Science • Technology • Quality • Regulatory • Community

PDA Letter

Volume XLII • Issue #9

October 2006

In This Issue…

Critical or Primrose Path: *Can the U.S. FDA Solve the "Pipeline Problem"?*

Walter Morris, PDA

Do not, as some ungracious pastors do,
Show me the steep and thorny way to heaven,
Whiles, like a puff'd and reckless libertine,
Himself the primrose path of dalliance treads,
And recks not his own rede.

Hamlet, William Shakespeare

Nothing is more important to the ongoing health of the pharmaceutical/biopharmaceutical industry than the launch of new therapies. All innovator companies rely on a healthy supply of new drugs to drive business growth, expand research and preserve jobs. In addition, the industry's stakeholders—healthcare practitioners/providers, patients and government—rely on new lifesaving medicines to continue to push quality of life improvements to higher levels.

The models for developing new products that once sustained the industry are now deemed outmoded, particularly in an age when the very same stakeholders who want new and innovative treatments are demanding lower costs.

In its report, *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products* (2004), the U.S. FDA noted that the cost of new drug development expanded 55% in 2000-2002. In that same period, the number of submissions for new molecular entities (NMEs) continued a downward slide. This troubling dynamic represents the "pipeline problem."

FDA believes it can play a central role in reinvigorating the drug product pipeline. In the Critical Path report, FDA discussed the need for a "new product development toolkit" that would include "powerful new scientific and technical methods" and "superior product development science." These are needed, FDA states, because medical innovation has outpaced the medical product development process.

"Because FDA is uniquely positioned to help identify the challenges to development," the Agency writes, "we need to work with the larger scientific community on developing solutions."

continued on page 21

PDA Parenteral Drug Association

Connecting People, Science and Regulation℠

Not *Everything* that happens in Vegas...

Stays in Vegas

SAVE $200
Register by December 29
www.pda.org/annual2007

PDA 2007 ANNUAL MEETING – MARCH 19-23

Putting Science and Technology into Practice

CONFERENCE | EXHIBITION | TRAINING COURSES

Take home the Knowledge, Connections and Experience that will make a difference all year.

What's new this year? The exciting setting of Las Vegas and an expanded schedule of networking activities make it easier than ever to meet colleagues, exchange ideas and have fun!

What has not changed? Our commitment to providing valuable bio/pharmaceutical knowledge, insights and training

Join PDA at the spectacular Red Rock Resort, Casino and Spa

- Develop your practical knowledge of science and technology
- Connect with decision makers and thought leaders
- Strengthen your role in advancing sound science and regulation

Expanded networking activities you can't afford to miss!

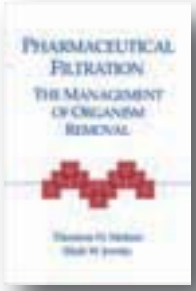
- PDA's 1st Annual Golf Tournament at Arroyo Golf Club
- Las Vegas signature shows and live entertainment
- Spouse/guest/child day programs
- Local sightseeing tours

PLUS: New member orientation, receptions, an expanded career fair and a gala event you won't forget!

PDA℠
Parenteral Drug Association

PDA Parenteral Drug Association Bookstore

Bestsellers



Pharmaceutical Filtration: The Management of Organism Removal

by Maik W. Jornitz and Theodore H. Meltzer, PhD

Offers a deep, comprehensive understanding of the all connections between the different aspects of the filtration universe.

Item No. 17235 PDA Member $225 Nonmember $279

Risk Assessment and Risk Management in the Pharmaceutical Industry: Clear and Simple
by James L. Vesper
Begins with history, definitions, how we think about risks and hazards, it gives overview of the risk management process and commonly used risk assessment methods and tools.
Item No 17219 PDA Member $210 Nonmember $260

Encyclopedia of Rapid Microbiological Methods, Volume I, II, III
edited by Michael J. Miller, PhD
Focuses on regulatory and compendial initiatives currently in place that help pharmaceutical microbiologists and managers implement RMM in their facilities.
Item No. 17252 PDA Member $730 Nonmember $899

Filtration Handbook Series
by Maik W. Jornitz and Theodore H. Meltzer, PhD
Item No. 17262, PDA Member $420 Nonmember $525

Environmental Monitoring, Volume I, Volume II and Protocol CD
edited by Jeanne Moldenhauer, PhD
Describes methods for developing and operating an appropriate, sustainable microbiological program both in the lab and during production. Numerous useful protocols are included on the CD.
Item No. 17239 PDA Member $530 Nonmember $659

PDA Archive on CD-ROM – PDA Archive Retrieval Index (2006 version)
Fully-searchable four disk CD-ROM archive includes all PDA Journal articles, Technical Reports and Monographs, Technical Bulletins and select Conference Proceedings.
Item No. 01101 PDA Member $395 Nonmember $590

Microbiology in Pharmaceutical Manufacturing
edited by Richard Prince
This book systematizes and updates the technical discipline of pharmaceutical microbiology. Providing valuable knowledge for the novice and expert alike, it contains the wisdom and guidance of 40 leading pharmaceutical microbiologists, engineers, and other thought leaders.
Item No. 17185 PDA Member $285 Nonmember $359

Laboratory Validation: A Practitioner's Guide (20% OFF)
edited by Jeanne Moldenhauer, PhD
This excellent guide and reference provides an overview of validation from a laboratory perspective.
Item No. 17201 PDA Member $295 Nonmember $369

Pharmaceutical Quality
edited by Richard Prince
How do you define quality? Pharmaceutical Quality offers examinations of quality from international, governmental, industrial, and individual perspectives.
Item No. 17207 PDA Member $285 Nonmember $359

Risk-Based Software Validation: Ten Easy Steps
by David Nettleton and Janet Gough
This book offers a systematic, ten-step approach, from the decision to validate to the assessment of the validation outcome, for validating configurable off-the-shelf (COTS) computer software that generates data or controls information about products and processes subject to binding regulations.
Item No. 17256 PDA Member $200 Nonmember $249

Table of Contents

Cover art: FDA aims to have the Critical Path to drug approvals operate less like a mountain pass and more like a superhighway.

Coming Next Month...
FDA and EMEA End of Year Wrap-Up

DECEMBER 6-7, 2006

Omni Shoreham Hotel

Washington, D.C. USA

ISPE and PDA Present

CHALLENGES OF IMPLEMENTING ICH Q8 & Q9

Practical Applications

Part of a new conference series co-hosted by the International Society for Pharmaceutical Engineering and the Parenteral Drug Association

www.ispe-pda.org/Q8Q9

PDA Thanks All the Members Who Visited 3 Metro Center…

We Look Forward to Seeing You at Bethesda Towers!

The following photos are of members and others who visited PDA's former location at 3 Metro Center in Bethesda during the last half of year we occupied the space.

The PDA Board of Directors meeting, December 2005. Facing the camera are (l-r) Bob Myers, Yoshihito Hashimoto, Jennie Allewell, Vince Anicetti and Stephanie Gray.

(l-r) Nikki Mehringer, Rebecca Devine, Eric Sheinin and Laura Thoma

Georg Roessling and Kathleen Greene

Lisa Skeens flashes a brilliant smile

The Board of Directors honored both Nikki Mehringer and Stephanie Gray. Nikki was presented a plaque and a gift for her two-years of service as Chair. Stephanie, who retired from the board, was presented a certificate of appreciation.

Members of the Regulatory Affairs and Quality Committee met on a beautiful spring day in Bethesda. Pictured are (l-r) Steve Mendivil, Amy Scott Billman, Bob Dana, Zena Kaufman, John Towns and Barbara Zinck.

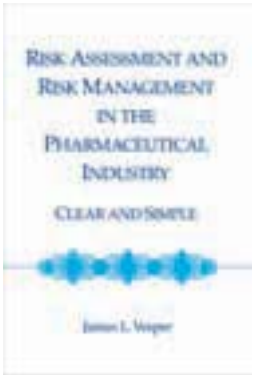
Bob Dana presents a certificate of appreciation to Amy Scott Billman for her two years of service as RAQC Chair.

PDA staff (l-r) Matt Clark, Gail Sherman and Bob Dana are presented a gift from a delegation of pharmaceutical representatives from Tunisia. The group visited PDA's headquarters to learn more about PDA and our Mission.

PDA
Parenteral Drug Association

Connecting People, Science and Regulation℠

Risk Management Series

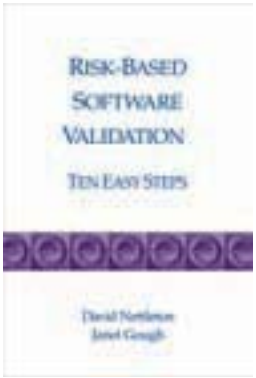


Risk Assessment and Risk Management in the Pharmaceutical Industry: Clear and Simple

James L. Vesper

Explores the history, definitions, and how we think about risks and hazards, offering an overview of the risk management process and commonly used risk assessment methods and tools.

■ Item No 17219 PDA Member $210 Nonmember $260



Risk-Based Software Validation: Ten Easy Steps

David Nettleton and Janet Gough

This book offers a systematic, ten-step approach, from the decision to validate to the assessment of the validation outcome, for validating configurable off-the-shelf (COTS) computer software.

■ Item No 17256 PDA Member $200 Nonmember $249

Multimedia Program

Shep's Risk Management Based Systems Audits of Quality Systems and Their Sub-Systems and Their Critical Quality Attributes

Each of these 19 narrated programs is a proactive management audit tool that identifies and evaluates specific quality systems within development, quality assurance, quality control and commercial production operations.

Individual program price: PDA Member $300 Nonmember $360

- API-Selected Operations [Item No. 11062]
- Buildings and Facilities [Item No. 11063]
- Calibration and Maintenance [Item No. 11064]
- Complaints System [Item No. 11065]
- Control of Components and Drug Product Containers and Closures [Item No. 11066]
- Equipment [Item No. 11067]
- Quality Control Laboratory Operation [Item No. 11068]
- Manufacturing [Item No. 11069]
- Out Of Specifications (OOS) Investigations [Item No. 11070]
- OOS Review Board [Item No. 11071]
- Packaging and Labeling Operations [Item No. 11072]
- Product Release [Item No. 11073]
- Production and Process Controls [Item No. 11074]
- QA/QC Operations [Item No. 11075]
- Recalls [Item No. 11076]
- Records and Reports [Item No. 11077]
- Stability Operations [Item No. 11078]
- Technology Transfer [Item No. 11079]
- Validation [Item No. 11080]

www.pda.org/bookstore

In Focus: The TR-1 Feedback Tour, Summer 2006

In the September issue of the *PDA Letter,* we included an update on the TR-1 feedback tour. Member's of the revision task force visited Cork, London, Pavia and Bethesda during the summer months. In this issue, we would like to share some great images from the tour!

Particpants in London: **front row (l-r)** Nick Hill, Keith Shuttleworth, Genevieve Lovitt-Wood, Nigel Halls, Georg Roessling, Steve Pickering; **second row (l-r)** Brian Reeks, Andrew Webb, John Spenn, Kris Evans, Rich Levy, Dave Karle, Paul Hargreaves, Jim Tyrrell; **back row (l-r):** Peter Bedingfield, Andrew Hopkins, Frank Talbot

MHRA's Paul Hargreaves discussing TR-1 in London.

Participants in Pavia: **front row (l-r)** Giuseppe Ruggirello, Gilberto Dalmaso, Barbara Sambuco, Emanuela Fabbri, Lorella Chiappinelli, Nigel Halls; **back row (l-r)** Mike Sadowski, Rich Levy, Volker Eck, Paul Hargreaves, Gabriele Gori, Georg Roessling, Bob Myers

Irving Pflug and Anne Nicholas listen to presentations in Bethesda.

Mike Sadowski (standing) speaks to the audience about TR-1 in Bethesda. Sitting are (l-r): Carlos Arenas, Keith Shuttleworth, Kris Evans and John Braun.

Barbara Sambuco, Chair of the Pavia meeting, welcomes attendees and speakers.

PDA Parenteral Drug Association

Connecting People, Science and Regulation SM

2006 PDA/FDA Joint Regulatory Conference

Web Seminars

Cost-effective ■ Convenient ■ On-Demand ■ No travel required

The latest science, technology and regulatory information recorded, live, and available on-demand, from the convenience of your computer.

Impact of ICH Q8, Q9 and Q10 Implementation on Regulatory Submissions – An Industry Discussion

Industry will discuss different strategies being used to incorporate the concepts from the Q8, Q9 and Q10 guidance documents into regulatory submissions (INDs, License Applications - NDAs, BLAs, Post-Approval Supplements).

Presenters
Jackie Schumacher, Associate Research Fellow – Regulatory CMC, *Pfizer Global Research and Development*
Sally Anliker, PhD, Manager, Global Regulatory CMC, *Eli Lilly and Company*
Neil Wilkinson, Director, *AstraZeneca*
Richard Saunders, PhD, Vice President, Pharmaceutical Development, *Wyeth Research*

Effectively Applying Failure Mode Analysis in the Pharmaceutical and Biotech Industry

A review of the principles of FMEA as well as the tools to apply it. Case studies are presented and discussed to provide participants with actual examples of FMEA being applied. This session is an interactive workshop allowing participants to ask questions of the two instructors regarding considerations and tips in effectively apply FMEA so as to extract its maximum value.

Presenters
Bikash K. Chatterjee, Chief Operating Officer, *Pharmatech Associates, Inc.*
Warford Reaney, Director, Operations, *Pharmatech Associates, Inc*.

Continuous Improvement

Bose Electronics has been a major leader in the electronics industry employingsuch techniques as Six Sigma to manufacture the highest quality sound equipment with limited defects reaching the consumer. This session will offer an overview of how they have achieved success in the area of continuous improvement.

Presenters
Todd Studer, Continuous Improvement Manager, *Bose*
Keith Webber, PhD, Deputy Director, Office of Pharmaceutical Science, *CDER, FDA*

Strategically Applying Regulations and Quality Management In the Business Environment

A focused presentation on the strategic importance and downstream value for quality from public health, regulatory and economic perspectives.

Presenters
Daniel Diermeier, PhD, *IBM*, Distinguished Professor of Regulation and Competitive Practice, *Northwestern University*
Scott Gottlieb, PhD, Deputy Commissioner for Policy, *FDA*

Industry Executives Discuss Strategically Applying Regulations and Quality Management In the Business Environment

An international panel of industry senior executives join Dr. Diermeier in an interactive Q/A session, discussing how they have strategically positioned quality in their companies. They discuss their roles, the roles of their executive team, the quality unit, and operations.

Presenters
Daniel Diermeier, PhD, *IBM*, Distinguished Professor of Regulation and Competitive Practice, *Northwestern University*
Josh Boger, PhD, CEO, *Vertex Pharmaceuticals*
Guy Villax, CEO, *Hovione*

Understanding the Impact and Applying the Concepts of ICH Q8, Q9, Q10

FDA officials and industry experts explore the concepts, opportunities, challenges, and downstream implications of these guidances.

Presenters
Louise Johnson, Vice President, Quality, *Vertex Pharmaceuticals*
Chris Joneckis, Senior Advisor for CMC Issues, *CBER*, *FDA*
Jon Clark, Associate Director for Policy and Development, *OPS*, *CDER, FDA*

Train your entire staff at one price

Price after 10% Off
Member $355
Nonmember $405

Price after Sept. 16
Member $395
Nonmember $450

Register at the conference and receive 10% Off!

All recorded sessions will be available after September 29, 2006 at:

www.pda.org/webseminars

PAT: Déjà vu All Over Again?[1]

Lynn D. Torbeck, Torbeck & Associates

The current Good Manufacturing Practice regulations were published in the Federal Register on September 29, 1978. Section 211.110(a) of those regulations contains several concepts that have substantially changed our industry since they were approved. I am particularly impressed by one specific sentence:

"Such control procedures shall be established to monitor the output and to *validate* the performance of those manufacturing processes that may be responsible for causing *variability* in the characteristics of in-process material and the drug product."

I enjoy pointing out to people that the words "validate" and "variability" occur in the same sentence. Not to be putting words in the mouths of those who wrote this section, but it always seemed to me that the authors were telling us to find, control, manage and, if possible, reduce variation as part of our validation studies.

I am supported in that idea by a journal article entitled, "The FDA Viewpoint," written in 1985 by Ed Fry (Fry, 1985) who was then Director, Division of Drug Compliance, CDER Office of Compliance, U.S. FDA. In that paper, speaking for the FDA, he made several profound and important statements about validation and its connection to variability:

Experiments are conducted (that is, validation runs) to assure that factors that would cause variability, are under control and will result in an output that meets the specifications within the limits of the ranges that you had previously established.… The regulations require validation of those processes responsible for causing variabilities in characteristics of in-process materials or finished products.…However, the regulation implies that not everything that takes place in a pharmaceutical manufacturing plant causes variability. Therefore, some things don't need to be validated. We never intended to require that everything [that] takes place in a manufacturing operation is subject to a validation study.

Are we coming full circle back to the original intention of the GMPs with process analytical technology? Is there a feeling of déjà vu in reading the PAT. Guidance? In that guidance, we find many references to statistics and variability:

- *What sources of variability are critical? (p. 5 of the guidance)*
- *How does the process manage variability? (p. 5)*
- *Facilitating continuous processing to improve efficiency and manage variability. (p. 5)*
- *A process is generally considered well understood when (1) all critical sources of variability are identified and explained; (2) variability is managed by the process; and, (3) product quality attributes can be accurately and reliably predicted over the design space. (p. 6)*
- *A flexible process may be designed to manage variability of the materials being processed. (p. 9)*

Variation is the Enemy

Variation (i.e. change or differences) is one of the great concept of statistics. In our personal lives, variety is the spice of life. We want and seek change in our foods, music and entertainment. But, in many areas, variation is the enemy and must be dealt with directly. In business processes, such as accounts payable or purchasing, variability is the source of errors, lost time and lost business. In clinical and preclinical studies, variation obscures and complicates the search for important medical effects. In quality and manufacturing, excessive variation often results in out-of-specification results, out-of-trend results, SOP deviations, data outliers, rejected and recalled lots, Form 483 observations, warning letters, massive fines, consent decrees and loss of business. Variation is the enemy of Safety, Strength, Quality, Identity and Purity, or SSQuIP. If we decrease variability we increase our ability to achieve our goals at less cost.

We, as individuals and as an industry, need to work every day to reduce variation and variability in our selves, our methods, materials, measurements, machines, processes, products and the environment. Each of us must ask ourselves and each other the question: "Where is the variability coming from and what have I, or we, done to manage it, minimize it, control it and, if possible, eliminate it?"

Statistics and statistical thinking (Torbeck, 2001) are the tools needed to address this unwanted variation. It is a natural progression to go from process design to statistical thinking, because:

Where there is process, there is measurement.

Where there is measurement, there is data.

Where there is data, there is variability.

Where there is variability, there is statistics.

Where there is statistics, there is statistical thinking.

Statistical thinking can be summarized with these ten concepts:

1. Work occurs in systems of processes and subprocesses of interconnected and interrelated steps. Processes have Suppliers that provide Inputs into the Process activity. The end result is the Output that then goes to the Customer (SIPOC). This model provides an overview that is useful for broadly defining the process.
2. Processes can be mapped, flowcharted, studied ➤

Let Our Expertise Be Your Safety Net

We're Texwipe®. We're Here to Help.

The technical expertise at ITW Texwipe is your assurance of the most reliable contamination control for your cleanroom. Our broad line of consumables includes the right product for your specific application.

When you specify Texwipe, we support you with training, educational tools and protocol recommendations.

Whether you operate a Class 1 or Class 100,000 cleanroom in a sterile or an industrial environment, our products ensure your operation runs as it should. We help you reduce your cost of ownership by providing the right products to optimize your cleaning protocols.

Visit our website to find the optimum solutions for your specific applications. Or call us. We're Texwipe. We're here to help.

Dry Wipers • Pre-Wetted Wipers • Swabs • Sterile Products • Stationery • Mops

ITW Texwipe®

Quality. Consistency. Support.

www.texwipe.com

	North America	Europe	Asia
Tel	201 684 1800	+45 87 400 220	+65 6468 9433
Fax	201 684 1801	+45 87 400 222	+65 6468 6772
E-mail	info@texwipe.com	europe@texwipe.com	asia@texwipe.com

systematically, understood, and improved. However, optimizing each step separately may result in a sub-optimum process.

3. Work is done by teams of people with differing backgrounds, education, expertise, skills, needs, and expectations all working for a common goal.
4. Process outputs vary due to both special or systematic causes and common or random causes.
5. Cause-and-effect relationships are the bedrock of science. These relationships can be found, quantitated, studied, understood and exploited to control special cause variability.
6. Excessive variability is the enemy of the cGMP's, validation, SSQuIP (safety, strength, quality, identity, purity), productivity, cycle time, efficiency and profits.
7. Variability can be measured using the standard deviation and thus quantitated, studied, and understood.
8. Statistics is the science of variation and uncertainty.
9. Excessive variability in processes can be reduced.
10. Organizations succeed and survive by continuous improvement using teams to reduce variation and to bring processes into engineering and statistical control.

Sources of Variation

A major advance in modern statistical thinking is that variability can not only be measured, it can be reduced through specific actions. Variation in our product and business processes is often thought of as coming from either a single source or from multiple sources.

The single source (called a special cause) of variation is addressed in the pharmaceutical industry by deviation investigation, root cause analysis, corrective action and where possible, preventive action or CAPA. We, as an industry, have more or less achieved this activity, but many CAPA's and investigations do not realize a real solution or find the root cause because of a lack of true process understanding. Ironically, there has been a historic disincentive to finding problems because of the fear of indicting a validated process.

In contrast, common causes are the result of a summation of many small sources of variations. This has not been well addressed in theory or in practice. Root cause analysis doesn't work for common cause variation since the results can be attributed to multiple small sources of variability all adding together. Textbooks tend to call this "inherent" variation, implying there is nothing that can be done to reduce it.

> ***If you can't describe what you are doing as a process, you don't know what you're doing.***
>
> **—W. Edwards Deming**

Root Cause vs. Common Cause

In its CGMPs for the 21st Century report, FDA defines "root cause" as the singular source of a deviation/process failure and "common cause" variability as inherent variability stemming from a number of sources: excipients, equipment, measurement systems, etc.

Controlling Common Cause Variation

However, I think there are specific actions that can reduce these sources of common cause variation. It does require, however, the concerted effort of many people working together, and thus becomes a management issue of implementation and culture change.

There are five variations on the theme of consistency that, when taken together, can have a real impact on the reduction of common cause variation.

1) Operational Definitions: Unlike a short dictionary definition, an operational definition can be several paragraphs or several pages long. Note that SOPs are a form of operational definitions. But, we can further reduce variation by applying the concept to situations in which it is not clear how things are to be performed. Activities considered to be "common practice" are usually done differently by different people.

For example, what does it mean to "sample the tank" or "soak until soft and pliable"? Consistent definitions and consistent actions will yield more consistent results and less variation.

2) Achieve the Target: Many characteristics or variables have specification criteria. The usual cultural attitude is, "If we can get within the limits of the criteria or specification, then we have met the goal." I propose, instead, that we all work to achieve the target every time, often the center of the limits, not just fall within the limits.

For example it is common to have a specification like 25 to 35 minutes. I suggest that it should be written as 30 (25, 35) minutes, thus forcing the reader to see the target first. Admittedly, if only one person does this once or twice, no progress is made. But if hundreds of employees adopt a personal goal of everyday always striving to achieve the target every time, we will begin to see variation reduce.

3) Flexible Consistency: Sounding contradictory, this idea is another way to minimize common cause variation. Often in our work, there is more than one acceptable way to perform an activity. People doing these activities should agree, as a group, to doing it one way, and then they all do it that way all the time without exception. If, at a later time, it is proposed that ➤

there is a better way, all of the people should change all at one time to the new way of doing the work.

For example, a test method has many activities that are not detailed in the method documentation. The analysts that use that method should agree on doing these activities the same way every time to minimize the method variability. Again, one incidence is negligible, but implementing the concept hundreds of times will reduce variation.

4) Hold Constant Controllable Factors: This is almost too obvious to mention, but controllable factors such as time, temperature, pressure and speed should not vary if they can be controlled and held constant. Don't let so-called "noncritical" factors vary if they can be held constant. Every little bit helps.

5) Mistake Proofing: We need to design our processes to make it impossible or nearly impossible to make a mistake. Examples include putting mechanical "stops" on equipment so that it is not possible to make a bad part.

One biotech company color coded two bioreactors blue and green and then used light blue and light green paperwork so that misplaced paper forms were obviously out of place. Another classic t example is that of a truck frame assembly process where a nut had to be torqued to a given level. At that station of assembly there were three operators. The person who was free had responsibility for tightening the nut with a torque wrench. Inevitably, the operators would mistakenly think the other person had torqued the nut. To prevent this confusion, the torque wrench was placed in a small bucket of white paint. If the nut had been tightened, the operators would see it clearly—white paint on the nut. If it had not been tightened, everyone on the assembly line would have a visual signal reminding them that it needed to be done. Expanding this concept a hundred fold can have dramatic results on variation. In business processes, for example, forms design can have a dramatic impact on reducing mistakes in recording information and data.

Conclusion

In summary, this paper proposes that the FDA has been asking the pharmaceutical industry for close to 30 years to reduce special and common cause variability as a key element of process validation. Now that same theme is an integral part of Process Analytical Technology and Quality by Design, QbD.

Notes:
1. Apologies to Yogi Berra

References:
CGMPs, *Federal Register* 43, September 29, 1978, page 45076

Fry, E., "The FDA's Viewpoint," *Drug and Cosmetic Industry,* Vol. 137, No. 1, July 1985

Torbeck, L., "Statistical Thinking," *Pharmaceutical Technology,* July 2001

U.S. FDA, *Guidance for Industry: PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance, 2004*

U.S. FDA, Innovation and Continuous Improvement in Pharmaceutical Manufacturing: Pharmaceutical CGMPs in the 21st Century, 2004, p. 12

Five Approaches to Limiting Common Cause Variability

This paper has recommended five specific approaches be used to reduce common cause variation and achieve to consistency. It is recognized that these approaches are easy to articulate and difficult to implement. They require a culture change. They require consistent support and reinforcement by management at all levels everyday in all aspects of business. While not easy, the rewards are real and financially substantial.

1. Operational Definitions
2. Achieve the Target
3. Flexible Consistency
4. Hold Constant Controllable Factors
5. Mistake Proofing

Clean Easily in 50% Less Time

DESIGNED TO ELIMINATE MESSY MOP & BUCKET SYSTEMS

CORE 2 CLEAN

- Incorporates the ability to use a Quick-Disconnect Sprayer, Trigger-Activated Mop and Multi-Direction Fogger from one source
- Provides superior wetting of the surface
- Presents a clean solution to the surface without the need to rinse
- Powered by compressed air and ASME rated to 100 psi
- Stainless steel construction can be completely steam sterilized
- Available in a 2 and 5 gallon tank sizes with easy, locking roll caster wheels
- Compatibility tested with all VAI sterile chemicals
- Bottom valve for easy drainage
- Easy-to-read pressure gauge
- Pressure release valve

SUPERIOR PRODUCTS • SUPERIOR IDEAS • SUPERIOR SOLUTIONS

vai
Veltek Associates, Inc.

(610)-644-8335
www.sterile.com

INNOVATIVE CLEAN ROOM PRODUCTS

Recent Sci-Tech Discussions: Total Organic Carbon in Cleaning Validation and Vet Drug Production in Human Drug Plants

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.

I've heard about use of Total Organic Carbon (TOC) in cleaning processes and validation and in application of cleaning methods. I'm glad to hear your opinions in this matter.

Respondent 1: In my opinion, TOC is the method of choice for cleaning validation. It is a simple technique and easy to develop methods for. There are those who try to dismiss TOC due to its non-specificity, but that is actually what is its greatest strength in cleaning validation. TOC responds to the presence of any organic compounds and the vast majority of Active Pharmaceutical Ingredients (APIs) and excipients are organic compounds. When a surface is truly clean, you will get no signal from TOC; meaning everything is gone. I like to call TOC the "Geiger counter" for cleaning validation. I don't care whether you're looking for uranium, plutonium or whatever, if there is no reading on the Geiger counter, then none of them are present. Same idea for TOC. If there is no TOC signal, then neither your API, nor your excipients nor your cleaning agents are there. TOC can tell you a great deal about your cleaning processes. The other complaint you still hear is that TOC cannot detect water-insoluble compounds. This is not true. From what I have seen there is no such thing as a completely water-insoluble compound. They are all water soluble to some degree and most are soluble well into the part per million range. TOC can easily detect down to the part per billion range and the trace amounts of residues that would result in these levels are easily solubilized from surfaces. At a former company, we demonstrated this for a number of compounds and I have been presenting this data at cleaning validation conferences for nearly 10 years now. Yet, you still hear people say TOC cannot detect water-insoluble compounds. So, as you can see TOC has my vote for use in cleaning validation.

Respondent 2: The Total Organic Carbon (TOC) assay is a useful one in cleaning validation, especially for biopharmaceutical products. Most biotechnology companies use the TOC assay for cleaning validation. It is not the only available assay and it may not be the most suitable one in all cases. A few things to consider:

1. You should know the organic carbon content of your products. Typically, globular proteins have around 50% carbon. The carbon content of other products may be determined using chemical references such as the Merck Index. In some cases, you may have to determine the organic carbon content experimentally.

2. The Total Organic Carbon assay measures *all* sources of organic carbon, whether they come from residual product, the swab, or the analyst's fingers. The assay cannot differentiate between different sources of organic carbon.

3. If the product contains significant inorganic components such as magnesium, aluminum, phosphorus, etc., these components may be selectively left behind by a cleaning process designed to remove organic components. You may want to add another assay such as Atomic Absorption or Inductively Coupled Plasma Etcher (ICPE) for the inorganic components.

4. Because TOC is a non-specific assay, it cannot determine the nature of any organic residues. Identification of the residues left behind by a cleaning process can be a valuable aid to cycle development.

To sum up my recommendations, take a look at the chemistry of your product, and use the assay(s) best suited to the product characteristics.

Respondent 3: I agree…that TOC is an extremely useful assay. I would still suggest that you know what your expected residues are before selecting your assay. TOC is useful for 95% of the products and processes used in pharmaceuticals. You need to be aware of the other 5% of the products and processes that TOC is not suitable for.

Respondent 4: While TOC theoretically detect residues well below 500 ppb, the practical limit is the TOC content of the water you are using for a blank. Typically, this will be around 100 - 200 ppb. For your example, if you use the 500 ppb laundry water as a blank, you will not be able to reliably detect TOC contamination below this level.

Is it acceptable to manufacture veterinary medicines in the same facility as human drugs? Are there any guidances regarding this? Where can I find them?

Respondent 1: Yes, it is acceptable to produce veterinary medicines in human facilities as many of the molecules used are the same, and the GMP and quality requirements for vet drugs are as stringent as that for humans. Of course the issues related to use of facility for potent molecules and specific classes of antibiotics applies.

Respondent 2: Yes, the same identical GMP rules apply. Only difference between human and veterinary pharmaceuticals are the number of legs the user has: two-legs for people vs. four legs for animals (usually!), and hence absolutely no impact on GMPs and manufacture.

Respondent 3: I looked at that question myself a couple of years ago, and will answer from a biologicals standpoint. I think the answer is it all depends. As far as I am aware, there are no specific guidelines dealing with such a scenario. In the EU GMPs apply to the manufacture of human and veterinary medicines. There are some differences depending on what type of product you make (e.g., biologics, proteins or vaccines etc., or chemicals). In the United States, both FDA and USDA regulate depending on the nature of the product. The USDA can be more strict in certain cases (for example, controlling the import and use on your site of pathogenic mircoorganisms). Outside of the USA, if you manufacture or do business on a global basis, with the USA and your own country, you could find yourself following USDA wishes over GMPs concerning your pharmaceutical development and manufacturing operations. Even if you make the same product(s) for human and veterinary use, you may find that your local regulatory authorities place restrictions on their manufacture that could make it easier to have two separate facilities (personnel segregation, material flows, cleaning validation, product storage). I strongly recommend that you discuss the issue with them (both human and veterinary), and having addressed all of the GMP issues in a risk analysis, demonstrate on a case by case basis that you can do it safely.

Respondent 4: I don't disagree, but: the European guidances on human and veterinary GMPs are now split so one might come into some difficulties if one assumes they are identical. In the United Kingdom, the medicines act has now been amended and treats veterinary GMPs quite differently from human GMPs, even if the text is the same or similar.

Respondent 5: This kind of question does arise at times. It is quite likely to be an issue in clinical manufacturing facilities. The usual relevant concept is as follows: With a multiple use facility, you should operate it at the highest applicable regulatory standard. If I presume that Human cGMP requirements call for "higher" levels of compliance, then you should not have a problem making vet products in this facility. You would still want to check for additional specific requirements for the specific vet products (if there are any). In most situations, if your facility is in compliance with human cGMPs, you could make products for any use, observing whatever additional precautions required the products. It is possible that cleaning validation may create some problems for you, depending on the vet products.

Respondent 3: I'm not convinced that human GMPs should be seen as having a "higher" standard than veterinary GMPs. On the biologics side (decontamination and cleaning) will certainly be an issue, particularly if one is using certain veterinary pathogenic microorganisms. However, I would like to come back to my comments in my previous email that one will need a well reasoned risk analysis and a watertight argument and data in order to convince some regulatory authorities that you can do both in the same facility.

Respondent 5: I do not have experience on the biological side. I expect you are right about that. Past GMP considerations, you are correct that there will still be a need for analysis of all factors. My thinking is that if the facility is in compliance with human GMP requirements, it should be feasible to deal with additional factors associated with specific products. But you would still need to be prepared, with data, to present your case.

Respondent 6: Good point [Respondent 4]. The GMP directives in the EU were always separate for human and veterinary medicines (91/356/EC (Human) and 91/412/EC (Veterinary)); however, 91/356/EC has now been superseded by 2003/94/EC, but 91/412/EC has yet to be updated. Fundamentally, they end up at the same point as far as the guidance goes—see the attached link to Eudralex volume 4: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev4.htm

Respondent 4: Agreed, but in the UK the regulations have also been split between human and veterinary, c.f. Statutory instruments 2005 2789 and 2005 2745. Even though the words (at the moment) may say the same thing, the two guidances now have different basis in law. Interestingly (sic) SI 2005 2789 references directly EU directives; therefore, once those directives get amended ipso facto those amendments become UK legal requirements, whereas in the past they did not do so until the regulations were updated. One can only assume that the motivation behind splitting the directives and the regulations between human and veterinary is that "someone" intends different requirements to be incorporated into them, but we shall see in the fullness of time. Personally I think it makes sense.

PDA Calendar of Events for North America

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

Conferences

October 10-11, 2006
PQRI Workshop on Excipient Testing and Control Strategies
Bethesda, Maryland

October 23-25, 2006
The Universe of Pre-Filled Syringes & Injection Devices
(Conference and Exhibition)
Bethesda, Maryland

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

December 6-7, 2006
2006 ISPE/PDA Joint Workshop: Challenges of Implementing ICH Q8 and Q9 — Practical Applications
(Conference and Exhibition)
Washington, D.C.

January 29-31, 2007
PDA Emerging Manufacturing and Quality Control Technologies Global Conference
(Conference and Exhibition)
San Diego, California

March 19-23, 2007
2007 PDA Annual Meeting
(Conference, Courses and Exhibition)
Las Vegas, Nevada

September 24-28, 2007
2007 PDA/FDA Joint Regulatory Conference
(Conference, Courses and Exhibition)
Washington, D.C.

Training

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

Laboratory Courses

October 5-6, 2006
Developing and Validating Cleaning and Disinfection Programs for Controlled Environments

October 24-25, 2006
Validating a Steam Sterilizer

October 26-27, 2006
Fundamentals of D, F and z Value Analysis

October 30-31, 2006
Environmental Mycology Identification Workshop

November 14-15, 2006
DoE Basics for PAT Applications

November 15-17,2006
Cleaning Validation

December 5-7, 2006
Practical Aspects of Aseptic Processing

January 22-26, 2007
Aseptic Processing Training Program

Lecture Courses

October 16-17, 2006
Computer Products Supplier Auditing Model: Auditor Training

October 23-25, 2006
Advanced Pharmaceutical Filtrations and Filters

Course Series

October 16-18, 2006
Boston Course Series
Boston, Massachusetts

Chapters

October 10, 2006
PDA Southeast Chapter
PDA Southeast Chapter Fall Meeting and Vendor Show
Chapel Hill, North Carolina

October 19, 2006
PDA Midwest Chapter
Dinner Meeting — Maintaining the Validated State of Analytical Laboratory Instrumentation GMP/GLP Environments
Indianapolis, Indiana

October 25, 2006
PDA Capital Area Chapter
Dinner Meeting — Evaluating Risk in Aseptic Processing: The Akers-Agalloco Method
Gaithersburg, Maryland

November 3, 2006
PDA Southeast Chapter
Social Networking — 2006 PDA Southeast Chapter Fall Golf Social
Cary, North Carolina

November 16, 2006
PDA West Coast Chapter
Dinner Meeting
Location to be determined

November 29, 2006
PDA Delaware Valley Chapter
Dinner Meeting
Malvern, Pennsylvania

November 29, 2006
PDA New England Chapter
Afternoon Workshop — Contract Manufacturing
Location to be determined

Europe/Asia-Pacific

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

Europe

October 5-6, 2006
PDA European Pharmaceutical Cold Chain Management Conference: A Global Approach to Harmonization
(Conference and Exhibition)
Berlin, Germany

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

November 9, 2006
PDA Italy Chapter
Roundtable — Review of the 2006 PDA/EMEA Joint Conference
Milan, Italy

November 10, 2006
PDA Italy Chapter
Course — Periodic Quality Review
Milan, Italy

November 23, 2006
PDA Italy Chapter
Roundtable — Review of the 2006 PDA/EMEA Joint Conference
Rome, Italy

November 24, 2006
PDA Italy Chapter
Course — Periodic Quality Review
Rome, Italy

November 25, 2006
PDA Italy Chapter
Course — Periodic Quality Review
Rome, Italy

December 5-6, 2006
Process Validation of Protein API Manufacturing Conference
Berlin, Germany

December 6-7, 2006
PDA Biotechnology Meeting
Paris, France

February 12-13, 2007
2006 ISPE/PDA Joint Workshop: Challenges of Implementing Q8 and Q9 — Practical Applications
Brussels, Belgium

Asia-Pacific

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

The right answer, every time.

Identify thousands of microbial species with the higest level of accuracy.
The MicroSeq® Microbial Identification System automatically identifies bacterial and fungal species with one standardized procedure. It doesn't matter if the organisms are gram negative or gram positive, healthy or unhealthy, dead or alive. The MicroSeq system gives you unprecedented speed, accuracy, and reproducibility—without the ambiguity common to phenotypic or biochemical identification methods.

Results in less than 5 hours

- Simplified workflow
- Validated libraries contain over 2800 species
- Automated sequencing and identification
- Based on gold standard 16S sequencing
- Includes features to assist with 21 CFR Part 11 compliance

For fast, definitive microbial identification, visit **www.microseq.com**.

Applied Biosystems

25 YEARS ADVANCING SCIENCE

Critical or Primrose Path:* Can the U.S. FDA Solve the "Pipeline Problem"?, *continued from cover

To this point, it is unclear what the impact of FDA's efforts will ultimately be. Long ago, the government acted to speed up drug approvals to assist companies in getting drugs to the market faster with the Prescription Drug User Fee Act. In spite of the government's best efforts in this area—including new staff, new guidances and other actions—the number of marketing approvals for NMEs and new biotech therapies has remained flat. The Pharmaceutical Research and Manufacturers of America reports that 20 new products were approved in 2005 (18 NMEs and 2 new biotech therapies), compared with 36 in 2004, 21 in 2003, 17 in 2002, 24 in 2001, and 27 in 2000.[1]

These results suggest that after two years at least, the Critical Path Initiative (CPI) has had little, if any, impact. The question posed here is, can a government-driven initiative have any real long-term impact? Or is FDA acting as one of Shakespeare's pastor—making speeches, issuing reports and guidances, conducting workshops, but in reality, effecting very little change in the product pipeline?

It might be too early to fairly answer these questions, but it is worth taking a look at what FDA has accomplished so far.

While some industry observers were questioning the progress of the initiative as the calendar turned to 2006,[2] the Agency was on the verge of releasing a number of key documents and making several important announcements regarding the CPI.

In March 2006, FDA issued its "Critical Path Opportunities List" and an accompanying CP opportunities report. The list maps out 76 specific projects that FDA is targeting for additional research to modernize the drug development process. These projects fall into the following six categories:

1) Evaluation Tools
2) Clinical Trials
3) Bioinformatics
4) Manufacturing
5) Urgent Public Health Needs
6) At-Risk Populations

The Science of Efficient Research

Through extensive consultation with stakeholders, FDA has determined that the most pressing priorities are the projects falling into categories 1 and 2—better evaluation tools and streamlined clinical trials. Advances in these areas offer the greatest opportunity of reducing research and development timelines and costs. Over half of the projects on the list fall into these two areas.

When it comes to better evaluation tools, FDA is placing great emphasis on the promise of new biomarkers. Biomarkers are measurable characteristics that reflect physiological, pharmacological or disease processes in animals or humans. Changes in biomarkers following treatment reflect the clinical response to the product. Common biomarkers in use today have been around for decades and are empirically derived, meaning they lack predictive and explanatory capabilities. Improved biomarkers and diagnostics offer researchers the ability to rule out poor therapies earlier in the process, thus reducing costs and streamlining research.[3]

Genomics, proteomics and metabolomic technologies offer potentially powerful biomarkers. In fact, FDA has recently approved several genomic tests for drug-metabolizing enzymes which allow researchers to identify patients who are at high risk for serious toxicity from cancer therapies. While a number of potential new biomarkers are in existence, qualification of these biomarkers has not been accomplished. The CP opportunities list identifies a number of efficacy and safety biomarkers that need to be developed and qualified.

At a July 10 Conference on Adaptive Trial Design in Washington, D.C., FDA Deputy Commissioner for Medical and Scientific Affairs **Scott Gottlieb,** MD, discussed the potential of biomarker research. He noted that much of the focus of the CPI thus far has been on the development of "better markers and evaluative tools."

Indeed, FDA announced earlier this year the formation of a Predictive Testing Consortium between the Critical Path Institute (C-Path) and eight large pharmaceutical companies: Bristol-Myers Squibb, GlaxoSmith-Kline, Johnson & Johnson, Merck and Co., Novartis Pharmaceutical Corporation, Pfizer, Inc., Roche Palo Alto and Schering Corporation. FDA entered into a memorandum of understanding with C-Path in October 2005.

In a March announcement about the consortium,[4] FDA Deputy Commissioner of Operations **Janet Woodcock** explained: "The use of predictive safety biomarkers in early animal and laboratory studies will strengthen the product's safety screening before it is introduced into humans. It will also enable researchers to better select initial human doses and monitor for side effects in early trials. As a result, pharmaceutical companies will be able to learn more from smaller clinical trials and get new, safer therapies to patients faster and at a lower cost."

In his July 10 speech, Dr. Gottlieb elaborated further on the flexibility offered by biomarkers, stating that they will facilitate "adaptive" clinical trials. "In an adaptive clinical trial," he said, "patient outcomes can be used as they become available to adjust the allocation of future patients or some other aspect of study design. This allows researchers to improve expected patient outcomes during the experiment, while still being able to research good statistical decisions in a timely fashion."

Dr. Gottlieb outlined some of the challenges in moving toward ➤

the adaptive clinical trial model:

"Adaptive approaches are not a panacea to all of our challenges, and enabling them is not a sure thing. Adaptive procedures are more complicated to design and to analyze, and in some settings are more difficult to implement. Sponsors need consensus and clarification on pivotal scientific questions related to when adaptive clinical trial design is most appropriate."

Cost reductions in clinical trials would go a long way in reducing the discrepancy between research costs and new drug launches. Stakeholders point to the costs of clinical trials as one of the largest barriers to innovation. FDA is also pressing for innovative alternatives to the traditional clinical trial model. The opportunities list outlines a number of possibilities in this area.

At the July 10 conference on adaptive research, Dr. Gottlieb announced that FDA will issue five guidances to help companies devise adaptive trials. The first will cover the use of multiple endpoints in the same trial. The other four will cover enrichment designs, noninferiority trial deigns, adaptive designs and missing clinical data. FDA will participate in a two-day workshop in November on adaptive designs.

At a Drug Information Association conference in June, Wyeth Assistant VP-Clinical Development **Michael Krams,** co-chair of the PhRMA working group on adaptive designs, discussed the trade group's ideas in this area.[5] Among the group's suggestions were: seamless Phase II/III trials, adaptive dose finding and sample size reestimation.

FDA as Director, Not Doer

FDA strategically labels its list of projects as an "opportunities" list because it cannot possibly perform most, if any, of the research needed to advance each project. Instead, the Agency will use its position as the central health authority in America to provide leadership and to encourage other stakeholders, especially the industry, to effect change.

In the "opportunities" report, Acting FDA Commissioner **Andrew von Eschenbach,** MD, elaborated on FDA's role: "Although we are only one organization among many with a role to play in moving innovative medical products to the marketplace, FDA is uniquely positioned to provide national leadership in this effort. Because FDA oversees testing of all medical products in the United States, and because our scientists have a special expertise in the sciences of product testing and manufacture, we can identify the scientific hurdles that commonly cause setbacks for companies."

According to von Eschenbach, the Agency believes it has the opportunity to promote innovation industry-wide "by setting standards and providing guidance." As a neutral party, he writes, "FDA can serve as the catalyst for the consensus development that is needed to identify new scientific standards."

FDA is looking to strategic collaborations to help advance the CPI. C-Path is one of them. Founded under a memorandum of understanding with the Agency in October 2005, the organization is an independent, publicly funded, non-profit organization dedicated to the Critical Path Initiative. C-Path aims are to foster research and educational programs intended to enable the pharmaceutical industry to safely accelerate the development of new medications.

Besides FDA, the University of Arizona and SRI International are founding collaborators with C-Path. SRI is formerly known as the Stanford Research Institute and is committed to discovery and to the application of science and technology for knowledge, commerce, prosperity and peace. The University of Arizona provides the home and infrastructure for C-Path.

Along with the aforementioned Predictive Testing Consortium, which involves eight drug companies, C-Path is working collaboratively with:

The Drug Information Association
The University of Utah/Intermountain Health Care
Bashas' United Drugs Pharmacies
The Arizona Poison and Drug Information Center
The Translational Genomics Research Institute
The Arizona Center for Education and Research on Therapeutics
Scientific Technologies Corporation, Inc.
The Ara Parseghian Medical Research Foundation

FDA is also collaborating with the Clinical Data Interchange Standards Consortium, Health Level 7, in an effort to move current clinical trial practices and computer systems to an electronic clinical trial environment.

The U.S. National Institutes of Health (NIH) is involved in CPI as well. NIH issued a "Roadmap for Medical Research," a series of far-reaching initiatives designed to help usher more innovations to market. The latest "roadmap" initiative was announced in October 2005. It targets the transformation of clinical and translational research so that new treatments can be developed more efficiently and delivered more quickly to patients. NIH also announced the "Clinical and Translational Science Awards" program, which is meant to energize the discipline of clinical and translational science at public health centers across the United States. The plan is to release US$30 mil. in grants towards such research in 2006. The ultimate goal, according to NIH, is to release a total of US$500 mil. by 2012.[6]

[**Editor's Note:** This article will not delve into other details of the CPI Opportunities List. The "manufacturing" category of the

continued on bottom of page 26

CLEAN & DISINFECT
FLOORS, WALLS & CEILINGS

Choose From More Than Seventeen Cleaning And Disinfecting Systems

We are the world's leading manufacturer, supplying a wide range of multi-bucket cleaning systems engineered to capture and isolate contaminants. Our TruCLEAN systems are designed to deliver uniform application of solutions to walls, floors and ceilings. Easy operator adaptability. Reliable performance. Consistent results. **GUARANTEED.**

All TruCLEAN Systems compatible with Gamma, ETO and Autoclave Sterilization.

FREE *PROFESSIONAL REFERENCE GUIDE*
CD ROM AND VIDEO ALSO AVAILABLE

PERFEX CORPORATION
Experts in Clean Systems for Controlled Environments
800-848-8483 USA & Canada • 315-826-3600 • Fax: 315-826-7471
E-MAIL: perfex@ntcnet.com WEBSITE: www.perfexonline.com

Solving the Over-Inspection Problem

Lothar Hartmann, PhD, F. Hoffmann – La Roche Ltd.

Health authorities inspect pharmaceutical manufacturers in order to ensure that patients receive medicines of high quality, ensuring safety and efficacy. Inspections help to control risks for the patient and help to protect them. Industry accepts the regulators' right to inspect.

So what is the problem?

…too many inspections: Until recently our manufacturers were inspected mainly by the national health authorities where they were located and by the U.S. FDA and the European Medicines Agency—the two largest "international inspectorates." Over the last couple of years, however, we have witnessed an enormous increase in the number of national inspectorates conducting international inspections, including those in Australia, Brazil, Mexico, Uganda, Korea, Libya, Iran, Saudi Arabia, Tanzania, Belarus, Pakistan, Nigeria and Yemen. .

And why is this a problem?

…it's not the inspectors, per se: The inspectors from the individual countries are not the problem (apart from a few health authorities with whom protection of intellectual property can be an issue). Overall, the inspectors are capable, highly educated and open-minded, and they conduct inspections in a reasonable manner.

The problem is…..

…time: The growing number of inspections that a single plant or facility now has to manage is the problem. In addition to internal audits and customer audits, some organizational units are facing up to ten inspections by different health authorities within one year. This burden is more the "norm" than the exception for the "riskiest" areas of production, such as sterile and biotech manufacturing.

In 2005, approximately 40 different national inspectorates conducted inspections outside their own borders, totaling close to 1500 "foreign" inspections. This translates into approximately 40-55 foreign inspections per global pharmaceutical company during 2005. The disturbing news is that the number of foreign inspections is trending upwards.

Calculating that industry needs approximately 120 man days per inspection (including pre- and post-inspection activities), one can imagine the huge resources involved to satisfy the foreign inspections alone, forgetting for a moment that local inspections are still occurring as well.

Is this the optimal use of resources on both sides—regulatory and industry?

…probably not: When we look at the inspection reports issued by various inspectorates, we realize that the majority of observations are of a similar nature. There are several reasons for this development. One reason is the disconnect between the global industry and the parochial health authorities. While global companies are reducing the number of manufacturing facilities needed to supply product to the entire world, national health authorities are still operating locally, with their primary concern being their home market. Local laws are being adapted to mandate inspections in more and more countries, and the scope is expanding, e.g., to APIs and biotech manufacturing. In many cases, local authorities do not share or accept inspection observations from other inspectorates.

Does this system add value to the patient? Is this the optimal way to provide the patient with safe medicines?

…probably not: There are several other problems that need to be addressed for the benefit of the patient, each of them being very challenging and requiring enormous efforts to be resolved:

- There are a number of markets around the world suffering from a high percentage of counterfeit products, and the problem is increasing.
- In some countries, resources are lacking to enforce local regulations properly.
- Worldwide, we have no harmonized understanding of the GMP requirements and their interpretation in the drug product arena (the exception being APIs through ICH Q7A).
- In some cases, when changes have to be made to registered manufacturing processes to improve the quality and robustness of products, industry might have to wait as much as eight years until all authorities worldwide have accepted the change.

These are only a few of the many issues which require all of us—industry and authorities—to increase efforts to improve the situation. One can only imagine the personnel and operational time which could be liberated by saving resources from redundant inspection programs. Nevertheless, it is clear that inspectorates still need to be concerned about their home market and still need guarantees that regulations are being met for the products imported to their country.

Are there possibilities to improve the situation?

…yes: If we conclude that one or two inspections per manufacturing unit each year are sufficient to ensure patient safety based on quality and compliance, we implicitly agree that inspectorates should work together to aim for this goal. This could mean that inspection reports will be shared, accepted and made accessible among the inspectorates. But it also implies that the quality and standards against which inspections are conducted are comparable among the inspectorates. ➤

BD

Helping all people live healthy lives

BD Preventis™

Needle Shielding System for Prefilled Syringes

Nurses keep control on each injection step:

- The injection technique won't change with the added needle shielding system
- Needle shielding system activation controlled by practitioners
- Easy assembly process

BD

BD Medical
Pharmaceutical Systems
Worldwide Headquarters
11, rue Aristide Bergès
38800 Le Pont de Claix
France
Tel: 33.4.76.68.36.36
Fax: 33.4.76.68.35.05
U.S. Headquarters
1, Becton Drive
Franklin Lakes, NJ 07417-1886 USA
Tel U.S.: (1) 800 225 3310
Outside of U.S.: (1) 201 847 4017
Fax: (1) 201 847 4847
www.bdpharma.com

This draws the attention to the Pharmaceutical Inspection Co-operation Scheme (PIC/S) as a possible platform to work towards a solution. Many national inspectorates are already organized in the PIC/S, and all members have to fulfill a defined quality standard which is assessed before membership applications are approved. In addition, a routine reassessment of the standard of the member inspectorates occurs.

In the past PIC/S launched an initiative that goes into the direction of sharing inspection reports: the International Medicinal Inspectorates Database (IMID). Unfortunately the IMID has for the time being been suspended. Modifications to this initiative and its relaunch could serve as the backbone of a concept in which inspectorates work more closely together and share available information, leading possibly to a situation in which most inspections would be conducted by local inspectorates. PIC/S could serve as the coordinator of inspection plans among its member inspectorates. In addition, PIC/S could set up and provide a training program and/or support regional activities assisting non-member inspectorates to achieve the required international level.

With the U.S. FDA becoming more active in PIC/S, the time is right to see what possibilities this organization can offer both the industry and the regulators in the coming years. There certainly would be many benefits from inspectorate communications, and perhaps eventually some relief from the amount of inspections conducted on the same manufacturing site.

If we accept the premise that PIC/S can create a solution to the over-inspection problem, we all should encourage inspectorates to apply for membership.

About the Author

Lothar Hartmann, PhD, is Head of External Relations—Global Quality at F. Hoffmann—La Roche Ltd., in Basel, Switzerland. He is an active contributor and speaker for PDA and is currently a member of the PDA Science Advisory Board. He can be reached at lothar.hartmann@roche.com.

Critical or Primrose Path: **Can the U.S. FDA Solve the "Pipeline Problem"?,** ***continued from page 26***

CPI discussed in the initial CPI white paper and the opportunities list/report includes the initiatives begun under the GMPs for the 21st Century initiative, many of which are routinely addressed in the *PDA Letter.*]

Where's the Beef?

One of the primary stakeholder expectations of the CPI is that FDA not stray from efforts to improve the overall regulatory process nor divert resources from marketing application reviews. FDA agrees.[7]

There still remains the question of where are the resources to fund the CPI? The U.S. Congress has not offered any significant funding. FDA received about US$6 mil. to devote to C-Path for fiscal year 2006—a figure FDA admits is not large at all.[8] FY 2007's budget might not include much more.

It has been a long two years since the initial CPI report brought to the fore the "pipeline problem." While it took some time, FDA did deliver on its initial promises to identify areas that need concerted and committed research in order to breathe new life into the drug development process.

So, to answer the question posed in this article's title—*Can FDA solve the "Pipeline Problem"?*— unlike Shakespeare's ungracious pastors, it appears FDA is very serious about its role in helping to pave a more efficient Critical Path to drug approvals. FDA's listing of 76 CP "opportunities" seems like a very good start to help focus the private, academic and government research sectors on key areas of need. On top of that, the Agency has expressed its willingness to walk down the Critical Path by accepting new clinical trial designs. The next question is: Will industry, the U.S. Congress and the American public follow the Agency's lead?

References

1. PhRMA, *New Drug Approvals in 2005,* http://www.phrma.org/files/NDA%202005.pdf, p. 14

2. Clinton, Patrick and Wechsler, Jill, "What Ever Happened to Critical Path," *Pharmaceutical Executive,* Jan. 1, 2006, http://www.pharmexec.com/pharmexec/article/articleDetail.jsp?id=282481

3. U.S. FDA, *Innovation or Stagnation: Critical Path Opportunities Report,* March 2006, p. R-9

4. FDA, "FDA and the Critical Path Institute Announce Predictive Safety Testing Consortium," FDA News Release, March 16, 2006

5. F-D-C Reports, Inc., "Adaptive Trials Going Mainstream with Industry White Paper, FDA Guidance," *"The Pink Sheet",* vol. 68, no. 30, p. 17

6. *Innovation or Stagnation: Critical Path Opportunities Report,* p. R-26

7. *Ibid,* p. R-21

8. Owens, Joanna, "Funding for Accelerating Drug Development Initiative Critical," Medical Progress Today.com, vol. 3, no. 10

FDA Posts New Level 2 Guidance on the cGMP Q&A Web Page

FDA launched a drug cGMP Q&A section of its website as part of the 21st century initiative. The goal is to provide timely answers to questions about the meaning and application of cGMPs to drug products. The answers to each question generally clarify statements of existing requirements or policy, and as such, are considered Level 2 guidance. CDER, CBER, CVM and ORA are cosponsoring the Q&A. PDA published several of the initial Q&A in the September 2004 issue of the *PDA Letter.* FDA has added three new Q&A's since the original posting, the latest on September 8, 2006 (two of the new Q&A's are included below). According to an Agency source, additional Q&A should be posted soon.

Can up to twelve month expiration-dating be assigned to oral solid and liquid dosage forms repackaged into unit-dose containers based on guidance in the May 2005 draft revision of Compliance Policy Guide, Section 480.200 (7132b.11), "Expiration Dating of Unit Dose Repackaged Drugs"? [From the "Laboratory Controls" category, posted September 8, 2006]

No. In May 2005, a Notice of Availability of the draft revision of FDA's Compliance Policy Guide Section 480.200 (CPG 7132b.11), "Expiration Dating of Unit-Dose Repackaged Drugs," was announced in the Federal Register. The draft CPG specifies certain conditions when it may be possible to assign up to twelve month expiration-dating to non-sterile solid and liquid oral drug products repackaged into unit-dose containers without conducting new stability studies to support the length of expiration-dating on the repackaged products. The draft CPG was prompted by United States Pharmacopeia (USP) standards for assigning up to a twelve month "beyond-use date" to non-sterile solid and liquid oral dosage forms dispensed in unit-dose containers. ("Beyond-use date" is USP's pharmacy dispensing term for specifying a date on a prescription container beyond which a patient should not use the product.) If finalized, FDA's draft CPG would replace the current version of CPG Section 480.200. The current version of CPG Section 480.200 was finalized in March 1995 and provides conditions under which FDA will not initiate action for assigning up to six month expiration dating for drug products repackaged into unit-dose containers without conducting new stability studies.

FDA is conducting a stability study of certain commercially repackaged drugs to determine the suitability of the draft revision of CPG Section 480.200. Until the stability study is complete and FDA evaluates all comments submitted to the public docket in response to the May 2005 Federal Register Notice of Availability, the agency does not intend to make a final decision on the draft revision of CPG Section 480.200. Consequently, at this time and until FDA announces a final decision on the draft CPG, the current CPG Section.480.200, which was finalized in March 1995, is in effect.

References:

- Compliance Policy Guide section 480.200 (CPG 7132b.11)
- Federal Register: May 31, 2005 (Volume 70, Number 103) pages 30953-30954
- CFR 211.137 and 211.166

Contact for further information:
Barry Rothman, CDER, barry.rothman@fda.hhs.gov

Can Total Organic Carbon (TOC) be an acceptable method for detecting residues of contaminants in evaluating cleaning effectiveness? [From the "Equipment" category, posted May 18, 2005]

Yes. Since the publication of the inspection guide on cleaning validation in 1993, a number of studies have been published to demonstrate the adequacy of TOC in measuring contaminant residues.

TOC or TC can be an acceptable method for monitoring residues routinely and for cleaning validation. In order for TOC to be functionally suitable, it should first be established that a substantial amount of the contaminating material(s) is organic and contains carbon that can be oxidized under TOC test conditions. This is an important exercise because some organic compounds cannot be reliably detected using TOC.

TOC use may be justified for direct surface sample testing as well as indirect (rinse water) sample testing. In either case, because TOC does not identify or distinguish among different compounds containing oxidizable carbon, any detected carbon is to be attributed to the target compound(s) for comparing with the established limit. Thus, a firm should limit 'background' carbon (i.e., carbon from sources other than the contaminant being removed) as much as possible. If TOC samples are being held for long periods of time before analysis, a firm should verify the impact of sample holding time on accuracy and limit of quantization.

References:

- 21 CFR 211.67: Equipment cleaning and maintenance.
- 21 CFR 211.160(b): General requirements (Laboratory Controls)
- USP 643 Total Organic Carbon
- Guide to Inspections of Cleaning Validation, 1993

Contact for further information:
Abi D'Sa, CDER, dsaa@cder.fda.gov/Brian Hasselbalch, CDER, hasselbalchb@cder.fda.gov

Picky about particulates?

Manic about microbes?

Count on Biotest

The HYCON® System for Environmental Monitoring: RCS Air Samplers, APC Particle Counters and Contact Slides.

APC Airborne Particle Counters and RCS Microbial Air Samplers combine to give you a clear picture of airborne contamination. Biotest Diagnostics Corporation offers a full line of reliably accurate, technically-advanced, hand-held, air monitoring devices. When you're picky about maintaining air quality standards, count on Biotest. Call today or visit our website at www.BiotestUSA.com.

Biotest

CE

Biotest DIN EN ISO 9001 HYCON

BIOTEST DIAGNOSTICS CORPORATION
66 Ford Road, Suite 220, Denville, New Jersey 07834
Phone: 973.625.1300 • 800.522.0090 • Fax: 973.625.9454
www.BiotestUSA.com

Regulatory Briefs

Regulatory briefs are compiled by PDA member volunteers and staff directly from official government/compendial releases. Links to additional information and documentation are available at http://www.pda.org/regulatory/RegNewsArchive-2006.html.

Europe

Updated Post-authorisation Guidance, Human Medicinal Products

The EMEA posted revisions to the Post-authorisation Guidance for Human Medicinal Products. (EMEA-H-19984/03, rev 6, August 2006.) The latest revision includes information on marketing and cessation notification and on sunset clause monitoring. It addresses questions which Marketing Authorisation Holders (MAHs) may have on post-authorisation procedures. It also provides an overview of the EMEA position on issues typically addressed in discussions or meetings with MAHs in the Post-Authorisation phase. (The information in this guidance is under review by the EMEA and is updated periodically following entry into force of the new pharmaceutical legislation on 20 November 2005.)

GCP Inspection Guidance

The EMEA revised text for Question 29 of the Pre-submission procedural guidance for human medicinal products, part of the guidance for *GCP inspections during the assessment of the application.* This guidance is updated from time to time and should be reviewed at the EMEA website.

Pre-Submission Guidance

The EMEA updated questions (6, 10, 12 13 and 32) and generated new questions (33-37) regarding pre-submission guidance.

List of Marketing Authorisations

The EMEA released the list of Medicinal Products with Community Marketing authorisation as of August 2006. A link to the 52-page list is available at the PDA regulatory news archive.

North America

U.S. FDA Posts Good Review Practices (GRPs) Webpage

The September 12 *Federal Register* included reference to CDER's new "Good Review Practice" webpage for human drugs. A link to the website can be found at the PDA regulatory news archive.

Good Review Practices, or GRP, is a "documented best practice" within CDER that discusses any aspect related to the process, format, content and/or management of a product review. GRPs are:

- developed over time as superior practices based on experience, and provide consistency to the overall review process of new products
- developed to improve the quality of reviews and review management. GRPs improve efficiency, clarity, and transparency of the review process and review management
- adopted by review staff as standard processes through supervisor mentoring, implementation teams and formal training when necessary

As GRPs develop, review staff will adopt them into their daily review activities. Since GRPs can change and evolve frequently as a result of new science, statutes, regulations, guidances, and accumulated experience, the policies will be updated regularly.

Review staff are expected to follow GRPs and may depart from them only with appropriate justification and supervisory concurrence.

U.S. FDA Publishes Views on Possible International Non-proprietary Name (INN) Policies for Biosimilars

On September 1, 2006, FDA posted its view on n Possible International Non-proprietary Name (INN) Policies for Biosimilars. The full report is can be linked to from the PDA regulatory news archive. In the statement, FDA said:

The United States Food and Drug Administration (U.S. FDA) continues to support the original purposes, premises, and uses of the INN and believes the system has provided many positive elements to the world's public health, especially in facilitating the exchange of scientific data and reports on various products with the same active ingredient(s).

The USA recognizes the INN system as a cataloging system whereby many products worldwide may share the same internationally recognized nonproprietary name based on drug substance. In this manner, the INN system provides a clear mechanism to health care professionals worldwide for identifying medicines and communicating unambiguously about them based on pharmacological class.

The U.S. FDA's concerns in today's discussion are (a) that the INN not be used in ways that could jeopardize the health of patients, and (b) that we not unnecessarily institute changes that could jeopardize the public health benefits of the present INN system.

Specifically, INNs should not be used to imply pharmacologic interchangeability of products with the same active ingredient(s) when no credible scientific data exist that demonstrate such. Likewise, INNs should not be used to differentiate products with the same active ingredient(s) when credible scientific data demonstrate that no pharmacologically relevant differences exist.

PDA Call for Speakers for Inclusion on a Newly Created Speaker List

PDA is currently in the process of creating a speaker list for its chapters to reference when planning future meetings and events. As the list is in its infancy stage, PDA would like to encourage members who are interested in speaking at chapter events to contact PDA Vice President of Quality and Regulatory Affairs Bob Dana at dana@pda.org or by phone at +1 (301) 656-5900 ext. 224. Contacting PDA about your interest will not guarantee inclusion on the chapter speaker list, however it will allow for further open communication between PDA, PDA Chapters and potential speakers. When submitting your name please include all necessary contact information as well as a bio and CV. Topic areas on which you are experienced in speaking are also requested.

The purpose of this list will be to encourage chapters and speakers alike to form relationships that will allow for easy communication and less legwork when chapters are searching for speakers on particular topics and within their region. By stating your interest in speaking at events, chapters will have access to a working list of contacts who have shown interest in speaking and participating at the local chapter level. Your area of expertise will be noted and a bio will also be included. Contacting PDA regarding this important program will not only help to create a quick reference for chapter leaders, but will also enable our chapters to bring new speakers and topics to their membership. The list will allow for reciprocal communication and opportunities amongst peers and create opportunities for both PDA chapters and speakers alike.

Worried about who's looking over your shoulder?

Relax. PDA's Career Center is 100% Confidential

- Create, edit and store your anonymous resume and cover letter for free
- Reveal as little or as much personal information as you like
- Search and apply to a variety of pharmaceutical and biopharmaceutical jobs ranging from entry level to executive level
- Receive e-mail job alerts that notify you of newly added jobs specifically matching your search criteria so you never miss out on an opportunity

PDA℠
Parenteral Drug Association

Connecting People, Science and Regulation℠

www.pda.org/careers

PDA's Emerging Manufacturing and QC Technologies Conference

January 29-31, 2007 • San Diego, California

Martin VanTrieste, Amgen and Program Planning Committee Chair

Everyone has heard the adage "Work smarter, not harder." As pharmaceutical and biopharmaceutical professionals in academia, industry or regulatory agencies, we constantly strive for continuous improvement and are always looking for smarter ways to accomplish our tasks. Striving to "work smarter," we seek out ways to make safer products, release products to the public sooner and produce products at lower costs.

On behalf of the program planning committee, I invite you to attend the first-ever *PDA Emerging Manufacturing and Quality Control Technologies Global Conference* in San Diego, January 29-31, 2007. The conference will introduce you to new technologies and allow you to explore their potential use as tools to drive continuous process improvement while increasing manufacturing efficiency.

Concurrent sessions led by industry and regulatory experts will cover a number of areas in which innovative technologies are available for implementation immediately or in the near future for many applications, including:

- Traditional manufacturing
- Disposable processing
- Restricted access barrier systems
- Aseptic filling
- Microarrays and microsensors
- Environmental monitoring
- Alternative biotech manufacturing
- Rapid microbial detection

I am pleased to tell you that, as a complement to these sessions, the conference will further explore the new and emerging technologies discussed with technology demonstrations. **Company representatives will be on hand to demonstrate the application of their new technologies and explain the science behind their development.** This should provide for a unique learning experience that gives you a first-hand look at the future of manufacturing and quality control innovations and at the same time brings you face-to-face with the companies that invented them.

No one knows exactly what the future holds for the pharmaceutical and biopharmaceutical industries, but one thing is certain—advances in technology and productivity are playing a large part in shaping that future. I hope that you will join me at the *PDA Emerging Manufacturing and Quality Control Technologies Global Conference* to get a "sneak peek" at new and emerging technologies and how they will impact the industry in the years to come.

The PDA Letter is published 10 times per year, exclusively for PDA members. Subscriptions are not available. Articles in the PDA Letter may be reproduced with permission—contact the PDA Letter Editor for details.

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

Advertising
Cindy Tabb, *Sales*
+1 (301) 656-5900, ext. 222
tabb@pda.org

Copy Editor
Evelyn Heitman

PDA Global Headquarters
Bethesda Towers
4350 East West Hwy., Suite 200
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

PDA

Parenteral Drug Association

Connecting People, Science and Regulation℠

PDA Emerging Manufacturing and Quality Control Technologies Global Conference

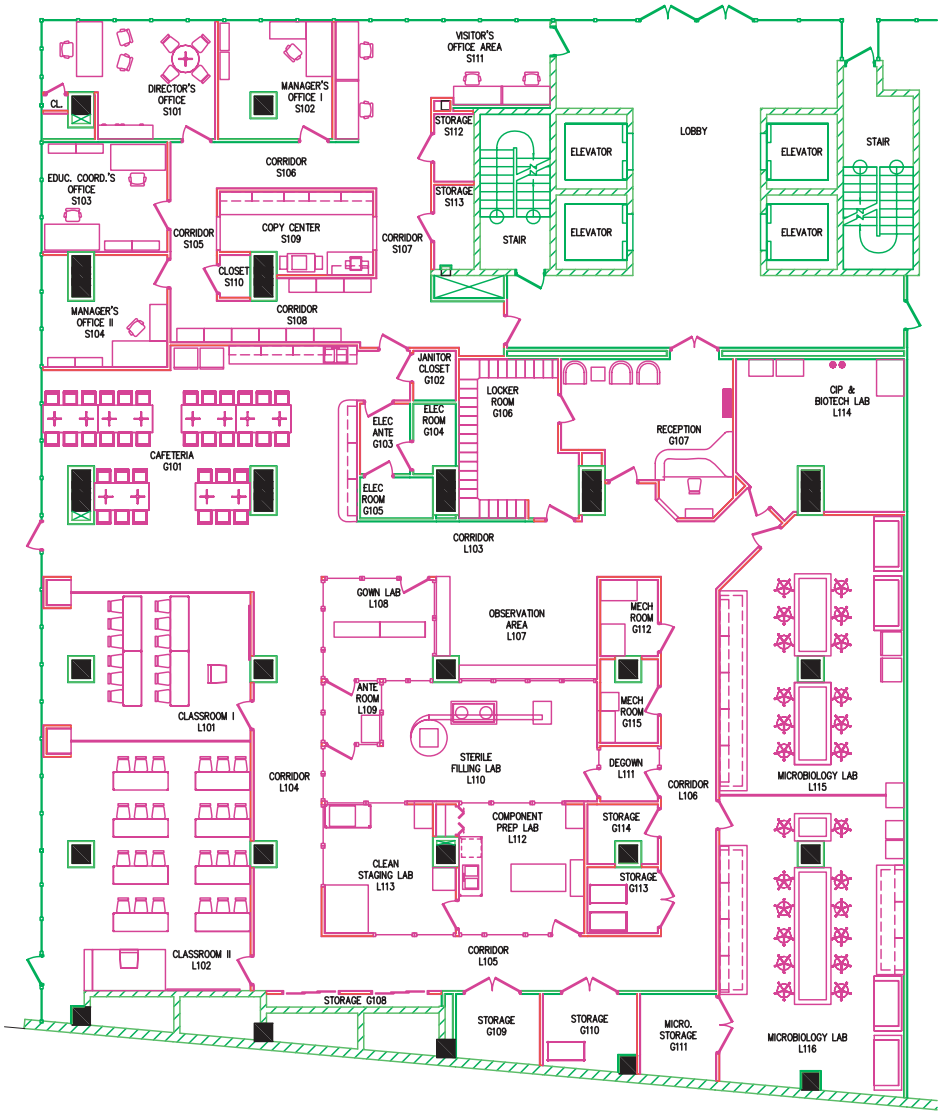
January 29-31, 2007
San Diego, California

Register before November 6th and save!

Get a first-hand look at new and emerging manufacturing and quality control technologies designed for the pharmaceutical and biopharmaceutical industries. Company representatives will be on hand to explore the use of new innovations as potential tools to drive continuous process improvement while increasing manufacturing efficiency.

www.pda.org/emerging

The TRI Move: New Floor Plan Completed!



The Floor Plan as devised by Vectech Pharmaceutical Consultants staff and PDA.

Bob Myers (l facing) and James Wamsley (center) work with Vectech's William Bennett and Robert Ferer to develop the floorplan for the new TRI facility

Gail Sherman and Bob Myers show off their hard hats and the designs for the new TRI facility at the 2006 PDA/FDA Joint Regulatory Conference

PDA
Parenteral Drug Association

Conference	Training Courses	Exhibition
13-15 November	16-17 November	13-14 November

2006 PDA Asia-Pacific Congress

Connecting People, Science and Regulation℠

Overview

The 2006 PDA Asia-Pacific Congress will provide important information on current and emerging regulatory, scientific and technical issues. Key health authority and expert industry speakers will present updates of regulatory requirements, including the revision of the Japanese Pharmaceutical Affairs Law and practical examples of quality systems, microbiological topics and manufacturing processes. The Congress will be a multi-track format focusing on new regulatory developments, pharmaceutical manufacturing, and microbiological issues relevant to the global pharmaceutical and biopharmaceutical industries.

Topics to Include:

- Revisions to Japan's Pharmaceutical Affairs Law – and Implementation
- Quality by Design
- 21st Century GMPs
- Pharmaceutical Harmonization
- Process Analytical Technology (PAT)
- Novel Manufacturing Processes
- Aseptic Processing
- Risk Management
- Rapid Microbiological Testing
- Viral Safety
- Active Pharmaceutical Ingredients (APIs)
- Computer Validation
- Disposable Technologies
- Environmental Monitoring
- Pharmaceutical Water
- GMPs During Clinical Development

Featuring:

- Regulatory updates and implementation strategies for Japanese and worldwide delegates
- New presentations by health authority leaders from U.S. FDA, EMEA, Japan and China
- First-time sessions on practical applications of revised Japan's Pharmaceutical Affairs Law
- Case studies examining novel manufacturing processes, new developments in microbiology, disposable technologies, PAT and more

Visit **www.pda.org/apcongress** for the full program

Interactive Training Courses

Presented by the PDA Training and Research Institute

Fundamentals of Pharmaceutical Filters and Filtration
Maik Jornitz, Group Vice President, Product Management, Sartorius Corp.
Theodore Meltzer, PhD, *Capitola Consulting*
16-17 November

Quality Programs – The Road to Continuous Improvement
Daniel H. Gold, PhD, President, *D.H. Gold Associates, Inc.*
16-17 November

Risk Assessment in Manufacturing
Hal Baseman, Chief Officer and Principal, *ValSource LLC.*
16 November

GMP Requirements for the Manufacture of Clinical Trial Materials (CTM's)
Robert Dana, Vice President of Quality and Regulatory Affairs, *PDA*
17 November

For complete course descriptions, visit **www.pda.org/apcongress/courses**

Tokyo, Japan

13-17 November 2006

Venue

Tower Hall Funabori
Tokyo, Japan
Hotel information available at
www.pda.org/apcongress

Registration

See registration form on reverse for full details, or visit
www.pda.org/apcongress

Full Congress and One Day registrations available!

Conference Inquiries

Japan
Yoshihito Hashimoto
E-mail: yohashimoto@ykh.chiyoda.co.jp

Outside Japan
Wanda Neal
E-mail: neal@pda.org

Training Course Inquiries

Japan
Yoshiaki Hara
E-mail: yoshiaki.hara@sartorius.com

Outside Japan
Gail Sherman
E-mail: sherman@pda.org

Exhibition and Sponsorship Opportunities Available!

For more information, contact:
Nahid Kiani
E-mail: Kiani@pda.org

"FINALLY...

A SINGLE SOFTWARE PLATFORM TO MANAGE ALL OF OUR QUALITY AND REGULATORY COMPLIANCE NEEDS."

TRACKWISE®

The Ultimate Tracking Software℠

Over 150 customers worldwide, more than 200,000 end users.

- ☑ *ENSURE COMPLIANCE*
- ☑ *ACHIEVE CONTROL*
- ☑ *ENHANCE COLLABORATION*
- ☑ *STREAMLINE OPERATIONS*
- ☑ *REDUCE COSTS*

YOUR SOLUTION FOR

- Deviations
- CAPA
- Customer Complaints
- Action Item Tracking
- Nonconformance
- Change Control
- Supplier Quality
- Audits/Audit Observations
- Preventive Maintenance
- Environmental Health and Safety Incidents
- HACCP Compliance
- Sarbanes-Oxley Controls
- *And more*

Meet FDA, OSHA, EMEA, SEC and ISO compliance requirements

Sparta Systems, Inc. *Quality Management Solutions*

Holmdel Corporate Plaza • 2137 State Highway 35 • Holmdel, New Jersey 07733 • (888) 261-5948 • (732) 203-0400 • FAX: (732) 203-0375
e-mail: info@sparta-systems.com • info-europe@sparta-systems.com • www.sparta-systems.com

SW-1282