator under actual conditions of use. Since the test is carried out under in-use conditions, the efficacy of the process can be accurately determined. Laboratory studies as often performed by suppliers of biological indicators are performed at standardized conditions which may not reflect the capabilities of the production vessel. This difference in lethal conditions is one major reason for anomalous results in validation studies.

One of the objections raised in relation to F-N studies is that the conditions within the isolator or other vessel may not be uniform and that this may adversely affect the accuracy of the results. While larger chambers may be more prone to variation in the internal concentration of the decontaminating agent and relative humidity than smaller ones, this variation manifests itself directly in the results of the study and no fur-

ther adjustment to the results is needed. This phenomenon makes the F-N approach particularly useful. The survival of microorganisms at some locations allows the estimation of the D-value at the prevailing conditions within the unit, which results in a higher D-value and consequently a longer decontamination process. This pragmatic information enables selection of the required cycle parameters to ensure the full inactivation of the challenge organism and ultimately the bioburden. Where the F-N approach is used for steam sterilization, the variability across the chamber is certainly reduced; however lack of variability is not a requirement for the application of the method. Cycles for EtO sterilization are ordinarily developed using this method with either single point or no measurement of gas concentration/relative humidity. The application of this approach to isolators is wholly consistent with well-established EtO sterilization validation methodology.

Variations in the relative humidity and/or concentration of the decontaminating gas/vapor within an isolator are an inherent part of the process. The use of the F-N approach in which resistant indicators are distributed throughout the chamber and subjected to a sub-lethal system will assess the impact of these variations on the delivered lethality. While a uniform concentration is always desired, deviations from the uniformity are incorporated into the D-value determination using the F-N method.

The letter also expresses concern that TR 34 supports the adequacy of a 3-log reduction for isolator decontamination. The task force was careful in its selection of terminology here, choosing the word decontaminate rather than sterilize. PDA believes that a 3-log reduction of resistant spores is sufficient for isolator decontamination. Although higher reduction levels are possible and have, in fact, been demonstrated in some instances, sterilization of the isolator interior has not been shown to result in increased product sterility assurance.

We hope this letter has clarified our position on these issues. Again, we appreciate your review of the draft TR 34 and look forward to your comments on the final version. We would be happy to meet at your convenience to further discuss these issues to resolve our differences.

Sincerely,
Russell E. Madsen
Senior VP Science and Technology
Enclosure

TM 1 Revision, Draft 12, Now Available for Comment

The latest draft of the revision to *PDA Technical Monograph No. 1: Validation of Steam Sterilization Cycles*, is available in the Members Only section of the PDA Web site for review and comment. This is a comprehensive rewrite of the original monograph, which was originally published in 1978 and draws upon the extensive technical information published on this subject in the intervening period. While this publication cannot possibly supplant the wealth of information published on this subject, the revision attempts to provide summary information on the subject while citing appropriate references for the reader to consult if necessary. The objective is to contemporize the earlier effort through the utilization of current definitions, recognition of improved temperature measurement and sterilization equipment and enhanced technologies. Different types of sterilization equipment, cycle choices and the possible validation methodologies which can be employed are also discussed.

Technical comments on the draft would be appreciated. Comments should be submitted by February 28, 2002, and be directed to:

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—Russell E. Madsen

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The Definition of "CGMP Compliance"

The following remarks are taken from an exchange in the Pharmaceutical Sci-Tech Discussion Group, a PDA-sponsored Online Forum held on the Internet at www.pda.org. PDA Online Forums are free of charge and open to the public. They serve as a platform for exchanging practical, and sometimes theoretical, ideas within the context of some of the most challenging issues confronting the pharmaceutical industry. If you are not currently a member of a discussion group, we encourage you to visit our Web site and join.

This month's posting...

Question

How does one define being in compliance with CGMPs?

Obviously doing correctly what the GMPs call for constitutes "compliance." But, in my opinion, "compliance" is a relative term, not an absolute. I feel that it also implies an attitude of genuinely wanting to and trying to do things correctly as opposed to taking unwarranted shortcuts. I doubt that many companies are fully "in compliance with the GMPs" 100% of the time, for very practical and unavoidable reasons. Audits and inspections merely give a snapshot of the degree of compliance at a specific point in time.

The GMP regulations are deliberately worded in broad terms as to what must be accomplished as opposed to "how to" accomplish the goals, in order to give each company latitude in equipment and procedures. But, this in itself makes it difficult to spell out just when one is or is not "in compliance." Similarly, some aspects of what we consider to be current GMP have not yet made it to the formal regulations in 21 CFR, cleaning validation being one example of many such details that we know FDA insists upon and that are enforceable by regulatory actions even in the absence of written regulations.

From a philosophical point of view (which sometimes also shows up in litigation), it would be interesting to know what our industry considers "in compliance" to really mean.

Response 1

One doesn't define being in compliance with CGMPs any more than one defines compliance with traffic regulations. One simply does one's best to comply (or not) according to one's interpretation of the regulation. Much the same way, different people have differing views of traffic regulations. At a stop sign, one driver comes to a complete halt, while others come to various interpretations of "stop." The traffic cop, in his duty of "protect and serve," will observe their processes and will make written citations or take other measures as judged appropriate.

Response 2

As an ex-Reviewer and also a member of the industry for over 15 years, I can speak form both sides. Compliance is generally in the eye of the reviewer! Based on their knowledge or the lack thereof, you may either pass or fail. Some ask intelligent questions, others ridiculous/non-applicable ones. It's simply the luck of the draw.

You may be the top facility in your field, as to compliance, yet receive a 483. It all depends on the reviewer. You can either challenge them or comply with their wishes, no matter how ridiculous they may be. Supervisors do no always challenge bad reviewers because that makes them look like bad managers. Companies do not always challenge bad citations because they are afraid of the Agency and look for the easiest way out.

Ergo, "compliance" simply means I passed this time. Look back to the Generic Drug Scandal and how many compliant firms became suddenly, non-compliant.

The bottom line is to always do that which is safe, prudent and good practice for your operations and pray you get a good reviewer and inspector(s).

Response 3

In case of GMP "what is current today is obsolete tomorrow" and hence it's always pre-fixed with the letter "C." The rules and guidelines published on GMP are always and invariably written in terms of "what" must be accomplished and never in terms of "how to" accomplish because of too many variables. All these factors contribute to inability to define the term "compliance," though all auditors and regulatory inspectors use the term.

Response 4

"The bottom line is to always do that which is safe, prudent and good practice for your operations and pray you get a good reviewer and inspector(s)."

I think this is thoughtful advice. I can only add that to be "compliant" (a term I am not very comfortable with) requires the following: Demonstrate

full knowledge and sustainable control of your manufacturing process. If you can do these things, you are faithful to CGMP irrespective of what any out-of-control investigator may say or do. While there is a multitude of regulatory, compendial and industry guidance extant, exactly how one demonstrates knowledge (data; information) and control of the process is up to the manufacturer. If you cannot demonstrate the "competency" of your process (i.e., predicated on knowledge and control), you are fair game to be picked apart by any trained investigator or auditor. For example, if you are aseptically producing batches using a process stream that has not been sufficiently microbiologically characterized, then you may be generating sterile-marketed batches but you are not doing so consistent with the intent of CGMP (i.e., know what's present and prove that what's present is being controlled). This "knowledge-control" mentality is central to "compliance." ■

—Compiled by Russell E. Madsen

International Calendar

2002

FEBRUARY

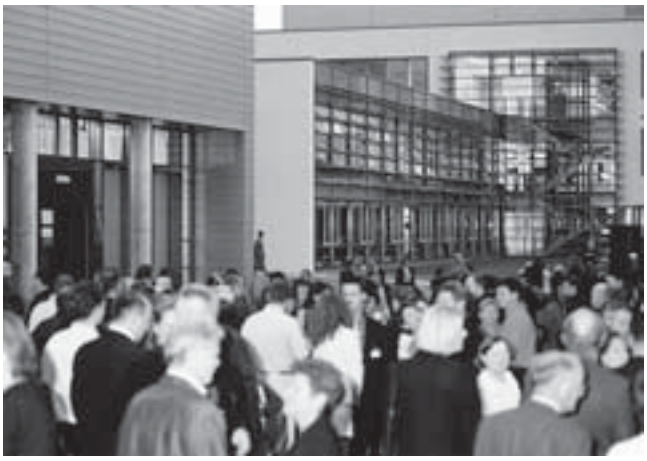
February 11–13, 2002
Basel 2002: PDA International Congress, Courses and Exhibition
Adding Value to the Pharmaceutical Industry—Leveraging the Future
Basel Convention Center
Basel, Switzerland
For Exhibit Information Contact:
Nahid Kiani, PDA
(301) 986-0293 ext. 128
kiani@pda.org

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

Company, Colleague & Product Announcements

German Chancellor Gerhard Schroeder officially put **Sartorius AG's "Plant 2001"** into operation on 28 September 2001, in Goettingen, Germany. Sartorius AG is a leading manufacturer of industrial filtration and measurement systems. The facilities are designed for the manufacture of the Biotechnology Division's filtration and separation products for the pharmaceutical and food industries. Executive Board Chairman and Group CEO, Dr. Utz Claassen, emphasized the significance of this day stating, "The new plant also entails a tremendous expansion of our production capacity and investment in quality and environmentally friendly manufacture. For us, the Plant 2001 will provide strategic leverage in the direction of attaining global market leadership in quality." In conjunction with the new plant opening, was the 1st Sartorius BioTech Forum with speakers from industry and research presenting the latest trends in biotechnology to over 200 participants from the pharmaceutical and biotechnology sectors. For more information, contact Sabine Niebch at +49(0) 551 308 3702 or sabine.niebch@sartorius.com or visit their Web site at www.sartorius.com.

German ChancellorGerhard Schroeder (left) and Sartorius CEO Utz Claassen at the grand opening.



Guests admire the state-of-the-art facility in Goettingen.

Magellan Laboratories, a full-service pharmaceutical contract development organization, has named **Lenie Valencia** as senior technical manager of Magellan's Microbiology Division. Valencia has 13 years experience in pharmaceutical research and most recently served as the Microbiology Department manager at Oread Laboratories, Inc., a contract pharmaceutical organization (CPO). For more information, visit www.magellanlabs.com.

Millipore Corporation recently announced the acquisition of technology that enables the sterile transfer of materials in barrier isolators and clean rooms used in the manufacturing of biotherapeutics and pharmaceuticals. Millipore acquired the technology from affiliates of IC Technology of Livingston, New Jersey. (A barrier isolator is an isolation chamber sealed off from the general atmosphere that surrounds a sterile filling line. The purpose is to prevent contamination of a sterile filling environment and avoid operator exposure to toxic drugs.) Millipore's SafePass Sterile Transfer System assures the safe transfer of components and materials required for aseptic filling, including stoppers, needles, fluids and aerosol systems. The SafePass system consists of a transfer port with a patented UV sterilizing source that provides a secure, sterile access to a barrier isolator or clean room as well as the expendable containers used to transfer components and materials. For more information telephone Technical Service at 1(800) MILLIPORE or visit www.millipore.com/safepass.

Cambrex Bio Science, Inc., a subsidiary of Cambrex Corporation, recently announced the manufacture of their first European approved commercial product. Cambrex Bio Science is now producing a newly approved orphan drug for one of its confidential, internationally recognized biopharmaceutical clients. The drug received the European Commission's marketing approval and is pending approval by the FDA. Cambrex Bio Science, Inc., www.bscp.com, is a bulk biopharmaceutical contract manufacturer located in Baltimore, MD and provides pre-clinical, Phase I-III, and commercial API Production. See www.cambrex.com for more information.

Contec® recently introduced the new DuPont™ Sontara® nonpyrogenic wiper—the first nonwoven sterile wiping product to be designed specifically for use in the pharmaceutical, medical device and biotech industries. Compatible with Class 100 cleanroom environments, this new wiper is made from Sontara® nonpyrogenic fabric, a proprietary blend of polyester and cellulose fibers developed with low levels of endotoxins, particles and extractables. Offering high sorbent rates and capacity, the DuPont™ Sontara® nonpyrogenic wipers are ideal for use in multiple cleaning applications including product wipe down and process equipment decontamination. For more information about the DuPont™ Sontara® nonpyrogenic wiper, or any of the products in Contec's sterile environments line, please call (800) 289-5762, visit www.contecinc.com or e-mail: wipers@contecinc.com. ■

—Joseph G. Bury

Send us your news . . .

. . . address news releases to Joe Bury via e-mail at bury@pda.org or mail hard copy to PDA headquarters in Bethesda.

2002 PDA Spring Conference, Courses and Exhibition

March 11–15, 2002 • Rosen Hotel, Orlando, Florida

Aseptic Processing and Environmental Monitoring: Reaching a Common Understanding of the Regulatory and Technical Requirements

Make your plans now to join PDA in sunny Orlando, Florida for the popular PDA Spring Conference. The conference will feature 2½ days of presentations in plenary session format.

With the ongoing internal review and revision of the 1987 Aseptic Processing Guideline by the FDA, the industry and regulators have been examining some of the more controversial environmental monitoring and aseptic processing issues.

Scientifically-based presentations will provide a chapter-by-chapter overview of the draft PDA Aseptic Processing guidance document and will provide participants with the opportunity to develop consensus positions that FDA might consider as it finalizes this guidance.

FDA representatives have been invited to present on the status of the Aseptic Processing Guidance.

The results of the PDA Survey on Aseptic Processing will be revealed for the first time at this conference.

Presenters will compare and contrast science-based aseptic process with current regulatory perspectives and will discuss the following topics:

I. Process Simulation Strategies and Practices, including:
- Interventions;
- Incubation Conditions;
- Growth Promotion Testing;
- Acceptance Criteria;
- Duration;
- Number of Units to Fill; and
- Incubation of Normally Excluded and Damaged Units.

II. Environmental Monitoring, including:
- Relevance of Alert & Action Levels;
- Relationship to Batch Release;
- Continuous Environmental Monitoring;
- Location and Frequency of Non-viable Air Monitoring;
- Viable Surface Monitoring;
- Application of Limits for Molds Viable Sampling of Product Contact Surfaces;
- Identification of Environmental Isolates; and
- Incubation Conditions for Environmental Monitoring Samples.

III. Personnel Control Issues, including:
- Training;
- Qualification/Disqualification;
- Technique;
- Supervision;
- Access;
- Monitoring;
- Gowning Practices;
- Reuse of Gowns; and
- Number of People.

IV. Materials Transfer

V. Cleaning and Disinfection

VI. Application of PDA Technical Reports 22 and 28 (Finished and Sterile Bulk Products)

Laboratory technicians, QA/QC, regulatory affairs and validation personnel who must have an understanding and appreciation for aseptic processing and environmental monitoring requirements and related regulations will benefit from participation in this important conference. ■

—Leslie Zeck

PDA/USP Joint Conference on Sterile Product Manufacturing

Sanibel Harbour Resort, Fort Myers, Florida • May 19–22, 2002

New regulations have been developed and changes in existing regulations have occurred since the last open conference on the topic of sterility assurance. PDA, in collaboration with the USP, will host an "open" conference on sterile product manufacturing to address this shifting regulatory climate. Participants in the conference will:

- Explore the continuum of the microbial control and test in the manufacture of sterile pharmaceutical products;
- Determine the inconsistencies in compendial, regulatory and industrial practices in microbial control and identify how they an be made more consistent; and
- Establish consensus positions whenever possible.

The conference will address the following topics:

1. Advanced aseptic processing;
2. Moist heat sterilization;
3. Environmental monitoring;
4. Criteria for processing simulation testing;
5. Sterilization by membrane filtration; and
6. Microbiological analysis.

Registration in this conference is limited to 300 participants to ensure scientifically useful feedback from participants. Please watch for the brochure on this important conference by visiting either www.pda.org or www.usp.org/conferences. ■

—Leslie Zeck

Q7A Training Workshops Enthusiastically Received

The Q7A Training Workshops on ICH Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (APIs) have been well attended and enthusiastically received by participants. The first two sessions held in Chicago and Princeton were filled to capacity; the two sessions currently on the schedule are expected to fill as well. Be sure to sign up for either the Newport Beach, California offering [February 25–27, 2002] or the San Juan, Puerto Rico session [April 8–10, 2002] quickly.

These workshops are the only joint Q7A training being sponsored by the FDA. Conducted by members of the Expert Working Group that developed the guidance, these training workshops are attended by FDA personnel as well as industry representatives.

A registration form for the workshops may be found on page 33. To download conference details in PDF format, visit http://www.pda.org/PDF/Q7ARegBro.pdf.

Plans are underway to conduct Q7A Training in Europe in 2002. Details will appear in the *PDA Letter* and on www.pda.org when available. ■

—Linda Williams

Basel 2002 from cover

- Biotechnology and Biologics Issues;
- Computer Issues;
- Current Management Issues for Manufacturing;
- Harmonization and Compendial Issues;
- Non-Sterile Products;
- Pharmacopaeial Issues;
- Regulatory Issues; and
- Sterilization

This three-day congress will attract more than 500 international professionals and scientists in the parenteral, sterile products, biotechnology and related fields for high-level education and dialogue among industry and regulatory experts. The prestigious benchmark congress, the seventh international congress PDA has hosted in Europe since 1992, will identify strategies for leveraging the future of the pharmaceutical industry.

All individuals interested in the future of pharmaceutical science and technology, including those engaged in manufacturing, production, quality assurance/quality control, engineering and maintenance operations, facility design, product and process development, scale-up, validation, compliance and regulatory affairs and research and development, will derive significant value from participation.

The congress and courses will be conducted in English; no translation will be available. The official proceedings and scientific papers presented at the conference will be published.

Posters featuring the latest science and technology will be featured during the Wednesday evening networking reception. If you would like to submit a poster abstract and be considered as a presenter, please e-mail zeck@pda.org with your topic and content information **by January 18, 2002**.

Exhibits

See the latest in pharmaceutical science and technology at PDA's Exhibition in Basel. For information on exhibiting and/or sponsoring an event, contact PDA via e-mail at kiani@pda.org or visit www.pda.org for details.

Courses

Training Courses to be offered at Basel International Congress are:

Basic Concepts in Cleaning and Cleaning Validation

This course covers the basic concepts in critical cleaning processes in pharmaceutical manufacturing, in addition to the validation of those cleaning processes. It is designed to cover the fundamentals of cleaning processes, including cleaning agents, cleaning methods, and cleaning process parameters, as well as the regulatory expectations and current practices of cleaning within the framework of validation expectations. This course is primarily a lecture format, with hands-on small-group exercises and other opportunities for class interaction.

Faculty: **Destin A. LeBlanc**, Cleaning Validation Technologies

Active Pharmaceutical Ingredients—Manufacture and Validation

This course is an in-depth two-day workshop designed to give the participant a thorough foundation in manufacturing operations related to the production of Active Pharmaceutical Ingredients. It is a course on how to operate an API plant. Every aspect of plant operations is covered, including how to manage the relationship with the regulatory authorities. Four sets of competencies are covered: 1) The Drug Regulatory and Compliance Process, 2) Operations, 3)Validation and 4) FDA Inspections.

Faculty: **Daniel H. Gold, Ph.D.**, President of D.H. Gold Associates, Inc.

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Failure Investigations and Change Control

This highly focused workshop will bring together the best of current thinking in the areas of failure analysis and problem investigations. Participants will benefit from the combined experience of a seasoned faculty member and the assembled group to pursue the issues surrounding this drastically important area of CGMP compliance. The course emphasizes not only the systems necessary to comply with current agency thinking on these issues, but also the rationale for why these procedures make good business sense.

Faculty: **Robert G. Kieffer, Ph.D., RGK Consulting**

Managing Risk Using Failure Mode and Effect Analysis (FMEA)

FMEA is a technique that considers three factors:

1) What can go wrong? What can fail? What is the probability of this failure occurring?
2) If the failure occurs what will be the consequences for the customer/patient, an employee or the company?
3) What is the likelihood of detecting the failure before any harm has been done? The goal of this exercise is to use this information to prioritize our corrective/preventive actions. Obviously, the worst case is a high probability of failure, severe consequences and no means to detect failure when it occurs.

Faculty: **Robert G. Kieffer, Ph.D., RGK Consulting**

For course content-related questions, please contact the PDA-Training and Research Institute (PDA-TRI) at (410) 455-5800 or info-tri@pda.org. To register for a course or the congress, visit www.pda.org, e-mail info@pda.org or call (301) 986-0293. ■

—Leslie Zeck

Q7A Training Workshop Registration Form

Chicago, IL – October 22-24, 2001
Princeton, NJ – November 7-9, 2001
Newport Beach, CA – February 25-27, 2002
San Juan, PR – April 8-10, 2002

ICH Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (APIs)

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

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

Job Title

Company (indicate full company name)

Business Address

City State/Province Zip + 4/Postal Code Country

☐ Substituting for

Business Phone Fax E-mail

(check here only if you are substituting for a previously enrolled colleague.

2. Fees. Please plan to attend all three days of this training workshop. One-day registration is not available. **Full Workshop Registration Includes:** Conference reference materials on site, Lunch on each day, Networking Reception on Day 1.

	Industry	Government*
Chicago, IL – October 22-24, 2001	☐ $995	☐ $395
Princeton, NJ – November 7-9, 2001	☐ $995	☐ $395
Newport Beach, CA – February 25-27, 2002	☐ $995	☐ $395
San Juan, PR – April 8-10, 2002	☐ $995	☐ $395
TOTAL FEES		$_____

*Government: You must be an employee of an official government agency to qualify for this discounted rate.

3. Please check the appropriate box

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

Account Number_____ Exp. Date _____

Name Exactly as on Card _____

Signature _____ Date _____

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

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

Federal Tax I.D. #52-1906152

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.

Please tell us how you learned about this event

- ☐ Advertisement
- ☐ Direct Mail
- ☐ Fax
- ☐ Internet
- ☐ Colleague
- ☐ Other_____

Confirmation: Written confirmation will be sent to you once payment is received. You must have written confirmation to be considered enrolled in this event.

Substitutions: If a registrant is unable to attend, substitutions are welcome and can be made at any time. If you are pre-registering as a substitute attendee, indicate this on the registration form. Refund deadlines and amounts are as follows:

Chicago, IL: If request for refund is received at PDA ***on or before September 24*** registrants will receive a full refund less a $35 (US) processing fee. If received ***after September 24 and on or before October 8*** registrants will receive 50% of the registration fee. After ***October 8***, no refunds can be made.

Princeton, NJ: If request for refund is received at PDA ***on or before October 8*** registrants will receive a full refund less a $35 (US) processing fee. If received ***after October 8 and on or before October 22*** registrants will receive 50% of the registration fee. After ***October 22***, no refunds can be made.

Newport Beach, CA: If request for refund is received at PDA ***on or before January 21*** will receive a full refund less a $35 (US) processing fee. If received after ***January 21 and on or before February 4*** registrants will receive 50% of the registration fee. After ***February 4***, no refunds can be made.

San Juan, PR: If request for refund is received at PDA ***on or before March 8*** registrants will receive a full refund less a $35 (US) processing fee. If received ***after March 8 and on or before March 22*** registrants will receive 50% of the registration fee. After that, no refunds can be made.

LTR12/01

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

New CGMP Trainer's Certification Course

PDA-Training and Research Institute (PDA-TRI) proudly announces the availability of CGMP Trainer's Certification Training, a course designed for the new CGMP Trainer. For those with little training experience, this hands-on course will convey the foundation of skills needed to be successful at developing and delivering CGMP, regulatory and technical training.

The PDA-TRI CGMP Trainer's Certification Training was developed in response to the demand from every segment of the pharmaceutical and related industries for an introductory-level new trainer preparation course. Not a lecture course, this hands-on training course requires participants to first set up their organization's training curriculum, then design training courses to meet these requirements and finally to deliver classes.

Location: PDA-TRI
Baltimore, MD

Duration: Five Full Days

Dates: February 25–March 1, 2002
April 29–May 3, 2002
November 4–8, 2002

The course will focus on five training skills. Course participants can expect to return to their companies with significant skill development in the following areas:

- The Role of Training
- CGMP Training Requirements
- Organizing the Training Function
- Platform Delivery of Training
- The Design of Training Courses

Who Should Attend?

Individuals selected by their organizations, as CGMP or technical trainers, will find this course a "must attend." The course is targeted to new and relatively new trainers, though any person wishing a thorough foundation in training skills would benefit from the course.

Details about this new course, as well as a registration form, are posted on www.pda.org. Because of the hands-on nature of the course attendance is strictly limited. Register early. ■

—Rick Rogers

Faculty in Focus

John Lindsay, Aseptic Solutions, Inc.

The PDA Training and Research Institute (PDA-TRI) would like to spotlight the educational contributions of John Lindsay, the year 2000 recipient of the James P. Agalloco Award. The James P. Agalloco Award is presented to the PDA faculty member each year who exemplifies outstanding performance in education.

Lindsay was selected because of his outstanding commitment to the PDA-TRI Aseptic Processing Training Program over the last two years. As one of the lead faculty and program coordinators for the course, he shares a wealth of knowledge and more than 20 years of pharmaceutical experience with students from around the world.

John Lindsay is currently President & Senior Consultant with Aseptic Solutions, Inc. His work history includes Senior Manager of Environmental Quality Assurance with Genentech, Inc. where he was responsible for the standardization and administration of all QA activities in the area of Environmental Control. He was also a Senior Consultant with KMI/PAREXEL, where he consulted to parenteral pharmaceutical manufacturers on sterility assurance, aseptic processing and environmental control issues.

Lindsay co-authored *Cleaning and Cleaning Validation: a Biotechnology Perspective*, the first book published by the PDA. He also co-authored *PDA Technical Report No. 13: Fundamentals of a Microbiological Environmental Monitoring Program.* Most recently, he has been involved with PDA's Microbiology Training Subcommittee and is co-author of *A Proposed Training Model for the Microbiological Function in the Pharmaceutical Industry.*

Lindsay is an active member of PDA and the American Society for Microbiology. He is a Certified Specialist Microbiologist—Consumer and Industrial Microbiology—by the National Registry of Microbiologists of The American Academy of Microbiologists.

Lindsay received his B.A. in Biology from Westminster College and his M.A. in Microbiology from the University of Kansas, Medical Center. ■

—Casey Weininger

Upcoming PDA-TRI Education Courses

These courses will be held at PDA-TRI in Baltimore, Maryland unless otherwise noted.

For course content information, call PDA-TRI directly at (410) 455-5800.

To register, call PDA headquarters in Bethesda, Maryland at (301) 986-0293. PDA-TRI Location/Hotel Information follows.

Aseptic Processing Training Program 2002—Lab Option 1: January 14–18 (week 1) and February 11–15 (week 2); Option 2: April 8–12 (week 1) and May 6–10 (week 2); Option 3: September 9–13 (week 1) and October 7–11 (week 2); Option 4: October 28–November 1 (week 1) and November 18–22 (week 2); $6,500 members/$6,695 nonmembers; *Various PDA-TRI Faculty*

Fundamentals of D, F & z Value Analysis—Lab January 24–25, 2002; $1,500 members/$1,695 nonmembers; *Faculty:* John T. Shirtz

Everyday Compliance January 29, 2002; April 17, 2002; September 18, 2002; $680 members/$875 nonmembers; *Faculty:* Rick H. Rogers

Environmental Mycology: Identification Workshop—Lab January 30–31, 2002; May 16–17, 2002; September 19–20, 2002; December 4–5, 2002; $1,500 members/$1,695 nonmembers; *Faculty:* John Brecker

Computer Products Supplier Auditing Process Model: AUDITOR TRAINING—2002 February 5–6, 2002; May 21–22, 2002; October 1–2, 2002; Fees to be determined; *Faculty:* Harvey Greenawalt

GMP Trainer Certification Course February 25–March 1, 2002; April 29–May 3, 2002; November 4–8, 2002; August 13–14, 2002; $2,795 members/$2,990 nonmembers; *Faculty:* Rick H. Rogers

Introduction to Developing Effective Audit Strategies for CGMP Cleanrooms—Lab March 5–6, 2002; August 13–14, 2002; $1,150 members/$1,345 nonmembers; *Faculty:* Strother D. Dixon

Introduction to Writing and Auditing CGMP Documentation March 7, 2002; August 15, 2002; $680 members/$875 nonmembers; *Faculty:* Strother D. Dixon

Cleaning Validation—Lab April 15–16, 2002; October 21–23, 2002; $1,900 members/$2,095 nonmembers; *Faculty:* Jon Voss, Robert O'Brien and Ron Kraus

Ensuring Measurement Integrity in the Validation of Thermal Processes—Lab April 18–19, 2002; $1,500 members/$1,695 nonmembers; *Faculty:* Göran Bringert

Contamination Control Basics—Lab April 26, 2002; October 18, 2002; $750 members/$945 nonmembers; *Faculty:* Sandra Lowery and Maureen Reagan

Designing Regulatory Training that Works May 15, 2002; $680 members/$875 nonmembers; *Faculty:* Rick H. Rogers

Advanced Regulatory Compliance Training for the Supervisor/Manager October 22–23, 2002; $1,010 members/$1,205 nonmembers; *Faculty:* Rick H. Rogers ■

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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:

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If you or your organization is interested in supporting training activities at PDA-TRI, please contact Casey Weininger, Senior Training Coordinator at (410) 455-5801 or weininger@pda.org.

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PDA Book

Cleaning & Cleaning Validation: A Biotechnology Perspective Authors: Roger Brunkow, David DeLucia, George Green, Shane Haft, John Hyde, John Lindsay, Jill Myers, Robert Murphy, John McEntire, Karen Nichols, Ray Prasad, Brenda Terranova, Jon Voss, Caroline Weil, Edward White; This book is intended to serve as a source of practical technical information for those persons in the biotechnology industry. Case studies and/or actual industry examples are used to support the text wherever possible. While much of the material contained within this text is equally applicable to non-biopharmaceutical processes, the emphasis has been focused directly upon biopharmaceutical manufacturing. Section I provides an in-depth analysis of the design concepts that lead to cleanable equipment. Also covered are cleaning mechanisms and cleaning systems. The first section is particularly useful to those persons faced with the task of designing systems that will be cleaned and also provides the biochemical background of the mechanisms associated with the removal of common biotechnology soils. Section II focuses on cleaning validation concepts. While the material is equally useful for single product cleaning, emphasis is placed upon multi- product cleaning validation. Included are general validation principles as they apply to cleaning validation, detailed analysis of cleaning process validation, sampling techniques, analytical methods and acceptance criteria. The material in Section II will be useful to anyone responsible for the development of a cleaning validation program. Section III provides an overview of multi-product biotechnology manufacturing procedures. Included an analysis of the risk to benefit scenarios associated with the various forms of product manufacturing, analysis of changeover programs, equipment considerations and material transport as they are affected by multi-product manufacturing strategies. 1995; 190 pages; $125 members/$145 nonmembers **Item No: 13002**

PDA/ISPE Books

Good Practice and Compliance for Electronic Records

Computer technology has changed the framework of business in every industry, transforming the way businesses operate. The pharmaceutical industry is just one of many industries transformed by computers and software. Industries involved in commerce and trade are not the only entities affected: governments have also been transformed, creating new laws and government programs that rely upon computers and Web technologies. PDA and the International Society for Pharmaceutical Engineering Good Automated Manufacturing Practices Forum (ISPE GAMP Forum) have operated two separate initiatives, but with close cooperation, to deliver industry guidance relative to electronic information and emerging governmental regulations. Both initiatives produced work products from different perspectives; however, the approaches are complementary and, collectively, they cover the broad issues that are associated with electronic records and signatures. The work products of both initiatives will be published as a series titled **Good Practice and Compliance for Electronic Records** for the benefit of practitioners involved in electronic records management programs in FDA- regulated companies. Part 2 of this three-part series is now available. Part 1 – Good Electronic Records Management (GERM), and Part 2 – Complying with 21 CFR Part 11, Electronic Records and Electronic Signatures will be released in 2002.

Part 2 – Complying with 21 CFR Part 11, Electronic Records and Electronic Signatures This document has been produced by a Special Interest Group of the GAMP Forum (pharmaceutical companies, suppliers, consultants and the Medicines Control Agency in the UK) in order to promote a better understanding of 21 CFR Part 11. It aims to provide industry and its suppliers with practical guidance on how to comply with the rule, while highlighting and addressing common issues of concern. The manuscript provides a management process for achieving and maintaining compliance with 21 CFR Part 11 in manufacturing environments. Specific guidance is provided for both new and existing systems in addition to the role of suppliers in supporting this approach. Appendices provide information, examples, templates, checklists, and a lifecycle for the management of electronic documents that are useful when implementing 21 CFR Part 11 compliance programs. A Glossary and References List are also included. 80 pages; $95 members/$190 nonmembers **Item 19001**

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PDA-DHI Books

To Order, Use Form on Page 43

Aseptic Processing: The Importance of Microbiology and Environmental Monitoring in Media Fill Validation Author: Michael Jahnke; The second in this series of four books. Provides current, practical techniques that focus on considerations in the preparation and monitoring of aseptic manufacturing, taking into account the national and international requirements, and guidelines concerning the validation of aseptic processing. Topics include: Risk analysis, HAACP, Documentation and qualification; Qualification and training of personnel; Scope of validation; Overall requirements; Release requirements; Documentation; Authorization. The guide also includes an excellent Manufacturing and Testing Master Batch Record, and 25 extremely valuable charts, graphs, and figures. 80 pages; $90 members/$109 nonmembers **Item 17181**

Change Control Author: Soren Schwartz; Edited by Chris Reid, this manual provides a well-organized, practical process for the management of changes to the Information and Control Systems used in GxP-related operations. 28 pages; $90members/$109 nonmembers **Item 17189**

Electronic Records and Electronic Signatures Compliance Assessment Authors: Chris Reid and Barbara Mullendore; *ERES* provides practical guidance on the interpretation of 21CFR Part 11 and the steps you need to take to address current and future compliance issues. 58 pages; $90 members/$109 nonmembers **Item 17177**

External Quality Audit, The Authors: Janet Gough and Monica Grimaldi; Will help you to effectively evaluate suppliers to determine reliability, quality and value. 100 pages; $120 members/$149 nonmembers **Item 17180**

GMP in Practice: Regulatory Expectations for the Pharmaceutical Industry Author: James Vesper; A quick guide to GMP, designed to simplify and enhance understanding of most of the current GMP expectations and how they apply to ongoing tasks in any given pharmaceutical manufacturing situation. 224 pages; $100 members/$124.50 nonmembers **Item 17191**

Hosting a Compliance Audit Author: Janet Gough; This is the guidance you need to host a compliance inspection. 106 pages; $120 members/$149 nonmembers **Item 17192**

Internal Quality Audit, The Author: Janet Gough and Monica Grimaldi; This book provides guidance for performing a systematic internal quality audit with guidelines and a common sense approach to an often difficult task. 175 pages; $120 members/$149 nonmembers **Item 17179**

Introduction to Environmental Monitoring of Pharmaceutical Areas Author: Michael Jahnke; Topics discussed include all aspects of cleanrooms, air handling systems, HAACP and risk analysis along with numerous useful charts, tables and figures. 80 pages; $90 members/$109 nonmembers **Item 17182**

Microbiological Risk Assessment in Pharmaceutical Clean Rooms Author: Bengt Ljungqvist and Berit Reinmuller; This monograph clearly explains the Limitation of Risk Method (LR-Method). 32 pages; $75 members/$90 nonmembers **Item 17175**

Microbiology in Pharmaceutical Manufacturing Author: Richard Prince, Editor; Providing valuable knowledge for the novice and the expert alike, many of the world's greatest pharmaceutical microbiologists and engineers, as well as other thought leaders, have invested their considerable talents and prestige in developing this comprehensive collection of timely information on this critically important subject. This book encapsulates current knowledge in a truly wide array of microbiological applications for the reader. It is hoped that this book will demystify the field of microbiology by describing it plainly and systematically from various scientific, technical, and functional perspectives. 750 pages; $240 members/$299 nonmembers **Item 17185**

Practical Change Control for Health Care Manufacturers Author: Angie Jamison; Quick Guide. 124 pages; $120 members/$149 nonmembers **Item 17173**

Quality Control Systems for the Microbiology Laboratory: The Key to Successful Inspections Author: Lucia Clontz; Addresses the main quality control systems that should be implemented in a microbiology laboratory with a focus on current issues and inspection trends. 175 pages; $120 members/$149 nonmembers **Item 17176**

Understanding Active Pharmaceutical Ingredients Author: Seigfried Schmitt; Written by a Chartered Chemist and Member of the Royal Society of Chemistry, and edited by Trevor Deeks, this succinct document provides an overview of API use, including regulatory and validation details. 60 pages; $80 members/$109 nonmembers **Item 17188**

Understanding GMP: An Expert's View on Merging Global Regulatory and Manufacturing Perspectives Author: Martyn Becker; This ex-MCA inspector, now at Merck, shares his expertise and perspectives on GMP regulations, legislation, applications, and practical challenges and solutions to applying GMP to the manufacturing environment. 224 pages; $120 member/$149 nonmember **Item 17174**

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

Select PDA Technical Reports Available

TR 34 Design and Validation of Isolator Systems for the Manufacturing and Testing of Health Care Products; This technical report addresses essential user requirements for the application of isolator technology to a broad range of manufacturing, development and testing applications in the health care product manufacturing industry. It covers not only product sterility assurance, but also the use of isolators for the containment of hazardous materials. 2001; 32 pages; $75 member $125 nonmember. **Item No. 01034**

TR 33 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. **Item No. 01033**

TR 32 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; 277 pp; $90 members/$140 nonmembers (paper copy; **Item No. 01032**); **CD**—$50 members/$75 nonmembers (CD-ROM format; **Item No. 01132**).

TR 31 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. **Item No. 01031**

TR 29 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. **Item No. 01029**

TR 13 Revised Fundamentals of an Environmental Monitoring Program; The purpose of this document is to identify microbiological and particulate control concepts and principles as they relate to the manufacture of sterile pharmaceutical products. It expands substantially upon the first edition of Technical Report No. 13 (Revised), *Fundamentals of a Microbiological Environmental Monitoring Program*, published by PDA in 1990. While this publication cannot possibly supplant the wealth of information published on this subject, it provides summary information and appropriate references for the reader to consult, if necessary. The objective was to contemporize the first edition through the utilization of current definitions, recognition of improved environmental monitoring procedures, and equipment. This document serves as a source on clean room environmental test methods, and although some non-viable particulate and endotoxin testing data are included, its primary focus is microbiological control. The concepts for sterile product manufacturing are the most stringent application, but these concepts can also be applied to non-sterile product manufacture. The focus is environmental monitoring as it relates to facility control and compliance. This document was compiled to aid in setting up a program that is meaningful, manageable, and defendable. 2001; 44 pages; $75 member $125 nonmember. **Item No. 01013**

PDA Archive on CD-ROM

PDA Archive on CD-ROM - PDA Archive Retrieval Index; The PDA Archive will give you easy access to more than 50 years of research papers written by highly qualified research scientists in the pharmaceutical industry. All PDA Journal articles, Technical Reports and Monographs, and selected Meeting Proceedings are available on this fully searchable CD-ROM. The archive is updated each year adding six issues of the PDA Journal, all PDA Technical Reports and Monographs, and selected PDA Meeting Proceedings. The archive is a 4-CD set.
Archive; Price: $395 members/$495 nonmembers. **Item No: 01101**

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Here is how it works: **1)** use this page or a photocopy, **2)** fill in the requested information, **3)** attach a check in US dollars, drawn on a US bank, net of all bank charges, for $75.00 (Parenteral Society), $25.00 ($R^3$-Nordic), or complete the credit card information and **4)** mail or fax to PDA. All secondary membership forms must be received by January 31, 2002. We are unable to process memberships received after this date.

PDA will forward all secondary membership applications directly to the Parenteral Society administrative offices in England, or directly to the R^3-Nordic administrative offices in Sweden. Under the terms of the agreement, this application must be renewed each year. If you have any questions, please contact Virginia Ventura at PDA, (301) 986-0293, ext. 122.

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LTR 12/01

Calendar begins on back cover

April 8-12, 2002
PDA-TRI Laboratory Course:
Aseptic Processing Training Program (week 1)
PDA-TRI Baltimore, MD

April 15–16, 2002
PDA-TRI Laboratory Course: Cleaning Validation
PDA-TRI Baltimore, MD

April 17, 2002
PDA-TRI Lecture Course: Everyday Compliance
PDA-TRI Baltimore, MD

April 18-19, 2002
PDA-TRI Laboratory Course:
Ensuring Measurement Integrity in the Validation of Thermal Processes
PDA-TRI Baltimore, MD

April 29-May 1, 2002
PDA Isolation Technology Conference
Hilton East Brunswick, East Brunswick, NJ

April 29-May 3, 2002
PDA-TRI Lecture Course: GMP Trainer Certification
PDA-TRI Baltimore, MD

MAY

May 6-10, 2002
PDA-TRI Laboratory Course:
Aseptic Processing Training Program (week 2)
PDA-TRI Baltimore, MD

May 15, 2002
PDA-TRI Lecture Course:
Designing Regulatory Training That Works
PDA-TRI Baltimore, MD

May 16-17, 2002
PDA-TRI Laboratory Course:
Environmental Mycology Identification Workshop
PDA-TRI Baltimore, MD

May 19-22, 2002
PDA/USP Joint Conference on Sterile Product Manufacturing
Sanibel Harbour Resort, Fort Myers, FL

May 21-22, 2002
PDA-TRI Lecture Course: Computer Products Supplier Auditing Process Model—Auditor Training
PDA-TRI Baltimore, MD

JUNE

June 3-5, 2002
PDA-TRI Florida Course Series
The Diplomat Resort Country Club & Spa, Hollywood, FL

AUGUST

August 13-14, 2002
PDA-TRI Laboratory Course:
Introduction to Developing Effective Audit Strategies for CGMP Cleanrooms
PDA-TRI Baltimore, MD

August 15, 2002
PDA-TRI Lecture Course:
Introduction to Writing and Auditing CGMP Documentation
PDA-TRI Baltimore, MD

August 27-29, 2002
PDA-TRI Vermont Course Series
Sheraton Burlington Hotel & Conference Center
Burlington, VT

SEPTEMBER

September 9-13, 2002
PDA-TRI Laboratory Course:
Aseptic Processing Training Program (week 1)
PDA-TRI Baltimore, MD

September 18, 2002
PDA-TRI Lecture Course: Everyday Compliance
PDA-TRI Baltimore, MD

September 19-20, 2002
PDA-TRI Laboratory Course:
Environmental Mycology Identification Workshop
PDA-TRI Baltimore, MD

September 23-27, 2002
2002 PDA/FDA Joint Regulatory Conference, Courses and Tabletop Exhibition
Hyatt Regency on Capitol Hill, Washington, DC

September 26, 2002
PDA-TRI Lecture Course:
Audit Process Model Management Overview Training
Hyatt Regency on Capitol Hill, Washington, DC

OCTOBER

October 1-2, 2002
PDA-TRI Lecture Course: Computer Products Supplier Auditing Process Model—Auditor Training
PDA-TRI Baltimore, MD

October 7-11, 2002
PDA 2002 Biennial Training Conference
Charting a Course for Success
Hyatt Regency Tampa, Tampa, FL

October 7-11, 2002
PDA-TRI Laboratory Course:
Aseptic Processing Training Program (week 2)
PDA-TRI Baltimore, MD

October 21–23, 2002
PDA-TRI Laboratory Course: Cleaning Validation
PDA-TRI Baltimore, MD

October 22-23, 2002
PDA-TRI Lecture Course:
Advanced Regulatory Compliance Training for the Supervisor/Manager
PDA-TRI Baltimore, MD

October 28-November 1, 2002
PDA-TRI Laboratory Course:
Aseptic Processing Training Program (week 1)
PDA-TRI Baltimore, MD

NOVEMBER

November 4-8, 2002
PDA-TRI Lecture Course: GMP Trainer Certification
PDA-TRI Baltimore, MD

November 18-20, 2002
PDA-TRI Las Vegas Course Series
Alexis Park Resort & Spa, Las Vegas, NV

November 18-22, 2002
PDA-TRI Laboratory Course:
Aseptic Processing Training Program (week 2)
PDA-TRI Baltimore, MD

DECEMBER

December 4-5, 2002
PDA-TRI Laboratory Course:
Environmental Mycology Identification Workshop
PDA-TRI Baltimore, MD

December 9-13, 2002
2002 PDA Annual Meeting, Courses and Exhibition
New Orleans Marriott, New Orleans, LA

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Return your completed PDA membership application, with payment made to: **PDA, 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.)*

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- ❑ Pharmaceutical Manufacturing
- ❑ Pharmacy
- ❑ Recruiter
- ❑ Other

Professional Interest (check all that apply)

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

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LTR 12/01

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Be sure to visit our booth #302 at the PDA Annual Meeting

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Calendar of Events

2002

JANUARY

January 14-18, 2002
PDA-TRI Laboratory Course:
Aseptic Processing Training Program (week 1)
PDA-TRI Baltimore, MD

January 16-18, 2002
PDA-TRI Lake Tahoe Course Series
Hyatt Regency Lake Tahoe Resort & Casino
Incline Village, NV
- **PDA-TRI Lecture Courses:**
- January 16
  - **A Comprehensive Guide to OOS Regulations**
  - **A Practical Guide to Change Control**
  - **Cost Effective Validation**
  - **Metrology and Calibration in the GMP Setting**
  - **Training for Performance**
- January 16-18
  - **GMP Training Manager Workshop**
- January 17
  - **GMP Fundamentals**
  - **Strategic and Practical Approaches to Part 11 Compliance**
- January 17-18
  - **Basic Concepts in Cleaning and Cleaning Validation**
  - **Validation by Design**
- January 18
  - **Basic Statistical Tools for Quality Assurance and Manufacturing Personnel**
  - **Designing Regulatory Training that Works**

January 24-25, 2002
PDA-TRI Laboratory Course:
Fundamentals of D, F & z Value Analysis
PDA-TRI Baltimore, MD

January 29, 2002
PDA-TRI Lecture Course: Everyday Compliance
PDA-TRI Baltimore, MD

January 30-31, 2002
PDA-TRI Laboratory Course:
Environmental Mycology Identification Workshop
PDA-TRI Baltimore, MD

FEBRUARY

February 5-6, 2002
PDA-TRI Lecture Course: Computer Products Supplier Auditing Process Model—Auditor Training
PDA-TRI Baltimore, MD

February 11-15, 2002
Basel 2002: PDA International Congress, Courses and Exhibition—*Adding Value to the Pharmaceutical Industry—Leveraging the Future*
Basel Convention Center, Basel, Switzerland
- **PDA-TRI Lecture Courses:**
- February 14
  - **Failures, Investigations and Change Control**
- February 14-15
  - **Active Pharmaceutical Ingredients (APIs): Manufacture & Validation**
  - **Basic Concepts in Cleaning and Cleaning Validation**
- February 15
  - **Managing Risk Using Failure Mode and Effect Analysis (FMEA)**

February 11-15, 2002
PDA-TRI Laboratory Course:
Aseptic Processing Training Program (week 2)
PDA-TRI Baltimore, MD

February 25-27, 2002
Training Workshop
ICH Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (APIs)
The Sutton Place Hotel, Newport Beach, CA

February 25-March 1, 2002
PDA-TRI Lecture Course: GMP Trainer Certification
PDA-TRI Baltimore, MD

MARCH

March 5-6, 2002
PDA-TRI Laboratory Course:
Introduction to Developing Effective Audit Strategies for CGMP Cleanrooms
PDA-TRI Baltimore, MD

March 7, 2002
PDA-TRI Lecture Course:
Introduction to Writing and Auditing CGMP Documentation
PDA-TRI Baltimore, MD

March 11-15, 2002
2002 PDA Spring Conference, Courses and Tabletop Exhibition
Environmental Monitoring and Aseptic Processing: Reaching a Common Understanding of the Regulatory and Technical Requirements
Rosen Hotels and Resorts, Orlando, FL
- **PDA-TRI Lecture Courses:**
- March 14
  - **Identification of Microorganisms Using Comparative DNA Sequencing**
- March 14-15
  - **A Practical Approach To Aseptic Processing and Contamination Control**
  - **Assessing Packaging and Processing Extractables/Leachables**
  - **Cleanroom Management**
  - **CMC Regulatory Compliance of Biopharmaceuticals**
- March 15
  - **How to Design an Effective Regulatory Training Program**
  - **Process Validation: An Introduction**

March 21-22, 2002
PDA Mountain States Chapter—Presentations and Courses
Omni Interlocken Resort, Broomfield, CO
- **PDA-TRI Lecture Courses:**
- March 21
  - **Assay Validation**
- March 22
  - **A Comprehensive Guide to OOS Regulations**
  - **Strategic and Practical Approaches to Part 11 Compliance**

APRIL

April 8-9, 2002
PDA Canadian Chapter/A3P International Conference & Exhibition
Holiday Inn Montreal Midtown, Montreal, Quebec Canada

April 8-10, 2002
Training Workshop
ICH Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (APIs)
Caribe Hilton, San Juan, Puerto Rico

Calendar continues on page 45

Be sure to watch
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for conference and course updates!