Volume XXXIX, No. 3

PDA Letter

March 2003

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

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PDA Board of Directors Names Neal G. Koller PDA President

by Floyd Benjamin, PDA Chair

Neal G. Koller

On behalf of the PDA Board of Directors, I am very pleased to welcome Neal G. Koller as President of PDA. Neal's first day on the job was Monday, January 27th. I know you will enjoy meeting Neal at PDA events and working with him to build PDA into an even stronger organization.

As you are all aware by now, Edmund M. Fry, who served PDA as chief staff executive for the past 11 years, resigned from the position in September 2002 to join IVAX Pharmaceuticals. PDA's Senior Vice President, Science and Technology Russ Madsen stepped in as Acting President and kept the organization moving forward while the Board found a successor. We are very grateful to him for leading the staff during the transition.

The PDA Board of Directors approached the finding of a new President with the utmost seriousness. A Search Committee was appointed which I chaired was comprised of Chair-Elect Nikki Mehringer, Treasurer Rich Levy, Immediate Past President Robert Myers and Board members Vince Anicetti, Stephanie Gray and Glenn Wright. We were charged with bringing a single candidate for confirmation to the Board.

Our first effort was to develop a profile of the type of executive we felt would be the most successful in achieving our goals and objectives as defined in the Strategic Plan. Next, an executive recruiter was hired to assist us in the search.

The Search Committee presented Neal Koller to the Board for approval as required by the By-laws. Neal's confirmation was unanimous by both the Search Committee and the full PDA Board of Directors.

We are all extremely pleased that Neal Koller has joined PDA. His track record as a highly successful global executive in this industry will insure that PDA maintains its strategic focus in this challenging environment.

Neal comes to PDA with more than 22 years of experience in medical devices and biopharmaceuticals. Most recently he was President of WelCare Group, Rome, Italy. Prior to WelCare, he was President and CEO of Dovetail Technologies, Incorporated, President and CEO of Sound Diagnostics, and had a long affiliation with Sherwood – Davis & Geck, subsidiary of Wyeth Pharmaceuticals.

He holds a B.S. in Biology from the University of Richmond. He further pursued graduate work in Biochemistry at the Medical College of Virginia.

Again I encourage you to meet Neal in the near future and make him aware of PDA's strong membership support. ■

PDA Meets With USP Water Committee

On January 15, 2003, members of the PDA Packaged USP Waters Committee met at the USP to discuss Extractables in Packaged Pharmaceutical Waters. Following is a letter from then Acting PDA President Russell Madsen to USP, explaining the PDA position on proposed specifications for Packaged Pharmaceutical Waters. Immediately following the PDA letter is a response from the USP Pharmaceutical Waters Expert Committee summarizing the meeting and outlining the next steps to be taken.

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

Neal G. Koller
President

Linda M. Williams
Director, Communications & Marketing

Joseph G. Bury, MBA, CIW
Editor/Web Editor

Janet Raysick
Manager, Publications & Production

Important Dates...

- **March 31st—deadline for comments on draft guidance for industry on the collection of race and ethnicity data, page 5**
- **April 1st—deadline for Annual Meeting Call for Papers, page 36**

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U.S. Regulatory Briefs

Draft Guidance for Industry on the Collection of Race and Ethnicity Data in Clinical Trials for FDA Regulated Products. The FDA has announced the availability of a draft guidance for industry entitled "Collection of Race and Ethnicity Data in Clinical Trials for FDA Regulated Products." This draft guidance recommends a standardized approach for collecting race and ethnicity information in clinical trials conducted in the USA and abroad for certain FDA regulated products. The standardized approach being recommended was developed by the Office of Management and Budget (OMB).

For more information contact, Katherine Hollinger, Office of Health Science and Coordination (HF-8), FDA, 5600 Fishers Lane, Rockville, MD 20857, (301) 594-5400; or Nancy Derr, Center For Drug Evaluation and Research (HFD-5), FDA, 5600 Fishers Lane, Rockville, MD 20857, (301) 594-5400; or Ilan Irony, Center for Biologics Evaluation and Research (HFM-576), FDA, 1401 Rockville Pike, Rockville, MD 20852, (301) 827-5378; or IDE Staff, Center for Devices and Radiological Health (HFZ-403), 9200 Corporate Blvd., Rockville, MD 20850, (301) 594-1190.

Submit written comments on the draft guidance by March 31, 2003 to the Dockets Management Branch (HFA-305), FDA, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Send electronic comments to www.fda.gov/dockets/ecomments. Include Docket No. 02D-0018 with the comments. For more information on this draft guidance, visit www.fda.gov/guidances.

Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers, FDA Draft Guidance for Industry and Reviewers. This guidance outlines a process (algorithm) and vocabulary for deriving the maximum recommended starting dose (MRSD) for "first in human" clinical trials of new molecular entities in adult healthy volunteers and recommends a standardized process by which the MRSD can be selected. The purpose of this process is to ensure the safety of the human volunteers.

The goals of this guidance are to (1) establish a consistent terminology for discussing the starting dose, (2) provide common conversion factors for deriving a human equivalent dose, and (3) delineate a strategy for selecting the MRSD for adult healthy volunteers, regardless of the projected clinical use. This process is diagrammed with a flow chart that presents the decisions and calculations used to generate the MRSD from animal data.

Toxicity should be avoided at the initial dose. However, doses should be chosen that allow reasonably rapid attainment of the phase 1 trial objectives (e.g., assessment of the therapeutic's tolerability, pharmacodynamic or pharmacokinetic profile). All of the relevant preclinical data, including information on the pharmacologically active dose, the full toxicological profile of the compound, and the pharmacokinetics (absorption, distribution, metabolism, and excretion) of the therapeutic, should be considered when determining the MRSD. Starting with doses lower than the MRSD is always a possible option and may be particularly appropriate to meet some clinical trial objectives.

The major elements "the determination of the no observed adverse effect levels (NOAELs) in the tested species, conversion of NOAELs to human equivalent dose (HED), selection of the most appropriate species, and application of a safety factor" are all discussed in greater detail in subsequent sections. Situations are also discussed in which the algorithm should be modified. The algorithm is intended to be used for systemically administered therapeutics. Topical, intranasal, intra-tissue, and compartmental administration routes and depot formulations may

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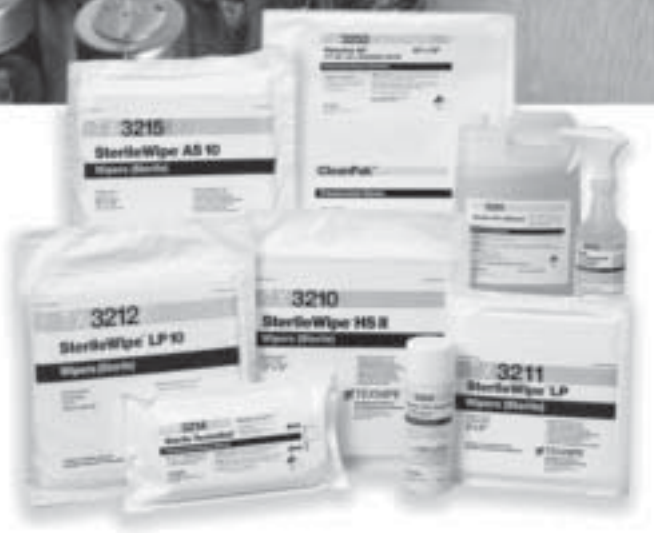

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have additional considerations, but similar principles should apply.

The entire draft guidance can be found at: www.fda.gov/cber/gdlns/dose.htm#ix. For questions regarding this draft document contact Robert Osterberg, FDA, Center for Drug Evaluation and Research, at (301) 594-5476 or Martin Green, FDA, Center for Biologics Evaluation and Research, at (301) 827-5349.

International Conference on Harmonization; Guidance for Industry Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products. A full study design is one in which samples for every combination of all design factors are tested at all time points. A reduced design is one in which samples for every factor combination are not all tested at all time points. A reduced design can be a suitable alternative to a full design when multiple design factors are involved. Any reduced design should have the ability to adequately predict the retest period or shelf life. Before a reduced design is considered, certain assumptions should be assessed and justified. The potential risk should be considered of establishing a shorter retest period or shelf life than could be derived from a full design due to the reduced amount of data collected.

Bracketing and matrixing are reduced designs based on different principles. Therefore, careful consideration and scientific justification should precede the use of bracketing and matrixing together in one design. Whether bracketing or matrixing can be applied depends on the circumstances, as discussed in detail below. The use of any reduced design should be justified. In certain cases, the conditions described in this guidance are sufficient justification for use, while in other cases, additional justification should be provided. The type and level of justification in each of these cases will depend on the available supporting data. Data variability and product stability, as shown by supporting data, should be considered when a matrixing design is applied.

Bracketing, as defined in the glossary to the parent guidance, is the design of a stability schedule such that only samples on the extremes of certain design factors (e.g., strength, container size and/or fill) are tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested.

Matrixing, as defined in the glossary of the parent guidance, is the design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations would be tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations would be tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in the samples for the same drug product should be identified as, for example, covering different batches, different strengths, different sizes of the same container closure system, and possibly, in some cases, different container closure systems.

The guidance was published January 15, 2003 and can be found at: www.fda.gov/cber/gdlns/ichq1d.htm.

FDA Releases Preliminary Results of Physician Survey on Direct-to-Consumer Rx Drug Advertisements. FDA has released results of its survey of 500 physicians about direct-to-consumer (DTC) advertising for prescription drugs. The results confirm that DTC advertising, when done correctly, can serve positive public health functions such as increasing patient awareness of diseases that can be treated, and prompting thoughtful discussions with physicians that result in needed treatments being prescribed-often, not the treatment in the DTC advertisement. This study also demonstrates that most physicians view DTC advertisements as one of many factors that affect their practice and their interactions with patients, both positively and, in some respects, negatively.

Highlights include:

- Many physicians believe that DTC can play a positive role in their interactions with their patients. For example, most agreed that, because their patients saw a DTC ad, he or she asked more thoughtful questions during the visit. Some thought that the ad made their patients more aware of possible treatments.
- Many physicians also thought that DTC ads made their patients more involved in their healthcare.
- Physicians also felt they had to provide additional information to patients beyond what patients retained from the DTC advertising. About 75 percent of physicians believed that DTC causes patients to think the drug works better than it did, and many physicians felt some pressure to prescribe something when patients mentioned DTC ads.
- However, eight percent felt very pressured to prescribe the specific brand name drug when asked about it. Instead, physicians suggested alternative courses of action for a variety of reasons: a different drug was more appropriate, there were side effects the patient did not know about, or a less expensive drug was available.
- According to the survey, one effect of DTC ads was to help educate patients about their health problems, and to provide greater awareness of treatments. The study demonstrated that when a patient asked about a drug, 88 percent of the time they had the condition that the drug treated. And

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Phase Two of CBER/CDER Product Consolidation Concludes

On January 8, 2003, Commissioner of the Food and Drug Administration Mark B. McClellan, M.D., Ph.D., informed employees of the Food and Drug Administration (FDA) that the Agency's Consolidation Working Group has completed phase 2 of the consolidation of certain biologic product reviews in FDA's Center for Drug Evaluation and Research (CDER). The consolidation of certain product review functions in CDER, announced last September, is expected to produce a more efficient, effective, and consistent review program for human drugs and biologics.

In an e-mail message to all employees in CDER and in FDA's Center for Biologics Evaluation and Research (CBER), McClellan announced the planned transfer of nearly $32.9 million from the biologics program to the human drugs program's budget. This amount reflects the full year costs associated with the transfer of therapeutic product reviews from CBER to CDER.

The categories of products that are being transferred generally include:

- Monoclonal antibodies intended for therapeutic use;
- Cytokines, growth factors, enzymes, and interferons (including recombinant versions) intended for therapeutic use; and
- Proteins intended for therapeutic use that are extracted from animals or microorganisms, other than human blood and blood components and derivatives.

The funds to be transferred represent approximately 208 full-time equivalents (FTE's) from CBER and 5 FTE's from FDA's field operations from FY 2002 staffing levels—and the possibility

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80 percent of physicians believed patients understood what condition the drug treats.

- Moreover, doctors believe that patients understand they need to consult a health care professional about appropriate treatment: 82 percent of physicians believe patients understand very well or somewhat that only a doctor can decide if the drug is right for the patient. This is important, because only 40 percent of physicians believe that patients understood very well or somewhat well the possible risks and negative effects of an advertised drug from the DTC ad alone.

These new results confirm FDA's current understanding about DTC advertising. Ads can and do help increase patient awareness about the availability of effective treatments for their health problems. But FDA's DTC policies must help prevent potential misperceptions about benefits and risks of the advertised treatment, and any actual prescribing decision should be based careful consultation between a patient and his or her health professional, to make sure that all relevant information is considered for the patient's case.

FDA will continue to scrutinize DTC ads closely to ensure that all essential information is communicated as clearly as possible, as outlined in the current policy. In addition, FDA will continue its comprehensive evaluation of DTC advertising and its impact on public health and FDA's policies and guidance.

This is the third survey conducted by FDA to help the Agency assess the impact of DTC advertising. FDA will continue to analyze these data, and will continue its comprehensive evaluation of DTC advertising and its impact on public health, to ensure that current DTC policies maximize the positive benefit that DTC advertising can play in the public health arena.

Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing, delaying the effective date until January 21, 2004. The FDA is putting in place a new comprehensive approach to the regulation of human cells, tissues, and cellular and tissue-based products (HCT[sol]Ps). The goal of the new approach is to improve protection of the public health without imposing unnecessary restrictions on research, development, or the availability of new products. The new comprehensive approach to the regulation of different types of HCT[sol]Ps is intended to be commensurate with the public health risks presented, enabling us to use our resources more effectively, increase consistency, and improve efficiency.

Due to the numerous comments submitted to FDA regarding the proposed donor suitability and Good Tissue Practices (GTP) rules, FDA will not be able to finalize these rules by January 21, 2003. Establishments that manufacture HCT[sol]Ps covered by the staggered effective date have been registering voluntarily, and FDA is willing to continue accepting such voluntary registrations.

For further information contact Paula S. McKeever, FDA, Center for Biologics Evaluation and Research (HFM-17), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, (301) 827-6210. To review the entire document see the *Federal Register*: January 21, 2003 (Volume 68, Number 13) Pages 2689-2691. ■

—William Stoedter

USP Water Committee from cover

January 9, 2003

Mr. Frank J. Barletta
United States Pharmacopeia
12601 Twinbrook Parkway
Rockville, MD 20852

Re: Extractables in Packaged Pharmaceutical Waters

Dear Mr. Barletta:

PDA appreciates the opportunity to comment on the proposal in the July–August 2002 Pharmacopeial Forum regarding changes to the monographs for packaged pharmaceutical waters. As you are aware, organic and inorganic compounds may be leached from product packaging. While the rubric to the proposed change acknowledges this phenomenon, we believe data, where they exist, are insufficient at this time to establish standards for TOC and conductivity.

We believe it would be inappropriate for USP to establish TOC and conductivity standards for packaged waters on the basis of the limited data and unpublished studies since any conclusions derived there from may be distorted. A program of substantial scope would be called for in order to compile information that provides a sound basis for modernization of the TOC and conductivity standards. For example, factors such as container size, container composition, surface to volume considerations, and lot-to-lot variability, examined over the duration of shelf-life, would necessarily need to be considered in order to establish meaningful standards.

USP's proposed limits of 6,000 ppb, (ref. July-August 2002 Pharmacopeial Forum) serve to reinforce our concern of establishing standards on the basis of limited data. For example, data described by Poirier-Meltzer found upper limits of about 6,100 ppb of TOC. Data reported by Baxter and Abbott found TOC values as high as 10,500 ppb (see accompanying data). Further, we believe that standards must not be set which preclude the continued marketing of commercially available product. We therefore reiterate the need for further investigation into this matter before standards are set.

There is another facet of the subject that calls for special consideration. Inevitably, it seems, the measurement of drug preparations for TOC, or conductivity, etc., becomes translated in the public mind as implying dangers to health; however, no physiological implications can be legitimately derived from conductivity and/or TOC specifications. USP and PDA have the obligation to prevent the distortion of technical findings. It should be clear that physiological conclusions cannot be drawn from the studies already completed, or presently being advocated.

We hope this explanation and the accompanying data prove useful to the USP Pharmaceutical Waters Expert Committee as they deliberate these issues. Please feel free to contact me if you have questions or would like additional information.

Sincerely,
Russell E. Madsen
Acting President

January 16, 2003

William Stoedter, RAC
PDA Director of Regulatory Affairs, PDA
3 Bethesda Metro Center, Suite 1500
Bethesda, MD 20814

Dear Bill:

We dedicated the first 45 minutes of our meeting to a discussion of packaged waters with Roger Williams and Eric Sheinin. Later in the morning, when the PDA representatives arrived, the Committee spent another 75 minutes discussing this matter. In the afternoon, the Committee met in closed session to again discuss the packaged waters tests revisions. We concluded that the use of the conductivity test in lieu of the qualitative wet chemistries for ionic substances is not an issue. We all agree to harmonizing with the EP standards. The Oxidizable Substances (OS) test remains to be the major "stumbling block." It is an archaic, qualitative test that has many documented difficulties associated with it. The Committee had proposed a TOC limit of 6 ppm based upon the only data available to us. The data that you submitted, just prior to our meeting, indicates that the limit should be closer to 30 ppm. The Committee is prepared to consider and perhaps propose that number, though we are not enthusiastic or unanimous. As a Committee, we all do not favor performing a lengthy study to establish an identification test for packaged water. We could support the study in order to achieve a better understanding of current capability, and the possible toxicological effects of certain species, but NOT at the expense of improving the testing today. We wish to resolve the issue during our tenure in this revision cycle. If the concerned PDA firms have additional data in its files that they want to share with the Committee now, we would be pleased to consider it.

As was discussed during your presence, the Committee is not wedded to the use of TOC, as alternative quantitative methods are always possible, but TOC is the most reliable state-of-the-art test for detecting gross organic contaminants. It is the surrogate test that can be regarded as a safety net when specific toxicity information is lacking. We recognize that the TOC will vary with the construction of container; size of container, agitation of container, storage conditions of the container, environmental conditions, time, and other parameters; however, the Committee believes that, when used together, conductivity and TOC testing will identify packaged water and distinguish it from other solutions. If the PDA can propose another suitable analytical technique or method to perform this function, the Committee would be anxious to consider it.

The Committee has postponed advancing the proposal to In-Process in the next available PF. However, it plans to have some revision become official in a supplement to USP 27, i.e., 2004, and to do so it must be advanced in PF within the next six months.

Thanks again for your participation. All communications should be addressed to Frank Barletta, the USP Liaison to the Pharmaceutical Waters Expert Committee.

Sincerely,
Anthony Bevilacqua, Ph.D.
Chairman, Pharmaceutical Waters Expert Committee

cc: Eric Sheinin Roger Dabbah
PWC Members Theodore Meltzer ■

Meet the Regulator

Editor's note: PDA will be posting short biographies of regulators so that PDA Members can get to know them better; both personally and professionally. We start our series with:

David Hussong, Ph.D.

Director Regulatory Scientist, DHHS/FDA/CDER/OPS, Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Office of Pharmaceutical Science
E-mail: husssong@cder.fda.gov

David Hussong is currently a microbiologist with the Food and Drug Administration (FDA). He joined the FDA's Center for Biologics Evaluation and Research (CBER) in 1979 after completing a Master's Degree in microbiology; however in 1980 he returned to the University of Maryland, to begin working on a Ph.D. with Drs. Ronald Weiner and Rita Colwell. During his Ph.D. program, he worked on research grants at the USDA/Agriculture Research Center, studying *Legionella* and *Salmonella* in natural materials and the environment. Some of his dissertation research was done with Dr. Emilio Weiss in the Rickettsial Disease Laboratory of the Navy Medical Research Institute, where he also developed rapid detection methods for unusual pathogens. His dissertation developed methods that demonstrated a viable but non-culturable phase of *Legionella pneumophila*. These methods were used in collaboration with the Public Health Laboratory Service (UK) investigation of the 1985 Legionnaire's disease outbreak in Stafford, UK.

In 1985, Dave returned to the FDA's CBER, in the Laboratory of Mycobacteria and Cellular Immunology, to regulate and research tests for tuberculosis and related organisms using monoclonal antibodies and radioimmuno assays. His Ph.D. in microbiology was awarded in 1986. Dave was commissioned as an officer of the US Public Health Service in 1987 (he currently holds the rank of Captain). In 1989 he transferred to FDA's Center for Drug Evaluation and Research (CDER) as a reviewer of pharmaceutical sterilization and manufacturing quality microbiology with Vivian Greenman and Dr. Peter Cooney. His official title today is Director Regulatory Scientist, and his primary job function is to review microbiological methods and acceptance criteria, manufacturing controls, and product attributes as described in new and supplemental NDAs and INDs. As a senior member of the team, Dave assists in other projects including guidance documents. A PDA member since 1993, Dave recently joined the PDA Science Advisory Board and has served on several committees. Dave is also the FDA ad hoc reviewer to the USP Expert Committee on Analytical Microbiology.

Dave and his family own a small hay farm where they enjoy horses, gardening, hunting, and fishing. He also loves motorcycles; a hobby of his since 1968. ■

—William Stoedter

Phase Two of CBER/CDER from page 8

of an additional 8 FTE's if the President's FY 2003 budget is adopted.

The Commissioner also announced that, because of important complementarities with other vaccine and cellular research in CBER, review of therapeutic vaccines (such as vaccines for cancer) would remain in CBER. Under the new structure, clinical review of therapeutic vaccine-associated Investigational New Drug applications (IND's) and Biologics License Applications (BLA's) will be fully coordinated with the appropriate area of clinical expertise in CDER. CDER and CBER will establish a process for conducting prompt, reimbursable consultations on product reviews when such consultation is necessary.

The Consolidation Working Group, co-chaired by Principal Associate Commissioner Murray M. Lumpkin, M.D., and Assistant Commissioner for Planning Theresa Mullin, Ph.D., will now move on to its third and final phase of work. This phase will focus on the logistics of the transfer and on developing procedures and timelines for actual transfer of review responsibilities for specific licensed/approved products and INDs from CBER to CDER. This phase is expected to be completed by early February. ■

—William Stoedter

European Regulatory and GMP News

Mutual Recognition Agreements (Sectoral Annex on GMPs) Internationally Harmonized Requirements for Batch Certification (Final, after revision 3—only explanatory note, date December 16, 2002)

Explanatory Note

In the framework of Mutual Recognition Agreements, the Sectoral Annex on Good Manufacturing Practices (GMP) requires a batch certification scheme for drug/medicinal products covered by the pharmaceutical Annex. The importer of the batch is to receive and maintain the batch certificate issued by the fabricator/manufacturer. Upon request, it has to be readily available to the staff of the Regulatory Authority of the importing country. This certification by the manufacturer on the conformity of each batch is essential to exempt the importer from re-control (re-analysis).

Each batch transferred between countries having an MRA in force, must be accompanied by a batch certificate issued by the fabricator/manufacturer in the exporting country. This certificate will be issued further to a full qualitative and quantitative analysis of all active and other relevant constituents to ensure that the quality of the products complies with the requirements of the Marketing Authorization of the importing country. This certificate will attest that the batch meets the specifications and has been manufactured in accordance with the Marketing Authorization of the importing country, detailing the specifications of the product, the analytical methods referenced, the analytical results obtained, and containing a statement that the batch processing and packaging quality control records were reviewed and found in conformity with GMP. The batch certificate will be signed by the person responsible for certifying that the batch is suitable for release for sale or supply/export at the fabrication/manufacturing site.

Where applicable this batch certificate shall also be used for non-finished medicinal products such as bulk, partially packed, intermediates, and active pharmaceutical ingredients.

These harmonised requirements have been agreed by the Regulatory Authorities of the following parties/countries: Australia, Canada, European Community, New Zealand, and Switzerland.

This Certificate shall also be used in the framework of Protocol to the Europe Agreement on Conformity Assessment and Acceptance of industrial products (PECA).

For further information please visit www.emea.eu.int.

Guidance for Comments

1. The Committee for Proprietary Medicinal Products (CPMP) and the Committee for Veterinary Medicinal Products (CVMP) during their December 2002 meetings have endorsed the revised Note for Guidance (NfG) on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathies via Human and Veterinary Medicinal Products, EMEA/410/01 Rev. 2. By virtue of Annex I to Directives 2001/82/EC and 2001/83/EC this NfG is mandatory. The revised document is now published on the Web site of the Commission for a three-month external consultation. Comments are requested before Tuesday, April 15, 2003 and should be sent by e-mail to Maurice.Robert@cec.eu.int or by post to the Unit F/2.
2. CPMP Position Paper on the limits of genotoxic impurities: A general concept of qualification of impurities is described in the guidelines for active substances (Q3A, Impurities in New Active Substances) or medicinal products (Q3B, Impurities in New Medicinal Products), whereby qualification is defined as the process of acquiring and evaluating data that establish the biological safety of an individual impurity or a given impurity profile at the level(s) specified. In the case of impurities with a genotoxic potential, determination of acceptable dose levels is generally considered as a particularly critical issue, which is not specifically covered by the existing guidelines. This Position Paper describes a general framework and practical approaches on how to deal with genotoxic impurities in new drug substances. In the current context the classification of a compound (impurity) as genotoxic in general means that there is clear evidence for its genotoxic activity usually from positive findings in *in vivo* mammalian test(s), with supporting evidence from *in vitro* test(s). These compounds are usually animal carcinogens and are suspected to be human carcinogens. The draft of this paper is released for consultation in December 2002 and the deadline for comments is March 2003. Comments should be sent to the EMEA, SWP Secretariat (fax +44 20 7 418 8613), before the end of March 2003. For further information contact http://www.emea.eu.int.
3. Note for Guidance on Summary of Requirements for Active Substances in the Quality Part of the Dossier (draft): This revised Note for Guidance is for application to both Human and Veterinary products. The original guideline "Requirements in Relation to Active Substances" (NTA, 3AQ6a Volume IIIA) came into effect in October 1991. The draft of this paper is released for consultation in January 2003. The deadline for comments is June 2003. For detailed information visit http://www.emea.eu.int. ■

—Gautam Maitra

Human Drug CGMP Notes

Volume 10, Number 2 • Second Quarter, 2002

A Memo for FDA Personnel on Current Good Manufacturing Practice for Human Pharmaceuticals Issued By: The Division of Manufacturing and Product Quality, HFD-320 Office of Compliance Center for Drug Evaluation and Research
Project Manager: Brian J. Hasselbalch

This document represents the agency's current thinking on Current Good Manufacturing Practice for human pharmaceuticals. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

In this edition:

Calibration

Nowadays, many leading analytical balance manufacturers provide built-in "auto calibration" features in their balances. Are such auto-calibration procedures acceptable instead of external performance checks? If not, then what should be the schedule for calibration?

Stability

Do CGMPs require that forced degradation studies always be conducted of the drug product when determining if a drug product stability test method is stability-indicating?

Equipment

Is there a list of CDER-approved drug manufacturing equipment?

Particulate testing

When a firm performs the USP <788> Particulate Matter in Injections test for a Large Volume Parenteral (LVP), is it acceptable to take the average among the units tested to determine if the batch meets its specification for this attribute?

Report-keeping

I recently inspected a firm and discovered that their policy is to destroy, internal audit reports and any attachments once the corrective actions are completed. The firm keeps only the date and auditor's identity. Is this acceptable practice?

General Comments

Welcome to another edition of Human Drug CGMP Notes, our periodic memo for FDA personnel on CGMP for human pharmaceuticals.

Remember that we are now publishing the Human Drug CGMP Notes EXCLUSIVELY for FDA personnel. ("Exclusively" means that we're not posting directly for public consumption, but each edition is fully releasable under FOIA.) With last year's promulgation of the Good Guidance Practices, publishing at our INTERnet website would require each edition to 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. Be assured, however, that every edition now published comes with the Division's seal of approval, as before.

Thank you. Brian

Questions and Answers

Nowadays, many leading analytical balance manufacturers provide built-in "auto calibration" features in their balances. Are such auto-calibration procedures acceptable instead of external performance checks? If not, then what should be the schedule for calibration?

No, the auto-calibration feature of a balance may not be relied upon to the exclusion of an external performance check. For a scale with a built-in auto-calibrator, external performance checks should be performed on a periodic basis but less frequently as compared to a scale without this feature. The frequency of performance checks depends on the frequency of use of the scale and the criticality and tolerance of the process or analytical step. Note that all batches of the product manufactured between two successive verifications would be affected should the check of the auto-calibrator reveal a problem. Additionally, the calibration of an auto-calibrator needs to be periodically verified—a common frequency is once a year—using National Institutes of Standards and Technology (NIST) traceable standards or NIST-accredited standards in use in other countries.

What should be the accuracy or acceptance level for process balances, i.e., balances used in manufacturing operations like dispensing and in-process weighing?

A measurement uncertainty (random plus systematic error) not exceeding 0.1 % (0.001) of the reading is generally accepted for laboratory scales. Please refer to USP Chapter <41> and ASTM standard E 617 for further information. However, applicability of this limit to your weighing scale in a process area would depend on the criticality or sensitivity of the particular step of a process. For this reason, acceptance limit for measurement uncertainty of a process balance should be set and compliance to CGMPs is evaluated based on sound scientific justification, on a case-by-case basis.

References:

—21 CFR 211.68: Automatic, mechanical, and electronic equipment

—21 CFR 211.160(b)(4): General requirements (Lab Controls)

—USP Chapter <41> Weights and Balances

—ASTM standard E 617: Standard Specification for Laboratory Weights and Precision Mass Standards (this standard is incorporated into the USP by reference; other widely recognized standards may be acceptable)

Contact for further information: Mike Gavini, HFD-324; (301) 827-7277; gavinim@cder.fda.gov

Do CGMPs require that forced degradation studies always be conducted of the drug product when determining if a drug product stability test method is stability-indicating?

No. It may not be necessary to conduct forced degradation studies of a drug product to determine if the test method is stability-indicating.

Section 211.165(e) of the CGMP regulations states that the accuracy, sensitivity, specificity, and reproducibility of test methods shall be established and documented. Further, section 211.166(a)(3) requires that stability test methods be reliable, meaningful, and specific.

To ensure compliance with the CGMP regulations in sections 211.165(e) and 211.166(a)(3), the stability test methods must be stability-indicating. That is, the test methods must be specific so that the content of active ingredient, degradation products, and other components of interest in a drug product can be accurately measured without interference.

The CGMP regulations do not specify what techniques or tests are to be used to assure that one's test methods are stability-indicating. However, evaluating the specificity of the test methods during forced degradation studies (i.e., exposing drug to extremes of pH, temperature, oxygen, etc.) of drug substance and drug product often is necessary to assure that stability test methods are stability indicating. But in certain circumstances conducting a forced degradation study of just the drug substance may be sufficient to evaluate the stability-indicating properties of a test method.

Generally, in determining whether it is necessary to conduct forced degradation studies of the drug product, the specificity of the test method should be evaluated for its ability to assay drug substance, degradants, and impurities, in the presence of each other, without interference. The evaluation also should provide assurance that there is not a potential for interaction between drug substance, degradants, impurities, excipients, and container-closure system during the course of the shelf-life of the finished drug product.

Drug product stress testing (forced degradation) may not be necessary when the routes of degradation and the suitability of the analytical procedures can be determined through use of the following:

- data from stress testing of drug substance
- reference materials for process impurities and degradants
- data from accelerated and long-term studies on drug substance
- data from accelerated and long-term studies on drug product

Additional supportive information on the specificity of the analytical methods and on degradation pathways of the drug substance may be available from literature sources.

Lastly, the rationale for any decision made concerning the extent of the forced degradation studies conducted as well as the rationale for concluding that a test method is stability-indicating should be fully documented.

References:

—21 CFR 211.137: Expiration dating

—21 CFR 211.165(e): Testing and release for distribution 21 CFR 211.166(a)(3): Stability testing

—Compliance Policy Guide, 7132a.04 (Section 480.100), Requirements for Expiration Dating and Stability Testing

—Inspection Technical Guide: Expiration Dating and Stability Testing for Human Drug Products

Contact for further information: Barry Rothman, BFD-325; (301) 827-7268; rothmanb@cder.fda. gov

Is there a list of CDER-approved drug manufacturing equipment?

No. CDER, through the CGMP regulations, neither approves nor prohibits specific equipment for use in manufacturing of pharmaceutical products (with the exception of asbestos and fiber-releasing filters, see 211.72), and accordingly we do not maintain a list of approved equipment. The CGMPs merely require that equipment be of appropriate design to facilitate operations for its intended use and for cleaning and maintenance (see 211.63 and 211.67). And, that any equipment surface in contact with components, in-process materials, or drug products not be reactive, additive, or absorptive so as to "alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements" (see 211.65).

Firms are afforded the flexibility to select equipment that best satisfies their particular needs and which is capable of meeting the relevant CGMP requirements. Each firm is responsible for selecting all equipment used in their manufacturing process to produce quality product in accordance with CGMP. They are also responsible for selecting the appropriate intended use for the equipment's operation, and are free to modify standard equipment designs to best suit their process. In this respect, then, compatibility considerations can often take on the most CGMP significance.

References:

—21 CFR 211.63: Equipment design, size, and location

—21 CFR 211.65: Equipment construction

—21 CFR 211.67: Equipment cleaning and maintenance

—21 CFR 211.68: Automatic, mechanical, and electronic equipment

—21 CFR 211.72: Filters

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When a firm performs the USP <788> Particulate Matter in Injections test for a Large Volume Parenteral (LVP), is it acceptable to take the average among the units tested to determine if the batch

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meets its specification for this attribute?
No. It is not acceptable to take the average among the LVP units tested, and therefore it would also be unacceptable to use the average to hide individual unit out-of-specification results when following the USP tests for particulate matter.

"Particulate matter" refers to small, sub-visible particles. USP <788> provides two scientifically sound tests for detecting such particulates—light obscuration and microscopic assay. Both are generally accepted for use in testing LVPs and small volume parenterals (SVP) for the determination of sub-visible particulate matter. Normally, samples are first tested by the light obscuration method; if the sample fails the specified limits, the microscopic assay method can then be used. However, the microscopic method can be the sole test if there is a documented technical reason or interference from the product under test that would make the light obscuration method unsuitable or the results invalid.

Confusion over when averaging data is and is not acceptable is probably due to the sample preparation method for the light obscuration test. At least 2, 5-mL aliquots from each sampled unit or the pooled sample (see below) are to be used in the particulate count determination, and the results from these aliquots are to be averaged for comparison with the specification. Note that the average is of the results from examining each aliquot and not between units. (The results of the first aliquot examined by light obscuration are to be discarded, and the subsequent aliquots—2 or more—are retained.) Pooling units prior to analysis is permitted only if the volume in each unit is less than 25 mL, in which case 10 or more units may be pooled. If the volume in the SVP or LVP is 25 mL or more per unit, single units are to be examined.

Results among the test units can not be averaged because particulate matter is assumed to be nonuniformly dispersed throughout the lot. The intent of assessing result from each individual unit is to ensure adequate representation of the lot and to detect potential variation within a lot.

How many individual units should be tested for LVPs and SVPs of 25 mL or more? The USP states that the number of units tested depends on "statistically sound sampling plans," and "sampling plans should be based on consideration of product volume, numbers of particles historically found to be present in comparison to limits, particle size distribution of particles present, and variability of particle counts between units." The USP also suggests that the total number of units tested for any given batch may be less than 10 units (for LVP and pooled SVPs) with proper justification. This is consistent with the CGMP requirements for statistical sampling plans.

References:
—21 CFR 211.160: General requirements (for lab controls)
—21 CFR 211.165(c),(d): Testing and release for distribution
—USP <788> Particulate Matter in Injections
—Draft Guidance: Guidance for Industry: Investigating Out of Specification (OOS) Test Results for Pharmaceutical Production

Contact for further information: Brenda Uratani, BFD-325; (301) 827-7269; uratanibncder.fda.gov

I recently inspected a firm and discovered that their policy is to destroy internal audit reports and any attachments once the corrective actions are completed. The firm keeps only the date and auditor's identity. Is this acceptable practice?
Maybe. It depends on what is in the report.

The CGMP regulations 21 CFR 210 and 211 for drug manufacturing do not specifically address the requirement to conduct or to keep records of internal audits. Our policy is that we do not either review or copy audit reports prepared as part of a firm's internal quality assurance program. The intent of this policy is to encourage firms to conduct internal quality assurance audits and self-inspections that are "candid and meaningful." (See Compliance Policy Guide 7151.02. Exceptions to this policy are described in this guide.) So, if the report in question is from a routine audit to verify the firm's quality system is operating as intended, then it would be acceptable for the firm to discard the report once corrections have been verified.

However, any documentation of corrective action as a result of such an audit would, of course, have to be retained. For example, if a routine internal audit finds a problem with a mixing step and the outcome is a change in mixing time, all affected procedures, including the master formula, are to reflect the necessary changes and such records are subject to FDA inspection as usual. Any investigation into the impact this problem had on related batches is to be retained and also made available for inspection by FDA.

As well, any reports of investigations or evaluations prepared in response to, for example, a product complaint (211.198), vendor qualification (211.84), periodic review of records and data (211.180(e)), and a failure investigation (211.192) are not internal audits as discussed above. Such records are subject to FDA inspection and must be retained for at least the time specified in the CGMP regulations.

References:
—Preamble to the Good Manufacturing Practices for Human and Veterinary Drugs, Federal Register, September 29, 1978 (vol. 43, no. 190), page 45015, paragraph 4 http://www.fda.gov/cder/dmpq
—21 CFR 211.84: Testing and approval/rejection of components, drug product containers, and closures
—21 CFR 211.180: General requirements
—21 CFR 211.192: Production record review
—21 CFR 211.198: Complaint files
—Compliance Policy Guide 7151.02, Ch. 1, sec. 130-300, p. 32 (http://www.fda.gov/ora/compliance_ref/cpg/)

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TR-32 UPDATE

by Dana Buker MBA, CPIM; QA Officer Innovatum and Harvey F. Greenawalt, ARC

Innovatum Joins the Audit Repository Center

Innovatum has developed DataThread™, the only 21 CFR Part 11 compliance solution for the AS/400 which was designed by using the FDA regulation as a functional requirements template. From the onset of the project, our goal was to create software that could be implemented over all applications running on the AS/400, without any changes to the underlying programs. Our software had to be robust, and be easily validated to the exacting standards of pharmaceutical and medical instrumentation manufacturers.

For the past 10 years, Innovatum has been delivering validated custom software systems to FDA-regulated industries. We recognize the importance of development protocols, which lead to quality software. As we developed DataThread™, we applied the lessons-learned at client companies to our own internal development. In fact, all of the internal DataThread test cases used in the performance of the OQ, IQ and PQ are shared with our clients, demonstrating our commitment to quality and creating a fast path toward validation. It was, therefore, with some excitement that we looked forward to our first audit by a major multi-national pharmaceutical company. As expected, the audit was rigorous and lasted two days. While the results were excellent, it became even more apparent that the cost of each audit would be significant to both Innovatum and our clients.

With a growing list of prospective clients, each wanting to perform a vendor audit, the potential productivity impact was severe. Under these conditions, one of our clients offered to perform a standard TR-32 audit and post the results to the Audit Repository Center (ARC). The logic seemed inescapable: one standardized pharmaceutical industry software supplier quality audit, to be shared by all participating members.

The outcome, for Innovatum, has been excellent. The audit itself has helped us further improve in our quest for quality. Even before the audit was finalized and posted to the ARC, we had potential clients who had expressed interest in reviewing the results. In January of 2003 the availability of our TR-32 audit has averted two client audits. We fully expect it to contribute to redirecting our efforts from audits, to R&D and customer support.

About Innovatum

Innovatum, Inc. (www.innovatum.com) is a software development and consulting firm specializing in regulatory compliance and the creation of sophisticated custom applications for Fortune 100 corporations. Innovatum also develops and markets off-the-shelf software such as DataThread™ a complete solution for 21 CFR Part 11. For those companies affected by HIPAA, DataThread can be used as a component of an overall remediation solution as well. Innovatum also offers ROPICS™, a validated radio frequency system with modules for manufacturing execution, warehouse management, and automation of other remote transactions for ERP.

Innovatum is headquartered in Sugar Hill, GA with sales offices located in Boston, MA.

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Auditor Training & Qualification

The next auditor-training course is scheduled for PDA-TRI Baltimore on March 25–26, 2003.

Information on applications for qualification and course registration is available on the PDA Web site at www.pda.org.

Availability of Audits

Currently, 54 audits are either under consideration, in process, or available for distribution.

Table 1.0 provides a summary of the Twenty-seven (27) audits that are currently available for distribution from the repository.

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

See Audits Currently Available from ARC on page 17…

PDA Technical Report No. 32—A Brief History

Auditing of Suppliers Providing Computer Products and Services for Regulated Pharmaceutical Operations

Companies who supply computer products and services (suppliers) to pharmaceutical companies (manufacturers) are required, by regulation or good business practices, to audit their performance. PDA Technical Report No. 32: Auditing of Suppliers Providing Computer Products and Services for Regulated Pharmaceutical Operations (TR-32) defines a six-step process for performing such an audit. Each of the steps represents a collection of activities to be accomplished by qualified auditors, manufacturers, and suppliers.

TR-32 followed in the aftermath of FDA's appeal to the regulated industry to standardize the auditing process for suppliers of computer products and ser-

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vices and establish a global repository for sharing audit information. The issues that concerned FDA included:

1. Uncertainty: Without an objective standard for all suppliers to follow, the obvious dilemma is that a supplier can never be reasonably certain that they are in compliance.
2. Inconsistency: Unless the objective standard is applied uniformly, from company to company, it is fair to say that all companies are not being treated alike. Some companies are more in compliance, while others are less compliant.
3. Redundancy: Because a supplier is often requested to submit to audits by a number of client manufacturers, a global repository makes sense since it would avoid a duplicative process.
4. Cost: Survey data at the time suggested that the beginning to close-out cost, per audit, was approximately $8,000 to $10,000 each to the manufacturer and the supplier. A global repository would reduce spiraling costs since suppliers are often audited several times in one year.

As a result of FDA's concerns, PDA issued TR-32 in January of 2000 to serve as a model for suppliers providing computer products and services for regulated pharmaceutical operations. The following year PDA licensed The Audit Repository Center (ARC) to serve as the global repository for all of its audits. ARC stores, then makes available via the Internet, the various audits submitted by suppliers. This allows manufacturing companies (subscribers) or participating suppliers to obtain easy access to the data. To acquire a copy of TR-32, visit www.pda.org. To learn more about the Audit Repository Center, or to subscribe to the growing number of audits available in ARC's repository, visit www.auditcenter.com. ■

Table 1.0 Audits Currently Available from ARC

	Supplier	Product
1	Access 360, Inc.	EnRole 4.0 (Provisioning Software)
2	Alacris, Inc.	IdNexus, Alacris products are designed to simplify identity management and maximize trust associated with Public Key Infrastructure (PKI) implementation and security technologies
3	Automation Tooling Systems, Inc.	Custom programming services for Process Control Software
4	Decision Management International, Inc. (DMI)	Regulus™ Document Authoring (DA) a member of the Regulus™ off-the-shelf solution set.
5	Documentum, Inc.	Content Authentication Services (CAS), eContentServer, DocControlManager (DCM) and GMPharama
6	Entrust Technologies Ltd.	Public Key Infrastructure Technology (PKI). Digital Security technology for enterprise resource systems.
7	Epicentric, Inc.	Foundation Enterprise Server 4.0, tool for coordinating information from disparate sources and for disparate users.
8	Fanuc Robotics North America	Robotic Controllers & Communications
9	Fisher Rosemount Systems, Inc.	Distributed Factory Automation, Delta V product Line
10	Foss NIRSystems, Inc.	SLE Near-infrared analysis of chemical and physical Properties
11	Infinity QS International (Lyle-Kearsley, Inc.)	Infinity QS Statistical Process Control Software
12	Inktomi Corporation	Enterprise Search Software (information retrieval solutions)
13	Innovatum, Inc.	Data Thread™ 21 CFR Part 11 compliance solution for the AS/400
14	Interwoven, Inc.	Web Publication management
15	Lexign Corporation	Lexign Flow EPR Software
16	Loftware, Inc.	Loftware print server (LPS) Label printing system
17	MARC Global Systems	Warehouse Execution Systems
18	Merant, Inc.	PVCS Dimensions & PVCS Replicator Configuration Management Systems
19	Mercury Interactive	Test management Tools: • QuickTest Professional • Astra Fast Track • Astra LoadTest • Astra Quick Test • Test Director • LoadRunner • LoadRunner TestCenter • WinRunner
20	Propack Data GmbH	Enterprise production Management System, PMX 3.2 with Solutions MES and CTM
21	SAP AG	MySAP.com e-business platform, specifically aspects of Supply Chain management, Product Lifecycle Management and Business Intelligence relevant to manufacturing operations.(Includes Product Lines: SAP R/3 4.5B and SAP R/3 4.6B/C)
22	Schlumberger	Secure ID Card
23	SSA Global Technologies, Inc.	Mid range ERP software for manufacturing, supply chain and financial application domains
24	Serena Software, Inc.	Serena ChangeMan Automating the Software Lifecycle
25	Sparta Systems, Inc.	Track Wise Software
26	Supply Chain Logic, Inc.	General use COTS Asset Tracking/Delivery Systems
27	The Sycamore Group	Custom IT Solutions, Integration Suite of COTS products and services to bridge data across multiple internal computer systems, including e-Commerce, LIMS, ERP, enterprise database, mainframe and wireless portable devices.

USP UPDATE

by Roger Dabbah, USP

The First Supplement of USP 26-NF 21 was published in February 2003 and will become Official on April 1, 2003. It has 15 new USP monographs. These include: Aminobenzoate Sodium; Amoxicillin Tablets for Oral Suspension; Bromodiphenhydramine Hydrochloride and Codeine Phosphate Oral Solution; Cyanocobalamin Co 58 Capsules; Depyridamole Injection; Felodipine Extended-release Tablets; Ganciclovir & Ganciclovir For Injection; Insulin Lispro & Insulin Lispro Injection; Lansoprazole Delayed-Release Capsules; Nabumetone Tablets; Paclitaxel Injection; Pentoxifylline Extended Release Tablets; Zileuton.

The first Supplement also contains 13 NF monographs such as Myristyl alcohol; Horse Chestnut, Powdered Horse Chestnut & Powdered Horse Chestnut Extract; Chondroitin Sulfate Tablets; Red Clover, Powdered Red Clover, Powdered Red Clover Extract & Red Clover Tablets; Alpha Lipoic Acid Capsules & Alpha Lipoic Acid Tablets; Saw Palmetto Extract & Saw Palmetto Capsules.

The USP Scientific Conference on Biological and Biotechnological Drug Substances and Products will be held April 1-4, 2003 at the Crystal Gateway Marriot, Crystal City, Virginia. This three-day conference will consist (on the first day—April 2) of a series of presentations on new technologies for biological and biotech products, followed by Workshops on Specification Development, Strategies for Establishment of Cell-banks for Production of Viral Products and Monoclonals, Immunogenicity of Therapeutic Proteins, and Well Characterized Biologicals Start with Well-characterized Raw Materials.

On the second day of the Conference, presentations will be given on Advances in Analytical Methodologies, Biopotency Assays, Pathogen Inactivation Technologies, and Surface Plasminogen Resonance. They will be followed by Workshops on Glycoprotein Glycan Analysis, Validation of Rapid Microbiological Procedures, Design and Analysis of Biological Assays, and Progress in Analytical Methodologies in Prion Detection.

The third day of the Conference will consist of a panel discussing issues on Equivalence of Biological & Biotechnological Ingredients and Products followed by interactive discussions with the audience. Additional details can be found on the USP Web site at www.usp.org. ■

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PDA Interest Group Updates

Several of PDA's Interest Groups met at the 2002 PDA Annual Meeting in New Orleans in December. Following are summaries and highlights from some of those meetings. More summaries were published in the February 2003 *PDA Letter*.

Drug/Device Combination Product Interest Group

Ray Pritchard, Alkermes, Inc.

A small but enthusiastic group met on December 10th at the 2002 PDA Annual meeting in New Orleans to discuss regulatory and quality issues unique to drug/device combination products. There were podium presentations by Michael Gross and Ray Pritchard, followed by a lively discussion session.

Dr. Gross presented a summary of the regulatory landscape. He reviewed the various kinds of drug/device combination products, and how they present their own unique challenges. He drew an analogy to the chimera, a fire-breathing monster that is part lion, part goat, and part serpent, making the point that device/drug combination products are a different kind of animal. Dr. Gross also gave the group a summary of the issues brought up at a recent FDA/Industry teleconference which covered many of the regulatory issues. FDA has become very much aware of the unique nature of drug/device combination products and has identified them as constituting a fourth product category. Dr. Gross then turned the podium, as well as the leadership of the Interest Group, over to Ray Pritchard.

Mr. Pritchard focused his presentation on the quality system challenges of drug/device combination products. While the drug GMPs (21 CFR 210, 211) and device GMPs (21 CFR 820) are similar in spirit, there are some significant differences that affect how they are applied. Quality professionals from the drug world seem to speak a different language than those in the device world. Do we need two quality systems for drug/device combination products? Mr. Pritchard suggested the integration of the two systems, starting with a sound drug GMP quality system and incorporating device quality concepts, as an example. He made the point that some of the features of device quality systems are already being adopted by pharmaceutical firms as current best practices.

A group discussion followed, with participants sharing their own experiences and difficulties in working with drug and device quality systems.

All PDA members who are interested in the issues surrounding drug/device combination products are urged to join the Interest Group and e-mail contact information to ray.pritchard@alkermes.com.

Isolation Technology Interest Group

Dimitri Wirchansky, Jacobs Engineering Group

The Isolation Technology Interest Group met during the 2002 PDA Annual Meeting on Wednesday, December 11th at the Marriott Hotel in New Orleans, LA. The meeting was attended by 56 members and consisted of three presentations and an open discussion.

Dimitri Wirchansky presented comments on Appendix 1 of the Draft Aseptic Processing Guidelines. Of particular interest is the Agency's statement that isolators offer an advantage over aseptic processing, appropriate background area classifications for isolator systems, and target log reduction for decontamination of isolator systems.

Paul Ruffeiux of Skan presented an overview of the implementation of isolators in pharmaceutical manufacturing and then proceeded to discuss future trends for isolator applications. Ruffeiux's focus is on filling and processing applications. Among the trends mentioned were integration of the isolator system with its associated equipment and the use of robotics to eliminate the use of gloves for specialized applications such as the processing of highly toxic actives.

Bill Friedheim of Carlisle (Walker) presented an overview of the latest trends in his company's applications. Friedheim's focus is on sterility testing, product development applications, containment, and powder processing. Among the trends mentioned were the desire to minimize the use of half suits and integrate Steritest equipment into the isolator floor for sterility testing, and an increase in the number of toxic and potent products for product development and powder processing. Friedheim also mentioned the use of robotics to eliminate gloves for specialized toxic product applications.

After the presentations, open discussion followed. There was considerable discussion around the advantages and consequences of using an automated CIP system to clean various systems such as filling lines, formulation isolators, and other processing systems. The advantages of using an automated CIP system are offset by some of the consequences. As an example, filling equipment is not usually set up for drainage of wash fluids, and if the system is wetted, it has to be dried before decontamination with vaporized hydrogen peroxide. If the product is not particularly potent or toxic, the complications of the automated CIP system in cycle time and validation may outweigh the benefits of automated cleaning. However, if the product is significantly potent or toxic, the benefits of automated cleaning are likely to outweigh the additional complications.

The next area of discussion focused on the decontamination level to validate to for the use of vaporized hydrogen peroxide. PDA Technical Report No. 34 recommends a minimum three log reduction. The FDA comments to this report, as well as the draft aseptic guidelines, favor the use of a six log reduction. One comment from the floor noted that the use of a log reduction figure was meaning-

less without the determination of the D value. It was also noted that some bioindicators have wide variations in D value from less than one to in excess of five. These are not appropriate for use. A bioindicator with a D value in the range of one to two is recommended. Most environmental isolates have D values less than one. Cycle development should be based on sound science, using bioindicators with appropriate uniformity and D value. Just doubling exposure time with the idea that more is better is not sound science. If a cycle is used for external decontamination of pre-sterilized, wrapped components, such as syringe tubs or environmental monitoring supplies, a three-log reduction is appropriate. However, if product contact parts or product component contact parts such as stopper bowls and tracks are part of the decontamination cycle, a six-log reduction is recommended. Anything less is difficult to justify. It should also be noted that the level of decontamination should be uniform throughout the isolator chamber since the peroxide should be distributed in a uniform way throughout the chamber.

This led to further discussions on how to verify uniform peroxide distribution in the isolator chamber. The peroxide sensors are expensive and cannot be distributed throughout the chamber like thermocouples in an autoclave. One suggestion was to use chemical indicators distributed throughout the chamber and to monitor the window of time required for all of the indicators to change color. Another suggestion was to monitor temperature uniformity. Paul Ruffeiux disagreed with this claiming that the temperature is not important. We were discussing this subject when time ran out on the session.

This was a lively informative session thanks to all those that participated. Comments on the discussions are welcome.

Lyophilization Interest Group

Edward H. Trappler, Lyophilization Technology

With a room packed with interested participants, the session was opened with introduction of an informal forum with the participants identifying topics for discussion.

These encompassed:

- Cleaning, agents and validation;
- Sterilization;
- Process Qualification;
- Cycle Validation;
- Broken Glass;
- Environmental Monitoring;
- Stoppering; and
- Visual Inspection

The question was asked about the necessity of cleaning the lyophilizer. A majority of the group acknowledged the importance of cleaning the interior of the lyophilizer, particularly for prevention of cross contamination. Methods noted were a sequence of cold, then hot WFI, only using hot WFI, with mention of using a disinfectant followed by rinsing with steam. The discussion then proceeded to what level of cleaning was appropriate. Use of automated CIP was acknowledged as preferred over manual cleaning and prominent equipment vendors indicating it to be a frequent option selected for new equipment. General consensus indicated the use of riboflavin was common for CIP system coverage during FAT and qualification studies. Verification of cleaning effectiveness ranged from visual inspection to TOC.

The discussions easily flowed from cleaning to sterilization. The group acknowledged that frequency of sterilization is needed to consider the potential of contamination during manual loading operations. Sterilization in preparation to processing a batch is considered routine. Campaigning of identical product batches then lead to considerations of risk analysis. Another interesting perspective affiliated with increasing popular use of autoloading systems; if the source of potential contamination is eliminated, i.e. manual loading operations, then what is the level of risk, and therefore need, for routine sterilization? A question on the status of VHP sterilization as an alternative was asked, with no indication that any of the companies represented was pursuing the method.

An additional reference to risk assessment was made during discussions on process qualification. Various positions included interests in instances of a different batch size, installing a new lyophilizer, and site transfer of a product to a different contract manufacturer. The first seemingly discontinuity of consensus appeared in this forum regarding terms. Terminology varied within the group, with references to consistency, demonstration and conformance lots being familiar to a variety of participants for "manufacturing scale" used to represent those batches for generating data in a production environment as part of a submission for regulatory approval. The technical issue left unresolved, suitability of using varied batch sizes for validation with a commitment for additional monitoring during routine manufacturing was seen as a reasonable approach. For the second time risk assessment was mentioned. As to the particulars of any circumstance, no one had elaborated.

As the discussion moved on to cycle validation, a impromptu survey of cycle length revealed the shortest mentioned process being five hours, with the record in length of thirteen days. Specifics of either case were not shared, thus valuable secrets and perhaps some embarrassment being avoided. Cycle validation discussions quickly progressed from robustness and consistency to demonstrating proven acceptable ranges and boundary studies. Bracketing tolerances, referring to level of achievable control of the lyophilizer, was pointed out as being one consideration. Again lively discussion aroused with a notion of conducting such studies in man-

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ufacturing environment. Consensus quickly developed on the suitability of establishing the boundary conditions as being an appropriate part of development activities. The focus progressed to treatment and testing of product samples processed during the boundary studies. Agreement on the need of finished product testing was prominent, with diversity on the suitability of testing under accelerated conditions to the use of an abbreviated stability schedule for such studies. Then the issue of how to deal with exceptions and synthesizing excursions to mock aberrant conditions injected an agreeable rationale when reflecting on the perceived mammoth task of boundary studies during development.

The session ended with a more pragmatic topic on concern and causes of vial breakage. A quick list includes product and formulation, fill volume, concentration, vial handling, along with stress and surface imperfections as potential contributing factors.

Running over in time, the forum was once again a lively discussion of a variety of topics, leaving others to begin the list our next session. With the welcomed opportunity to share inquiries, issues, observations, and experiences, and walking away with greater knowledge and insight on current topics of interest, this group and the format of an open forum proved to be a valuable resource for those attending. I will again look forward to being a part of such a session at the next PDA meeting.

With appreciation due to all that participated, thanks! And to all that quietly listened, I welcome hearing from you at the next session.

PS: As promised, considerations and references to lyophilization in the "Sterile Drug Products Produced by Aseptic Processing Draft" along with the reference mentioned during discussions on cleaning will be posted in the near future on the PDA Web site.

Ophthalmic Interest Group Meeting

Chris Danford, Alcon Laboratories, Inc.

The following topics were discussed as part of the December IG meeting:

- Terminal Sterilization vs. Aseptic Processing—Effects on Ophthalmic Products;
- What size media fill runs and acceptance criteria provide the most protection?
- Form-Fill-Seal Applications for Ophthalmic Products; and
- Particulate Matter Specification Changes (USP).

It was decided that a working group would be formed to draft a position paper regarding terminal sterilization versus aseptic processing and the effects of terminal sterilization on ophthalmic products.

Pharmaceutical Water Interest Group

Theodore H. Meltzer, Capitola Consulting Co.

The pharmaceutical water interest group was attended by some 18 people, some of whom "came and went." Perhaps inevitably, the topics raised often related singularly to the needs of the questioner. There was, however, a repetition of themes that dominated the previous meetings of the group:

- Small microbe removal;
- Are filters permitted in water systems;
- Specifications for Packaged Water;
- European new water classifications;
- European requirements for Lyo-api applications;
- Current regulatory trends;
- Passivation; the practice and its purposes; and
- Rouging—causes and prevention.

The Chair's Observations:

- Obviously, answers to some questions require guessing the intentions of regulatory personnel; uncertainty abounds.
- Certain questions of a perennial nature, relate to important issues the answer to which are not yet available to the technical community.
- Otherwise, the Interest Group serves as an information bank.
- A greater participation in group discussions is desired.

The Chair considers it his obligation to promote this.

Training Interest Group Meeting

Thomas Wilkin, Ph.D., Schering-Plough Corporation

The meeting was opened with a review of the very successful October 7–9, 2002 Training Conference held in Tampa, Florida. Planning has begun for the 2004 Training Conference to be held in Spring 2004 in Puerto Rico.

The discussion of current issues centered on the following topics:

- Compliance issues within training;
- How can training drive culture change?
- Vendor training—how and when to use;
- Training within a virtual organization;
- Training for new facilities; and
- Developing interest and investment in training.

Interactive discussion, with very good participation among the 30 plus attendees, was held.

Information and ideas were developed, discussed, and reviewed by the group in a solution-oriented manner.

Vaccine Interest Group Meeting

Frank S. Kohn, FSK Associates, Inc.; Doris Conrad, GlaxoSmithKline; Edward Fitzgerald, Fitzgerald Consulting; Carmen M Wagner, Strategic Compliance International, Inc.

The Vaccine Interest Group had approximately 28 people in attendance for the meeting. A number of critical issues affecting our industry were discussed. Some the issues are listed below:

Critical Issues & Concerns:

- Aseptic Processing;
- Determining Alert/Action Levels;
- Environmental Monitoring;
- Team Biological Inspections (CBER);

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OOS and Outliers

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

In the 1993 decision US vs. Barr, Judge Wolin very firmly stated that outlier testing could not be used with chemical analyses to invalidate an OOS. FDA's policy on this is the same, such that today, outlier testing is virtually unknown in QC chemistry labs as a means of invalidating OOS results. But statistician friends tell me that the outlier test has statistical validity. That being the case, could someone shed light for me on why Wolin and FDA are so adamantly against the use of outlier tests?

Response 1

What you say is true and this part of the decision caused a lot of discussion. Define the type of outlier test and when it will be applied in the method (SOP) and it will be okay. I had an assay where it was convenient to measure 10 times, rank the data and through the highest and the lowest data point out, disregarding the fit. This is a good method used in physics. Anchor the type of outlier test, e.g., Dixon, in your SOP. It may have to be applied every time the assay is run (an outlier may pull an out of specification result into the accepted range, creating a false positive).

Response 2

One of the reasons companies were using outlier testing was to eliminate bad results without investigating the reason for the bad result. Even though it is statistically valid, it may hide manufacturing problems (product uniformity among them) or analytical problems (not the right method), human error, or a combination of all of the above.

Response 3

The primary reason that Wolin wrote in the 1993 US v. Barr decision that outlier testing should not be used in chemical testing was that USP was "silent" on this issue and specifically mentioned its use for Biological/microbiological analyses. USP has since corrected this impression that its "silence" on use of outliers to eliminate OOS values was just that, silence, since it did not at that time have a definitive position. Since then the Wolin judgment has become dogma (ensures acceptable practices as observed by FDA) but in the past few years and with the help of some solid statistical analysis linked with analytical work, some companies are using outlier testing under certain conditions and always along with a preponderance of analytical evidence that OOS is shown through an extensive investigation and retesting protocol, not to be part of the original and new retest population. Wolin was also aware of the abuse of outlier testing in the late 1980s to the point with some companies that only a meager investigation for root cause was performed (where no assignable cause was usually found). The outlier testing was taken as the primary reason for exclusion of the OOS result and QA batch release or generation of Stability data. Its frequent use was not "analytically" based and diminished the perceived need for a thorough lab investigation for assignable cause.

Response 4

Having read the repeated questions about the "OOS," out-of-specification results, it seems that most have gotten ahead of themselves when it comes to "outlier" testing. To use any statistical "population" test, one must first have established what the distribution of valid results is for the population being tested. To establish that distribution of valid results, one must test a set of sample units that is representative of the population.

In the drug industry, the test samples most often giving results that one would want to characterize as an "OOS" result are typically those found for active content and active release (in solid-dosage, semi-solid-dosage drug products) or fill volume (in the case of liquids) and active release (in suspensions requiring such testing).

Luckily, ISO 3951:1989 establishes the minimum number of sample units that must be tested before, at the 95% confidence level, for

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

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

OOS and Outliers from page 23

different population sizes, one can validly assess population membership, provided the underlying distribution of results is "normal" or "pseudo-normal." Provided the samples tested are from all parts of the population, then, provided that number has been properly tested, one might be able to argue that an appropriate statistical "outlier" test could be applied.

Unfortunately, when a population is larger than 150,000 units as it is for tablets and capsules, that minimum number would be 200 for cases where one or more "valid" results appear to be significantly different from the others. If one asserts that "one" unit has given an apparently valid "OOS" result, one is also asserting that the process used to make that unit may not have been in control.

If the valid results, obtained from the testing of 200 representative units, are not "normally distributed," then a minimum of 300 population representative results are needed before one could validly begin to justify the use of an appropriate statistical "distribution free" "outlier" test.

To those who truly understand analytical testing, the recent article that addresses applying "outlier" testing to the USP "assay" case—where the lab must do whatever is necessary to homogenize the sample before it tests for "assay"—were, at best, a weak attempt to justify the use of an "outlier" test without revealing the large number of samples that would need to be tested in the "real world" cases.

Factually, if a firm complies with the USP and verifies that its homogenizing procedures do, in fact, homogenize the composite 20 or more units that make up a proper USP "assay" sample, as the USP specifies, before any aliquot is taken for testing, a valid USP "assay" test cannot produce an "outlier."

A priori, the sample work up or testing must have been flawed in such cases and any "outlier" establishes that sample, sample work, or sample test was deficient.

In my experience, when a valid set of 200 representative samples have been tested, most often, the distribution of values observed has included the "OOS" result in cases where the lab was found to be operating in full compliance with what is now ISO 17025. Often, I find that labs are not well controlled. For example, the QC laboratory has glassware that is neither identified nor calibrated. In the worst instances, the graduated cylinders being used did not even meet the accuracy of ASTM Class B or unidentified volumetric pipettes with chipped tips and internal "scratches" were being used OR poorly controlled environmental conditions (an "air conditioned" QA lab in the United States whose average within-day temperature varied from 21 to 30 degrees C in the summer).

In many of the instances where a laboratory has reported a "valid" "OOS" result value, a rigorous "root cause" investigation has found that laboratory controls were insufficient to prove the validity of any of the values it was reporting, or the samples tested were biased by the less than adequate inspection (sampling and testing plans, or both poor controls and plans and procedures were found).

In some "dry blending" processes, the "outlier" source was traced to the composition of the material in the "boundary layer" adjacent to the "Final Blend" blender's surfaces. In those instances, reformulation was needed to eliminate this "outlier" source. In other cases, the "root cause" was a weak blending process. In a population of hundreds of thousands or millions, the finding of "one" value (in "30" in a USP CU Test or in "24" in a USP Dissolution or Drug Release Test) that "appears" to be an "outlier" needs to be put into proper perspective—that "one" and "24" or "30" are "one" and "24" or "30" in "x" hundred thousand.

Until a representative sample has been tested, no statistically valid differentiation test should be applied. Moreover, 1) since most pharmaceutical manufacturing processes lack rigorous controls on the critical physical properties of all the components and 2) most do not test batch representative samples, it is rare that the performance that was seen in a previous batch or previous batches can validly be used as a basis for decision-making in the current batch. Therefore, if a firm can prove that the sample tested is batch representative and is willing to test 200 or more samples, then, after the lab has established that all of the results obtained are valid, the lab might be able to justify using a valid "outlier" test when, after such testing, a value still appears to be an "outlier."

My experience has been that, whatever their reasons, few firms are willing to do the inspection required. If anyone reading this knows of a firm that does use such an inspection plan, please let me know of them. Finally, since the FDA does not require firms to test appropriate batch-representative samples at the end of each step that may affect adversely in-process and drug-product uniformity as required by 21 CFR 211.110(a), it is, or should be, obvious it would not be scientifically sound or appropriate to entertain the use of an "outlier" test.

Response 5

Nice science and theory. The Dixon Test allows you to identify outliers with as little as three samples and it works fine.

Response 6

The comment that outlier testing should be described in the SOP is clearly stated in the FDA's OOS guidance.

The method described is used in physics and is a statistical method known as Winsorizing. I don't believe it would be acceptable to FDA w/o experimental, investigatory evidence.

Response 7

It is the use of outlier testing/explanation, to disqualify nonconforming data that was the issue. The 1998 draft FDA OOS Guidance is very clear on this. It allows the consideration and investigation of outliers, clearly suggests outlier be considered but it does not permit the disqualification of nonconforming data on the sole basis of it being an outlier and clearly explains the reason why.

May I suggest you speak to Sanford Bolton who was the statistician consultant at the trial? Professor Bolton is at Arizona State University (or is it the University of Arizona?).

Two years ago I spoke to a former FDAer who participated in the trial and the decision for several hours. I also met the industry person who was there from Barr. I cannot discuss what I learned but it was quite an emotional trial and not everything was scientifically based.

Later this week, when I have more time to write, I would like to describe disqualification on the basis of outlier determination that I believe is scientifically valid. I have one or two examples to propose and would be interested in the responses.

Response 8

The Dixon Criterion is, at best, a weak criterion for you to use to make a rejection decision for all of the following reasons:

1. It only determines the degree that a given sample result differs from the results found for the few other samples tested;
2. In addition, it was developed for use in experiments where the researcher must rely on only a few experimental values—not for the cases in which "large" numbers (>25) of population-representative sample dosage units can be, or are required to be, tested;
3. Moreover, as some authors of statistics texts that discuss "outliers" admit, it is just a set of statistical rules for "those who simply want justification for what they would have done anyway"; and
4. Unless your overall population is small, the Dixon Criterion cannot "determine" if the different "one" is, or is not, a valid member of the population (batch) from which the samples were taken—technically, the population is all the valid sample results associated with the sample units in the population (batch).

Thus, the Dixon Criterion ("Dixon") should only be used by labs engaged in a research activity (See Point 2).

Regarding "QCU" testing and CGMP, by their very nature, a "QCU" lab doing work in support of the CGMP regulations is engaged in a monitoring activity—not a research activity. Such labs are required by 21 CFR 211 to test a set of sample units that is representative of the batch from which they were taken. 21 CFR 211 requires both the in-process samples (21 CFR 211.160(b)(2)) determination of conformance to written specifications and

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OOS and Outliers from page 25

a description of sampling and testing procedures for in-process materials. Such samples shall be representative and properly identified, and drug product samples (21 CFR 211.160(b)(3)) determination of conformance to written descriptions of sampling procedures and appropriate specifications for drug products. Such samples shall be representative and properly identified and tested to be representative of the batch.

Until a lab has tested a representative sample, they have not met the legally binding minimum requirements set forth in 21 CFR 211. That the FDA does NOT enforce these clearly written requirements is their choice. However, this does not change the reality that manufacturers are supposed to test batch-representative (i.e., population-representative) samples and only apply scientifically sound and appropriate statistical tests that establish population membership or non-membership.

The Dixon Criterion is an "any sample" test. Thus, it is not scientifically sound to use "Dixon" to make a POPULATION decision when the population is typically larger than 150,000 units and the requisite minimum sample number that must be tested to comply with CGMP is not less than 42 batch-representative dosage units when the drug-product manufacturing process is well controlled (and NLT 200 batch-representative units when it is not) for drug-product tests such as active content ["Content Uniformity"], active release ["Dissolution"], and active release rate ["Drug Release"]).

As discussed previously, the compositing & homogenization that is allowed and should be done for tests such as "assay," "water," "impurity," and "other" drug-product tests precludes any valid test result from being an "outlier."

Those finding an "OOS" result for such tests should be focused on: finding the "root cause" of the test failure and reducing the risk of a recurrence. ■

—compiled by Russell E. Madsen

Interest Group Updates from page 22

- Assay Validation;
- Rework of Product;
- Failure Investigations/Change Control;
- Cleaning Validation;
- Inspection Trends; and
- Process Validation.

The interest group expressed the need to continue this interest group separate from any other interest group. The meeting included active participation by the members present on the items shown on the agenda above. In addition, several of those present shared their company experiences on several of these critical issues. One area of discussion was on the use of 0.45-micron vs. a 0.22-micron filter for biological processing steps, prior to filling, as a means for bioburden control vs. sterility. The group felt that we should have a vaccine interest group meeting at the spring PDA meeting on Biotechnology to further discuss several of these items.

Visual Inspection Interest Group

John G. Shabushnig, Pharmacia Corporation

The Interest Group met twice in 2002, with the last meeting being held during the PDA Annual Meeting in New Orleans last December. A summary of FDA 483 observations associated with inspection processes was presented. This summary can be found in the Interest Group Web page on the PDA Web site. Four themes were identified from these observations and discussed. These included the requirements to establish a maximum allowable rejection rate, to control reinspection (including when such reinspection is appropriate, reinspection conditions, and number of reinspections permitted), to use a statistically valid sampling plan for AQL inspection after 100% inspection, and to train and document training of inspectors. Jules Knapp provided an update on progress to develop a scientifically meaningful and practical definition of the compendial requirements for injectable products to be "essentially free" of particulate matter.

A Task Group within the Interest Group has been developing a draft position paper on this topic and expects to post this draft for member comment in the first quarter of 2003. A brief summary of the PDA Special Forum on Visual Inspection held September 16, 2002 in Frankfurt, Germany was also provided. The program for this meeting contained presentations on both manual and automated inspection methods.

Finally, another Task Group is repeating the survey of inspection practices originally conducted in 1996. The results of that survey are available on the IG Web page. If you would be willing to participate in this survey, please contact Tom Pamukcoglu (thomas.pamukcaglu@abbott.com) or John Shabushnig (john.g.shabushnig@pharmacia.com). A summary of survey results will be presented at an upcoming meeting in 2003 and posted to the IG Web page. 2003 IG meetings are currently planned to be held during the PDA/FDA Joint Regulatory Conference and the PDA Annual Meeting. ■

—compiled by Russell E. Madsen

Company, Colleague & Product Announcements

The **United States Pharmacopeia (USP)** announced that **Souly Phanouvong** has joined USP as technical advisor for drug quality control in the organization's Global Assistance Initiatives department. In his new position, Phanouvong will provide technical leadership for drug quality assurance activities. Phanouvong comes to USP from the World Health Organization (WHO), where he served as technical officer for access to anti-TB drugs and quality assurance. Before joining WHO, Phanouvong served as an electronic publishing officer at the Australian Therapeutic Guidelines Ltd.; a lecturer in the School of Public Health at La Trobe University, Melbourne, Australia; deputy-director, National Food and Drug Quality Control Centre, Ministry of Public Health in Laos; co-project manager and coordinator, Lao-Swedish International Development Authority Health and Pharmaceutical Cooperation Project, Ministry of Public Health, Laos; and acting division chief, Drug Quality Control, Inspection and Drug Information, Ministry of Public Health, Laos. USP is a non-government organization that promotes the public health by establishing state-of-the-art standards to ensure the quality of medicines and other health care technologies. These standards are developed by a unique process of public involvement and are recognized worldwide. For more information, visit www.usp.org/e-newsroom.

KMI, a division of PAREXEL International, LLC, has announced the further expansion of its European Operations Group to better serve clients in Europe and worldwide. Keith Wickert has been appointed Compliance Consultant having previously worked for the UK Blood Plasma Fractionator, the Bio Products Laboratory, and for Pall Corporation. He is based at the KMI office in Uxbridge, UK (near London). To create the European Operations Group, KMI has combined their existing compliance consultants, validation staff, and information technology consultants into one group in order to better respond to client needs. KMI now has experts based across Europe with offices in UK, France, Italy, and Switzerland. For further information, contact KMI at Europe@kminc.com or visit www.kminc.com.

Send announcements on personnel changes and new products . . .

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

David Lansky has opened **Lansky Consulting, LLC**, a statistical consulting and training service. The primary focus will be on supporting the biotechnology industry in the analysis, development, and validation of biological assays. For further information, contact David Lansky at (802) 865-0155 or david@lanskyconsulting.com.

CloriDiSys Solutions, Inc. recently introduced Steridox Chlorine Dioxide Sterilizers. Designed for use in any pharmaceutical, manufacturing, laboratory, research or surgical setting, the sterilizers provide a rapid and highly effective method to sterilize medical devices, sterile products, instruments, and components at ambient temperatures and feature a sophisticated sterilent concentration monitoring system to assure a tightly controlled sterilization process facilitating parametric release. All instrumentation, including the photometer for concentration monitoring, is easily calibrated to traceable standards. The process is easy to validate due to the repeatable cycle, tight process control, and highly accurate sterilent monitoring system. For more information, call ClorDiSys Solutions, Inc. at (908) 236-4100 or visit www.clordisys.com.

BD Diagnostic Systems, announced that it has recently launched a program built around its partnership with Compliance Software Solutions Corporation (CSSC), the developer of a unique software that automates data management for environmental monitoring. The partnership enables BD customers to enjoy the unprecedented advantages of CSSC's Environmental Monitoring Software System, known simply as EMSS. EMSS can collect, document and trend environmental monitoring data for audits and inspections, and can likewise provide critical information on the quality of the aseptic processing environment during manufacturing. This is especially beneficial for industries charged with meeting ever more stringent and changing regulatory requirements. EMSS can greatly im-

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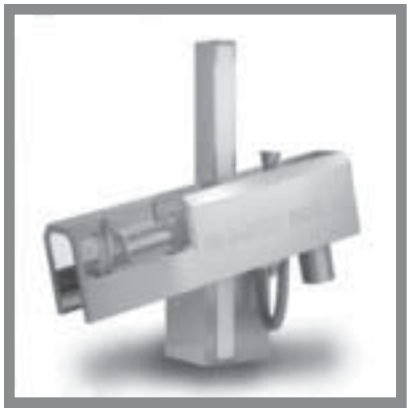
pact businesses where environmental monitoring data is often only tracked manually via logbooks and spreadsheets—making data difficult to manage and use effectively. EMSS offers BD customers a means to achieve compliance with industry regulations such as those outlined by the FDA, CFR, ISO and CGMP. EMSS will be distributed exclusively by BD. For more information about EMSS, please call 1(800)638-8663 or visit www.bd.com.

L. B. Bohle has introduced a unique, new granulator that allows for continuous throughput of materials. The BCG Continuous Granulator, combines granulating, drying and milling in a single operation, and allows for the production of formulations with active concentrations as high as 96 percent. The higher active content allows for a smaller, easier-to-swallow tablet using a significantly lower volume of excipient. A unique kneading action of the system allows the introduction of water that enables the granulation of even hydrophobic actives. The system also enables the introduction of specific amounts of nitrogen gas into the granulation. This allows the user to determine the porosity of the granules, which greatly expands formulation capabilities. Constructed to meet 21 CFR Part 11 requirements, the system features all stainless steel construction with full computer process and recipe documentation. For additional information, contact Reinhard Sievert at (215) 785-1121 or reinhardsievert@lbbohle.com. ■

—compiled by Joseph G. Bury



New Release

Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2002, Sixth Edition (The "Orange Guide")

This book, commonly known as the "Orange Guide," brings together the main pharmaceutical Regulations, Directives and Guidance, including GMP and GDP, which manufacturers and wholesalers are expected to follow when making and distributing medicinal products in the European Union and European Economic Area.

Key features:

This 2002 edition has been substantially updated to include the following:

- New annexes 15, 16, 17 and 18 to the EU guidelines in Good Manufacturing Practice including the ICH GMP for active pharmaceutical ingredients.
- Revised annexes in the Guide to GMP on the manufacture of sterile products (annex 1), medicinal gases (annex 6) and on products derived from human blood or plasma (annex 14)
- The updated version of the UK's Code of Practice for Qualified Persons
- A new section on the Inspection and Enforcement Division of the Medicines Control Agency including notes on mutual recognition agreements for manufacture, supply of unlicensed products and the services of the Division.

Published by the Medicines Control Agency (MCA), ISBN 011-322559-8, 343 pages
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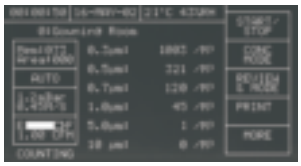

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April 10–11, 2003

2003 Taormina International Conference and Tabletop Exhibits for Senior Executives in the Pharmaceutical Industry

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The design of the conference, including formal presentations, informal discussions and social events, is specifically designed to enhance interaction among attendees and speakers.

Highlights include:

- Expert executives from leading pharmaceutical firms, presenting industry experiences, perspectives and solutions;
- Outside technical experts;
- Legal and regulatory perspectives on consent decrees and other consequences, and how to avoid them;
- Discussion on the development, implementation and execution of a new quality management system;
- Identification of key elements of building an effective quality system; and
- Discussion on supply chain management and strategic contracting.

Space at the conference is very limited. Please review the official brochure and online registration now available at www.pda.org. ■

—Leslie Zeck

For Information on Tabletop Exhibits, contact Nahid Kiani at **kiani@pda.org** or (301) 986-0293 ext. 128.

2003 International Calendar 2003

MARCH

March 31, 2003
PDA Presents—
Basel Pharmaceutical Forums
UBS Ausbildungs-und, Konferenzzentrum
Basel, SWITZERLAND

APRIL

April 10–11, 2003
2003 Taormina International Conference and Tabletop Exhibits for Senior Executives in the Pharmaceutical Industry
Managing for Quality in a Cost-Focused Environment
Conference: April 10–11
Tabletop Exhibits: April 10
Grand Hotel Timeo & Villa Flora, Taormina, Sicily ITALY

MAY

May 5–9, 2003
2003 PDA International Congress, Courses and Tabletop Exhibits
Congress: May 7–9
Courses: May 5–7
Tabletop Exhibits: May 7–8
The Ritz Carlton Millenia, SINGAPORE
PDA-TRI Lecture Courses:
May 5–6
A Practical Approach to Aseptic Processing and Contamination Control
Basic Concepts in Cleaning and Cleaning Validation
Active Pharmaceutical Ingredients: Manufacture & Validation
May 5–7
Requirements and Preparation of Pharmaceutical Grade Waters

May 12–14, 2003
ICH Q7A Training Workshop—*Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*
Hotel TBA, Tokyo, JAPAN

JUNE

June 23–25, 2003
PDA-TRI Toronto Course Series
Westin Harbour Castle, Toronto, CANADA
PDA-TRI Lecture Courses:
June 23
Failures/Deviations and Change Control
Achieving CGMP Compliance during Development of a Biotechnology Product
June 23–24
Basic Concepts in Cleaning and Cleaning Validation
Active Pharmaceutical Ingredients: Manufacture & Validation
CGMP & Compliance
June 23–25
Tablet Formulation
June 24
Knowledge & Skills of the Successful QA/QC Manager in the Pharmaceutical Industry
Z1.4 Attribute Inspection Sampling in a CGMP Environment
June 25
Assay Validation
Designing, Monitoring and Validation of Pharmaceutical Manufacturing Ventilation Systems
Radiation Dosimetry & Calibration

June 23–27, 2003
PDA Italy Chapter Presents
Sterile Manufacturing Practices in the Third Millennium: A Regulatory and Industry Perspective
Melia Milano Hotel
Milan, ITALY
Conference: June 23–25
Course: June 25–27
PDA-TRI Lecture Course:
June 25–27
Design, Engineering and Validation of Isolators for Pharmaceutical Applications

June 30, 2003
PDA Presents—
Basel Pharmaceutical Forums
UBS Ausbildungs-und Konferenzzentrum
Basel, SWITZERLAND

SEPTEMBER

September 29, 2003
PDA Presents—
Basel Pharmaceutical Forums
UBS Ausbildungs-und Konferenzzentrum
Basel, SWITZERLAND

DECEMBER

December 15, 2003
PDA Presents—
Basel Pharmaceutical Forums
UBS Ausbildungs-und Konferenzzentrum
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Stay tuned to **www.pda.org** for the most up-to-date calendar information

PDA
An International Association For Pharmaceutical Science And Technology

2003 PDA International Congress, Courses and Tabletop Exhibits

Congress: May 7–9
Courses: May 5–7
Tabletop Exhibits: May 7–8

The Ritz Carlton Millenia Singapore

Join PDA for the first conference in Singapore featuring presentations by industry and health authority experts on critical issues in pharmaceutical industry manufacturing. A variety of educational courses will provide additional opportunities for unprecedented worldwide education, training, and applied research in pharmaceutical sciences and associated technologies. An interactive exhibition will feature the latest advances in technology and services in the industry.

Singapore

Courses at the PDA International Congress in Singapore

May 5–6

- **A Practical Approach to Aseptic Processing and Contamination Control**
- **Basic Concepts in Cleaning and Cleaning Validation**
- **Active Pharmaceutical Ingredients: Manufacture & Validation**

May 5–7

- **Requirements and Preparation of Pharmaceutical Grade Waters**

Who Should Attend?

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.

Congress Overview: Regulatory and industry experts will discuss:

- FDA Systems Based Inspections;
- Regulatory Procedure in the EU;
- Biotechnology Issues;
- Outsourcing;
- Aseptic Processing Issues;
- ICH Issues;
- Pharmacopeial Issues; and
- Process Analytical Technologies.

Registration and hotel information will be available soon on the PDA Web site, www.pda.org. ■

—Leslie Zeck

Opportunities for tabletop exhibits are being offered to a limited number of companies. For details please contact Nahid Kiani at (301) 986-0293 ext. 128 or Kiani@pda.org.

Conference on Current Issues in Pharmaceutical Manufacturing

San Juan, Puerto Rico—May 19–20, 2003
Vancouver, British Columbia—June 9–10, 2003

Tropical Puerto Rico and majestic Vancouver are the sites for two important conferences on pharmaceutical manufacturing. Each conference will provide a forum to discuss current issues and to review case studies. These conferences are intended to bring industry and agency representatives together to ignite dialogue in the following programming areas:

- Aseptic Processing;
- Systems-based Inspections;
- Part 11;
- Training Issues; and
- Current Compliance Issues.

In addition to the above programming, Puerto Rico will offer sessions on environmental monitoring, disinfection, rapid methods, and cleaning validation.

A newly renovated oceanfront resort on Isla Verde Beach in one of San Juan's most sophisticated beachfront residential areas, the Inter-Continental San Juan offers a blend of ocean and city-view rooms, an oceanfront spa & fitness center, a variety of quality restaurants and lounges, concierge and tour desk services, executive business center and conference services, outdoor lagoon pool and whirlpool amidst waterfalls, and a tropical garden. PDA Rates ($149 USD single/double) are available three days pre- and post-conference. Hotel room cut-off date: April 25, 2003. For reservations call (787) 791-6100 ext. 53, or (800) 443-2009.

In addition to the captioned programming, the Vancouver conference will have a biopharmaceutical component with sessions on process validation for biologics; inspection of biotech facilities, preparing for FDA inspection, and Canadian regulatory issues.

In one of the most remarkable cities you will ever visit, Vancouver sits at the edge of the Pacific Ocean, nestled snuggly in and around the slopes of the snow-capped Coast Mountains. The Hyatt Regency Vancouver is centrally located in the heart of the downtown business and entertainment core with a location overlooking a mountain-rimmed harbor, adjacent to exclusive shopping in Royal Centre, two blocks from Robson Street and Pacific Centre. The hotel is also close to sports complexes and theatres, 1,000-acre Stanley Park, and Granville Island and Grouse Mountain for skiing and recreation. PDA rates ($215 CDN single/double) are available three days pre- and post-conference. Hotel room cut-off date: May 19, 2003. For reservations call (604) 683-1234, or (800) 633-7313.

FDA representatives have been invited to present at both conferences. Take advantage of unique networking opportunities and participate in question-and-answer sessions at the conclusion of each session. Details on these two important new conferences will be posted in the near future on www.pda.org. ■

—Lisa Wade

September 8–12, 2003

PDA/FDA Joint Regulatory Conference, Courses and Tabletop Exhibits

Navigating CURRENT GMPs: Catch the Compliance Wave

Conference: September 8–10

Courses: September 11–12

Tabletop Exhibits: September 8–9

Omni Shoreham Hotel • Washington, D.C.

Striving to keep your head above water with all the latest global regulatory and scientific information that crosses your desk? Don't get caught-up in the undertow. Instead, catch the wave at the PDA/FDA Joint Regulatory Conference; the place where industry leaders go to get updated from the trend setters. PDA/FDA is your one-stop shop for the latest detailed information on current and evolving industry practices.

Learning Objectives:

- Discuss emerging and dynamic perspectives and interpretations of CGMPs;
- Identify today's global industry trends with case studies and real life examples;
- Describe how to anticipate continuous looming new trends; and
- Identify new technologies and their applications.

Who Should Attend?

Individuals involved in pharmaceutical, biopharmaceutical product development, regulatory approval, production, and quality assurance including those associated with drug product manufacture, service providers, contract services and USA and international regulatory authorities.

The FDA Keynote address on information for the industry will be presented by Lester M. Crawford, DVM, Ph.D., Deputy Commissioner of FDA. Even if you attended Crawford's stellar presentation last year, you won't want to miss-out on the opportunity to hear him again as he describes the latest industry updates, from the point-of-view of the FDA.

Session discussion topics will include:

- Navigating Legal Waters & Compliance Currents;
- Riding the Changing Compliance Tides;
- Hot Regulatory Issues: Drug Device Combinations;
- Biopharmaceutical Process Validation Issues;
- Laboratory Issues/Case Studies;
- Inspection Trends in the USA and Europe;
- Role of the Quality Unit/Building Quality Culture, Its Evolution and Where is it Going?
- HACCP, ISO Implementation;
- Dispute Resolution;
- Outsourcing and the Quality Agreement;
- Global Supply Chain: Strategic Management;
- Corrective Action/Preventive Action;
- Aseptic Processing Issues;
- Using Process Analytical Technologies; and
- Engineering and Facilities Issues.

Mark your calendar now! Preliminary information will be available soon at www.pda.org. ■

—Leslie Zeck

PDA-TRI Lecture Courses at PDA/FDA

September 11

Biopharmaceutical QA/QC for Senior Management

A Risk Based Approach to CGMPs

September 11–12

Cleanroom Management

CGMP & Compliance

Preparing for an FDA Pre-Approval Inspection

September 12

Failures/Deviations and Change Control

For more information on Tabletop Exhibits, contact Nahid Kiani at kiani@pda.org or call her at (301) 986-0293 ext. 128.

2003 PDA Spring Conference Exhibitors Listing

AAI International, Inc.	604
Abbott Laboratories OEM Group	304
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Lloyd's Register Serentec, Inc.	106
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Patheon Inc.	314
PML Microbiologicals, Inc.	505
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Raven Biological Laboratories, Inc.	515
Saint-Gobain Desjonqueres	210
Sartorius Corporation	504
SCA Thermosafe	608
Schering – Plough Corp	512
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Siemens Energy & Automation, Inc.	105
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2003 PDA Spring Conference and Tabletop Exhibition

March 17–19, 2003

San Diego, CA

www.pda.org

Tel: (301) 986-0293
Fax: (301) 986-0296
E-mail: info@pda.org

List current as of 02/19/03

2003 PDA Annual Meeting, Courses and Exhibition

November 10–14, 2003 • Atlanta Hilton Hotel

Save the Date! Plan to be in "Hotlanta" in November!

PDA is committed to continuing the tradition of providing the best tools for your professional development and facilitating networking opportunities at the 2003 Annual Meeting. Slated to be held in Atlanta this fall, the Annual Meeting will offer participants opportunities to participate in a variety of multi-tracked scientific and technical sessions, educational courses and an interactive exhibition.

Highlights of the conference will include sessions focusing on key compliance issues. Whatever your role in your company, you won't want to miss presentations on such key topics as:

- Compliance Leadership;
- Creating a Corporate Compliance Policy;
- Corporate Compliance Responsibility and Training;
- Quality Compliance; and
- GMP Enhancements.

If you are interested in making a presentation on new research, please send your biography and a brief abstract of the presentation to zeck@pda.org by April 1.

Interest Group and Task Force meetings will provide opportunities to discuss key issues in pharmaceutical manufacturing in an open forum atmosphere on such topics as:

- Lyophilization;
- Vaccines;
- Biotechnology;
- Filtration;
- Sterilization/Aseptic Processing;
- Microbiology/Environmental Monitoring;
- Visual Inspection of Parenterals;
- Contract Manufacturing;
- Solid Dosage Forms;
- Stability;
- Inspection Trends/Regulatory Affairs;
- Pharmaceutical Water;
- Training; and
- Cold Chain Management.

See you in November in Atlanta! ■

—Leslie Zeck

PDA-TRI Lecture Courses at the 2003 PDA Annual Meeting

November 13

- Designing, Monitoring & Validation of Pharmaceutical Manufacturing Ventilation Systems
- Auditing Techniques for CGMP Compliance

November 13–14

- Basic Concepts in Cleaning and Cleaning Validation
- Computer-Related Systems Validation
- A Practical Approach to Aseptic Processing and Contamination Control

November 14

- Managing in a GMP Environment
- Change Control & Documentation

2003 PDA Annual Meeting Atlanta, Georgia

May 4–7, 2003

PDA Good Electronic Records Management Conference (GERM) 2003

Achieving FDA Part 11 Compliance with GERM

Conference:
May 5–7
Courses/Tutorials:
May 4
Westin Hotel
Chicago, IL

In 2001, PDA produced its groundbreaking conference on Good Electronic Records Management (GERM). Much more than the typical pharmaceutical "Part 11" conference, GERM 2001 showcased leaders on the forefront of digital records issues from technology, legal, and regulatory backgrounds. Conference delegates were presented with a comprehensive view of the future of digital record issues within, and well beyond, FDA-regulated industries.

In May, GERM 2003 will build on the strong foundation laid earlier, with an even greater emphasis on the critical needs of those responsible for managing all aspects of electronic record and signature environments. Several sessions will address topics from the recently-published GERM guide—Part 1 of the PDA-ISPE series on Good Practice for Electronic Records and Electronic Signatures. Additional sessions will highlight selected topics from Parts 2 and 3 in the PDA-ISPE trilogy of Good Practice guides. The focus will be on concepts and principles to consider when building, maintaining, managing, and transitioning electronic record environments. The Conference will provide a forum for information exchange based on practical experiences, building on lessons learned from real-life electronic records management.

Major Topics Covered

- Risk Management (record policies, practices, and QA of record processes)
- Information Technology (implementing, validating, and maintaining operating computing environments, storage media management)
- Project Management (legacy remediation, managing outsourced EDC systems, new computing solutions, revising record strategies and management buy-in)
- Records Management (creating records, record content management, signing records, coexistence of paper and electronic worlds)
- Digital Preservation (record retention, archival and retrieval, processability)
- Education (training and education in e-records)
- Legal (critical considerations beyond the technical and regulatory boundaries)

Faculty for this multi-track program of lectures, panels, forums and tutorials, will speak on topics that represent a broader view of the legal, regulatory, and strategic issues facing the electronic record and electronic signature world today. These leaders are on the cutting-edge of this digital information age, actively involved in establishing the groundwork for the future of electronic records and electronic signatures. Featured faculty are from Food and Drug Administration (FDA), FDA-regulated establishments, Judiciary, consultancies for records management, and technology research organizations.

Some of the Guest Speakers

- Charles M. Dollar, Ph.D., Senior Consultant with Cohasset Associates, Inc. Dollar has extensive experience in dealing with the impact of digital technology issues on archives and records management. From 1974 to 1994 he was on the staff of the National Archives and Records Administration where he specialized in electronic storage media issues.
- Raymond Lorie, Research Staff Member at the IBM Almaden Research Center and ACM Fellow. Lorie is conducting groundbreaking research in the development of the Universal Virtual Computer (UVC), a Digital Preservation Solution for long-term storage and retrieval of electronic records.
- Gordon B. Richman, Chem. Eng., J.D., Vice President, Strategic Compliance Consulting and General Counsel of EduQuest. Previously Richman was Director of Worldwide Quality Strategy in GlaxoSmithKline's Global Manufacturing and Supply operations. Prior to GSK, he spent several years in FDA regulatory practice with law firms in Washington, D.C.
- Jeffrey Rothenberg, Ph.D., Senior Computer Scientist in the Social Policy Department of the RAND Corporation. Rothenberg is the author of the landmark Scientific American article, "Ensuring the Longevity of Digital Documents," in which he called for immediate action to prevent future loss of today's electronic documents.
- Gary W. Secrest, M.S. (National Security Strategy), Director of Worldwide Information Security at Johnson & Johnson. Prior to joining J&J, Secrest held senior executive positions with the National Security Agency, including head of the Network Security Group and Director of the DoD Public Key Infrastructure Program.

Pre-conference Tutorials Offered

Electronic Records Management on Trial – Ken Winters, Esq., Federal Judicial Center, United States Courts — Responding to court ordered electronic records discovery requests is an increasingly important component of electronic records management. In this multifaceted, role playing tutorial, a hypothetical electronic records management program will be developed. The participants will then defend (or challenge) that program in a mock court case before a real judge. The key concepts of records management law, discovery procedure, and courtroom evidence addressed in this tutorial are applicable in all government and business electronic records management planning. This will be truly a unique and in-

continues on page 38

GERM from page 37

cisive event that will help you get prepared.

Managing Electronic Records: A Practical Approach – Laurie Fisher, Cohasset Associates, Inc. — This popular, information-packed, tutorial will provide an overview of the challenges facing all organizations in the management of their electronic records. It presents a tested practical model for incorporating e-records into a records management program – an approach based on solid project management methodologies (risk management, quality management, and resource management) as well as well-established techniques. Throughout this interactive tutorial, common pitfalls and short comings will be highlighted – to help you avoid making similar mistakes. Participants also will have the opportunity to "test" the concepts and methodologies presented in the tutorial — via worksheets and key concept tables.

What is Part 11? – John McKenney, SEC Associates, Inc. — This comprehensive tutorial is designed to provide participants with an in-depth understanding of the 21 CFR Part 11 Electronic Records; Electronic Signatures Rule. It will also address the implications on the predicate rule record keeping requirements for FDA-regulated activities. Participants will evaluate each section of the rule as it relates to their specific job roles. This widely acclaimed tutorial is intended for individuals who need a thorough understanding of the basic concepts and principles embodied in Part 11. Its easy-to-understand presentation format is ideal for those who are new to the subject.

Digital Preservation; Examination of Migration and Emulation Options – Dick Fisher and Charles Dollar, Cohasset Associates, Inc. — This tutorial will be presented by two of the nation's foremost experts on digital preservation. They will begin with their insights on the problem of digital preservation and its impending consequences when information is lost or inaccessible. They then will analyze the available options and detail their advantages as well as disadvantages. The focus of this tutorial will be a comprehensive examination of the two primary digital preservation options: migration and emulation. Participants will take away a clear understanding of the issues and options of an increasingly important problem. Avoid major future problems by preparing now! ■

—Leslie Zeck

Chapter News

Sterile Manufacturing Practices in the Third Millennium

A Regulatory and Industry Perspective

by Volker Eck, Ph.D., Pharmacia

23–25 June 2003

Milan, ITALY

Manufacturing sterile products has followed an organic and evolutionary development over a relatively long period of time. Only lately, new concepts have been introduced, that bear the potential to induce a revolutionary change of what was considered well established. Indicators of those are the new Concept Paper on Aseptic Manufacturing, issued by FDA in September 2002, the search for new and more rapid microbiological methods and their insertion into the frame of Process Analytical Techniques, promoted by FDA in late 2002.

The whole puzzle fits, considering the move by FDA to change the approach of evaluating adherence to CGMP from following line by line and word by word—what has been laid out in guidelines—to a conceptual hazard or risk assessment and defining rigid controls on a scientific basis from there. After all, the intent is to achieve a built in quality not only a tested one.

This movement is very much mirrored by similar initiatives of individual health authorities in Europe and gives rise to the sensation of something substantial that is going to change.

To see more clearly the impact on these activities, which when viewed separately may not be well-understood; the PDA Italy Chapter is organizing a conference on Sterile Manufacturing Practices on the rise of the Third Millennium. The conference aims to give a comprehensive overview of what it takes to come to a sterile product, following the process from starting materials to the final packaged good that goes out. It will give a holistic picture of the interactions, often not seen and taken into account, that may interfere when it comes to risk assessments and failure investigations of any kind. It is by design focused on practical, day-to-day problems and new approaches to resolve them.

The conference, therefore, will be of major advantage to professionals in development and production areas, who deal with pharmaceutical and analytical issues. It also will address many questions and problems for those dealing with manufacturing sterile products from a Quality Assurance perspective. And for those dealing with submissions for registration, addressing the concepts of risk and hazard assessment and learning to delineate the consequences in designing premises, processes and controls and their respective regulatory documentation will be beneficial.

There will be an opportunity to discuss "What Comes Next?" with representatives from health authorities and how to accommodate these emerging requirements.

Don't hesitate! Register now for this important venue. Details will soon be available on the PDA Web site. ■

Aseptic Processing Training Program at PDA-TRI...

Option 1, Week 1, January 2003

Training in making aseptic connections to the filling line.

Real-time training in set-up and performance of media fill simulations of aseptic filling processes.

Hands-on practice in proper gowning techniques.

Upcoming PDA-TRI Education Courses

Courses listed in alphabetical order

Aseptic Processing 2003 Training Program—Lab **Option 2**: April 7–11, 2003 and May 5–9, 2003; **SOLD OUT** **Option 3**: August 25–29, 2003 and September 22–26, 2003; **Option 4**: October 27–31, 2003 and November 17–21, 2003; $7,500 members/$7,695 nonmembers; *Faculty:* John Lindsay and David Matsuhiro

Cleaning Validation—Lab May 19–21, 2003; October 13–15, 2003; $3,000 members/$3,195 nonmembers; *Faculty:* Jon Voss and Bob O'Brien

Ensuring Measurement Integrity in the Validation of Thermal Processes—Lab April 28–29, 2003; November 6–7, 2003; $2,000 members/$2,195 nonmembers; *Faculty:* Göran Bringert

Environmental Mycology Identification Workshop March 13–14, 2003; May 15–16, 2003; October 2–3, 2003; December 4–5, 2003; $2,000 members/$2,195 nonmembers; *Faculty:* John Brecker ■

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

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

For registration information, call PDA headquarters in Bethesda, MD at **(301) 986-0293**.

PDA-TRI Location/Lodging Information

Unless otherwise noted, PDA Institute courses are held at: PDA Training and Research Institute, 1450 South Rolling Road, Baltimore, MD 21227, Tel: (410) 455-5800; Fax: (410) 455-5802.

PDA has not secured any specific room blocks for participants attending courses at the Training and Research Institute. There are several hotels in the Inner Harbor (downtown Baltimore) and BWI airport areas. These include, but are not limited to:

Baltimore Hilton & Towers Inner Harbor
(410) 539-8400
(410) 625-1060 - fax

Courtyard by Marriott–BWI
(410) 859-8855
(410) 859-5068 – fax

Baltimore Marriott Inner Harbor
(410) 962-0202
(410) 625-7892 - fax

Embassy Suites BWI
(410) 850-0747
(410) 850-0816 – fax

Homewood Suites BWI*
(410) 684-6100
(410) 684-6810 – fax

Holiday Inn Inner Harbor**
(*Special Rates for our courses Attendees*)
(410) 685-3500
(410) 727-6169 – fax

Hyatt Regency Baltimore Inner Harbor
(410) 528-1234
(410) 605-2870 – fax

Sheraton International Hotel BWI
(410) 859-3300
(410) 859-0565 - fax

Courtyard Baltimore Downtown/Inner Harbor
(443) 923-4000
(443) 923-9970 – fax

Holiday Inn—BWI***
(410) 859-8400
(410) 684-6778 – fax

* no on-site restaurant

** **A discounted rate** is available for **Holiday Inn Inner Harbor of $99**, to receive this rate call the number above and mention the PDA-TRI Corporate Rate (ID# 100196574) when making your reservations, **rooms based on availability**.

*** **A discounted room rate** is also available from the **Holiday Inn—BWI**. You must call the number above and mention the PDA Corporate Rate (3-PDA) when making your reservations.

For additional hotel information, please visit ww.baltconvstr.com, the Baltimore Convention and Visitors Bureau's Web site.

Transportation to PDA-TRI: All listed hotels are no more than a 15–20 minute taxi ride to the Training and Research Institute. All hotels can assist you with taxi arrangements. Registrants may prefer to rent a car for easier access to and from the Institute.

PDA-TRI Thanks the Following...

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

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

Membership Number

Job Title Company

Business Address

City State/Province ZIP/Postal Code

Tel Fax E-mail

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

LTR 03/03

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

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

3. Please check the appropriate box:

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

Account Number_____ Exp. Date _____

Name _____
(exactly as on card)

Signature_____ Date _____

Payments must be made to PDA in US dollars by check drawn on a US bank, or by American Express, MasterCard, or VISA.

Payment must be included to be considered registered.

4. Return completed form with payment made to:

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

Federal Tax I.D. #52-1906152

Deadline*: Enrollment is limited for the benefit of all attendees; this necessitates early registration. Paid registrations must be received one week prior to the event.*
Confirmation*: Written confirmation will be sent to you once payment is received. You must have this written confirmation to be considered enrolled in a PDA event. Please allow one week for receipt of confirmation letter.*
Substitutions*: If a registrant is unable to attend, substitutions are welcome and can be made at any time, even on-site. If you are pre-registering as a substitute attendee, indicate this on the registration form.*
Refunds*: Refund requests must be in writing. If received one month prior to start of an event (course series, conference, etc.), a full refund, minus a $55.00 handling fee, will be made. If received two weeks prior to the event, one-half of the registration fee will be refunded. After that time, no refunds will be made.*
Event Cancellation*: PDA reserves the right to modify the material or instructors without notice or to cancel an event. If the event must be canceled, registrants will be notified as soon as possible and will receive a full refund of fees paid. PDA will not be responsible for discount airfare penalties or other costs incurred due to a cancellation.*

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

PDA Books

Good Practice and Compliance for Electronic Records

published jointly with ISPE

Part 1—Good Electronic Records Management (GERM): Electronic Information Assurance for the Regulated Industry—Guide to Current Good Practice for Electronic Records and Signatures What you need to know about positioning regulated establishments for achieving electronic information assurance—the concepts and principles that need to be considered when building, maintaining, managing and transitioning electronic environments—can be found in Good Electronic Records Management (GERM), Part 1 of the PDA–ISPE series on Good Practice and Compliance for Electronic Records and Electronic Signatures. Focusing on requirements and concepts rather than technical implementation details, this resource document is a valuable tool for the architects of electronic records environments. Whether your mission is to define the requirements, policies and procedures or to construct the physical environment, you will find that Good Electronic Records Management (GERM) is a must for your bookshelf. Key elements of the document include: prerequisites; electronic records; organizational controls; operations and infrastructure; transactions; records retention; personnel qualification and training; hybrid systems and controls; legal; glossary; and further reading.

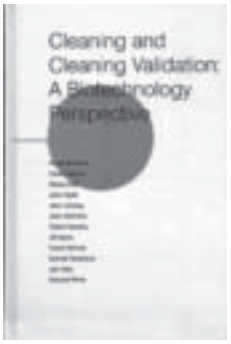
This document was produced through the collaboration of several industry groups (FDA regulated companies, system suppliers, legal experts, and consultants). It represents a compendium of current thinking on good electronic record management from an FDA regulated industry perspective. GERM attempts to present these practices at an abstraction level that is descriptive. The stated practices and concepts are meant to educate the reader when considering options for electronic records management. No endorsement of specific technologies is made, nor are there any specifics that direct a standard for the implementation of concepts. Current thinking on the topics presented means that this compendium is intended to evolve as experience with electronic recordkeeping grows. Application of concepts may require a paradigm shift in some organizations with regard to the treatment of electronic records. Such changes are a conscious business decision and not an intentional prerequisite for implementation of any of the concepts presented. 2002; 104 pages; $95 PDA members/$190 nonmembers **Item No. 19003**

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.

Part 2—Complying with 21 CFR Part 11, Electronic Records and Electronic Signatures; 80 pages; $95 members/$190 nonmembers
Item 19001 (English)

Part 2—Complying with 21 CFR Part 11, Electronic Records and Electronic Signatures; 80 pages, $95 PDA members/$190 nonmembers
Item 19002 (German)

Part 2—Complying with 21 CFR Part 11, Electronic Records and Electronic Signatures; 80 pages, $95 PDA members/$190 nonmembers
(Spanish)—*The Spanish version must be ordered directly from:* Ediciones VR, Av. Belgrano 3786, Of. #2, (1210) Buenos Aires, Argentina, Attn: Ms. Florencia Viscaino; E-mail: subscripciones@edicionesvr.com; Fax: 54 11 4931 4861 ext. 36



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 13002**

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TR 35 A Proposed Training Model for the Microbiological Function in the Pharmaceutical Industry; Many firms today have separate departments with different training requirements. Employees associated with the Microbiological Function do not always receive consistent training. This can lead to varying microbiological control practices within a manufacturing facility. This Technical Report was produced by the PDA Subcommittee on Microbiology Training, formed in January 2001, to develop an industry vision and guidance for instituting a step-wise, competency-based training program for microbiologi-

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cal training of individuals engaged in work activities connected to contamination control and microbiological testing of pharmaceutical articles. 2001; 24 pages; $75 members/$125 nonmembers. **Item No. 01035**

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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; 37 pages; $75 member/$125 nonmember. **Item No. 01013**

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For a complete PDA Calendar beyond September 2003, please visit **www.pda.org**.

2003 Calendar from back cover

May 15–16, 2003
PDA-TRI Laboratory Course: *Environmental Mycology Identification Workshop*
PDA-TRI Baltimore, MD

May 19–20, 2003
PDA Puerto Rico Conference on Current Issues in Pharmaceutical Manufacturing
Inter-Continental Hotel, San Juan, Puerto Rico

May 19–21, 2003
PDA-TRI Laboratory Course: *Cleaning Validation*
PDA-TRI Baltimore, MD

May 22, 2003
UK & Ireland Chapter Meeting
Directive 2001//20/EC and Annex 13
Britannia International, Canary Wharf, London, UK

JUNE

June 6, 2003
PDA Southeast Chapter Golf Outing
Location TBA

June 9–10, 2003
PDA Canada Conference on Current Issues in Pharmaceutical Manufacturing
Hyatt Vancouver, British Columbia, CANADA

June 23–25, 2003
PDA-TRI Toronto Course Series
Westin Harbour Castle, Toronto, CANADA
PDA-TRI Lecture Courses:
June 23
Failures/Deviations and Change Control
Achieving CGMP Compliance during Development of a Biotechnology Product
June 23–24
Basic Concepts in Cleaning and Cleaning Validation
Active Pharmaceutical Ingredients: Manufacture & Validation
CGMP & Compliance
June 23–25
Tablet Formulation
June 24
Z1.4 Attribute Inspection Sampling in a CGMP Environment
June 24–25
Knowledge & Skills of the Successful QA/QC Manager in the Pharmaceutical Industry
June 25
Assay Validation
Designing, Monitoring and Validation of Pharmaceutical Manufacturing Ventilation Systems
Radiation Dosimetry & Calibration

June 23–27, 2003
PDA Italy Chapter Presents—*Sterile Manufacturing Practices in the Third Millennium: A Regulatory and Industry Perspective*
Conference: June 23–25
Course: June 25–27
Melia Milano Hotel, Milan, ITALY
PDA-TRI Lecture Course:
June 25–27
Design, Engineering and Validation of Isolators for Pharmaceutical Applications

June 30, 2003
PDA Presents—*Basel Pharmaceutical Forums*
UBS Ausbildungs-und Konferenzzentrum
Basel, SWITZERLAND

JULY

July 15–16, 2003
PDA-TRI Lecture Course:
PDA Computer Products Supplier Auditor Process Model: Auditor Training
PDA-TRI Baltimore, MD

AUGUST

August 11–15, 2003
PDA-TRI Lecture Course:
CGMP Trainer's Qualification Program
PDA-TRI Baltimore, MD

August 14–15, 2003
PDA-TRI Lecture Course:
Compliance Auditing of Cleanrooms and Controlled Environments
PDA-TRI Baltimore, MD

August 19–21, 2003
PDA-TRI San Francisco Course Series
The Fairmont, San Francisco, CA
PDA-TRI Lecture Courses:
August 19
GMP Fundamentals
August 19–20
Sterile Pharmaceutical Dosage Forms: Basic Principles
Computer-Related Systems Validation
CGMP & Compliance
August 19–21
Introduction to Competency Based Training
August 20
Managing in a GMP Environment
August 21
Good Documentation Practices in the Pharmaceutical Industry
Analytical Problem Solving for CAPA Systems
Annual Product Reviews: How to Comply with FDA & ICH Requirements

August 21–22, 2003
PDA-TRI Laboratory Course:
Fundamentals of D, F, and Z Value Analysis
PDA-TRI Baltimore, MD

August 25–29, 2003—**SOLD OUT!**
PDA-TRI Laboratory Course: *Aseptic Processing Training Program—Week 1*
PDA-TRI Baltimore, MD

SEPTEMBER

September 3, 2003
UK & Ireland Chapter Meeting
Training Strategies
Royal Pharmaceutical Society, UK

September 8–12, 2003
2003 PDA/FDA Joint Regulatory Conference, Courses and Tabletop Exhibits
Conference: September 8–10
Courses: September 11–12
Tabletop Exhibits: September 8–9
Omni Shoreham Hotel, Washington, DC

Information on these conferences and courses will be posted on the PDA Web site as they become available.

Visit often to get the latest information!

www.pda.org

PDA
An International Association For Pharmaceutical Science And Technology

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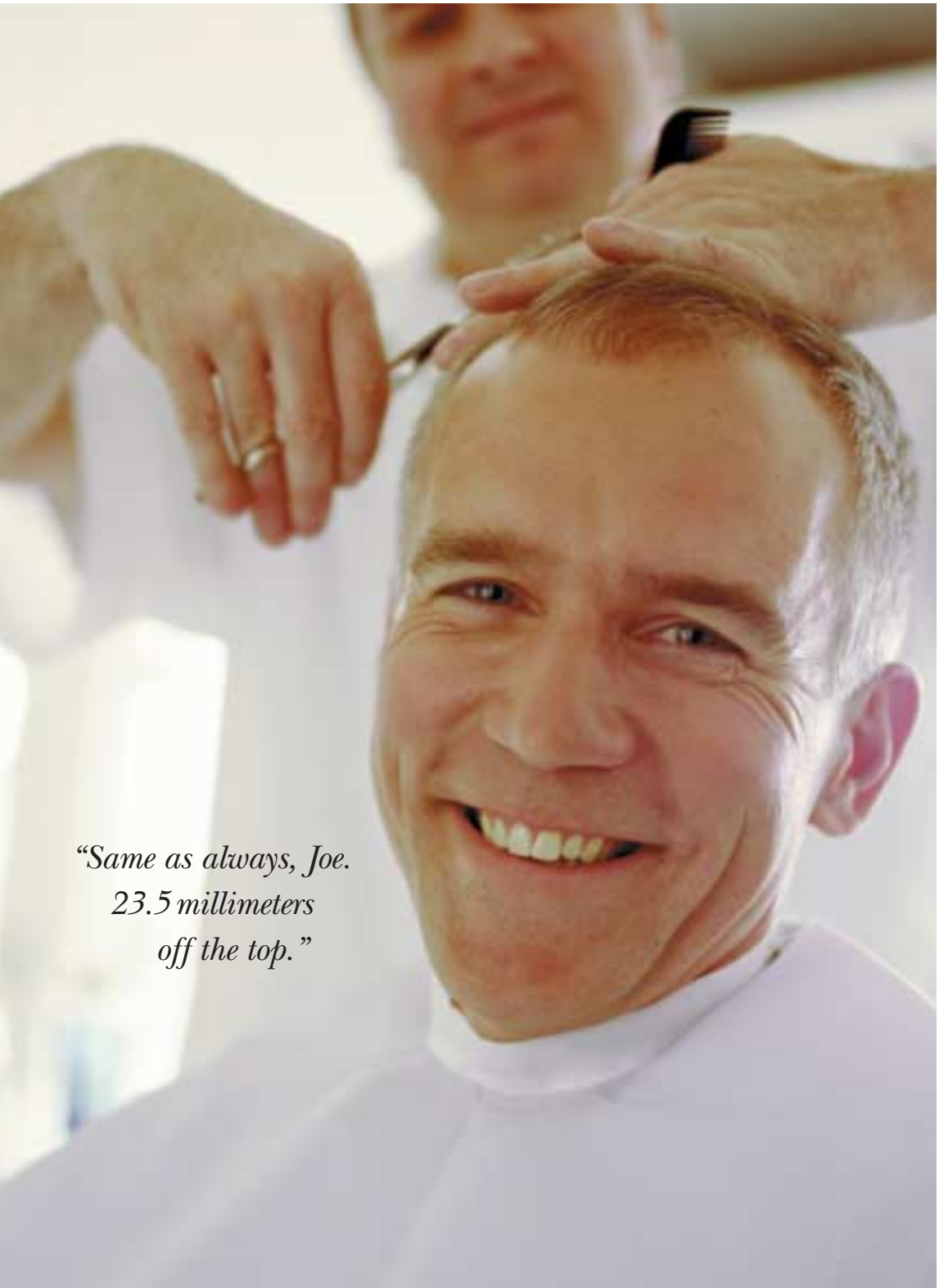

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Calendar of Events

PDA
An International Association For Pharmaceutical Science And Technology

March

March 13–14, 2003
PDA-TRI Laboratory Course: *Environmental Mycology Identification Workshop*
PDA-TRI Baltimore, MD

March 17–21, 2003
2003 PDA Spring Conference, Courses and Tabletop Exhibits—*Bridging the Gap between Science and Compliance: The Impact of Today's Regulatory Environment on Biopharmaceutical Development and Approval*
Conference: March 17–19
Courses: March 20–21
Tabletop Exhibits: March 17–18
Paradise Point Resort, San Diego, CA
PDA-TRI Lecture Courses:
March 20
Achieving CGMP Compliance during Development of a Biotechnology Product
Good Documentation Practices in the Pharmaceutical Industry
March 20–21
A Practical Approach to Aseptic Processing and Contamination Control
Assessing Packaging and Processing Extractables/Leachables
Preparing for an FDA Pre-Approval Inspection
Validation: An Introduction
March 21
Conducting Compliant Deviation Investigations for Pharmaceutical Industry

March 25–26, 2003
PDA-TRI Lecture Course:
PDA Computer Products Supplier Auditor Process Model: Auditor Training
PDA-TRI Baltimore, MD

March 31, 2003
PDA Presents—*Basel Pharmaceutical Forums*
UBS Ausbildungs-und Konferenzzentrum
Basel, SWITZERLAND

April

April 2–4, 2003
PQRI Good Regulation through Good Science Workshop
Gateway Marriott Hotel, Crystal City, VA

April 7–11, 2003—**SOLD OUT!**
PDA-TRI Laboratory Course: *Aseptic Processing Training Program—Week 1*
PDA-TRI Baltimore, MD

April 10–11, 2003
2003 Taormina International Conference and Tabletop Exhibits for Senior Executives in the Pharmaceutical Industry
Managing for Quality in a Cost-Focused Environment
Conference: April 10–11
Tabletop Exhibits: April 10
Grand Hotel Timeo & Villa Flora, Taormina, Sicily ITALY

April 16, 2003
PDA Delaware Valley Chapter Presents
Compliance Concerns with Sterile Products
The Desmond Hotel, Malvern, PA

April 17, 2003
PDA Southeast Chapter Spring Meeting
Sheraton Imperial, Research Triangle Park, NC

April 28–29, 2003
PDA-TRI Laboratory Course: *Ensuring Measurement Integrity in the Validation of Thermal Processes*
PDA-TRI Baltimore, MD

May

May 5–9, 2003
2003 PDA International Congress, Courses and Tabletop Exhibits
Congress: May 7–9
Courses: May 5–7
Tabletop Exhibits: May 7–8
The Ritz Carlton Millenia, Singapore, SINGAPORE
PDA-TRI Lecture Courses:
May 5–6
A Practical Approach to Aseptic Processing and Contamination Control
Basic Concepts in Cleaning and Cleaning Validation
Active Pharmaceutical Ingredients: Manufacture & Validation
May 5–7
Requirements and Preparation of Pharmaceutical Grade Waters

May 5–9, 2003—**SOLD OUT!**
PDA-TRI Laboratory Course: *Aseptic Processing Training Program—Week 2*
PDA-TRI Baltimore, MD

May 12–14, 2003
ICH Q7A Training Workshop—*Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*
Hotel TBA, Tokyo, JAPAN

May 14–16, 2003
PDA-TRI Baltimore Course Series
Wyndham Inner Harbor, Baltimore, MD
PDA-TRI Lecture Courses:
May 14
Environmental Monitoring in Pharmaceutical Manufacturing
Introduction to Writing and Auditing CGMP Documentation
Annual Product Reviews: How to Comply with FDA & ICH Requirements
May 14–15
Fundamentals of Tableting for Pharmaceutical Scientists
May 14–16
GMP Training Manager Workshop
May 15
Improving Sterile Drug Submissions to the FDA
Beyond the GMP/ISO Basics—Practical Strategies for Everyday Compliance
May 15–16
Pharmaceutical Water Systems: A Practical Approach
May 16
Z1.4 Attribute Inspection Sampling in a CGMP Environment
Maximizing SOPS—An Untapped Resource of Training Solutions
Analytical Problem Solving for CAPA Systems

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