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PDA Letter

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April 2006

In This Issue…

Past Leader Spotlight: Michael Korczynski, PhD, PDA President 1990-1991 6

Advancing the Science of Microbiology: Encyclopedia of RMM . . 8

Are You Ready? Have You Made Training A Winning Strategy? 30

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Personnel Training: A Growing Compliance Concern

Walter Morris, PDA

The U.S. FDA is paying more attention to drug manufacturers' training programs under its quality systems approach to inspections.

While personnel training is not the hottest compliance topic in the pharmaceutical GMP literature, it is a frequent U.S. FDA investigator observation, is appearing on a growing percentage of warning letters, and has been involved in some of the highest profile FDA regulatory actions in recent years.

It is no secret that regulatory authorities around the world expect proper investment into staff training. The U.S. drug cGMPs codify training in the very beginning of the regulation, 21 CFR Part 211 Subpart B, "Organization and Personnel," 211.25, "Personnel Qualifications;" the same requirements are in the cGMPs for biological products. Article 7 of the EU GMPs also addresses personnel. Likewise, the World Health Organization's cGMPs require proper personnel training.

Yet, a number of companies are found to be out of compliance with these expectations each year. Problems range from inadequate or no training to the failure to properly document training. An analysis of human drug and veterinary GMP warning letters issued by the FDA in the fiscal years FY 2000-2004 shows that 22% (55 letters out of 253) cite insufficient or no personnel training.[1] In this five-year period, FY 2000 saw the most letters containing training citations, with 17 out of 71 total letters (24%); the fewest in this period occurred in FY 2003, with 6 out of 29 (21%). While there were more warning letters issued overall in the previous four fiscal years ('96-99), the percentage citing violations related to personnel training was much lower, 11% on average (see Figure 1, page 14, for a year by year comparison). When looking at FDA's Turbo EIR data, training ranked very high on the list of common cGMP violations. Office of Regulatory Affairs (ORA) Senior Compliance Officer Philip Campbell informed PDA that observations regarding personnel training were the eighth most frequent according to FDA's Turbo EIR database, which has captured inspection data from all FDA districts since 2003.

continued on page 14

April 2006

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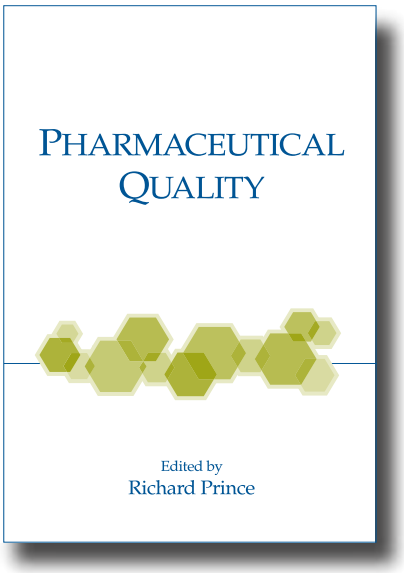

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Announcement and Call for Papers

PDA's 1st Annual Global Conference on Pharmaceutical Microbiology

Bethesda, Maryland ◆ October 30 – November 1, 2006

Call for Papers/Call for Exhibitors

Dear Friends and Colleagues,

The 2006 PDA Pharmaceutical Microbiology Program Committee invites you to submit a scientific abstract for presentation at PDA's 1st Annual Global Conference on Pharmaceutical Microbiology. We are looking for submissions on the following hot topics:

- Microbial control in closed and open systems
- Disposable systems
- Global harmonization
- Water systems
- Disinfectant qualification
- Environmental excursions
- Sterilization processes
- Environmental monitoring in sterile areas
- Environmental monitoring in non-sterile areas
- Filter performance and ratings
- Inspection readiness
- Isolator/barrier technologies
- Emerging and innovative technologies
- Risk analysis in microbiology
- Global pharmacopoeial topics
- Industrial practice for microbial ID – bacteria and fungi

****All submitted abstracts will be reviewed by the Program Planning Committee for inclusion in the meeting or for poster presentation.****

VISIT WWW.PDA.ORG/MICROBIOLOGY2006 TO SUBMIT YOUR ABSTRACT.
ABSTRACTS MUST BE RECEIVED BY MAY 15, 2006 FOR CONSIDERATION.

Please include the following information in your abstract and follow the steps identified in the Precis Abstract Manager.

- Submissions received without full information will not be considered -

- Title
- Presenter's biography
- Additional authors
- Full mailing address
- E-mail address of the presenter and co-presenters
- Two-three paragraph abstract, summarizing your topic and the appropriate forum (case study, discussion, traditional, panel, etc.)
- Target audience (by job title/department)
- Audience take-home benefits
- Key learning objectives

Commercial abstracts featuring promotion of products and services will not be considered. Upon review by the program committee and after May 15, 2006, you will be advised in writing of the status of your abstract. PDAwill provide one complimentary registration per presentation. Additional presenters are required to pay appropriate conference registration fees. All presenters are responsible for their own travel and lodging, with the exception of health authority speakers.

ATTENTION EXHIBITORS

PDA is seeking vendors who provide excellent products/services in support of this conference. Space is limited and is on a first come, first serve basis. To reserve your space, please contact Nahid Kiani at kiani@pda.org or 301-656-5900 x 128.

Table of Contents

Features

Cover **Personnel Training: A Growing Compliance Concern**
19 **Application of Regulatory *Principles* is Key to Analytical Testing in Clinical Trials**

PDA News & Notes

6 Celebrating 60 Years – Past Leader Spotlight: Michael Korczynski, PhD, PDA President 1990-1991
7 PDA Congratulates 2005 Honor Award Winners
7 PDA TR #1 Update; New Membership Manager

Science & Technology

8 Advancing the Science of Microbiology: Encyclopedia of RMM
10 Recent Sci-Tech Discussions: GLP/GMP and ISO 9000 Regulations

Quality & Regulatory Affairs

26 Regulatory Briefs

Membership Resources

28 PDA Chapter Contacts
29 Special Offer from *"The Gold Sheet"* for PDA Members

Programs & Meetings

3 PDA's 1st Annual Global Conference on Pharmaceutical Microbiology: Call for Papers/Call for Exhibitors
30 Are You Ready? Have You Made Training A Winning Strategy?
32 Nano-Pharmaceuticals – The Road Ahead

TRI • Education

34 Vice President's Message: Questions (and Answers) About Training
36 A Call for New Material

Technical Resources

2 April's Top Ten Best Sellers
8 Advancing the Science of Microbiology: Encyclopedia of RMM
13 What's New from the PDA Bookstore: Spring 2006

Cover art: Students prepare samples for incubation at PDA's Training and Research Institute.

Coming Next Month... Quality Systems

PDA
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Connecting People, Science and Regulation℠

For the first time, the PDA Training and Research Institute is partnering with a PDA Chapter to offer valuable job-focused training at a Chapter event.

PDA Training and Research Institute

Vancouver Training Course Series

June 13-14, 2006
Vancouver, British Columbia

In conjunction with the PDA Canada Chapter Annual Meeting, June 12

Courses offered include:

- Achieving cGMP Compliance During Development of a Biotechnology Product
- API – Qualification and Validation of API Facilities and Processes
- Approaches to Performing Self-Inspections as Part of a Total Quality System
- Change Control: A Practical Workshop
- Recombinant DNA Technology and Nucleic Acid-based Therapeutics

To register for the PDA Canada Chapter Annual Meeting, June 12, 2006, visit www.pdacanada.org.

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Celebrating 60 Years – PDA Past Leader Spotlight: Michael Korczynski, PhD, PDA President 1990-1991

Walter Morris, PDA

This year, in celebrating PDA's 60th anniversary, the *PDA Letter* is publishing a series of articles highlighting important contributors to the Association. This month, the "Past Leader Spotlight," continues.

In January of this year, we in PDA were saddened to learn of the sudden passing of **Michael Korczynski**. He was identified as one of our important past leaders and is the subject of this month's Past Leader Spotlight, although we were not able to conduct our normal interview. PDA owes Dr. Korczynski a debt of gratitude for his hard work in helping to build the association into what it is today. His hand was heavily involved in the three areas that have most shaped PDA over the last 15 years—Chapters, International Activities and Education.

As PDA Executive Director and Vice President in 1988, Dr. Korczynski and a group of PDA leaders including **James Agalloco** and **Clarence Kemper**, advocated for the creation of a PDA chapter structure, a novel concept for the highly centralized organization of the time. As Dr. Korczynski wrote in the *PDA Journal of Pharmaceutical Science and Technology's* special 50th anniversary edition (vol. 50, no. 5, p. 273), "the chapter structure was initially designed to bring PDA to the membership." The chapters became an important vehicle for extending to the membership more opportunities for participating in the association. PDA understood that companies were not willing or able to send large cadres of employees to PDA's national events. The chapters, therefore, were designed to allow PDA to provide more of its activities to members at a regional and local level.

A vocal advocate of an increased global role for PDA, Dr. Korczynski foresaw that the association "could no longer afford the luxury of thinking domestically." He and the other members who supported the move to a chapter structure considered the chapters an opportunity for PDA to extend its activities into regions outside the United States. In the nineties, PDA's involvement with international regulatory developments took off, influenced by the founding of chapters in Europe and Japan, the advent of the International Conference on Harmonisation and the establishment of ties with pharmaceutical associations/communities in Europe and Asia. Additionally, Dr. Korczynski was part of a team of PDA experts who participated in the development of International Organization for Standardization technical standards for clean rooms and controlled environments sterilization.

Dr. Korczynski's vision of localized service and international growth has matured into a strong legacy for the association. PDA now boasts 24 chapters worldwide, including six in the Asia-Pacific region and six in Europe. In addition, PDA has established ties with A3P in France, the Parenteral Society in the United Kingdom, and R^3-Nordic in northern Europe. Furthermore, PDA has sponsored a major meeting in Europe every year since 1992, and the number of chapter events there is rising each year. In recent years, PDA established a full service office and European branches of eight Interest Groups. Likewise, PDA and PDA chapter offerings are growing throughout the Asia-Pacific region. PDA has received recognition for the value of its members' contributions internationally.

To recognize Dr. Korczynski's strong leadership in helping launch the Association's international activities, PDA created the Michael S. Korczynski Grant and "Korczynski Paper" in 1994. He was the recipient of PDA's most prestigious award, Honorary Membership (2001) and the Frederick J. Carleton Award (1996) for service on PDA's Board of Directors.

Dr. Korczynski's contributions continued in the late 1990's as one of the founders of PDA's Training and Research Institute. He served as the Institute's first director from 1997-2000, helping to launch the first training laboratory in the industry. It remains a unique facility for training to this day. His dedication to training and personnel development was evident through his many writings, including a chapter in the 2001 PDA/DHI book, *Microbiology in Pharmaceutical Manufacturing*.

Outside of PDA, Dr. Korczynski was an accomplished executive at Abbott Laboratories and an excellent scientist. He was twice the recipient of Abbott's "Researcher of the Year Award" (1989 and 1994).

PDA, along with his family and colleagues, will miss Dr. Korczynski, and we will continue to build upon the strong foundation of localized service, international contribution and education that he helped create.

PDA Congratulates 2005 Honor Award Winners

Honorary Membership:
Kunio Kawamura, PhD and **Russell Madsen**
This is PDA's most prestigious award, conferring lifetime membership benefits to the recipient. The award is given in recognition of very long service, of a very significant nature, to PDA. The award requires unanimous approval of the PDA Board of Directors.

Gordon Personeus Award:
John Geigert, PhD
Presented in memory of the late Gordon Personeus, past PDA President and long-time volunteer, this award is intended to honor a PDA member, other than a Board member, for long-term acts or contributions that are of noteworthy or special importance to PDA.

Frederick J. Carleton Award:
Richard Levy, PhD
Presented as a tribute to lifetime contributor, past President, past Executive Director, and Honorary Member Frederick J. Carleton, this award is designated for a past or present Board member whose services on the Board are determined by his/her peers as worthy of such recognition.

Michael S. Korczynski Grant:
Syracuse University
This past January the PDA Community was saddened to learn of the passing of Michael S. Korczynski, PhD.

This 2005 PDA Korczynski Grant funds were donated "In Memory of Michael S. Korczynski" to Syracuse University in support the university's summer biology intern program.

Distinguished Service Award:
Edmund Fry; Louise Johnson; James Lyda; Michael Miller, PhD; Toshiaki Nishihata, PhD; and, **Martin Van Trieste**
This award is given in recognition of special acts, contributions or service that has contributed to the success and strength of PDA.

Service Appreciation Award:
Howard Drake
Given for special acts, contributions or service that has contributed to the success and strength of PDA's Exhibit Advisory Board.

James P. Agalloco Award:
David Matsuhiro
The James P. Agalloco Award is presented annually to the PDA faculty member who exemplifies outstanding performance in education. The selection is based on student and faculty evaluations and is named for James P. Agalloco in honor of his work in developing the PDA education program.

Frederick D. Simon Award:
Dennis Jenke, PhD; Molly Chacko; Tom Couch; Eric Edgcomb; Liqiong Fang; Mary Jo Garber; and, **Steve Swanson** for:
"Strategy for Assessing the Leachables Impact of a Material Change Made in a Container/Closure System"

The Frederick D. Simon Award is presented annually for the best paper published in the *PDA Journal of Pharmaceutical Science and Technology*. This award is named in honor of the late Frederick D. Simon, a previous PDA Director of Scientific Affairs.

Chapter Volunteer Award:
James Agalloco; Spyros Fetsis; Lisa Hollis McCulley; Joachim Leube, PhD; Thomas Quinn; Byong-Ho Youn, PhD; Maggie Sparhawk; and, **Randall Tedder**
The Chapter Volunteer Award recognizes the contributions of PDA members who participate at the chapter level. The award is a special way to acknowledge the extra effort put out by chapter volunteers.

Distinguished Editor/Author Award:
James P. Agalloco; Lucia M. Clontz; Maik W. Jornitz; Theodore H. Meltzer, PhD; and, **Jeanne Moldenhauer, PhD**
This award is presented annually for the best editor/author of PDA-DHI co-published books as selected by PDA members.

PDA Technical Report No. 1 Revision Update

Revision of PDA's seminal work, Technical Report No. 1: *Heat Sterilization* enters the final stages of work. The revision process has taken several years and 17 drafts. Now, a small group of PDA staff and scientists are working on draft 17 to tailor it to the specific needs of our membership. The final version of the rewrite will be more focused on material included in the original TR#1. The schedule for completion is to present a draft for comment by June 2006. Currently, no draft versions of the document are sanctioned by PDA.

New Manager for Membership and Chapters Joins PDA

Marc Povell joins PDA as Manager, Membership and Chapters. Marc brings five years of association experience to PDA, all with the American Immigration Law Foundation. His most recent position with the Foundation was Public Education Associate, where he performed a number of member-related services. Marc will work closely with PDA Senior Chapter Liaison Henry Kwan, PhD (see the March 2006 *PDA Letter*) and PDA Marketing, Membership and Chapters Director, Matthew Clark.

Advancing the Science of Microbiology: Encyclopedia of RMM

Michael Miller, PhD, Eli Lilly and Company

One of the greatest contributions to the field of microbiology came from the kitchen. In 1881, scientist **Walter Hesse** was searching for a solid medium that could be used to cultivate bacteria. Unlike gelatin (the growth medium of choice at that time) the material had to be stable at high temperatures, allow a variety of microorganisms to be separated easily, and resist digestion or liquefaction by certain microbial species. **Fanny Angelina**, Hesse's wife and laboratory assistant, had the answer: agar, a gelling agent that she used in her jellies and puddings. This simple kitchen ingredient revolutionized the science of microbiology, allowing the separation and culturing of microbes to become a routine procedure. Now, almost 125 years later, microbiology agar remains the most important and widely used microbial growth medium available today. Fanny would be proud... but should we be proud as well?

From Innovation to Stagnation

Although the growth of microbial cells on agar surfaces provides the laboratory with critical information about the amount and the type of organisms that may be present in a sample under evaluation, the time to result is usually longer than what is desired. Days and even weeks may elapse before microbial colonies are visually detected, and in most cases, confluent growth prevents individual organisms from being isolated, necessitating subculture onto additional agar media, delaying the time to result even further. Additionally, many laboratories are discovering that microorganisms, when stressed due to nutrient deprivation, or following exposure to sublethal concentrations of antimicrobial agents, such as preservatives, disinfectants, heat or decontaminating gases, may not replicate when cultured on artificial media, because the environment is not truly optimal for the resuscitation and subsequent proliferation of organisms that may be present. For these and many other technical and business reasons, the modern microbiological laboratory should look toward developing innovative approaches to the detection, quantification and identification of microorganisms. Fortunately, technology is now available, or close to being available, that will speed up microbiological analysis and provide results in real time, allowing pharmaceutical manufacturing to embrace the concepts of Process Analytical Technology (PAT) and the use of rapid microbiological methods (RMM).

21st Century Solution

The *Encyclopedia of Rapid Microbiological Methods* is a culmination of many years of research, development and implementation of new technologies by a number of industry sectors, including pharmaceuticals, medical device, cosmetic and personal care, health and clinical, food and beverage, and municipal water, as well as government agencies and their subsidiaries, including biodefense laboratories, first responders and homeland security. Furthermore, support for novel ways in which to conduct microbiological assays is becoming the norm for both regulatory agencies and pharmacopoeias, as demonstrated in recent initiatives and guidance documents provided by the U.S. FDA, EMEA, USP and Ph. Eur. The encyclopedia attempts to pull together the opinions of these organizations, suppliers of new microbiology platforms, and the laboratories and end users of the technologies discussed within its pages.

Volume 1 provides an overview of microbiological methods and opportunities for industry, regulatory and pharmacopoeial perspectives and validation strategies. Topics include: the history of microbiological methods; risk-based approaches to pharmaceutical microbiology; the realities and misconceptions of implementing rapid methods in the manufacturing environment; the use of rapid methods in the biodefense and the food industries; PAT; comparability protocols; 21 CFR Part 11; and practical guidance on RMM validation and implementation.

Volumes 2 and 3 explore specific rapid microbiological methods, technologies and associated instrumentation, from both a supplier and an end-user viewpoint. Volume 2 concentrates on growth-based and viability-based rapid microbiological technologies, including flow and solid-phase cytometry, ATP bioluminescence, impedance microbiology and a variety of microbial identification platforms relying on physiological responses.

Volume 3 concentrates on artifact-based and nucleic acid-based technologies, the detection of mycoplasma, and the use of micro-arrays, biochips and biosensors. Some of the platforms discussed include fatty acid analysis, MALDI and SELDI-TOF mass spectrometry, portable endotoxin testing, 16S rRNA typing, DNA sequencing, PCR, advances in micro-electro-mechanical systems (MEMS)

continued on page 12

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Recent Sci-Tech Discussions:
GLP/GMP and ISO 9000 Regulations

The following unedited remarks are taken from PDA's Pharmaceutical Sci-Tech Discussion Group, an online forum for exchanging practical, and sometimes theoretical, ideas within the context of some of the most challenging issues confronting the pharmaceutical industry. The responses in the Sci-Tech Discussions do not represent the official views of PDA, PDA's Board of Directors or PDA members. Join at www.pharmweb.net/pwmirror/pwq/pharmwebq2.html.

In this month's PDA Pharmaceutical Discussion Group selections, we are featuring a debate over the value of conforming to ISO standards to a GMP/GLP-compliant pharmaceutical manufacturer/laboratory. The debate started over a simple question about the difference between ISO 9000 and the regulations. We pick up the debate with the ninth respondent. We will continue this thread in the next issue.

What are the differences between GLP/GMP and ISO 9000 regulations in the pharmaceutical industry? Are GLP/GMP fully compatible with Total Quality Management? For me, the fundamental difference between GMP and ISO is that both have different agendas: GMP is mandatory; ISO is an unnecessary complication.

Respondent 9: I have read the past stream of posts…in quality-driven firms, like the pharmaceutical industry…the reality should be cGMP and ISO in the United States and GMP and ISO in the EC—because ISO and cGMP/GMP are not adversarial in nature.

Moreover, if firms are truly interested in the accuracy and precision of their test and calibration results, these firms would be operating with all areas, including lab and production, which make test, evaluation and calibration measurements in full compliance with ISO 17025 (formerly ISO/IEC Guide 25), in addition to the general ISO 9000 series and other applicable ISO standards and all applicable CGMP and/or GMPs.

Hopefully, this posting will be read for the positive advice it suggests, and nothing else.

Respondent 10: We all know that if you are operating in a GMP-compliant manner, then the authorities are delighted. And in fact, there is no regulatory reason to also become ISO 9000 certified. But, let's ask the question the other way around: Can anyone think of any benefits or advantages for a GMP-compliant facility to want to venture to become ISO 9000 certified? Any advantages from a regulatory, or marketing, or efficiency, or profitability, or any other perspectives?

Respondent 11: To the extent that any applicable ISO standard is recognized as a "universal" quality standard for any aspect of the pharmaceutical industry's unit operations, then—as the quality system regulations that constitute the cGMP for medical devices clearly recognizes—compliance with all applicable ISO standards is required for a firm to meet the minimums for compliance with "current good manufacturing practice" *because* these applicable ISO standards are the worldwide recognized minimum quality standards for the activities and operations covered by each applicable standard.

Therefore, in the United States, to be truly compliant with the statutory expectations for cGMP as set forth in 21 U.S.C. Section 351(a)(2)(B), a drug firm must comply with all applicable cGMP regulations as set forth in 21 CFR Parts 210 through 226, as well as all applicable recognized international ISO standards for any of their activities, since these ISO standards establish the minimum expectations for quality in the activities and systems covered in a given applicable ISO standard.

Thus, while a drug firm need *not* be third-party registered to be in compliance with all applicable ISO quality standards (e.g., [Respondent 10's] "... no regulatory reason to also become ISO 9000 certified"), each drug firm should be operated in a manner that meets or exceeds the minimum expectations set forth in all the applicable ISO standards in the United States, *since* the applicable ISO quality standards are obviously part of the cGMP for manufacturers in general, including the drug firms whose products are regulated by the U.S. FDA.

For example, in my limited experience, drug "test and calibration" operations that do not meet the minimums set forth in ISO 17025 have value traceability and/or reliability issues that cast doubt on the validity of the results reported by said operations and, because they are not complying with ISO 17025, have difficulty in proving the "root cause(s)" of suspect results.

The European GMP system seems to address the issue of GMP somewhat differently but tends to rely on ISO standards, where ➤

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such are available, in setting the expectations for quality production.

Hopefully, those firms claiming to operate in a quality-driven manner see the advantage of the ISO standards and adjust their "cGMP"/"GMP" practices to incorporate the applicable ISO standards as the "established basis" for their quality operations because doing so minimizes the level of documentation required by a firm to *justify* and/or *establish* the validity of its operational practices.…

It would seem that the FDA and ICH moves in the areas of quality systems and quality risk management would require that one's "unit" systems be based on some recognized standard with applicable ISO standards being the preferred "recognized" standard in all areas not explicitly addressed by statute or legally binding regulation.

Respondent 12: Previously some of my colleagues and I also assumed that if we had applied GMP, then we should not apply ISO 9000. But when we finally applied ISO 9000 in our site, we had a lot of advantages, especially how to conduct documentation more properly. For example, GMPs explicitly do not guide us how to conduct documentation hierarchy, while ISO 9000 does, GMPs explicitly do not guide what kind of documentation and data needed to perform feedback to other parties, while ISO 9000 does.

It's true that most of ISO 9000 guidelines have been covered in GMP, but it's true also the ISO 9000 guidelines complement and make the GMPs [easier to implement].

Besides quality, ISO 9000 also deals with continous improvement. This topic is not limited to quality-related issues only, but also the other areas, e.g., cost saving, production efficiency, etc. This point is not covered in GMPs.

For some companies, having ISO 9000 certification will [help] them to export their products to the EU. While for the local market, ISO certification can increase their company's value, since ISO is [better] known than GMP.

Respondent 13: [Respondent 12], I agree with most of your response to [Respondent 10], especially regarding the customer focus angle one adopts with ISO 9000:2003. This for me is the benefit of it.

You are quite wrong to imply ISO 9000 certification will ease export of products to the EU. It will not. Export of products into the EU will be subject to a satisfactory audit of the manufacturing facilities, approval of a Marketing Authorization in the EU, appointment by the exporting company of a "distributor" in the EU, which has a Manuafcturing Authorization for the products imported into that member state. You will need the services of analytical testing facilities in the EU, together with a QP to certify products as meeting the requirements of EU GMP, compliance with the Manufacturing & Marketing Authorizations.

Advancing the Science of Microbiology: Encyclopedia of RMM,
continued from page 8

including lab-on-a-chip systems, and a novel instantaneous and real-time optical detection technique for airborne microorganisms.

These are very exciting times for the rapid detection, quantification and characterization of microorganisms. The information presented in the Encyclopedia of Rapid Microbiological Methods provides the reader with a comprehensive collection of technology reviews and validation strategies that will encourage today's microbiologists to move away from centuries-old techniques and to embrace the next generation of novel, more-sensitive and rapid microbial detection platforms. I am optimistic that the material presented will provide a framework for all industry, clinical and government sectors required to evaluate the environment, products, processes and test samples for the presence of microorganisms to embrace the rapid methods that are available today, and what will be forthcoming in the years ahead. And yes, I am certain that Angelina would be proud!

About the Author

Dr. Michael J. Miller holds the position of Senior Research Fellow in the Manufacturing Science and Technology function of Eli Lilly and Company. He is responsible for providing technical leadership in microbiology and sterility assurance within manufacturing, quality, engineering, and product development. He is also accountable for leading Lilly's corporate initiatives for PAT, barrier isolation technology and rapid microbiological methods. He volunteers extensively with PDA on various committees and advisory boards and serves on USP Technical Committee 18, Working Group 6 on RMM.

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From the PDA Bookstore

Spring 2006

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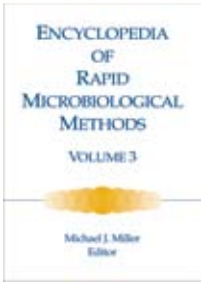
New Releases



Encyclopedia of Rapid Microbiological Methods: Volume I, II, III
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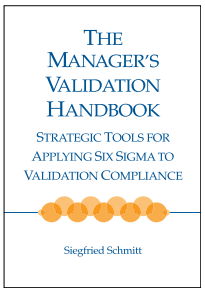


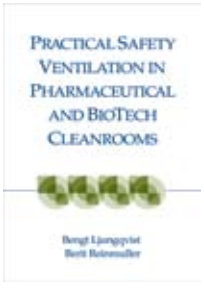
The Manager's Validation Handbook: Strategic Tools for Applying Six Sigma to Validation Compliance
Author: Siegfried Schmitt
Item no. 17234
Member: US$ 200
Nonmember: US$ 249

PDA Technical Reports

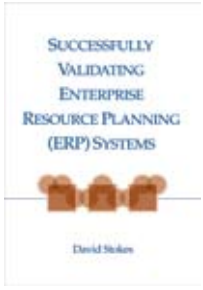
PDA Technical Report No. 39 Cold Chain Guidance for Medicinal Products: *Maintaining the Quality of Temperature-Sensitive Medicinal Products Through the Transportation Environment*
Item No.01039
$75.00 member
$150.00 nonmember

PDA Technical Report No. 42 Process Validation of Protein Manufacturing
Item No.01042
$75.00 member
$150.00 nonmember

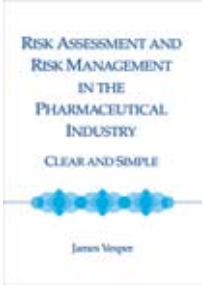
Coming Soon This Spring



Practical Safety Ventilation in Pharmaceutical and Biotech Cleanrooms
Authors: Bengt Ljungqvist and Berit Reinmuller
Item no. 17233
Member: US$ 225
Nonmember: US$ 279
Spring 2006



Successfully Validating Enterprise Resource Planning (ERP) Systems
Author: David Stokes
Item no. 17245
Member: US$ 225
Nonmember: US$ 279
Spring 2006



Risk Assessment and Risk Management in the Pharmaceutical Industry: Clean and Simple
Author: James L. Vesper
Item no. 17219
Member: US$ 210
Nonember: US$ 260
Spring 2006

Pharmaceutical Filtration: The Management of Organism Removal
Authors: Theodore H. Meltzer and Maik W. Jornitz
Item no. 17235
Member: US$ 200
Nonmember: US$ 249
Spring 2006

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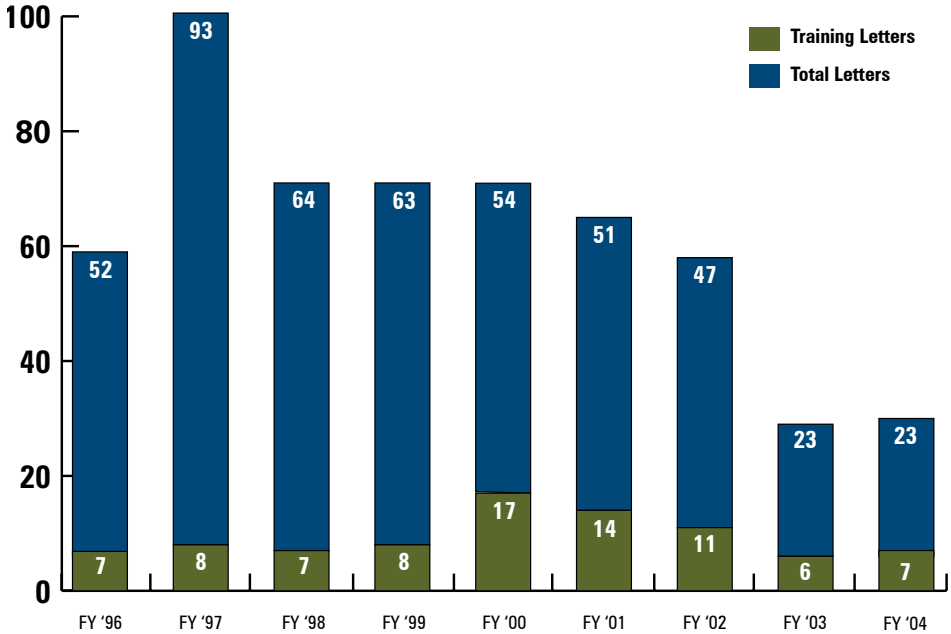
Personnel Training: A Growing Compliance Concern, continued from cover

Figure 1: **Drug and Vet cGMP Warning Letters Citing Training/ Total Drug and Vet cGMP Warning Letters, FDA Fiscal Years 1996-2004**



Training Courses

The PDA Training and Research Institute is offering courses aimed at keeping you compliant and ahead of the curve.

Achieving cGMP Compliance During Development of a Biotechnology Product
June 14, 2006

A Comprehensive Guide to OOS Regulations
September 14, 2006

Auditing Techniques for cGMP Compliance
September 15, 2006

Analytical Problem Solving for CAPA Systems
October 17 -18, 2006

Biopharmaceutical QA/QC for Senior Management
October 16, 2006

What Every Biotech Startup Needs to Know about CMC
October 17, 2006

For more information on these and other courses, visit www.pda.org.

Training Ante Raised

The increased frequency of inspection observations dealing with personnel training over the last five years conforms with FDA's shift to systems-based inspections, whereby the focus of each GMP inspection is on the company's quality control unit (QCU). Regulations for the QCU are in Part 211 Subpart B, 211.22 (a) (b) (c) and (d). FDA has clearly articulated over the last five years that a company's QCU, and management support for the "quality system" in general, will be examined closely during each cGMP and preapproval inspection.

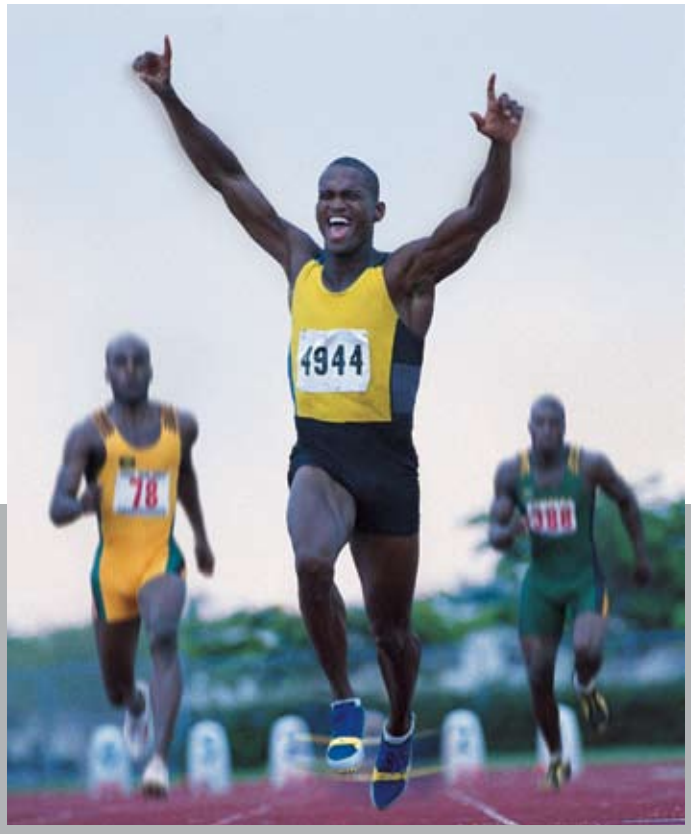
As an important component of the quality system, training is being evaluated more intently. In its 2004 quality systems draft guidance, FDA raises the stakes on personnel development by listing it as one of the metrics for judging a company's overall commitment to quality manufacturing and by emphasizing management's responsibility for evaluating the effectiveness of training. In addition, FDA advises that the effects of training should be seen in the performance of the employees. The guidance states:

Typical quality systems training would address the policies, processes, procedures, and written instructions related to operational activities, the product/service, the quality system, and the desired work culture (e.g., team building, communication, change, behavior). Under a quality system (and the CGMP regulations), training is expected to focus on both the employees' specific job functions and the related CGMP regulatory requirements.

Under a quality system, managers are expected to establish training programs that include the following:

- *Evaluation of training needs*
- *Provision of training to satisfy these needs*
- *Evaluation of effectiveness of training*
- *Documentation of training and/or retraining*

When operating in a robust quality system environment, it is important that supervisory managers ensure that skills gained from training be incorporated into day-to-day performance.[2] ➤



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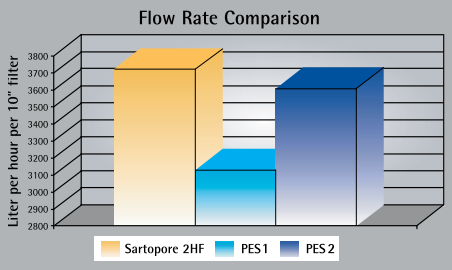

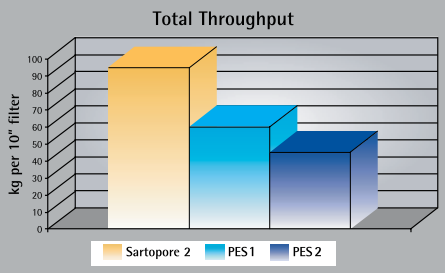

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Commitment Key to Effective Training

Professional trainers generally agree with FDA's linkage of the corporate commitment to training and the overall quality culture. Effective training occurs when a company's culture properly motivates personnel to take the lessons seriously.

MedImmune Sr. Manager of Corporate QA Compliance **Barbara van der Schalie** points out that the quality systems draft guidance for the first time articulates FDA's expectation that company management evaluate the effectiveness of their personnel training programs. Companies with a strong commitment to quality systems and personnel training are probably already on top of this. Van der Schalie points to MedImmune as an example, stating that the training program is "tremendous," and that the firm values training not only for its compliance implications, but also for the business payoff.

It is true, however, that ascertaining the effectiveness of training is difficult and can be a matter of interpretation. One of the problems is there are no good certification programs involving cGMP compliance or most manufacturing operations. Certification in these areas is difficult because it would have to be done in a manufacturing setting, which is often impractical.

Develop a Risk-Based Approach

To build an effective program, van der Schalie advises companies to utilize a risk-based system. When evaluating the training needs of a particular employee, van der Schalie begins with their job description and then analyzes the specific jobs or tasks the employee will perform. A risk analysis can then be performed on each task as it relates to the cGMPs: What is the risk of not performing a particular step? What is the risk of not documenting the step? etc. This exercise will help a company find the optimal training solution to maintain compliance and execute a sound quality system. PDA's **Gail Sherman**, VP of Training and Director of TRI, says evaluating training is never "cut and dry." Companies that believe they have invested adequately in training still might find themselves on the receiving end of an investigator observation. The most important factor in ensuring effective training programs is a corporate culture conducive to human resource development, she asserts. "The example should be set from above." A lot of time, she notes, training is "not a priority," and when companies hit hard times, money for training is "cut first."

To build an effective program, van der Schalie advises companies to utilize a risk-based system.

Having worked for FDA's Center for Biologics Evaluation and Research for 13 years as a trainer, Sherman can appreciate an organization committed to human resource education. With the advent of the Prescription Drug User Fee Act, Congress mandated that the Agency invest resources into personnel training for new product reviews. The pressure from the highest level of FDA management to see tangible improvements in review times set the tone for an effective training program with willing trainees. This massive training effort focused on the actual process of review management, review consistency and project management; the result of which was the reduction of approval times to 10 months for NDAs and BLAs.

Training Problems Affect All Company Types

The 55 FDA warning letters containing personnel training observations in the fiscal years 2000-2004 reveal that the issue affects many types of companies: large and small firms; generic and research-based; and license-holders and contract organizations (see box, page 18).

Drug repackers were overrepresented in the training warning letters. Twenty-two percent (12 of 55) of these letters were sent to repackers; overall, repackers received less than 10% of the total GMP warning letters issued in ➤

Recommended Resources

You may find these resources to be excellent references for your cGMP compliance program.

On-Demand Recording

CAPA Systems: Common System Failures & Measuring Performance

International GMPs: Meeting U.S. and European Requirements

For more information or to purchase an On-Demand Recording, call Vicky Acosta at +1 (301) 656-5900 ext. 158.

Publications

Quality Assurance Workbook for Pharmaceutical Manufacturers – Best Seller

GMP in Practice: Regulatory Expectations for the Pharmaceutical Industry – Third Edition

Pharmaceutical Quality – Best Seller

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Biotechnology: Overview of Principles, Tools, Processes and Products
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St. Louis Training Courses | August 7-9 | *St. Louis, Missouri*

Offering nine one-, two- and three-day courses:

- Basic Concepts of Cleaning and Cleaning Validation
- Environmental Monitoring in Pharmaceutical Manufacturing
- Managing the Microbiological Quality of Non-Sterile Pharmaceutical and OTC Drug Products New Course!
- Pharmaceutical Water Systems, Design and Validation
- Root Cause Investigation for CAPA
- Sterile Pharmaceutical Dosage Forms: Basic Principles
- Validation by Design®
- CIP System Design and Engineering Integration Options and Impacts New Course!
- Risk Management

Computer Products Supplier Auditing Model: Auditor Training
September 20-21 | *Baltimore, Maryland*

Boston Training Courses | October 16-18 | *Boston, Massachusetts*

Offering eleven one- and two-day courses:

- Analytical Problem Solving for CAPA Systems
- Approaches to Performing Self-Inspections as Part of a Total Quality System for Pharmaceutical Product Development and Manufacture New Course!
- Bioassay Development and Validation
- Biopharmaceutical QA/QC for Senior Management
- Design of Experiments for Efficient and Practical Assay Development and Validation New Course!
- Managing the Microbiological Quality of Non-Sterile Pharmaceutical and OTC Drug Products New Course!
- Preparing for an FDA Pre-Approval Inspection
- Overview of FDA QSR Requirements for Device Inspection Approaches
- Risk Management in Thermal Validation New Course!
- What Every Biotech Startup Needs to Know About CMC New Course!
- Minimizing the Legal, Quality and Compliance Pitfalls of Contract Manufacturing

Advanced Pharmaceutical Filtrations and Filters New Course!
October 23-25 | *Baltimore, Maryland*

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the five-year period (25 out of 253).

Testing laboratories were similarly overrepresented in the "training" letter pool: 9% (5 of 55) of the letters referencing training went to testing labs, while only 5% (12 of the 253) total letters went to such firms.

Many of these letters are instructive as to how FDA decides a training program is inadequate.

In a letter sent to a firm in 1999, based on an inspection of an aseptic processing plant, FDA questioned the effectiveness of the firm's training program. In the letter, FDA wrote: *The observations made during this inspection indicate that personnel performing and/or supervising aseptic processing operations did not always possess the knowledge to perform their assigned functions in such a manner as to provide the assurance that aseptically filled drug products have the safety, identity, strength, quality and purity they are purported or represented to possess.* The specific example provided by the investigator to support this allegation were: 1) The failure of personnel who review, approve and implement SOPs to detect a "defective" SOP. 2) The failure of a HEPA filter reliability maintenance engineer responsible for the air handling system to know the air handling system specification for air flow to the aseptic area. 3) The failure of all employees to participate in an annual media fill operation.

In another letter sent to the same firm in 2000, FDA observed that "the gowning procedures and the corresponding training program have not been shown to be effective," with no further explanation. Later in the same warning letter, FDA noted that the company's response to the FDA 483 "failed to provide documentation of employee training and qualification of gowning technique."

FDA warned another company for a poor training program based on employee performances. In a 1999 letter to the company, FDA wrote: *Your firm's analysts performing sterility analysis on powder products are inadequately trained. An analyst failed to fully dissolve the [drug] lot [number] powder being analyzed for 12 of [redaction] vials, as witnessed on July 12, 1999, and as required by the method. In addition, the letter noted that not all employees who enter the sterility core participated in media fills.*

continued on bottom of page 24

The following drug and veterinary companies were cited in warning letters for inadequate or no personnel training or for no records of employee training, during the U.S. FDA fiscal years 2000-2004 (Oct. 1, 1999-Sept. 30, 2004). Included below is the name of the firm receiving the warning and the date of the letter.

A&L Labs. ..... *June 30, 2000*
AJD Laboratories dba Ulmer Pharmacal ..... *Oct. 2, 2001*
Akorn ..... *Sept. 28, 2000*
American International Industries ..... *March 30, 2000*
Apothecary Products ..... *May 25, 2000*
Argus Analytical ..... *Oct. 2, 2000*
Bigmar-Bioren SA ..... *Aug. 8, 2004*
Biological Research Solutions ..... Jan. 16, 2001
Cardinal Enterprises ..... Dec. 7, 2001
Cardinal Health (International Processing) ..... July, 10, 2001
CASA Lab ..... July 2, 2001
Certified Processing ..... Apr. 4, 2000
Chemrich Holdings ..... Dec. 11, 2000
Chemrite Industries ..... Oct. 19, 1999
ChemSource ..... Nov. 15, 2002
Clinical Science Labs. ..... July 5, 2000
COATS Aloe ..... May 1, 2001
Earlham Analytical Labs ..... July 29, 2002
Farouk Systems ..... Aug. 1, 2001
Fort Dodge Animal Health ..... March 31, 2004
Gemeindezentrum ..... Apr. 10, 2000
Grafor Manufacturing ..... Apr. 20, 2001
Hoffman-LaRoche ..... Dec. 17, 1999
Icon Labs. ..... Feb. 4, 2003
Imperial Drug & Spice ..... Jan. 16, 2002
Integrity Pharma. Corp. ..... July 11, 2000
JOAMACA Chemical Products ..... Nov. 13, 2002
K.C. Pharma. ..... Nov. 19, 2002
Med-Pro ..... Apr. 26, 2000
Natchez Animal Supply ..... Oct. 10, 2002
Natureplex ..... Aug. 18, 2004
Navajo Manufacturing ..... Dec. 2, 2002
Old Hickory Medicine Company ..... Apr. 21, 2004
Opti-Med Controlled Release Lab ..... Jan. 9, 2002
Organon ..... Sept. 19, 2000
Pharmaceutical Corporation of America ..... Feb. 17, 2000
Pharmaceutical Distribution Systems ..... Jan. 3, 2002
Pharmaceutical Formulations ..... May 5, 2004
Pharmacia & Upjohn ..... Dec. 2, 1999
Pharmacia & Upjohn ..... Feb. 3, 2000
Pharmakon Labs ..... Sept. 7, 2001
Pierre Fabre ..... Nov. 5, 1999
Pride & Power ..... March 3, 2003
Robin Drug (Reed Drug) ..... Sept. 24, 2001
Sani-Pure Food Labs. ..... June 14, 2000
Shanghai Medicine ..... Feb. 10, 2004
Sybron Chemicals ..... Nov. 13, 2000
Truett Labs. ..... Apr. 19, 2001
Trusted Care ..... Dec. 14, 2001
TYA ..... Aug. 6, 2002
Ultra-Seal ..... July 22, 2004
Unique Labs. ..... Nov. 13, 2000
Wallace O'Farrel ..... Aug. 7, 2002
Wazata Bay Products ..... Dec. 19, 2001
Weber Labs ..... Jan. 25, 2000
Zenith ..... May 22, 2001

Application of Regulatory *Principles* is Key to Analytical Testing in Clinical Trials

Katalin Abraham and Karen Hencken, Merck & Co.

During human clinical trials for vaccines and biologics, the effectiveness of the product, including the immune response of the recipients, is assessed. The clinical assay results are important for the determination of immunogenicity or surrogate markers for efficacy and the establishment of label claims for the product. Therefore, it makes sound business sense to establish processes that assure that the samples to be tested are secure and properly stored, that the methods employed are documented and perform as intended, and that data integrity is maintained. Regulatory agencies expect these attributes to be evident. While these attributes are captured in GLP and GMP regulations, clinical testing is not covered by these regulations. Nevertheless, to assure these attributes, the underlying principles of the GLP and GMP regulations should be considered rationally during clinically trials.

The GMP regulations are intended for product manufacture, primarily commercial product manufacture, and GLPs, for nonclinical animal safety studies. There is no statutory requirement to follow either GMPs or GLPs in the clinical analytical lab. The scope for GLPs is clearly captured in 21 CFR 58.1 (a) that states, "This part prescribes good laboratory practices for conducting nonclinical laboratory studies…." Nonclinical laboratory studies are then defined in Sec. 58.3 (d): "Nonclinical laboratory study means in vivo or in vitro experiments in which test articles are studied prospectively in test systems under laboratory conditions to determine their safety. *The term does not include studies utilizing human subjects* or clinical studies or field trials in animals." 21 CFR 210.1 (a) states that GMPs as "set forth in this part and in parts 211 through 226 of this chapter contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the *manufacture, processing, packing, or holding of a drug* to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess."

There is no statutory requirement to follow either GMPs or GLPs in the clinical analytical lab.

Furthermore, strict adherence to these regulations is neither meaningful nor cost-effective for clinical assays. None of the predicate rules or Clinical Laboratory Improvement Amendments was intended for this application. (Although test methods in CLIA-certified laboratories may be utilized for clinical assays, the sample results are used to establish surrogate markers for the efficacy of a product. These data are not intended for diagnostic use.)

It is inferred that these CFR regulations were developed for situations in which the deliverable is a product lot or a patient's test result, where each individual value is scrutinized separately against the expected result. In clinical trials, the product's characteristics being evaluated determine the sampling performed. The testing laboratory is blinded to the individual sample demographics. The deliverable in this case is not a result for a lot of product. The deliverable is a reproducible test method, properly controlled, executed and documented. The "product" is an assay where there is confidence that the sample results are reliable and comparable across studies and over time.

For example, 21 CFR 211.84, "Testing and Approval or Rejection of Components, Drug Product Containers, and Closures," subsection (b) states: *Representative samples of each shipment of each lot shall be collected for testing or examination. The number of containers to be sampled, and the amount of material to be taken from each container, shall be based upon appropriate criteria such as statistical criteria for component variability, confidence levels, degree of precision desired, the past quality history of the supplier, and the quantity needed for analysis and reserve where required by Sec. 211.170.* Component is defined in 21 CFR 210.3, "Definitions," subsection (a) (3) as: *Any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product.* The directions are clear. Test or examine each component lot before use to determine whether it is acceptable. In clinical testing, "component" would refer to the reagents, controls, supplies (such as microtiter plates), etc., used in the given assay. Clearly this level of scrutiny, examination or testing, for all components where the

continued on page 22

PDA Calendar of Events for North America

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

Conferences

April 24-28, 2006
2006 PDA Annual Meeting
(Conference, Courses and Exhibition)
Anaheim, California

April 26-27, 2006
Workshop on Biotech Process Validation
Anaheim, California

May 8-12, 2006
2006 PDA Biennal Training Conference
(Conference, Courses and Exhibition)
Philadelphia, Pennsylvania

September 11-15, 2006
PDA/FDA Joint Regulatory Conference
(Conference, Courses and Exhibition)
Washington, D.C.

October 23-25, 2006
Prefilled Syringes and Drug Delivery Systems
(Conference and Exhibition)
Bethesda, Maryland

October 30, 2006
PDA's 1st Annual Conference on Pharmaceutical Microbiology
(Conference and Exhibition)
Bethesda, Maryland

Training

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

Laboratory Courses

April 10-11, 2006
Developing and Validating Cleaning and Disinfection Programs for Controlled Environments

May 22-24, 2006
Developing a Moist Heat Sterilization Program within FDA Requirements

June 1-2, 2006
Environmental Mycology Identification Workshop

July 18-21, 2006
Pharmaceutical and Biopharmaceutical Microbiology 101

August 7-11, 2006
Rapid Microbiological Methods

Lecture Courses

May 15-17, 2006
Biotechnology: Overview of Principles, Tools, Processes and Products

September 20-21, 2006
Computer Products Supplier Auditing Model:Auditor Training

Course Series

April 27-28, 2006
PDA Annual Meeting Course Series
Anaheim, California

May 11-12, 2006
PDA Biennial Training Conference Course Series
Philadelphia, Pennsylvania

June 13-14, 2006
Vancouver Course Series
Vancouver, British Columbia, Canada

August 7-9, 2006
St. Louis Course Series
St. Louis, Missouri

September 14-15, 2006
PDA/FDA Joint Regulatory Conference Course Series
Washington, DC

Chapters

April 5, 2006
PDA Metro Chapter
First Annual PDA Metro Chapter Day: Microbiology Update
Clark, New Jersey

April 6, 2006
PDA Mountain States Chapter
Multiple Topics for Round Table Discussion
Longmont, Colorado

April 18, 2006
PDA Delaware Valley Chapter
Pre-Approval Inspections
Malvern, Pennsylvania

May 9, 2006
PDA Metro Chapter
Microbiological Considerations for Oral Solid Products
Clark, New Jersey

May 16, 2006
PDA Southeast Chapter
Operational Excellence in Pharmaceutical and Biotechnology Manufacturing
North Carolina Biotech Center

Chapters (cont.)

May 18, 2006
PDA Midwest Chapter
Vendor Night and Discussion Groups
Northbrook, Illinois

June 7, 2006
PDA Metro Chapter
Viral and Mycoplasma Clearance
Clark, New Jersey

June 12, 2006
PDA Canada Chapter
Annual Meeting
Vancouver, British Columbia

July 14, 2006
PDA Delaware Valley Chapter
Risk Assessment
Malvern, Pennsylvania

July 20, 2006
PDA Midwest Chapter
Application of Bacterial Spore Inactivation Kinetics to Risk Estimation in Sterilization Processes
Northbrook, Illinois

August 4, 2006
PDA Midwest Chapter
2nd Annual Golf Outing

Europe/Asia Pacific/Middle East

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

EUROPE

May 23-24, 2006
Process Understanding and the Future of Validation
(Conference and Exhibition)
Barcelona, Spain

June 19-20, 2006
PDA Training Workshop 2006: FDA's Aseptic Processing Final Guidance
(Workshop and Exhibition)
Prague, Czech Republic

September 27-28, 2006
Visual Inspections
Berlin, German

October 10-13, 2006
PDA/EMEA Joint Conference
(Conference, Courses and Exhibition)
London, England

MIDDLE EAST

November 22-23, 2006
PDA and the PDA Israel Chapter
Quality Tools for the 21st Century
Tel Aviv, Israel

ASIA/PACIFIC

November 13-17, 2006
2006 PDA Asia-Pacific Congress
(Congress, Courses and Exhibition)
Tokyo, Japan

Application of Regulatory Principles is Key to Analytical Testing in Clinical Trials, continued from page 19

product is a valid assay, and not a finished pharmaceutical, would pose undue burden. Application of the principle is appropriate, however. There should be confidence that the materials used in the assay perform as intended. What that entails depends upon the component. Assay development and characterization must evaluate the components, identify the critical ones and then determine what the acceptance criteria are for using a new lot of a critical component. That testing and evaluation must then be performed and documented for each new lot. However, for other components, specification of a manufacturer and catalogue number in the SOP may be adequate. For these noncritical components, the lot number may not even be captured on the batch record. In manufacturing, the batch records thoroughly capture all lot numbers applicable to the batch.

Another example is the requirement from 21 CFR 58, "Good Laboratory Practice for Nonclinical Laboratory Studies," for standard operating procedures. Sec. 58.81 (a) states: *A testing facility shall have standard operating procedures in writing setting forth nonclinical laboratory study methods that management is satisfied are adequate to insure the quality and integrity of the data generated in the course of a study. All deviations in a study from standard operating procedures shall be authorized by the study director and shall be documented in the raw data. Significant changes in established standard operating procedures shall be properly authorized in writing by management.* The goals of ensuring the quality and integrity of the data through application of consistent procedures and demonstrating control of laboratory operations through management of deviations and changes certainly would logically apply to analytical data generated during a clinical trial. One difference is related to the role of the study director, which is a specific GLP requirement that is not applicable in a clinical laboratory setting, where testing for a number of studies occurs concurrently and control of an assay is more critical than control within a specific study protocol. Another difference is evident in 58.81(b), in which the requirement for procedures for laboratory tests and data handling, storage and retrieval would apply, but such procedures as animal room preparation and handling of animals found moribund or dead during the study would not.

Review of FDA 483s confirms that the Agency does have certain expectations for clinical testing...

Care should be taken not to randomly select regulations, since this tends to subvert their original intent. In the absence of guidances and regulations designed specifically for clinical testing, selecting an available guidance that appears to address the need but is intended for another application may seem reasonable at first. It is risky to remove any regulation from the framework for which it was intended. Assumptions built into the guidance may not be obvious or relevant for the unintended application and, as a consequence, may impose undue burden. Conversely, one may assume the applied guidance provides sufficient safeguards while a needed safeguard is altogether unaddressed. A process, once applied, is not easily abandoned in a regulated environment, and it must be recognized that clinical testing is viewed as a regulated area, even though specific regulations have not been codified.

Review of FDA 483s confirms that the Agency does have certain expectations for clinical testing, even if these expectations are not articulated in regulations or guidances. Clearly, the EU views clinical testing as regulated. Directive 2001/20/EC (GCPs) Article 15, Verification of compliance of investigational medicinal products with good clinical and manufacturing practice states: "1. To verify compliance…, Member States shall appoint inspectors to inspect the sites concerned by any clinical trial conducted, particularly, the trial site…*any laboratory used for analyses in the clinical trial…*"

It is important to be familiar with the regulations that have been promulgated to understand the expectations of regulatory agencies and then apply the relevant principles practicably.

A laboratory performing clinical testing must consider the following principles. Most fundamental is a complete, accurate and secure documentation system from which the appropriate information can be readily retrieved. Personnel must be competent and adequately trained, the facility must be appropriate, methods and instruments must perform as intended, and samples and data integrity must be maintained. Quality must be built into every step of the process. The process must be evaluated to determine where quality checks are meaningful, and then those checks should be applied. The process that captured these attributes and confirmed that they are in evidence must be documented so that it is ➤

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available for reference, review and refinement, when required. The procedures followed by the laboratory need to be clearly defined. A versioning system must be in place, so that it is evident what procedure was followed for each time period and each group of samples. To the same end, change must be controlled, and a process for evaluating planned changes or improvements as well as identifying, evaluating and managing atypical events must be established.

The integrity and retrievability of electronic records must be addressed, but 21 CFR 11 does not apply specifically to clinical studies, because there are no predicate GLP or GMP rules governing clinical work. The FDA's August 2003 guidance on Part 11 states that "Part 11 applies to records in electronic form that are created, modified, maintained, archived, retrieved or transmitted under any records requirement set forth in Agency regulations." Nevertheless, upstream clinical testing generates records that are subsequently used as source documents for records to which Part 11 does apply. Therefore, the principles of Part 11 should be applied. For example, firms should address security, audit trails and retrievability of electronic records. Doing so is part of any good documentation practice and makes good business sense.

The data generated during clinical trials for vaccines and biologics in a controlled research mode is pivotal to support product approval and label claims. Practicable application of key regulatory principles contained in the GLPs and GMPs yields accurate, valid and defendable clinical data.

[**Editor's Note:** PDA spoke with Kati Abraham about her article to learn more about the subject. To be clear, the recent release of a new regulation and guidance for Phase 1 (see the March *PDA Letter*, page 24) relates specifically to the application of cGMPs to the material prepared for subjects of the clinical trials, not to the labs that test the samples taken from the patients. In the authors' situation, they are discussing the latter—the labs that test the samples from patients in the trials. These labs can be audited by FDA, although the cGMPs and GLPs do not cover them. One of the authors' concerns is that a manufacturer's QCU, and sometimes FDA investigators, might expect these labs to be in compliance with the cGMPs and/or GLPs, which could lead to missed opportunities for the firm and unwarranted FDA 483 observations from the investigators.]

About the Authors

Katalin Abraham is Associate Director, Regulatory Compliance Management, Vaccine and Biologics Research, Merck Research Laboratories, Merck & Co., Inc. She is responsible for the establishment and management of the regulatory compliance infrastructure necessary for the proper conduct of clinical testing and early development activities for vaccine and biologics in accordance with the applicable regulatory principles.

Karen Hencken is Associate Director, Worldwide Nonclinical Quality Assurance Resources, Worldwide Quality Assurance Resources, Merck Research Laboratories, Merck & Co., Inc. She is responsible for providing quality assurance oversight for laboratories conducting testing in support of clinical research and for GLP studies conducted to assess the safety of products in development.

Personnel Training: A Growing Compliance Concern, continued from page 18

Training practices have come into question in more serious enforcement actions. In these cases, observed training inadequacies went hand in hand with other cGMP issues, which, combined, potentially indicate larger compliance problems.

The most recent example of this is a well-publicized case from 2005. The firm in question ultimately shut its doors following findings of serious compliance deficiencies at its New Jersey facility.

The situation unfolded rapidly, beginning with two recalls in early 2005, a two month FDA inspection, additional recalls affecting all products in distribution, the suspension of operations and the resignations of the CEO and his successor. Finally, on July 18, Able filed for Chapter 11 and the company's board of directors decided to put the company up for sale.[3]

The cGMP infractions observed during the two-month inspection centered on laboratory data integrity and the responsibilities of the QCU for OOS results.

The QC lab came under intense scrutiny and drew a number of investigator complaints, including training of lab analysts. The conclusions drawn by the Agency demonstrate the consequences of not training employees properly for critical compliance functions, lending credence to the idea of using a risk-based system for training, as proposed by MedImmune's van der Schalie (see page 16). ➤

Observation 8 of the FDA 483 stated that the company's employees were not given training in cGMPs and written procedures. Among the SOPs that analysts were not "routinely" trained in were those for deviation investigations and acceptance/rejection of OOS analytical results. FDA concluded that the firm's management was to blame for inadequate training:

This lack of training and oversight by management contributed to the nonreporting of OOS in the QC laboratory.

Another case demonstrating that the combination of alleged poor training practices and the lack of a strong quality system can land a company in serious trouble with FDA resulted in a well-publicized consent decree in 2002.

The observations noted on a number of FDA 483s preceding the decree were extensive and included poor laboratory practices and questionable data integrity. Training also figured prominently in the investigator findings. In a June 13, 2001 FDA 483 from an inspection of one of the firm's offshore plants, Agency investigators stated that the training for analysts in 2000 and 2001 was inadequate, based on a number of laboratory findings.

In one instance, the company attributed an OOS result to an analyst pipetting error. FDA observed that the plant possessed no records showing that the analyst was trained in the technique. Yet, the Agency investigators noted, the very same analyst provided training to other analysts and supervisors in glassware handling and pipetting "as a corrective action after additional OOS results were attributed to pipetting errors."

Another OOS result attributed to analyst error prompted the investigators to cite another example of poor training practices. In this case, the company had concluded that one OOS result occurred because of improper cleaning. However, FDA observed, the company had no records demonstrating that analysts were retrained in the cleaning procedure.

FDA also faulted the firm for "questionable" training practices, observing that *numerous training sessions are performed during the same day*. The example cited on the FDA 483 indicated that one employee attended eight training sessions, including analytical tests for release of bulk compounding, operational procedure for pH determination in cream samples, analytical laboratory documentation policy, analytical laboratory investigations, and rounding and reporting data. Moreover, the investigators found discrepancies in employee training records. Training record discrepancies were also observed at another of the company's offshore facilities, according to a Feb. 16, 2001 FDA 483.

While these cases are extreme examples of companies running afoul of FDA expectations for personnel training, the warning letter and FDA TurboEIR data demonstrate that Agency investigators are routinely observing questionable or inadequate training programs. When combined with other compliance failures, particularly with the QCU, FDA is apt to conclude that the corporate culture at the offending firm is not committed to ensuring

continued on page 38

"Training War Story" from PDA Pharmaceutical Sci-Tech Discussion Forum

[**Editor's Note:** The discussion threads on the PDA Sci-Tech Discussion Forum can be very technical, lively and sometimes amusing (or aggravating, depending on your point of view). For more information on the PDA Pharmaceutical Sci-Tech Discussion Group, see page 10. In response to one participant's request for "training war stories," one of the forums frequent contributors offered the following anecdote. This story illustrates how some companies just don't get it. Enjoy!]

You want training war stories, here is one (of many in my closet).

Once upon a time .....

I was auditing a company with severe regulatory problems. One of the problems was that their training had been deemed by the authorities to be quantitatively and qualitatively inadequate. I was asked to audit the company.

In response to the training criticism, the company had improved its training systems by, amongst other things, including a ten-question multiple choice quiz at the end of each training session to determine whether the "students" had in fact learned anything. On reviewing the results of the quiz over the past several months, I found that every student (worker) had gotten 100% on every quiz. Intrigued how this could be I attended the next 1 hour training session for night shift workers that started at the end of their shift at 5:00 a.m. During the session, given by a superb trainer, I noticed that all the students fell asleep during the training (most for at least half of the session).

At the end of the session, the instructor read out the multiple-choice questions, and then told the students specifically which answer to circle. No wonder every student (worker) got genius grades!

This is what I call "training to satisfy the regulators."

—Michael Aniseld, GlobePharm Consulting

Regulatory Briefs

United States and Europe

Cross-Atlantic Cooperation to "Intensify"

The European Medicines Agency (EMEA) and the U.S. FDA are reporting that the implementation plan for the EU-FDA confidentiality arrangement was judged by all parties to have been a success. Both sides reached this conclusion at a review meeting in Brussels on March 13, 2006.

Following positive feedback from both regulators and industry that parallel scientific advice can facilitate the development of safe and effective medicines, it was agreed to extend the pilot phase for this process. Another area of particular benefit is pharmacovigilance, where close collaboration on a number of important issues has enhanced patient safety.

This review resulted in an agreement to intensify transatlantic cooperation in the area of medicinal products, with particular focus on vaccines (including preparedness for an influenza pandemic), medicines for children, medicines for rare diseases (orphans), oncology and pharmacogenomics.

Other public health priority areas will be explored in the coming months, such as counterfeit drugs. The arrangement has strengthened interactions between the regulatory authorities and has contributed to improving the promotion and protection of public health.

Background
The confidentiality arrangement allows the European Commission/EMEA and FDA to exchange information as part of their regulatory processes. The types of information covered by the arrangement include legal and regulatory issues, scientific advice, orphan drug designation, inspection reports, marketing authorisation procedures and post-marketing surveillance.

For more information, go to www.pda.org/regulatory/regnewsarchive-2006.html.

Europe

EMEA Meets with Avian Flu Vaccine Manufacturers

EMEA met with avian influenza vaccine manufacturers, European veterinary vaccine experts and representatives from the European Commission to promote the availability of authorized influenza vaccines for birds in the European Union.

The meeting, held at the Agency's offices in London on March 8, 2006, considered the recent reflection paper from the Agency's Committee for Medicinal Products for Veterinary Use (CVMP) on data requirements for emergency avian influenza vaccines. There was consensus from all parties that the reflection paper should be developed into a full guideline as a priority.

As part of the Agency's preparedness for avian influenza, Thomas Lönngren, the Agency's Executive Director, has agreed to grant fee waivers for all applications made to the Agency for avian influenza vaccines. Waivers will be given for scientific advice, follow-up scientific advice, applications for marketing authorisation and variations relating to the pandemic use of the vaccine.

The CVMP has also recently adopted a guideline on accelerated assessment, which can be used by applicants for avian influenza vaccines. It was confirmed that the CVMP is committed to reviewing any application as quickly as possible, while still ensuring a scientifically sound and thorough assessment.

The meeting with interested parties is part of the Agency and the Committee's ambition to provide a clear route to the rapid approval of influenza vaccines for use in birds throughout the European Union. This should, in turn, ensure the availability of safe and effective vaccines to Member States when they decide to use emergency vaccination within the context of their national control programs against avian influenza.

For more information, go to www.pda.org/regulatory/regnewsarchive-2006.html.

EMEA Issues Final Similar Biological Medicines Guides; Publishes Two New Concept Papers

EMEA published a set of five final guidelines on similar biological medicinal products. They are intended to give guidance to industry in the development of this new type of application for marketing authorization. A general regulatory guideline on similar biological medicinal products was finalized in September 2005. The guidelines give guidance on quality, nonclinical and clinical issues. The product class-specific annexes to the guideline on non-clinical and clinical issues give guidance for certain classes of medicines: those containing insulin, somatropin and recombinant granulocyte-colony stimulating factor. The guidelines come into effect from June 1, 2006.

continued on page 38

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Chapter Contacts

The following is a list of the PDA Chapters, organized by the regions of the world in which they are located. Included are the Chapter name, the area(s) served, the Chapter contact person and his or her e-mail address. Where applicable, the Chapter's Web site is listed. More information on PDA Chapters is available at www.pda.org/chapters/index.html.

Asia Pacific

Australia Chapter
Contact: Greg Jordan
E-mail:
greg.jordan@signet.com.au

India Chapter
Contact: Darshan Makhey, PhD
E-mail:
dmakhey@hotmail.com

Japan Chapter
Contact: Katsuhide Terada, PhD
E-mail: terada@phar.toho-u.ac.jp
Web site: www.j-pda.jp

Korea Chapter
Contact: Woo-Hyun Paik
E-mail: whpaik@naver.com

Southeast Asia Chapter
Contact: K. P. P. Prasad, PhD
E-mail: prasad.kpp@pfizer.com

Taiwan Chapter
Contact: Shin-Yi Hsu
E-mail: shinyi.hsu@otsuka.com.tw
Web site: www.pdatc.org.tw

Europe

Central Europe Chapter
Contact: Erich Sturzenegger, PhD
E-mail:
erich.sturzenegger@pharma.novartis.com

France Chapter
Contact: Jean-Louis Saubion, PhD
E-mail: ufch@wanadoo.fr

Italy Chapter
Contact: Gabriele Gori
E-mail: gabriele.gori@bausch.com
Web site: www.pda-it.org

Prague Chapter
Contact: Zdenka Mrvova
E-mail: zdenka.mrvova@zentiva.cz

Spain Chapter
Contact: Jordi Botet, PhD
E-mail: jbotet@stegroup.com

United Kingdom and Ireland Chapter
Contact: Frank W. Talbot
E-mail: ftpharmser@aol.com

Middle East

Israel Chapter
Contact: Sigalit Portnoy
E-mail: sig@taro.co.il

North America

Canada Chapter
Contact: Hein Wick
E-mail: hwick@hwmr.ca
Web site: www.pdacanada.org

Capital Area Chapter
Areas Served: MD, DC, VA, WV
Contact: Barry A. Friedman, PhD
E-mail:
barry.friedman@cambrex.com
Web site: www.pdacapitalchapter.org

Delaware Valley Chapter
Areas Served: DE, NJ, PA
Contact: Art Vellutato, Jr.
E-mail: artjr@sterile.com
Web site: www.pdadv.org

Metro Chapter
Areas Served: NJ, NY
Contact: Nate Manco
E-mail: natemanco@optonline.net
Web site: www.pdametro.org

Midwest Chapter
Areas Served: IL, IN, OH, WI, IA, MN
Contact: Madhu Ahluwalia
E-mail: madhu@cgxp.com

Mountain States Chapter
Areas Served: CO, WY, UT, ID, NE, KS, OK, MT
Contact: Sheri Glaub
E-mail: sglaub@hotmail.com
Web site: www.mspda.org

New England Chapter
Areas Served: MA, CT, RI, NH, VT, ME
Contact: Myron Dittmer, Jr.
E-mail: mditt7845@aol.com

Puerto Rico Chapter
Contact: Silma Bladuell
E-mail: bladues@wyeth.com

Southeast Chapter
Areas Served: NC, SC, TN, VA, FL, GA
Contact: Lisa Eklund
E-mail: lisa.eklund@hospira.com
Web site: www.pdase.org

Southern California Chapter
Areas Served: Southern California
Contact: Saeed Tafreshi
E-mail:
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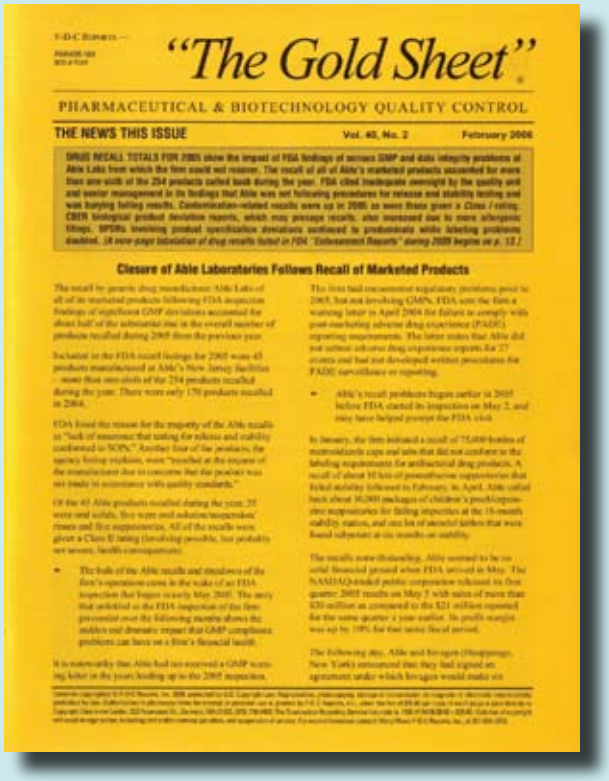
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Are You Ready? Have You Made Training A Winning Strategy?

Joanne W. Cochran, Program Committee Chair

There's not much time to register for the 2006 PDA Biennial Training Conference. From May 8-10, the Philadelphia Convention Center will be the hub of PDA training activity. The conference will provide overviews of a variety of training-related topics; post-conference PDA Training and Research Courses will provide in-depth instruction on the business-side of training.

Why come?

The FDA Connection

Hear what FDA has to say about current training and regulatory topics, including the latest FDA inspection strategy. One of the speakers is a member of the Pharmaceutical Inspectorate of the FDA. Learn what this means for you and your company.

35 Different Concurrent Sessions

Learn from your peers, the people who are managing and training employees in regulatory compliance. Discover how curriculums add to GMP training. See how different training techniques are used in various pharmaceutical companies and what they've found to be most effective. How are internal auditors trained? What about supervisors? How can you maximize your production downtime to take advantage of training? These are just a few of the topics that will be presented at the conference.

This conference is presented by compliance training professionals for training professionals. The experiences that they bring may be similar to your's.

Keynote Presentation Developed for This Conference Audience

This presentation has been tailored to the conference audience through collaboration with some of the PDA member firms and the Rummler-Brache Group. The tools that you will receive will help you to set metric targets and goals aligned with your corporate strategy for GMP compliance.

Trainer's Choice Awards

Find out how other trainers do training at *their* company and what they use. Take the opportunity to see what materials they have developed and how they have used them for their programs. Vote for the ones that you like!

Networking

The conference design provides many opportunities to network with other training professionals, both on an informal and a formal basis. Take advantage of these and share training experiences with other training professionals.

Training Vendors Focused on GMPs

The vendors that will be providing information and services are focused on compliance and GMP training. All have worked within the pharmaceutical industry and within the GMPs.

This conference is focused on you, a training professional in the pharmaceutical industry. Attend and use the three jam-packed days to strengthen your compliance training programs.

As Ben Franklin said: "Does thou love life? Then do not squander time; for that's the stuff life is made of."

Hurry and get your registration in!

I'll be looking forward to meeting you at the May 8-10 conference.

2006 Biennial Training Conference Exhibitors

Company	Table
Gx P Partners	13
Jeiven Pharmaceutical Consulting, INC.	2
Lehecka Pratt Associates, INC.	12
Quality Is Learned, INC.	9
Skills Plus International, INC.	14
Training & Communications Group, INC.	1
Working Words, INC.	10

2006 Biennial Training Conference TRI Courses

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Technical Training as an Integral Part of an Aseptic Operation Quality System
May 11, 2006

The Manager's Role in Training
May 11, 2006

The Evolution of Training: Keeping Pace with the Business and Regulatory Requirements
May 12, 2006

Making the Grade with the FDA
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Nano-Pharmaceuticals – The Road Ahead

D.F. Chowdhury, PhD, Aphton Bio-Pharma and PDA Nanotechnology Interest Group Leader

One thing that was clear at PDA's Nano-Pharmaceutical Conference, held in London in November, was the vast and exciting possibilities that nanotechnology has to offer to pharmaceuticals. Conference delegates were privileged to be able to hear and interact with several prominent figures in the field of nanotechnology, including representatives from the U.S. FDA, the U.S. National Aeronautic and Space Administration (NASA) and the London School of Pharmacy. Innovations are expected to include an almost infinite range of possibilities, from simple manipulation of materials for improving solubility profiles of poorly soluble drugs, to complex nano-electronic devices, targeted and self-regulating drug delivery systems, sophisticated multifunctional particulate systems, and the creation of new mechanisms for drug delivery and therapy, with consequent fading of the boundary between drugs, devices and combination therapies.

The focus of the conference was on risk and safety of nano-based pharmaceutical products and the regulatory implications. It is well understood that with new technologies there are always new risks and hazards which must be addressed. There has already been a call by some for a moratorium on the development of nanotechnology. However, as with all technological advancements, the same moral and ethical obligations and principles apply, but these should be addressed systematically and constructively, rather than bringing the process of knowledge creation to a grinding halt. It is well established that pharmaceutical products undergo some of the most rigorous regulatory scrutiny compared to most other products. Cosmetic products, for example, are not governed by a central regulatory authority, yet these are some of the first class of consumer products to have nanotechnology engineered into them and are already in use.

The current thinking is changes to the regulatory framework specifically for nanotechnology is unnecessary.

Health and safety regulation is risk based, and as such knowledge must be generated to assess the potential risks. The current thinking is changes to the regulatory framework specifically for nanotechnology is unnecessary. **Dr. Nakissa Sadreih**, chair of the CDER Nanotechnology working group, FDA, stated that there were no perceived needs for additional regulation of nano based products. We should bear in mind that nanoparticulate systems have been in development for over 20 years with several approved products incorporating nano-particulates, which despite their size range have not so far raised any peculiar or exceptional safety issues. So, rather than obstruct the path to innovation and scientific advancement, the ambience is one of a concerted effort to accelerate the knowledge generation process. FDA is seeking to speed up innovation and has established the critical path initiative, with the objective of assessing those areas in the pharmaceutical product development process that appear to be stifling innovation. Nanotechnology is one of the subject areas that falls under this initiative.

Moving forward there was a general consensus on the need for a focus on the characterization of materials and better understanding of their functionalities and properties and potential applications. After all, nanotechnology is, by definition, about manipulating matter at the nano scale in a way that imparts new, enhanced and novel properties that open up new uses and applications for the materials. This is an endeavor that potentially requires a whole host of new tools to also be developed and adequately validated for the purpose of characterization. In the pharmaceutical industry this calls for a paradigm shift in inter- and multidisciplinary collaboration by the industry. Professionals at all levels, from scientists to regulatory and quality will also need to undergo an element of education to grasp the basic fundamentals of nanotechnology, though in essence, although the production and characterization technologies may change, the basic principles of the drug development process still apply.

With more and more blockbuster drugs coming off patent, and big pharma in the aggressive pursuit of new products for their pipelines, emerging nano-pharmaceutical technologies are expected to have a dramatic impact on the industry. PDA's Nanotechnology Interest Group continues to work to bridge the gap between academia, industry and regulatory bodies through conferences and workshops.

[To get involved or find out more, contact Dr. Chowdhury, PDA's Nanotechnology Interest Group Leader, Europe, at Fazc@aol.com.]

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Vice President's Message

Gail Sherman

Questions (and Answers) About Training

In sitting down to write this month's message, I realized that I have exhausted topics such as *Here's what TRI did, Here's what TRI is doing, Here's where TRI has been* and *Where TRI is going*. So, I thought maybe I would focus on a topic that is sometimes not understood if you are not a trainer: training. There are many questions one may have about training, and I hope to address some of them here.

First of all: What is training? What are trainers? And how does training fit into PDA's mantra of career-long learning? The components of career-long learning are training, conferences, publications, task forces and interest groups. Each of these provides, in its own way, a mechanism for learning.

Let's get back to training. The Merriam-Webster Dictionary defines training as: *to make skillful or proficient; to bring to a desired standard by careful instruction*. The industry defines training as affecting a change in behavior. Those of us in the training field view training as a change in attitude, skill and/or knowledge. So, where is this going?

When a manager says "train them," the first question a trainer asks is: "Why? Is there a behavior (attitude) that needs to be changed, or a skill that needs to be learned? And is training the appropriate way to get to the end?" The trainer will conduct a "needs assessment" to determine if this particular issue is a training need. The easy way out is often to provide training, not as a proactive learning tool, but as a reactive response to a situation, which could often be external to the issue at hand and not one easily resolved by training.

Training Versus Conference Presentations

When we talk about training at PDA, we mean six hours daily of classroom instruction focused on a specific topic or area which will provide the participant with material which can be used to enhance a skill, change a behavior, or provide knowledge directly related to their work environment. When a potential instructor comes to TRI with a proposal to train, we ask them to complete a course proposal, which includes questions like: course description, number of days, target audience, rationale and learning objectives. We review the focus of the particular suggestion in terms of the take-away information that the student will receive. We want to know if there is enough information for the student to implement a process, or "to get their arms around," when they return to their workplace. And herein lies the difference between training and a presentation at a conference: the typical conference presentation will be much broader in scope, covering the big picture and should, when effective, whet one's appetite for more specific learning which then evolves as training!

There are challenges to providing training which aren't as obvious in other venues, formats or settings. For example, if you look at the definitions above, there is a need to provide information that will change a behavior and/or improve a specific skill set. In a conference setting, you can lecture for 30 or 60 minutes on a hot topic, but you usually can provide no more than an overview (the tactical/strategic issues) of the subject matter addressed but not the "take home get your arms around it stuff!"

And now, another question: So you want to be a trainer? There are many challenges involved with being a good trainer. A trainer does not put everything he/she knows on a slide and read it to the class, hoping that it sinks in and the class goes away happy. A trainer puts a few words on the slide and discusses the information with practical examples and case studies and interacts with the audience to assure that the trainer's knowledge is transferred in a form or format that will enhance the students' learning. Being an instructor has unique qualifications—the most important is the ability to transfer learning, to engage the audience in the content being taught (no matter how boring or how exciting) and to make your students think that you love what you are doing, and you really want to be there—working with them, interacting with them, and most importantly, teaching them something that they will take home with them and put into play in their work environment.

continued on page 38

We couldn't have said it better.

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

FDA Guidance For Pharmaceutical cGMPs
September 2004

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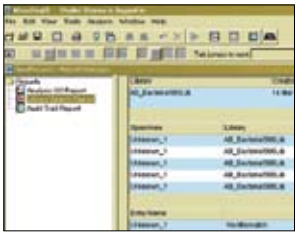

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A Call for New Material

Jessica Petree, PDA

Have a novel idea for a course? Do you know someone who would be a great instructor? Do you feel you're an expert in your field and have much to offer your colleagues? Then contact us! We would love to hear your ideas for new course topics and material. We have many experts teaching many courses, but we can always add more to our growing roster!

How many times have you been looking for a course and not found exactly what you needed or wanted? Why not tell us what your specific needs and wants are? We continually accept proposals for new courses and want to hear your ideas. Please tell us what you, our members, are looking for when seeking training. For a more in-depth explanation of what training is, look to Gail Sherman's VP Message in this issue (page 34), which focuses specifically on this topic.

Currently we are assembling our 2007 course series and are interested in adding some new hot topics to our schedule. If you feel that there are topics important to the industry that aren't currently getting the attention they deserve, please let us know. No one knows better about what you need than you do!

We have offered and will be offering many conferences focused on specific topics, such as Cold Chain Technology and Biotech Process Validation, and there have been many new developments in general FDA guidances. Combine these with the developments in ICH guidances specifically, and there are a number of topics to cover. The PDA Training and Research Institute is very interested in developing courses which complement the meetings you attend, so that we can further your education in those important topics. Because learning is a process that happens every day, we want to provide even more opportunities to promote it.

If you have thoughts on topics to cover, courses to offer, or if you are interested in teaching a course for us, please feel free to contact me via email or phone. I will do my best to accommodate as many requests as possible.

[Contact Jessica at petree@pda.org or +1-410-455-5800.]

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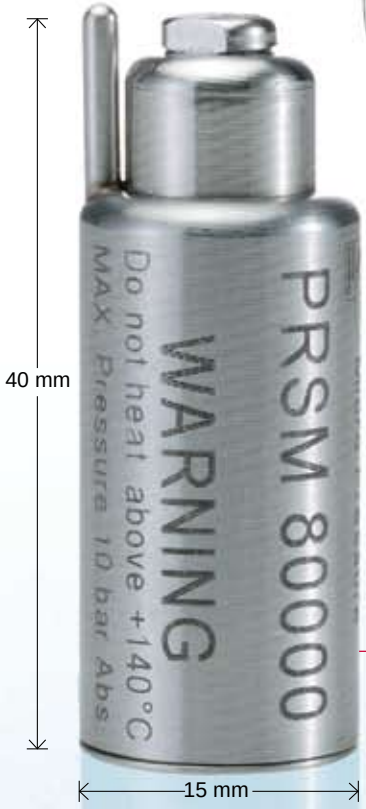

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Personnel Training: A Growing Compliance Concern, continued from page 25

a strong quality system, which could then result in more serious regulatory action.

Notes

1) PDA based the analysis of warning letters issued in FY 2000-2004 on data contained in the following issues of "*The Gold Sheet*": vol. 35, no. 4; vol. 36, no. 4; vol. 37, no. 4; vol. 38, no. 4; vol. 39, no. 3.

A warning letter was counted as citing training only if the citation specifically referenced training as an issue. Nevertheless, other observations might imply training was at issue.

2) FDA's draft guidance for industry: Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations, section IV, The Quality System Model, subsection B(2), Resources (Develop Personnel)

3) "*The Gold Sheet*", vol. 40, no. 2, pp. 1-5.

Regulatory Briefs, continued from page 26

In addition, a further class-specific annex for medicines containing epoetin will be available shortly. The finalization of the guidelines follows an extensive public consultation exercise, including a workshop held in Paris in December 2005, which generated feedback from regulators, industry, academia, health care professionals and patient groups. In accordance with the Agency's commitment to transparency, an overview of comments received will be published shortly.

In parallel, the Agency has also published two new concept papers. The first is a concept paper on the comparability of biotechnology-derived medicinal products after a change in the manufacturing process (nonclinical and clinical issues). The second is a concept paper on the immunogenicity assessment of therapeutic proteins. The public consultation period on these two concept papers is open until June 1, 2006.

Questions (and Answers) About Training, continued from page 34

I hope this helped you understand what training is. I also hope that those of you who have the gift, and want to help train others, will find us, talk to us, and yes, train for us! I leave you with two quotes that further define the art and science of training:

"Who dares to teach must never cease to learn"— *John Cotton Dana,* lawyer, engineer and librarian

"Tell me and I forget. Show me and I remember. Involve me and I understand."—*Chinese proverb*

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

Advertising
Dorothea McGuire, Sales
+1 (301) 656-5900, ext. 150
mcguire@pda.org

Copy Editor
Evelyn Heitman

Layout
Lisa Baehr

Printing and Distribution
H&N Printing and Graphics, Inc.

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

PDA European Office
Industriestrasse 31
6300 Zug
Switzerland
Tel: + 41 41 720 33 07
Fax: + 41 41 720 33 08
E-mail: info-europe@pda.org

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

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FOR FURTHER INFORMATION PLEASE GO TO *www.pda.org*

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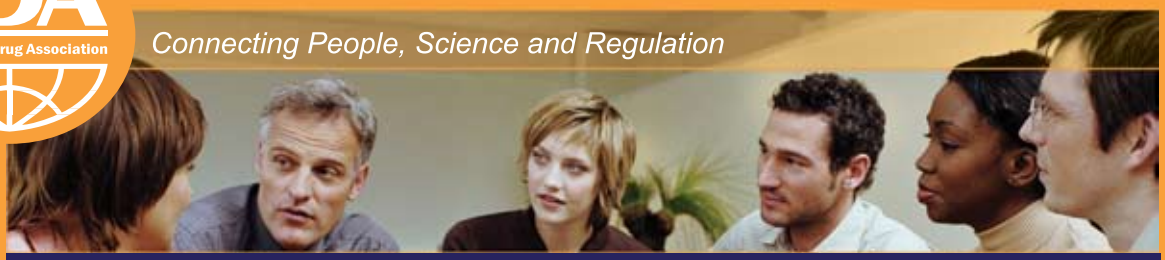

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