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PDA Letter

Volume XLVI • Issue #8

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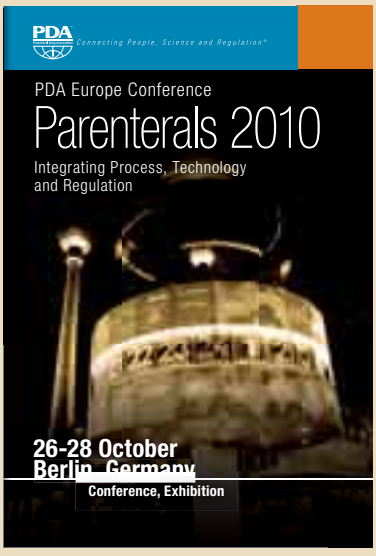
September 2010

In This Issue:



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Acting Right Can Facilitate a Good Regulatory Inspection

Sue Schniepp, OSO BioPharmaceuticals and Karen Ginsbury, PCI Pharmaceutical Consulting

Regulatory inspections are a fact of life for manufacturers of drug products. They are the ultimate test of a company's ability to demonstrate in a very short period of time and under stressful conditions how well it is adhering to its regulatory submissions, SOPs, policies and the CGMPs. With the regulatory ante raised in 2009 (enforcement will become "swifter, more aggressive and effective," announced U.S. FDA Commissioner **Margaret Hamburg**) and over 43 warning letters sent to pharma companies since 2009, **(1)** companies need to redouble their efforts in preparing for regulatory inspections. Doing so doesn't just mean getting all of your documents in order; it also means fostering good behaviors to facilitate a positive inspection.

Of course, no behavior—good or bad—can overcome a poor quality system and blatant noncompliance. This article, therefore, is intended for companies that are honest and serious about quality and compliance—the majority of companies out there. While your firm has worked hard developing a modern, effective quality management system designed to encompass the product and process life cycle, a lack of experience in handling a regulatory inspection can undermine your good work. The inspectors find themselves wasting precious inspection time because they are waiting for documents, receiving answers with no relevance to the questions asked, and/or dealing with interruptions—all behaviors that can leave the inspector with the impression that your company has inadequate control, poor understanding of GMPs, and lack of or weak leadership of the quality management system. A bad result can leave you and your firm feeling cheated, certain that your quality system does not justify the inspection observations or warning letter received.

The following are some tips and some case studies to show you how to present your company's quality system in the best possible light and in the shortest possible time. Providing the inspector with what he or she is looking for in the broadest context, but in the most concise and precise manner, is the surest way to a positive inspection outcome.

[Editor's Note: For more help in preparing for inspections, see related articles on pages 13 and 18.**]**

Company Policies for Handling Inspections

There should be a company policy for handling inspections, assigning roles and

continued on page 24

Interact with Over 100 Regulators

Official ICH Quality Implementation Working Group (Q-IWG) Integrated Implementation Training Workshops for ICH Q8, Q9 and Q10

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The impact of ICH Q8, Q9, and Q10 is already being felt on the regulatory side of our business, and this impact will continue to grow. Don't miss the opportunity to interact with more than 100 regulators and learn from the industry experts involved in the development of these guidelines. Contribute to a new era of refined pharmaceutical development by registering for this space-restricted event, the only such program presented by ICH in North America.

These unique workshops will include one day of case studies followed by one day of topic-specific Breakout Discussions. Participants will be divided into four teams and will rotate through each of four specified Discussion Breakouts covering Design Space, Control Strategy, Pharmaceutical Quality System, and Quality Risk Management. To maximize your experience, we encourage companies to send delegates to participate in each team.

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Manufacturers and distributors of pharmaceutical, biologic and medical device products face the challenge of optimal performance and improvement in an unprecedented economic environment. PDA recognizes that this challenge reflects a global need and that is why the *2011 PDA Annual Meeting* will emphasize knowledge management.

Session topics will include:

- **Development Science:** Advances in dosage form delivery systems, automated sterilization technologies, contamination control/facility management control, cell culture/line development and more.
- **Manufacturing/Process Science:** Aseptic processing, automated manufacturing systems, barrier/isolators/RABs/blow fill seal/robotics, building management and control and more.
- **Quality Science:** Compliance monitoring and trending, environmental monitoring, LIMS and lab management systems, microbiological methods and trends and more.
- **Outsourcing:** Quality contract and agreement development, transfer of critical information and knowledge, audit of suppliers, supply chain integrity and more.
- *New in 2011!* **Basics and Fundamentals:** Sterilization, aseptic processing, cleaning, contamination control, analytical testing, documentation and more.

The PDA Training and Research Institute is offering courses in conjunction with this meeting.

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CONFERENCE April 11-13, 2011 | **EXHIBITION** April 11-12, 2011 | **COURSES** April 14-15, 2011

Table of Contents

Volume XLVI • Issue #8 www.pda.org/pdaletter

Cover art:
When being inspected, your firm is under extreme scrutiny; how you prepare prior to and act during the inspection can impact the final result.

Coming Next Issue:
PDA Training

Editor's Message

A Topic for any Season

This issue's theme, preparing for inspections, is both timely and timeless. We chose it in view of the new regulatory posture at the U.S. FDA, but regardless of regulatory prerogative, there is never a time when improving your preparedness for an inspection is a bad idea. A number of authors volunteered to share their knowledge of and expertise in inspection preparation. These veterans of many regulatory inspections draw on years of experience to inform their opinions and recommendations.

The cover article gets us going with a unique discussion of how to behave when investigators are doing their thing. I've encountered numerous articles, courses and conference discussions on the paperwork and people that must be organized prior to an inspection, but **Sue Schniepp** and **Karen Ginsbury** delve deeply into the nuances of body language and words that can easily be overlooked in the best of prep plans.

There is a first time for everything, and the authors of our second feature try to help first timers to the inspection game by outlining a plan for preapproval inspection (PAI) preparation. Not all PAIs occur at newbie facilities, but for most, the first inspection they ever experience precedes product approval. **Melissa Smith** and **Lorraine Murphy** offer advice to help ease the nerves of those gearing up for their first PAI, and in doing so, provide a remarkably useful list of references.

I'm in the publishing business, so I could write volumes about procrastination, but when it comes to getting your team ready for an inspection, it is best not to delay. However, according to **John Avellanet**, things happen and firms sometimes find themselves only days away from I-day (inspection day) without being prepared. He offers seven tips that should help you make the best of situations like these.

"The time to repair the roof is when the sun is shining."

— John F. Kennedy

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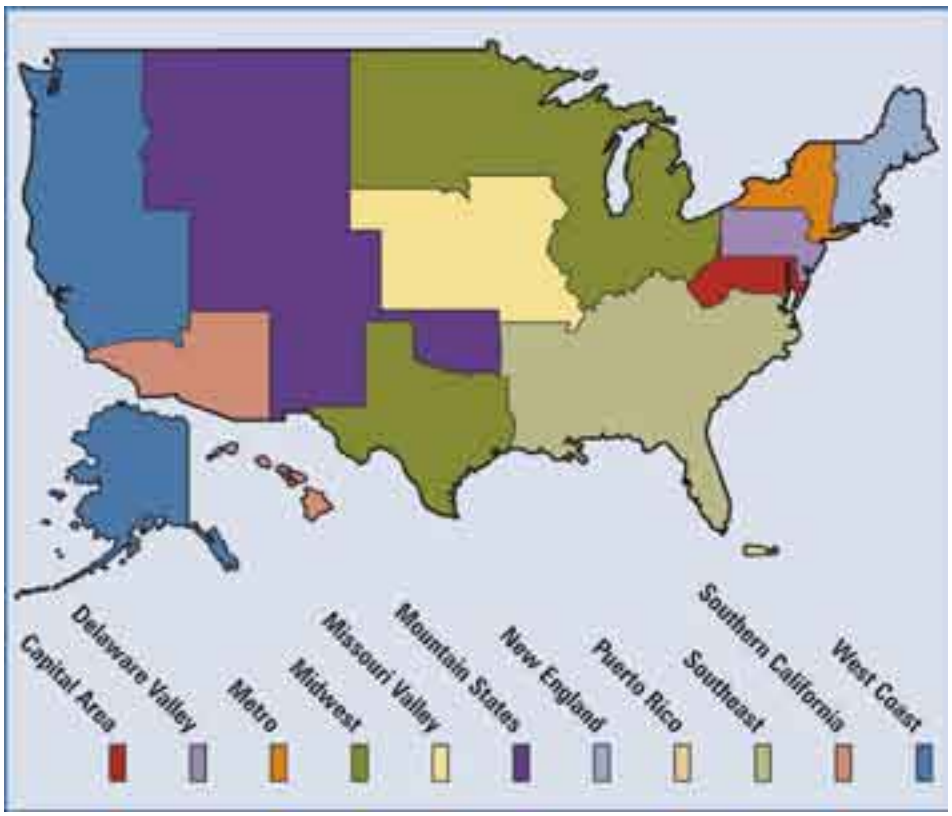
PDA Announces Establishment of Missouri Valley Chapter

PDA is proud to announce the founding of the Missouri Valley Chapter, which will serve PDA members in Iowa, Kansas, Missouri and Nebraska.

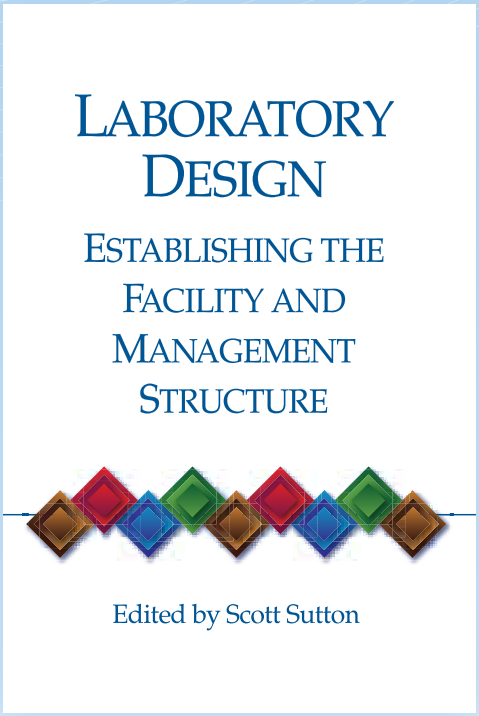
"This new chapter will bring excellent local programming to a significant segment of the PDA membership, and hopefully will attract new members who have not had the chance to experience the benefits of PDA before," said PDA President **Richard M. Johnson**.

Based in the Kansas City and St. Louis areas, the chapter will cater especially to PDA members and industry leaders in the same territory as the Kansas City U.S. FDA District. **Thomas Pamukcoglu**, SAFC Biosciences will serve as the first Missouri Valley Chapter President. He will be joined by Chapter President-Elect **Kenneth Boone**, Covidien; Chapter Treasurer **Keith Koehler**, Acceleration; and Chapter Secretary **Jeff Hargroves**, ProPharma Group.



New Release

New Release at the PDA Bookstore



Laboratory Design: Establishing the Facility and Management Structure

Edited by Scott V. W. Sutton, PhD

Gain an in-depth understanding of effective ways to organize your microbiology laboratory while meeting corporate requirements and reflecting your organization in the facility and through laboratory procedures and training.

By describing today's best practices available for design planning, technical proficiency and careful data analysis you will learn how to minimize your likelihood of error and how to maximize the ability of your staff to get their work done in an efficient and effective manner.

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www.pda.org/LaboratoryDesign

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Science & Technology *Snapshot*

PDA/ISPE Table Top Exhibit at PDA/FDA Meeting

Rich Levy, PhD, PDA

There will be a table top exhibit at the upcoming *2010 PDA/FDA Joint Regulatory Conference* in Washington, D.C., which will highlight two key scientific/quality initiatives sponsored by PDA and ISPE. Known as Paradigm Change in Manufacturing Operations℠ (PCMO) and Pharmaceutical Quality Life Cycle Implementation® (PQLI), these are sponsored by PDA and ISPE respectively. Both initiatives are comprised of task-force driven projects with the goals of establishing "best practice" documents and/or training events.

The PCMO and PQLI's initiatives are already facilitating communication among experts from industry, academia and regulators, as well as experts from the respective ICH Expert Working Groups and Implementation Working Group. Both initiatives are expected to contribute to a practical approach to implementation of International Conference on Harmonization (ICH) Guidances Q8 (R2), *Pharmaceutical Development*, Q9, *Quality Risk Management* and Q10, *Pharmaceutical Quality System*, as well as the more recently initiated topic, Q 11, *Development and Manufacture of Drug Substances*.

The table top exhibit discusses ongoing efforts by PDA and ISPE to co-examine these two key initiatives in order to ensure project coordination and to prevent unnecessary duplication. This tabletop will highlight that effort and the individual projects which make up the proposals.

We hope you will stop by the tabletop to learn more about these initiatives.

The below is a list of PCMO groups that will hold closed meetings at the PDA/FDA conference:

- **PCMO 2.1 "Capture Knowledge Management"**
- **PCMO RO1a "Quality Risk Management & Biotechnology Manufactured APIs"**
- **PCMO RO1 "Risk-Based Manufacturing"**
- **PCMO 2.2 "Management of Suppliers & Contractors"**
- **PCMO RO6 "Risk-Based Auditing"**
- **PCMO 1 "Process Validation & Verification: A Lifecycle Approach"**
- **PCMO RO5 "Quality Risk Management for Packaging & Labeling"**
- **PCMO Task Force Leader's Meeting**

Learn more about *2010 PDA/FDA Joint Regulatory Meeting* at www.pda.org/pdafda2010

Technical Report *Watch*

In Board Review: Following technical editing, TRs are reviewed by PDA's advisory boards (SAB, BioAB). If/when approved, the PDA Board of Directors (BoD) makes the final decision to publish or not to publish the document as an official PDA TR. Balloting at each level can take several weeks or longer, depending on the questions posed or revisions required.

- *Technical Report No. 22: Process Simulation Testing for Aseptically Filled Products* **(BoD)**
- *Biological Indicators for Gas and Vapor-Phase Decontamination Processes: Specification, Manufacture, Control and Use* **(BoD)**
- *Technical Report No. 3: Validation of Dry Heat Processes Used for Sterilization and Depyrogenation* **(BoD)**
- *Technical Report No. 13: Fundamentals of Environmental Monitoring* **(SAB)**

In Publication: TR is approved and ready for publication.

- *Technical Report No. 50: Alternative Methods for Mycoplasma Testing*

Available at the PDA Bookstore now!
Technical Report 50: Alternative Methods for Mycoplasma Testing

Journal *Preview*

Cell Substrates

Volume 64, No. 5 is dedicated to the proceedings of the 2009 PDA Cell Substrate workshop. Editor **Govind Rao** writes of the articles in his editorial: "Cell substrates are the 'seed corn' of the biotechnology industry. There are many competing cell lines that have emerged as favored expression systems. Each has its own advantages and disadvantages and particular media requirements and regulatory challenges. The reader should also note that some of the papers are written by the developers of the system and have a commercial interest in their further adoption." The papers provide good background material for the upcoming PDA/FDA Adventitious Viruses in Biologics workshop and should be useful to anyone currently wrestling with the never-ending challenges of cell bank use and maintenance.

Editorial

Michael Wiebe, "Introduction"

Research

Sally Baylis, "Regulatory Expectations of Validation/Qualification of Adventitious Virus Assays"

Lajos Baranyi, "Lentiviral Vector Mediated Genetic Modification of Cell Substrates for the Manufacture of Proteins and other Biologics"

Stephen Brown, "Avian EBx® Cell Lines, Application to Vaccines and Therapeutic Protein Production"

Dayue Chen, "Root Cause Investigation of Unusual Results Experienced"

Ruth Cordoba-Rodriguez, "Raw materials in the manufacture of biotechnology products: regulatory considerations"

Gay Gauvin, "Gamma-Irradiation of Serum for the Inactivation of Adventitious Contaminants"

Linda Hendricks, "Apparent Virus Contamination in Biopharmaceutical Product at Centocor"

Arifa Khan, "Testing Considerations for Novel Cell Substrates: A Regulatory Perspective"

Arifa Khan, "Regulatory Considerations for Raw Materials Used in Biological Products"

Andrew Kerr, "Adventitious Viruses Detected in Biopharmaceutical Bulk Harvest Samples Over a 10-Year Period"

John Petricciani, "Animal Cell Substrates: Back to the Future"

Cherylene Plewa, "Application of Lentiviral Vectors for Development of Production Cell Lines and Safety Testing of Lentiviral-derived Cells or Products"

Penny Post, "Safety Testing and Use of Insect Cells for Recombinant Protein Production"

Barbara Potts, "(Transcript) TSE Case Studies Associated with Japanese and Other Regulatory Authorities"

Mike Rubino, "Experiences with HEK293: A Human Cell Line"

Interest Group *Watch*

Join a PDA Interest Group

Georg Roessling, PhD, PDA

PDA interest groups were formed in 1995 and have stimulated member involvement ever since. PDA Interest Groups provide a vehicle for people with common interests to interact with one another, exchange information, network and directly impact the science, technology and regulation of bio/pharmaceutical manufacturing.

Any PDA member can join one or more interest groups. Most members join PDA interest groups, because it not only is an excellent source of specialized information; it also serves as a springboard for involvement in leading-edge activities such as the drafting and final publication of PDA technical reports and PDA technical bulletins.

Participate and get involved! This is your chance as a PDA Member to learn, influence future program content and become more actively connected with the mission of PDA. For more information, go to www.pda.org/interestgroups or email **Iris Rice**, rice@pda.org.

Mike Rubino, "Raw Materials Case Histories"

Ranga Sampath, "Rapid Molecular Assays for Microbial Contaminant Monitoring in the Bioprocess Industry"

Robert Weaver, "Evaluation of UVC and HTST Media Treatment for Viral Risk Mitigation in Mammalian Cell Cutlure Processes"

Michael Wiebe, "Summary of the Synthesis Session"

Recent Sci-Tech Discussions: Internal Audit v. Self Inspection

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.

Questioner: **Dear Forum Members,**

This is a topic of debate with inspectors or within organizations about the difference between an internal audit and self inspection. The term self inspection is commonly heard in WHO documents, but nothing is mentioned about internal audits.

The following are the key questions:

1. Is it a confusion of terminology or do these two words have separate meaning and procedures to be followed with a regulatory background?

2. Is it possible to use only one term (self inspection or internal audit), if both mean the same thing?

3. If different, what are the basic steps concerned in each of these terms and what is the minimum acceptable frequency to conduct them in a year?

Forum's valuable inputs are awaited.

Regards.

Respondent 1: Words don't matter! You should be able to prove that there is an internal, independent QA authority which is overseeing the operations and has control over quality systems and that corrective actions are being taken and documented. The principles of quality assurance control over compliance of quality systems are well documented in the U.S. FDA's quality initiative document and internal audit/self inspection are part of that.

Respondent 2: PICS and Eudralex have the following statement:

There is a procedure for self inspection and/or quality audit which regularly appraises the effectiveness and applicability of the quality assurance system–so one might be led to believe that there is a difference.

It would seem to me that the FDA prefers the term internal audit and the European Medicines Agency, self inspection. In any case, a better term might well be that they are "first-party" inspections. If you go through the various guidances, as I have done, I do not think that you will come up with a clear distinction between the two, but maybe someone has found something.

Respondent 3: Words and their meaning do matter.

In my experience, self inspection is a compliance activity conducted within a department or a functional activity by a member of that department, whereas an internal audit is an independent compliance activity conducted by the quality unit or a corporate audit group that is reported to your management with a timetable for response and corrective action.

Respondent 1: Such a requirement or definition is not specified in any guideline, and it is becoming more like a poem with everyone interpreting depending on his own imagination and stake. The bottom line is: Assess/audit your own quality systems as inspectors…. Hence, words don't matter but essence and requirement does!

Respondent 4: Hi [Questioner],
I believe that internal audit and self inspections are synonym; the internal audit or self inspections program helps to ensure the compliance with all relevant GMP and regulatory requirements. Therefore, this SOP defines the procedure and responsibility for the self inspection planning, implementation and follow-up to assure the site is compliant with regulatory, cGMP and site quality procedures.

Respondent 5: Colleagues:
[Respondent 1] is not quite right when he states that self inspections are not required or defined in any guideline. While it is true that the U.S. GMPs do not specify this requirement, all other world-relevant GMP regulations and Guidelines do. Please refer to:

- Health Canada's 2009 GMP Guidelines
  - Quality Control, Section 4.2.3:1.4
- The WHO 2006 GMP Guide (Quality Assurance of Pharmaceuticals: A Compendium of Guidelines and Related Materials, Vol. 2, Good manufacturing practices and inspection. –2nd ed.)
  - Self Inspections, 8.1 through 8.6
  - Quality Audits, 8.7
  - Supplier Audits, 8.8-8.9
- The 2006 EU GMPs
  - Quality Assurance, Chapter 1, Section 1.2 ix
  - Self Inspections, Chapter 9

It is also important to remember that even if FDA investigators don't have legal access (in the United States) to the results of self inspection audits, they can get to them in various ways via your CAPA reports, incidents, discrepancies, failures, OOS, Complaint Investigation Reports or obtain a court order (in the United States) to be granted access if they believe a firm's management has chosen to consistently ignore the findings of self inspection reports or ask the local regulatory agency (during foreign inspections) if the investigator's suspect similar behavior.

However, regarding the difference between internal audits and self inspections (which was the subject of the initial query), only the WHO makes the distinction between various types of audits, i.e., self inspections, supplier audits and quality audits. The latter to be performed by experts (either from within the firm or third party) with the intention of improving the quality management system, leaving self inspections and internal audits

to mean essentially the same.

Respondent 6: [Respondent 1], Please note that going solely by whether it is "required" or "defined" in the regulation is a wrong approach when it comes to the U.S. GMPs. If taken [literally] it ultimately could lead into significant product-quality related issues and FDA warning letters as well. These regulations were written in 1978 or so, and only a few changes have been made since then. Some of the regulations in other parts of the world came much later from the U.S. GMP regulations and have been made better.

Interpreting U.S. GMP regulations requires a different mindset. The GMP regulations have remained the same. But, what we have in the United States is the "c" in GMPs. The "c" stands for "current." In other words, we need to comply with the Current Good Manufacturing Practices (cGMPs or CGMPs). The "c" keeps changing over time based on industry best practices. It takes considerable effort to track and monitor these changes in the interpretation of the same good-old GMP regulation. The cGMPs require internal audits (or inspections). There are no ifs or buts about it.

Respondent 7: I must disagree on one point, there is a U.S. GMP requirement, Sec. 820.22 Quality Audit, that says:

Each manufacturer shall establish procedures for quality audits and conduct such audits to assure that the quality system is in compliance with the established quality system requirements and to determine the effectiveness of the quality system. Quality audits shall be conducted.…

While this is not CFR 210 or 211, it is applicable to any quality system where FDA has authority. Internal quality audits have been common practice in the U.S. pharmaceutical industry for at least 20 years, so it would be very difficult to argue that they are not cGMP.

As for the difference between internal audits and self inspections, if you believe that there is a difference, define it in your SOPs. The only time I have seen them defined as different, the internal audit was performed/sponsored by the corporate quality group and a self audit (inspection) was performed by each functional unit within each facility. For example, the chemistry lab manager at site A did a self audit of their chemistry labs, and later corporate QA assigned the site A micro lab manager to perform an internal audit of the chemistry labs.

On a recent 483, I saw a reminder that "Under the law, your firm is responsible for conducting internal self-audits…" So, maybe just mash all the words together and be done with it!

Respondent 8: There have been several different interpretations of what is and what is not required—together with differences on what the name should be. Does it matter, providing that there is a system to assess your GMP compliance? If there is not a system, the only check is when the investigator/inspector visits. If this check finds big problems, we all know the consequences. Have an internal system and occasionally use an external resource that can give an independent view. The external resource can be corporate quality or consultants.

Respondent 9: I agree with [Respondent 3's] common sense approach. Words do matter, but sometimes semantics create issues of their own without effectively addressing the actual problem.

Join the discussion at www.pharmweb.net/pwmirror/pwq/pharmwebq2.html

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Arm Yourself with Knowledge for Your First Inspection

Melissa Smith, MJQuality Solutions and Lorraine Murphy, GTC Biotherapeutics

The preapproval inspection represents, in many cases, a first for your firm and for the U.S. FDA. It is your first experience with the Agency's inspection process and their first evaluation of your facility, procedures and people. Understanding how to prepare for this first look is as important to your success as having sound processes, controls and compliance activities. While this article focuses on preparing for this preapproval inspection, the basic approach to inspection preparation can be applied to a post-approval inspection.

Inspection Basics

Consider the following questions in the preparation stage for Preapproval Inspections (PAI), which form the basics of the "who-when-what-where-how" elements.

Who
Who is likely to be coming?
How many inspectors will there be?
When
When are they coming?
For how long might they come?
What
What are the triggers for inspection?
What are the assigned roles and responsibilities for the inspection?
Where
Are they also likely to go to contract sites-which ones, when and are they ready?
How
Will you get a schedule for the inspection?
Will you get an agenda?

Since this is the organization's first inspection, it is likely to be triggered by the filing of a submission. If a BLA, NDA or PMA (for a combination product), an audit can be expected prior to approval, and the organization should be inspection ready at time of filing. In these cases, the Agency will provide notification on the timing and duration of an audit.

A comprehensive reference for this information is the CDER Preapproval Inspections is the Compliance Program Guidance Manual 7346.832. **(1)** This 47 page manual describes in detail CDER's role in the preapproval process. The objectives and responsibilities of CDER when conducting preapproval inspections are described in detail for all areas inspected, making this a useful document for reference.

The CDER manual also outlines the strategy for assigning inspections, the notification process, the team responsibilities and the areas covered by inspection. It reviews the decision making method for the assignment of a PAI on a priority basis or discretionary basis. The criteria listed in the CDER manual for a priority based PAI should be reviewed by the PAI team as part of the planning process, as this may affect the timeline and risk prioritized preparation route.

Another thorough reference for basic preapproval inspection preparation is a book entitled, *Preparing for FDA Preapproval Inspections.* **(2)**

The Plan for Preparation

For a preapproval inspection, there is an expected timeline which is part of the overall master project plan for the product, along with process validation lots, regulatory submission and launch activities. Basic first activities are to define the inspection timeline, team and type of inspection, with these activities taking place as part of an overall inspection readiness plan. Note that the inspection readiness plan should address all relevant sites: Contract Manufacturing Organizations (CMO), Contract Research Organizations (CRO), packaging, labeling, suppliers and so on. The elements of risk management also play a role in the inspection preparation as each item in the plan is assessed for risk impact and has a resource estimate associated with it, including manpower and timeline. The primary inspection team can delegate work through multiple work teams as required by the readiness plan. Inspection readiness dates for all sites are included in the plan. Various tools are part of the project management toolbox that can be used for managing the project, assessing risk, tracking progress and risk-based filling of gaps.

Preparing for Inspection Procedures

Ensure that policies and procedures covering essential elements for a U.S. FDA inspection are in place and that staff at all levels within the organization, from president to maintenance workers, are trained as appropriate. The clearly written procedures and training should:

- Define roles and responsibilities and designate by name or title a person to serve as the coordinator or escort for the inspection
- Address admission of an inspector into the plant. The receptionist should know people within the organization to be notified. The inspector should be asked to show credentials and the purpose of the visit (i.e. routine or for cause), including the Notice of Inspection (form FDA 482), which authorizes the inspection and officially begins the inspection when presented.
- Cover the copying of records, sampling of items, picture-taking and proprietary information (i.e., take duplicate samples or photographs).

Maintaining an "audit binder" is an excellent way for an organization and the audit coordinator to stay prepared. The binder may include: company annual report, names, phone numbers, biographies of key employees (regulatory and legal personnel), an organization chart, facility information, location of appropriate records (permits, master files and product/process specific information), plant layout drawing, flow chart of manufacturing process, lists of components, etc.

For a PAI audit, expect subcontractors to be included in the audit agenda (especially if they are geographically convenient,

otherwise the agency may schedule a separate visit). Make sure quality agreements are up to date. Agreements should address communication and responsibilities for agency audits. Plan to be available—even on site—during the contractor audit. Afterwards, it is important to obtain a copy of any observations and to make sure follow up activities are completed.

Define Roles and Responsibilities

The roles and responsibilities for inspection preparation are part of the readiness plan. Roles and responsibilities for conduct during the inspection need to be defined or assessed. The primary contact person needs to be able to contact the inspection team and assemble them as quickly as possible. There should always be backups for members of the inspection team which includes the subject matter expert (SME).

The following should be readily available to the front desk, regulatory management, quality management and upper management:

- Inspection team list
  - Including SME
  - Phone numbers (including off-hours and backups delegates)
- Contact list for key contract sites
  - CMO, CRO, Off-site document storage

The inspection team should ensure the following is always available and kept updated:

- Company Presentation
- Organizational Chart
- System Chart (i.e. documentation flow)
- Site Plan

Determine if there is a contract inspection team who needs to go to contract sites. If so, define the roles and responsibilities of the team members (as in all the inspection teams) ahead of time. When the time comes, this activity ensures the quick action of the team to respond to the needs of the inspection.

The roles and responsibilities of each type of team should be thoroughly defined and understood by all team members as part of the inspection readiness process within the company.

Once the scope of the inspection is determined, the expectations of the inspection revealed (follow-up, annual…) and the roles and responsibilities of the teams defined, the teams are ready to determine what tools and systems to use to prepare for the inspection.

Inspection Tools–Gap Analysis

Key areas to assess for inspection readiness can be identified through a gap analysis. The primary areas of focus for the gap analysis can differ depending on the conditions under which the inspection is taking place, but these gap analyses still draw on the same comprehensive list of inspection areas. Both the total timeframe of the inspection and lead-time can differ, as well as the likely areas in which the inspection may focus. One can obtain various gap analysis list based ➤

Potential Sources of Information

- **Internal audits**
  - Have audits been comprehensive, at a minimum, addressing critical or high risk systems
  - Are there any audit findings still open?
  - Assess all open findings. Ensure that you have a plan to close and that the plan is being followed
- **Annual Quality Review (3)**
  - Review last quality review
  - Consider updating if more than 6 months old
  - CAPA
    - Which ones are still open?
    - Ensure timely closure
    - Preventive action taken
    - Effectiveness of action taken
    - Trending
  - Deviations
  - Change controls
  - Audit
- **Annual Product Review**
  - Adverse Event Reporting
  - Trending
  - Major Process Changes
  - Stability
- **External Audits**
- **Training System**
  - Job descriptions up-to-date
  - Training modules
  - Training files
- **Change control history**
  - Software (including spreadsheets)
  - Documents
  - Equipment
  - Methods
- **Supplier Qualification and monitoring**
- **Validation readiness**
  - When were validations done?
  - Do they need to be updated?
  - Is this discussed as part of Annual Product Review?
  - If not, review status
  - Links to change control and revalidation as needed
- **Facility compliance audits**
  - Plant-Mfg, Packaging, Labeling, Distribution
  - Lab
  - Equipment
  - Materials
  - Facility-Equipment-Process control measures
  - Process Validation program
- **Chemistry-Manufacturing-Controls submission**
- **Competitor's inspection reports may have similar products and relevant problems may be identified in their inspection**

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on the regulatory requirements (21CFR 11). Overall, the intent is similar to that stated in the FDA compliance manual, to assess the readiness for commercial manufacturing, to check for compliance against the regulatory application filed, and to assess data integrity which supports the first two assessments. **(1)**

A gap analysis assesses the current state of control against the requirements of the relevant CFR, the quality systems in place, and the compliance of the systems, facility and data with what was submitted in the CMC. A mock audit is also an important tool to PAI as it assesses the readiness of the systems, facility and personnel for the inspection, especially if it is treated like a regulatory inspection and not as an external vendor inspection. There are other tools in routine use which help keep a facility prepared for audit, such as the annual quality/product review and the internal/external audit program.

The major areas which are assessed within a gap analysis and/or mock inspection can be mapped within the major areas of system readiness, personnel readiness and facility readiness, which are outlined in **Figure 1**. Preparation of reports, quality documents, process documents, facility, personnel, vendors and suppliers are also part of this overall readiness plan. Additional details regarding manufacturing elements which can be assessed as part of the gap analysis are outlined in another compliance guide, *Drug Manufacturing Inspections: Compliance Program Guidance Manual 7356.002* as well as many of the associated guidelines referenced in this manual. **(4)**

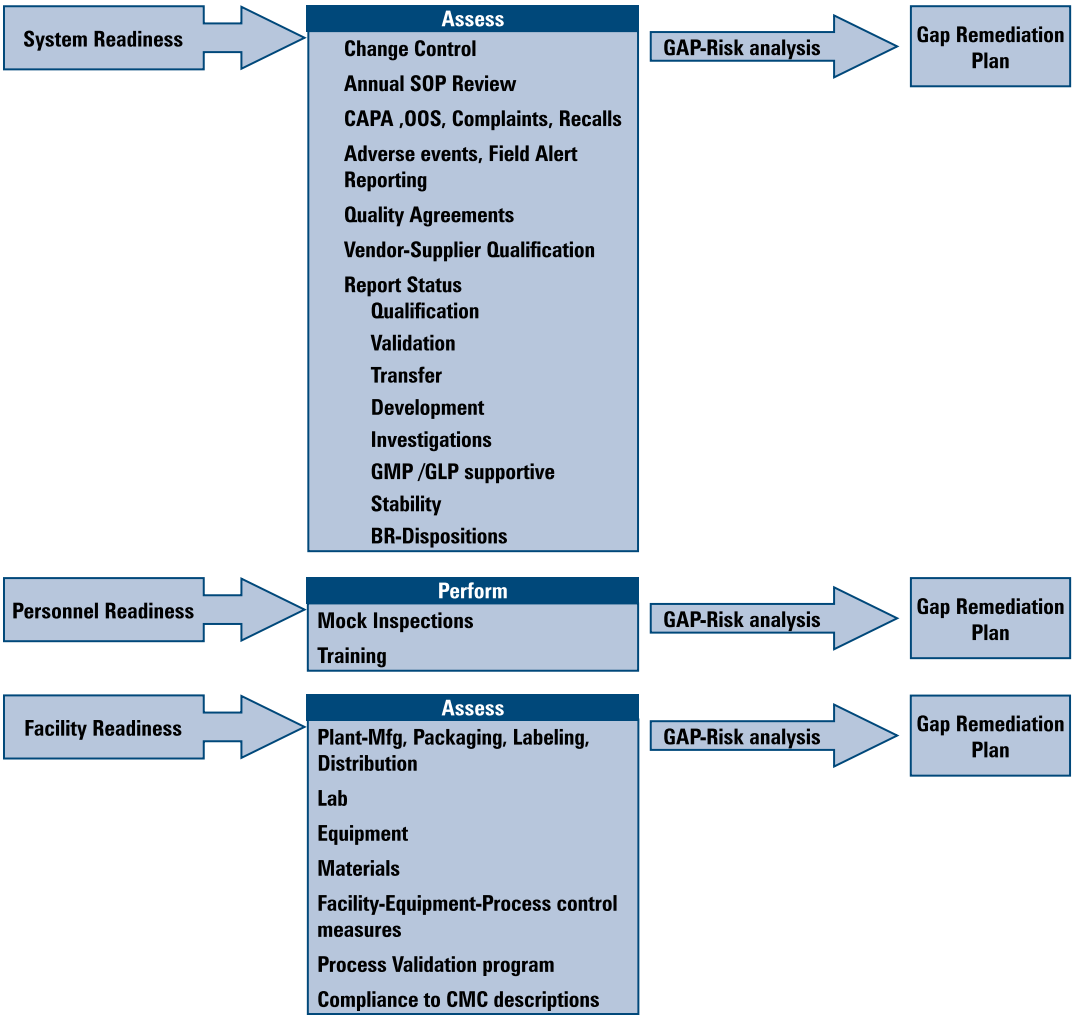
Sources of information for a gap analysis include internal and external audits and annual product and quality reviews. Knowledge of CMC content (and supportive content) in addition to relevant guidelines are also important when deriving the key elements of the gap analysis. **(5)** The references cited in the FDA compliance manuals are another good source of information that can be useful in generating this gap analysis list. **(1)** When examining these systems, the following areas or questions are some that can be assessed as sources of inspection readiness elements.

As experience with inspections is gained, the need for separate inspection readiness tools are reduced

Documentation is also reviewed as part of the system analysis. Included in this review are the documents/procedures for a regulatory inspection, training system, vendor approval list, annual quality review, annual product review, internal audit reports and biological product deviations. As part of the document review process, the following areas can be covered:

- Identify key documents based on type of inspection
- Notify off-site storage for key documents
  - Who is responsible for this?
  - How easy are the documents to retrieve-paper and electronic
  - Are the proper resources assigned to retrieve them in timely manner?
  - What is a timely manner?
- Do you have the following documents ready?
  - SOP's up for review (are they up to date?)
  - Validation reports pending completion
  - Qualification reports pending completion

Figure 1: System, Personnel and Facility Readiness



- Outstanding CAPA
- Training documents
- Reports that contain justification for change controls, OOS investigations
- OOS closures
- Outstanding change controls
- Complaint (AER) investigations (if any)

Once gaps have been identified and risks assessed and prioritized through the gap assessment process, develop an action plan to address the gaps. The inspection readiness team should actively track this plan to ensure adequate completion within the expected timeline with consideration of the established priorities. Risks should be assessed, mitigated and managed.

As experience with inspections is gained, the need for separate inspection readiness tools are reduced, replaced by the effective management and continual improvement through the quality tools—i.e., annual product review, annual quality review, internal audit program and external audit program.

Assessing Readiness

Once all the teams have been assembled, the systems, documents, facility and personnel readiness assessed and the gaps analyzed, the inspection readiness team is then responsible for reviewing and approving the action plan, which includes risk assessment, resources required and the overall timeline for task completion.

The form this plan takes can be varied, but the elements require the definition of task, priority, man-hours, equipment/resources needed and timeline along with the associated risk. The task, responsibility, commitment required and assessment of completion is required to be detailed to enable the inspection team to review for appropriate completion. The inspection gaps are filled, according to the readiness plan/team by priority/risk keeping in mind the inspection readiness date for all sites.

Part of this plan can be a type of preventive action. It is an opportunity to see what changes to the inspection readiness systems can be instituted in order to ensure inspection readiness is more easily achieved in the future with fewer resources or with more effective utilization of resources.

How to Handle the Inspection

Another important element to consider in inspection readiness is to ensure you have all the systems and personnel in place to handle the inspection. This should be part of what has already been tested out during the mock inspection and revised as needed to cover the gaps. Some of the things to consider in this plan are:

- Do you have a system to record copies of all documents reviewed?
- What is your policy for?
  - Copies of documents
  - Allowing inspection of internal audit results
  - Photographs
  - Materials and Samples
  - Has this been covered in your inspection SOP?
- What paperwork will the inspectors have for the audit?
  - What is an inspection notice?
  - Who received it?
  - Who reviews it?

For practical consideration, the following items can be reviewed to see if they should form part of your plan. **(6)**

- Generally, the FDA will provide an agenda and a list of auditors for the visit. Be prepared to provide an overview of the company and product(s).
- Set aside a suitably sized, comfortable room for the inspector's use during the visit. Make sure it does not contain any confidential records. If possible, the room should be isolated and away from areas where casual conversation may occur.
- An introductory meeting at the start of the inspection is typical. Officers of the company may attend. Be prepared to provide a concise overview of the company and product(s).
- QA and the Audit Coordinator should be prepared for long days, with staffing of multiple shifts of essential functions, if necessary. Staff should be on hand before the inspectors arrive in the morning to prepare audit rooms and copies of documentation, for example. At the end of each day, there will likely be a closing meeting with the Agency. After the daily closing meeting, plan to hold a follow-up internal strategy meeting to review and prepare for the next day.
- Persons should be assigned to take notes during the audit. If possible, there should be a person assigned to each inspector.
- Plan ahead of time for how documentation will be handled during the audit. Have a list of company SOPs and only provide documents that are specifically requested. Keep lists of documents and versions provided. Leaf through the pages of the documents to insure completeness and absence of extraneous information. It's a good idea to make an additional copy for internal review. Whenever possible, subject matter experts should be encouraged to review documents ahead of time in anticipation of questions. Consider having a separate staging area to keep the documents that are going back and forth organized.
- The Agency will usually hold an exit interview at the completion of the audit. Officers of your company may wish again to be present. Serious deficiencies, if any will be discussed and documented in a form 483. Whenever possible, make corrections before the inspector(s) leave the premises.

Preparation is Key

This is just a basic review of preparation for a preapproval inspection. The references cited give more detail in each of these summarized areas. Expectations for the inspection (who, what, when, where, how), a readiness plan, inspection teams, use of tools (gap analysis, mock inspection, documentation review), closing the gaps and inspection preparation are the basics to help you plan and execute, in order to be ready for an inspection.

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continued on page 22

Rapid Deployment Tips to Prepare for an Inspection Quickly

John Avellanet, Cerulean Associates

On the desk sits the letter with blue and black letterhead from the U.S. Food and Drug Administration informing you that Agency inspectors will arrive at your facility the Thursday after next.

Now what?

Drafting an Action Plan

Most regulatory and quality professionals would agree that a best practice is to have a pre-defined inspection preparation action plan at the ready, rather than assembling and executing one in an ad hoc manner under a tight timeline in an environment suddenly fraught with the tension and anxiety inevitably accompanying the announcement of an impending inspection.

And yet, day-to-day activities, projects, interruptions, distractions and business, as usual, gobble up good intentions. Defining a comprehensive action plan is often postponed. Tasks that might have been planned and executed ahead of time are left undone. Now, given the arrival of a U.S. FDA inspector in ten days or less, time is short and the firm must get the biggest impact for its preparation efforts. In this light, there are seven rapid impactful activities:

1. Review the notification letter
2. Review previous inspection records
3. Review the FDA quality system inspection technique (QSIT) manual
4. Review the relevant FDA inspection manuals
5. Review relevant harmonization guidelines
6. Prioritize likely areas of scrutiny
7. Hold an inspection expectation overview meeting

These are all in addition to those activities typically covered in a regulatory inspection and third-party audit handling standard operating procedure (SOP) such as setting aside two rooms, one for the inspector and one for company use only. **(1)**

The key to proper inspection preparation is divining where the inspector may go and having knowledgeable personnel and records ready to meet him or her. While these seven steps may seem like they will take significant time, experience has shown that they are accomplishable in ten days or less with two caveats: **1)** Upon notification of an impending inspection, preparing for that inspection is the number one priority for the next 80 hours or less, and, **2)** Reviewing the regulatory documents discussed below is vital for making educated guesses as to what is most likely to be asked by the inspector.

Review the documentation for specific areas of concern on the part of previous inspectors

1. Review the Notification Letter

With luck, the letter will spell out the type of inspection the Agency intends to conduct, including the records the inspector expects to review. This may be a preapproval inspection (PAI), "statutory" inspection, a "for cause" inspection or a "follow-up" inspection. In such cases, the inspection is largely confined to those areas identified in the letter; although, the inspector can, and sometimes does, ask about and review supporting documentation for other areas of relevance. For example, one notification letter, sent by the FDA, informed a recipient that the Agency intended to conduct an inspection related to a whistleblower complaint around data integrity associated with clinical trial production or finished product contamination. In that case, the inspection led to a review of risk evaluations for pilot plant production and process parameters, the risk evaluation, qualification and oversight of the active pharmaceutical ingredient manufacturer and so on, not just pilot plant batch records, electronic record integrity and clinical trial production quality control data.

In any "for cause," PAI or "follow-up" inspection, the Agency will likely provide some level of insight into the areas of the compliance program and the records the FDA intend to review. And while no inspection is good news per se, this will at least help focus preparation far more than a general inspection based on calendar year timing.

2. Review Previous Inspections

Assuming the firm has been inspected by the Agency before, previous establishment inspection reports (EIRs) and FDA Form 483 observations should be available for review. Companies that have not yet been inspected by the Agency can turn to their critical suppliers such as a contract manufacturer (CMO) or contract research organization (CRO). This is especially important if the company is receiving a preapproval inspection or if a "for cause" inspection cites clinical or manufacturing oversight concerns. The CMO or CRO may have been inspected by the Agency. If so, they will have EIRs and Form 483s that can be reviewed.

Review the documentation for specific areas of concern on the part of previous inspectors. For instance, if the previous report cited inconsistencies in calibration records for a specific titrator, the inspector might want to either look at more calibration records for other equipment or focus on the overall maintenance program from equipment logs, cleaning records and even personnel qualifications (or supplier qualifications if maintenance is outsourced).

Records that raised questions and led to further scrutiny of supporting activities and their documents are good candidates to be examined again. Since the last inspection, how has the company attempted to resolve questions raised by the previous inspector? And what track record of improvements does the firm have to show? From a review of previous FDA observational forms and any related correspondence, compile a list of the records reviewed. This should provide a good idea ➤

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of where the inspectors will at least start their review.

3. Review the QSIT Manual

The third step is to review the FDA's Quality System Inspection Technique (QSIT) manual. **(2)** Originally written to help inspectors of medical device and diagnostic firms since the publication of FDA's *Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach* with its emphasis on a holistic compliance framework and quality system, the QSIT is well worth the time to review; it provides example questions to which the FDA inspector might seek answers. For instance, in order to assess the role of senior management in promoting and overseeing FDA compliance at a firm, the inspector may make sure to obtain answers to questions such as:

- Have measurable quality policy objectives been implemented?
- Are quality audits conducted?
- Does the quality unit have appropriate responsibility, authority, and resources?

This is not to say the inspector will outright ask such questions; rather, the inspector will ask questions of both senior management and other personnel while looking for records (e.g., proof) that substantiate and/or answer the above questions.

4. Review the FDA Inspector Manuals

At this point, it's time to start sketching out the likely path the inspection will follow. The agency has provided some help in the guise of three publications:

- Investigations Operations Manual
- Inspection Guides
- Compliance Program Guidance Manual

For the Investigations Operations Manual, review chapters four, "Sampling," and five, "Establishment Inspections." **(3)** If scrutiny is expected around oversight of an international supply chain, examine chapter six, "Imports." If review of product recall handling is anticipated, take a look at chapter seven, "Recall Activities."

There are a number of inspection guides, so skim the detailed listing on the FDA website to see which best apply. **(4)** Remember, the objective is to make a quick list of the likely targets of scrutiny within the firm. Thus, if a preapproval inspection is expected given a recent submission, look specifically at the guide *Pharmaceutical Quality Control Labs*. **(5)**

Multiple chapters in the Compliance Program Manual deal with specific subcomponents of regulatory expectations. **(6)** The inspector will try to ascertain the company's level of compliance with these expectations, so a review of his/her default inspectional objectives can be helpful. The two most useful sections for uncovering specific expectations will be 7346.843 on Post Approval Audit Inspections, **(7)** and 7346.832 on Preapproval Inspections/ Investigations. **(8)**

The key to proper inspection preparation is divining where the inspector may go

Be aware that while a review of the statutes and regulations may also be helpful, particularly if it has been some years since the statutes, regulations and their preambles have been read. Each of the publications referenced above cites specific regulatory sections for the inspector. Given the limited time available in preparing for the inspector's arrival, other inspection preparation activities may preclude a more comprehensive regulatory review. Keep in mind the goal is to rapidly identify questions most likely to be asked by the inspector. As stated earlier, this seven step preparation process assumes approximately ten days or less (e.g., 80 hours or less). Thus, use the time available before the inspector arrives be a guide as to how in-depth statutes, regulations and preambles are reviewed in order to get the greatest return on investment given the limited preparation time available.

5. Review Relevant Harmonization Guidances

Just as the FDA QSIT and the three FDA publications noted above can help guide rapid preparation by identifying potential questions to be prepared to answer, so too can guidance documents from the International Conference on Harmonization (ICH) and the Global Harmonization Task Force (GHTF). In practice, however, ICH guidelines can be of limited value in time-sensitive situations such as preparing for an inspector's imminent arrival. GHTF guidelines, while ostensibly written for the device industry, are much more specific in terms of questions to be answered and the documentation to be kept around quality systems; thus, much more helpful when preparing for an inspection.

The more virtual the biopharmaceutical firm (i.e., the more the firm outsources development, manufacturing and/or distribution), the more likely the FDA inspector is to focus on supplier selection, evaluation, qualification and oversight. Given such a supplier management focus, the most relevant GHTF document to look through is the *Guidance on the Control of Products and Services Obtained from Suppliers*. **(9)** Pay particular attention to the end of each section entitled "Objective evidence may include" as well as any sentence ending with the phrase "...should be kept." This will help quickly identify examples of records that will support the answers to the questions the inspector may ask.

Be aware that FDA is slowly converging its regulatory compliance infrastructure expectations for device, biologic and drug firms to a common set of holistic, risk-based quality system controls **(10)**; thus, biopharmaceutical quality and regulatory affairs personnel who ignore recent harmonization guidelines directed more at medical device firms may unwittingly be doing themselves a disservice. If a harmonization guideline addresses common quality system and other core compliance infrastructure issues, the guideline document is well worth a quick review to ascertain if it has specifically applicable advice. **(11, 12)**

6. Prioritize Areas of Scrutiny

With the list of potential questions and possible documentation to provide, it is time to prioritize likely inspection points. Identify between 5-10 likely areas that will be reviewed. For instance, if the review indicates the agency is concerned about

management involvement and support for the company's quality system, then what is it about management involvement and support that is likely to draw inspector scrutiny? For a more virtual pharmaceutical firm, one specific area might be the effectiveness of supplier oversight in the context of management involvement. In this case, expect to provide the inspector with copies of records such as:

- Quality system management review SOP
- Quality system management review summaries and action plans
- Training SOP
- Training records, including effectiveness assessments, for management
- Executive resumes
- Organizational chart
- Management job descriptions
- Supplier evaluation and selection SOP
- Documented risk evaluation of various suppliers and supporting documentation showing management involvement
- Documented decisions and rationales on which suppliers to use and the controls to be put in place, including supporting documentation showing management involvement
- Quality or technical agreements with critical suppliers, and any supporting documentation showing management involvement
- Documentation showing management review of supplier deviations and/or investigations

It is important to be prepared to answer and provide proof as to if management trained on supplier evaluation and selection *prior to* vendor selection, and if management trained on risk management *prior to* execution of a quality agreement. After-the-fact training will spark questions as to how the firm made informed decisions if management was unaware of its current obligations, company processes and the potential impacts of supplier problems. Further document scrutiny might reveal that although a risk evaluation clearly showed one supplier would be more problematic from a drug safety and efficacy issue, the price was much better and the supplier was chosen *with no additional controls or safeguards put into place* given the increased level of risk. It is then easy to call into question whether the firm is operating in a state of control capable of consistently producing a safe and efficacious product.

7. Conduct an Inspection Expectation Overview

With those 5-10 specific areas in hand, and a list of documents to be expected to turn over for each area, schedule a meeting to review the preceding analysis's results and obtain feedback. This meeting should be cross-functional, including senior representatives from the quality department, regulatory affairs, information technology (IT/ICT), manufacturing, clinical and so on. The meeting should try to update everyone on inspection expectations and identify items that may

have been overlooked. Closeout this meeting by briefly reviewing your firm's regulatory inspection and third-party audit handling process.

Final Thoughts

These seven steps will help a firm meet an inspection with confidence. The seven steps are accomplishable within ten days or less under two assumptions: first, preparing for the inspection becomes the top priority for those 80 hours or less, and second, reviewing the regulatory agency documents referenced above is strictly for rapidly estimating what is most likely to be asked by the inspector, and not for the purpose of training or in-depth comprehension. This lean compliance, seven-step preparation assumes that many of the requirements spelled out in statutes and regulations are already accounted for in a firm's 21st century quality system and compliance infrastructure.

Preparing for an impending FDA inspection is like preparing for a suddenly announced visit from new in-laws. Knowing what to expect can save hours of anxiety, headache, and heartburn. The seven steps outlined above can help executives excel in less than ten days.

Are you ready?

About the Author

John Avellanet is the author of *Get to Market Now! Turn FDA Compliance into a Competitive Edge in the Era of Personalized Medicine*. He has gained tremendous acclaim for his speeches, corporate workshops and business-savvy compliance consulting work with clients and conference venues around the world. John can be directly reached through his independent advisory firm, Cerulean Associates LLC, on the web at www.Ceruleanllc.com or through his award-winning blog at www.ComplianceZen.com.

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Arm Yourself with Knowledge for Your First Inspection, continued from page 17

Lorraine Murphy has over 20 years experience in the biotech industry, having held leadership positions in R&D and quality at several organizations.

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Acting Right Can Facilitate a Good Regulatory Inspection, continued from cover

duties, and designating a person who will be responsible for hosting and managing the inspection. The policy should ensure that someone accompanies the inspector(s) at all times in order to see and hear everything that they do and, wherever possible, document this. Do this to avoid misunderstandings and to provide explanations where you believe inaccurate or unclear information was provided. Documenting the inspection will also serve as a reference point for placing inspectional findings in context when responding to the observations.

Inspections can be announced or unannounced, so make sure that the receptionist is familiar with the "handling inspections" policy and calls the designated host to collect the inspectors. You can and should ask the inspectors to present their credentials. Assign them a visitor tag and ask them to wear it at all times. Log them into the company visitor register and provide them with a copy of the company's safety and GMP rules for visitors. They should sign this document to indicate that it has been read and understood. Do not provide them with contradictory instructions. For example, one company said, "no cameras allowed." However, the safety instructions read, "no cameras allowed without prior authorization." If an inspector asks for authorization, you would be wise to provide it.

Accompany the inspector(s) to the designated conference room. If there are none available (unannounced inspections), ask others to leave the designated room. If there is one rule everyone in the company needs to internalize, it is that during an inspection there is no other priority than the inspection. Anything else can and will wait. It is useful to have an up-to-date, brief, introductory presentation ready at all times with the company history, ownership, organizational chart and numbers of employees, a current list of products manufactured at the site (or outsourced) and a facility layout drawing. A list of key personnel (names and job titles) that can be presented to the inspector(s) saves them from having to spend time gathering this information.

Inspection Readiness at All Times

A company's quality management system should be operating at a level where an unannounced inspection can be managed with a positive outcome at any time. The only instance where this might not be the case is for a start-up company planning for their very first preapproval inspection. In this case, the company will more or less be able to determine the timing of the inspection such that they should have an inspection readiness plan in place. In either case, a firm should be ready to activate their plan at the time of the inspection.

Mobile phones, laptops and other devices have no place in the conference room, except as a tool to aid the hosting facility.

There are some observations that are obvious and easy for inspectors to catch, so your firm should have a zero tolerance policy at all times for:

- Piles of old, unsigned printouts stacked anywhere in the company but where they should be, in particular a warehouse and/or a laboratory
- Unauthorized instructions written in marker pen or printed but not signed or clearly identified with a version number, and stuck on equipment, walls, drawers or white boards. Likewise for uncontrolled photocopies of SOPs or work instructions
- Uncontrolled printed labels found anywhere in the facility
- Expired reagents, materials, calibration stickers, reference standards, etc
- Puddles, rust, dust and dirt, as well as general disorder

Basic Behavior During an Inspection

Listen to and respect the inspector and acknowledge that they have a job to do. The easier you make their job, the more likely you are to end the inspection on a high note.

Write down every request for documents or data and periodically verify that the inspectors have received what they asked for. Do not leave them sitting in the conference room for lengthy periods without any information to review, this is wasting their time. If they ask for a document that might take a while to find, tell them "this is in our archive and might take about half an hour to arrive. In the meantime, we have the cleaning validation/batch record, etc. that you had asked for and can show you that." At the end of the day, ask if they have received everything they needed. Remind them if they did not get a document they requested, it could be due to a misunderstanding on your part. So, if they wouldn't mind repeating the request, you can provide it to them tomorrow or even send it on to them if they have finished the inspection. Most inspectors are very open and understanding to such an approach.

Mobile phones, laptops and other devices have no place in the conference room, except as a tool to aid the hosting facility. The inspectors should receive the undivided attention of everyone present, including people waiting their turn for questioning. All personnel in the company should know that they may be asked to enter the conference room while another person or persons are presenting a different topic. They should sit on the side, quietly, follow what is going on, and avoid starting conversations with anyone else in the room, texting or doing any action that might distract the inspectors or persons involved at that time.

Remember, the inspection belongs to the inspector(s). They are responsible for determining the agenda and working hours, within reason, and you should accommodate them. They are going to ask for a site tour or to visit specific areas (e.g., chemistry and microbiology laboratories) either immediately or at some point during the inspection. When you escort the inspector on the facility tour, do not allow "hangers-on." The touring party can become unmanageably large with department personnel listening in and crowding the

inspector. It becomes difficult to hear requests, and the inspector gains the impression of a facility with inadequate space and the likelihood of mix-ups. Creating the right atmosphere can be critical to the outcome of an inspection. Make sure personnel know if they are supposed to join the tour; otherwise they should continue to go about their business in a quiet and competent manner such that the inspector(s) see a well-run and organized business being managed by proficient and skilled staff. As soon as an employee draws attention to themselves or their activities (e.g., by shouting to a colleague or running around), this is likely to lead to a request for training records and close scrutiny of the activities and person.

Paul Hargreaves, one of MHRA's most experienced inspectors, explained that GMP is a philosophy; therefore, when reading a sentence in the text, you have to look at it in relation to your company's quality system and apply it. This is the heart of what an inspector is looking for: Does your company understand the requirement? Is it implemented? Is it adopted in an appropriate manner for the types of product that you are manufacturing?

Listen Before You Answer an Inspector's Question

Listen carefully to each question and wait until the inspector has finished the question before answering. If you are not sure that you have heard correctly or did not fully understand the question, ask the inspector to repeat it. Do not be shy to say (particularly during the tour where there may be noisy machinery or other distractions), that you didn't catch the question and could they repeat it.

Answering questions is stressful, and instinctively we want to get it over with. However, answering without fully understanding the question results in providing the wrong information, often unconsciously leading the inspector directly to an area that is troubling you but in which they really weren't interested.

The below is an example of such a case:

Question: *Can you describe how you perform sampling for….*

Answer: (Before question is finished and knowing that you had a rejected raw material sample from one of your major suppliers the previous day) *The samples are logged in here and then sent for testing.*

Next Question: *Can I see the logbook….*

In the above example, the inability to wait until the question was completed led the inspector to the logbook and before you knew it, he/she was asking about the rejected sample. If the auditee had waited for the question to be completed, the outcome might have been very different. as demonstrated below:

Question: *Can you describe how you perform sampling for the product xxx during the granulation step?*

And the answer, because you waited to

Don't apologize—explain what your company's practice is as briefly as possible.

hear the question, takes you and the inspector to a different place.

Try to place the question in the context of your QA and GMP knowledge, so as to focus your answer. Even if you do not have the exact document the inspector is looking for, they will be reassured to hear that you at least understand why this is a problem and are capable of fixing it in a reasonable timeframe.

Selection of Inspection Support

It is important to have an established list of appropriate subject matter experts (SME) who have been trained and briefed on inspection procedures and on how to act in front of the regulatory authorities. These individuals should be selected for their knowledge of a specific subject, such as microbiology, chemistry, etc. However, their expertise in the subject should not be the sole criteria for determining their suitability. They should also be chosen for their ability to answer questions succinctly without embellishing and to deal with scientific facts, not theoretical opinions. The company's audit lead and preparation room leaders should remind the SMEs of how to behave appropriately before they are allowed to enter the audit conference room. It is just as important to clear people for entry into the audit room as it is to clear documentation that is being presented to the regulator.

Justifying Interpretation of Regulations

Many of the regulations are subject to interpretation. Some manufacturing sites may interpret information differently than a sister-manufacturing site. It is important for companies to identify these differences prior to an inspection and to have one scientific justification explaining the company's interpretation of a regulation or requirement. This documentation should be formally written down. Once the paper is completed, it should be signed, dated, and made available to the manufacturing sites, in case they need to explain the position during and inspection. For example, a scientific rationale is necessary when a company chooses to deviate from a compendial procedure.

Fullfilling a Document Request

When a document is requested, make a careful note of the request, record the SME who will be required to present the topic and record as much context surrounding the request as you can provide. This allows the SME to bring the relevant documentation into the room, rather than coming with huge files and having to spend time searching for the relevant portion. In general, it is preferable to present only the requested document rather than full files. The very worst possible scenario would be to present the file to the inspector and tell them "it's in there."

In one case, the inspector asked for pest control records for monitoring station #31. The SME brought in the entire file and spent five minutes going through it looking for the requested record. The inspector observed, "The person in charge of pest control is not familiar with the records." If asked about pressure differentials and filtration in the microbiology laboratory, an auditee will annoy the inspector if the engineer shows up with a layout drawing without pressures on it. Likewise, it is not acceptable for the microbiology head to say, "I don't know if there are pressure differentials or filtration." They should know of their existence as it could affect work flows and gowning practices. It would be acceptable to say, "There are differentials, and filtration but I prefer that our engineer provide you with the exact details."

Handling the Stress of an Inspection

It is fine to tell the inspector that you or one of your staff is nervous. In one case, an analyst was called in to describe work in their notebook. Their face was bright red and they could hardly get a word out. Inspections are stressful. The inspector asked them to run through a calculation they had performed, and the analyst couldn't do it. The QA Director turned to the inspector and said, "Would you excuse her for a moment, as you can see, she is quite nervous. I would like her to step outside, take a drink of cold water and come back once she has had a moment to review the notebook alone." The inspector understood and moved on to another topic. Ten minutes later, the analyst came in and calmly explained the work. The inspector was satisfied and moved on to a new topic.

Interactions with the Inspector

Let the inspector determine the pace of the inspection. If they have asked a question, don't answer if they are reading or writing, because you might disturb their train of thought (which is irritating). If they want you to reply, they will tell you, "It's ok you can answer." Don't push documents under their noses while they are writing or tell them, "It's important." Sometimes they are trying to catch their breath and capture an issue that is running through their mind, so give them space.

Don't apologize—explain what your company's practice is as briefly as possible. If the inspector states or looks dissatisfied, try to explain how you believe you have implemented a GMP requirement for your product and use phrases such as "it seemed logical at the time," "if this is wrong, we will review and correct it as needed," or "maybe we need to look at it again, we will do that." Don't push the inspector into a corner by being too emphatic regarding your practices. Another useful phrase is "we are always open to improvement" or "continuous improvement is a foundation of our quality system, so we will get this put right." If you based your practice on a guideline, try "we interpreted the guidance to mean… but we will revisit it and we appreciate/understand your concern." This is far more acceptable than "the guidance supports our practice," or even as once stated, "FDA wants it done this way, the last inspector told us that." The trouble is that the last inspector probably didn't tell you that, you misinterpreted them or practices have changed. Therefore, the best approach is to justify ➤

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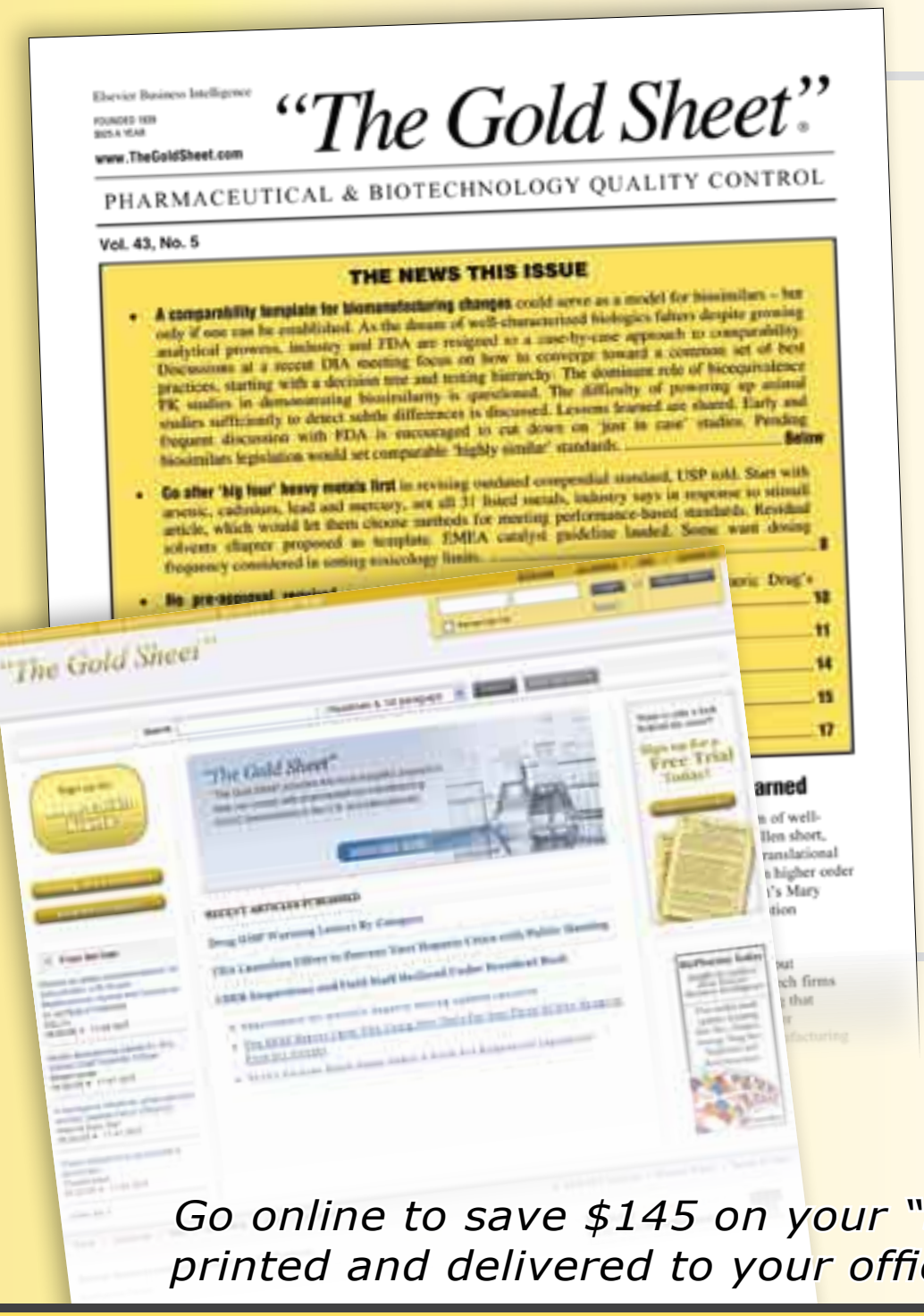

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Never ***correct documents or errors in front of the inspector after they have pointed them out.***

your position based on knowledge and risk management.

Below is a case study on how to justify your approach to an inspector:

Question to warehouse manager: *Do you have a copy of the list of approved suppliers?*

Reply: (after brief worried expression discussion in foreign language) *Can we leave this topic for tomorrow when the supply chain person comes back?*

Question: *Does the warehouse person have a copy of the list?*

Reply: (eventually after further discussion) *They have a purchase order showing the name of the supplier so that they confirm they received what was ordered, and the purchasing manager has a copy of the list.*

This answer has the inspector thinking:

The warehouse doesn't have a copy of the list and there is no mechanism for controlling entry of material from an unapproved supplier. I can tell they are worried because of all the back and forth discussion and the worried looks.

Had the firm anticipated why the inspector was asking the question (i.e., the GMP concern) the situation might have been handled as follows:

Question: *Do you have a copy of the list of approved suppliers?*

Reply: (confidently) *The purchasing manager keeps the list of approved supplier. The purchasing manager is authorized to order materials only from suppliers who appear on that list. The warehouse receives a copy of the purchase order and verifies that the manufacturer on*

The following are a series of case studies that show if you think before you speak, you will show the inspector that your company is not on the defensive.

Case study #1: During the site tour, the inspector comments that the doors to the warehouse are not fully sealed. A space at the bottom could allow insects to enter. The company responded by showing the inspector a UV insecticutor located high on the wall. The inspector's reaction, possibly not stated out loud but most likely to appear in the detailed report of findings, is, "These guys aren't serious. There is nothing to stop insects from crawling in, and they are trying to defend this practice?" A better response would have been, "We have already issued a purchase order to replace the doors," if this is the case, or "We noted this during a recent internal audit, and the doors will be fully sealed within xx days/weeks." Another response could have been: "We understand your concern. We will address this and we will also see if there are any similar instances anywhere else in the facility and fix those if found."

Case study #2: A company had a deviation concerning the depyrogenation tunnel used for sterilizing vials for an aseptic filling process. On the deviation report they wrote, "Root cause microbial load too high prior to sterilization." The inspector questioned this. "You haven't explored other possible causes, so how do you know that this was the root cause?" The VP QA instinctively thought: "It was obvious." However, remembering that the investigator is also a professional, she bit back that response and replied as follows: "You are right. You know, at the time, it seemed so obvious to us that this was the root cause that we didn't think it necessary to continue the investigation. However, there could well have been other factors and one of them might have been the root cause with this as only a contributing factor. We will revisit this investigation." The item did not appear on the list of inspectional observations, nor was it mentioned in the detailed inspection report. The reason was that the inspector was satisfied that they were dealing with a professional who understood the problem and was going to handle the issue.

Case study #3: During an inspection of a non-sterile manufacturing process, the inspector reviewed the microbiological monitoring SOP and noticed that there were no action limits for fungi.

Inspector: "You should have action limits for fungi."

Response: "We haven't set them yet."

This was a bad answer. A better one would be, "We are collecting data in order to allow us to determine an alert and action level based on historical data."

Inspector: "In my country, any repeat counts of fungi (more than 1cfu) should be an action limit."

The instinctive response might be, "This is nonsense, we are not talking sterile operations." But, breathe deeply and then answer.

Response: "We will set alert and action levels, taking your concerns into consideration and bearing in mind that this is a non-sterile, dry production process (no water involved), so fairly low risk for contamination."

The inspector moves on to another topic and in the observations records, "No action levels have been set for maximum amount of fungi allowed." Had an argument developed, that finding might have been "there is no response to repeat counts of fungal contamination and no alert or action levels have been set," which would be a far worse outcome.

the label of the material delivered is the same name as that on the purchase order; otherwise, they raise a deviation."

In the second case, the scenario plays out with the inspector gaining the impression that the situation is under control, and a good outcome is achieved by the company.

A final tip, do not contradict any of your colleagues.

Occasionally, let your genuine emotion show. In one case, after four days of very intensive inspection, a researcher was asked to demonstrate the reconciliation of all the API material used in the development work. Every experiment was documented and all material reconciled, except for 200g. The researcher could remember what it had been used for, but apparently had forgotten to write it down. The inspector looked at the researcher and asked, "Why didn't you write it down?" Her reply (with tears in her eyes), "Believe me, I am asking myself that exact same question, and I just don't have an answer. I only wish I did." The inspector believed her and did not make an audit observation about the missing 200g.

Don't point out mistakes that you have noted, that is not your job. Just answer the question asked. For example, "Who cleaned the tank?" Wrong answer: "I know we have no signature on the sign." Right answer: "I will check in the batch record and tell you." Even if the inspector has noticed the lack of signature, you have reassured them that there is a record of who performed the cleaning.

If you feel a "situation" developing, you should act fast to try and defuse it. In one case, the inspector found a stability sample that was not recorded in the sample receipt log. The inspector asked if this was part of the routine stability program, and was told, "No, it is a batch with a deviation." The inspector then said, "I want to see the deviation when we go upstairs."

At this point the company should have answered: "We will have the deviation report waiting for you. We will investigate why the sample was not logged in, and we will share our findings with you." At least you have now shown the investigator that you too are concerned and that you understand the potential seriousness of the findings. Once upstairs, the inspector immediately asked for the deviation. Someone should have been waiting with the report in the room, but they weren't. Instead, the inspector was told that the deviation was not complete. At that point, the investigator was certain that the company was trying to hide something/was holding back, and things started to turn hostile. It is really difficult to recover from this kind of situation, so try hard not to go there in the first place.

Don't Destroy Your Creditability

Never provide unverified answers. Credibility takes a long time to build and seconds to destroy.

Question: *Does your company use outside contractors to perform any job functions?*

Answer: *No.*

During the site tour, the inspector asks about the guard at the gate:

Question: *Is he a permanent employee?*

Answer: *No, he is contracted from an outside company.*

In this case, the inspector actually stated, quite angrily, "You told me that your firm does not use contractors." Now a bad atmosphere has been created, and each of your future answers will be viewed with suspicion. In this particular case, the person responding salvaged the situation by immediately apologizing: "I am really sorry, I misunderstood your original question. I was thinking about contracted manufacturing operations and so didn't consider the guards. Of course you are quite correct, there are contract services. By the way, our cleaners are also on contract. I apologize for the misunderstanding." This went down quite well.

Try not to justify situations where you give the inspector the wrong information by shifting your mistake onto the way the inspector asked for the information; it is best just to correct the problem. For example, don't say, "No, you misunderstood me," which implies that you have given the right information but the inspector does not understand it. Or worse, don't put words into the inspector's mouth by justifying your error with phrases like "you were asking about manufacturing."

Do not try to justify the unjustifiable. If an investigator observes a practice or identifies a situation that contradicts GMPs, either directly or current industry interpretation of that practice or even if you notice that they don't like a particular practice, don't become defensive and try to show at any cost why you are correct. Give it one shot, "It was our understanding that…," but if the response is negative (either verbal rejection or body language), let it go. You may not fully understand the inspector's concern, so let them write it up and you will get another chance at understanding it during the wrap-up. You can take it under advisement/consultation prior to providing a detailed written response and corrective action plan.

Do not ask the inspector questions. In answer to a query about line clearance procedures, one participant asked the inspector, "What is line clearance?" The participant was a member of the engineering staff, and while he may never have encountered the procedure or exact terminology, the impression created was "here is a company where personnel do not even recognize the language of GMP." This was very frustrating for the VP QA who obviously did know and had the answer.

Do not answer questions if you are not the SME. It is legitimate to reply, "This is not within the scope of my job," or even "I don't know the answer to that." But then, try to be helpful, e.g., "I will call the person responsible."

Never correct documents or errors in front of the inspector after they have pointed them out. This can be interpreted as an attempt to destroy evidence. Once an inspector pointed out that there was a date missing on a form and asked for a photocopy. A "helpful" employee took

the form and filled in the date before making the copy. It took three hours for the company to convince the inspector that this was not an attempt at fraud and that the employee had thought they were being helpful. The inspection almost ended at that point. In another case, the inspector pointed out that incubated agar plates with colonies on them were stored in a container marked "sterilized equipment." Again, a "helpful" employee tore off the label in front of the inspector. The required response should be "we will investigate how this came about."

Avoid absolutes, "all," "never," "of course," "always." For example, "Do you recalibrate pH meters if you move them to a new location?" "Always." The inspector will now start reviewing records often with the deliberate intention of finding a single instance where you forgot to do it and then proving you as a "liar" or unreliable. It is preferable to answer, "Our SOP requires that." At least if there is an inconsistency found, it can be investigated, but your credibility is not harmed because the SOP does indeed require it, but you didn't say it "always" happens.

A final tip, do not contradict any of your colleagues. If you hear someone giving a response that you believe to be incorrect, do not start arguing or correcting him or her in front of the inspector. Let the situation play out, and then take the inspection host aside and explain what happened. They will decide if and how to rectify the situation.

Inspections are by their nature stressful. A successful outcome requires a well-versed team where each player knows their role and the boundaries of that role. The easier you make the inspector's job and the more comfortable you make them feel with your quality system, the better the inspectional outcome. Periodic review of procedures and policies is well advised as are periodic "mock" inspections which allow proactive corrective actions, both relative to the quality system itself and to the process of handling the inspection.

About the Authors

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Quality & Regulatory Snapshot

Hailey's Comments

Korea's Evolving GMPs

Hailey (HeeYoung) Park, PDA

The Korean Good Manufacturing Practices (KGMPs) cover finished pharmaceuticals, active pharmaceutical ingredients (APIs) and biologics. For this article, I will focus on KGMPs general provisions for chemical and biologic products, both finished and APIs.

In 1969, the World Health Organization recommended that their members apply GMPs to domestic regulations, which prompted the Ministry of Health and Welfare (MHW), the forerunner of KFDA, to introduce GMPs into Korea. In 1974, the Korean Government founded the KGMP Development Council, which had representatives from both academic and industry for a smooth transition to the application of GMPs to the domestic pharmaceutical industry. The KGMP Development Council researched the established GMPs of other regions and developed a localized model.

About a decade later, the Korean Government issued the first KGMPs, but these were not required; they were viewed as guidances. The industry did not readily accept the KGMPs, because, in its view, the regulations required additional investments, such as upgrades to the manufacturing process. In a nutshell, the industry did not see any advantages in adopting the regulations. By 1984, only 14 out of 250 pharmaceutical manufacturers had voluntarily implemented KGMPs. As a result, the Korean Government established the KGMP Preparation Council to develop a KGMPs certification procedure. In 1982, the council came up with an evaluation checklist for KGMPs certification and it was finalized in 1984.

In 1985, the Korean Government began issuing KGMPs certifications to firms who applied and passed their evaluations. The MHW reviewed the documents and inspected the site and received opinions from GMP professional groups (KGMP Evaluation Council) who were represented by the Korean Pharmaceutical Manufacturers Association, Korea's

Regulatory *News*

Moving Tow@rds eCTD Submissions

Barbara Jentges, PhACT GmbH

Only a decade ago, the ICH steering committee agreed upon the Common Technical Document (CTD), providing for a harmonized structure and format for marketing authorization applications that are submitted to regulatory authorities. **(1)** With the "electronic Common Technical Document" (eCTD), the submission is going paperless worldwide, providing a wide range of benefits for regulators, as well as for applicants in the reduction of administrative overheads from less paper to the reduction of physical archiving space. **(2)**

The specification for the electronic Common Technical Document (eCTD) is based on "Extensible Markup Language" technology and was created by the multidisciplinary ICH M2 Expert Working Group (EWG). An eCTD submission process is initiated by the applicant and allows the submission of the eCTD in a one-way direction from applicant to regulator. Throughout the life cycle of an eCTD, additional information will be "submitted to update or modify the information contained in the initial submission." **(3)**

However, before an eCTD can be submitted successfully, a number of IT-technical and organizational hurdles need to be overcome by the applicant. An additional burden is the formal document requirements that need to be considered when preparing "navigable eCTD compliant documents." These document requirements include bookmarks, intra- and inter-text hyperlinking and a number of additional formal requirements regarding fonts, page orientation, page size and margins, etc.

But more than that, although the ICH eCTD standard has been specified, there "is no single ICH approved validation test suite against which (software) vendors may test their tools." **(4)** The result is "inconsistent interpretation by software developers in areas where specifications or regional guidances are ambiguous." **(4)** This leads to numerous problems with the interoperability and compliance of these tools.

continued on page 34

counterpart to the Japan Pharmaceutical Manufacturers Association, Pharmaceutical Research Manufacturers of America, and European Federation of Pharmaceutical Industries and Associations.

Facing external pressure, the Korean Government opened its domestic pharmaceutical market to the world, and in 1990, the KFDA published GMP guidances for bulk APIs (bulk GMPs). Local companies realized that in order to develop foreign markets, GMP compliance was necessary to export drugs. During 1985 to 1991, 71 manufacturing firms received KGMPs certification, while 48 were preparing applications.

KFDA Legalizes KGMPs

The increase of KGMPs certified firms made the Korean Government more confident in legalizing the KGMPs as an article of the Pharmaceutical Affairs Act. As of July 1994, no facilities could distribute pharmaceutical products without proving KGMPs compliance.

The KGMPs evaluation was run with six classified categories, not based on a product-based approach. Once a drug product was certified to be KGMP compliant in a category, additional products in that category could be exempted from other KGMP evaluations at the manufacturing site. This categorized KGMPs certification was only applied to local firms until the product-based preapproval inspection was introduced in late 2008.

In 2000, bulk GMPs were combined with KGMPs regulations, but were not enforceable until 2002. The year 2000 also saw the addition to the KGMPs of a mandatory Annex for biologics that almost immediately reflected advanced principles of other countries' GMPs.

Updated Quality Systems

In 2005, KFDA started conducting intensive inspections to update quality systems within the industry. In order to focus more on KGMPs management and on the improvement of quality systems throughout the industry, KFDA established the GMP Evaluation Team in 2006, the forerunner of the Pharmaceutical Quality Division. The GMP Evaluation Team realized that the KGMPs were dated and advanced ideas were now being employed in other regions, like in the United States and in Europe. Therefore, KFDA worked on revisions to the KGMPs in order to update them; these were published in 2008, along with a a handbook to help manufacturers fully implement the new regulations.

The significant changes focused on six specific areas, as well as updating older sections of the KGMPs. The changes included:

- Detailing the previous articles in KGMP
- Introducing product-based preapproval inspection
- Enhancing requirements about automatic or computerized system
- Supplementing requirements about validation
- Increasing requirements about annual/quality review
- Amplifying requirements about change control system
- Boosting requirements about self-audit

The KFDA has acknowledged that the Korean Pharmaceutical Manufacturers Association and academic institutes have played a vital role in developing the KGMPs.

Preapproval Inspections

KFDA's inspections can be classified in three catagories: preapproval, periodic and for cause inspections.

In KGMPs history, the origin of preapproval inspections came from the biologics annex, which closely reflected the world's current thinking in quality science. By 2002, preapproval inspections were gradually applied to other products, like chemical APIs, by introducing drug master files. In 2008, preapproval inspections were also applied to chemically finished drugs. (The preapproval inspection at a foreign site was initiated with the start of the product-based preapproval inspection since 2008.)

After a drug approval application, which is required, and a preapproval inspection document is submitted, the document will be sent either to the Pharmaceutical Quality Division or the Biopharmaceutical Policy Division. The division that is responsible will examine the documents and determine if a site visit is needed. If it is, the Pharmaceutical Quality Division or the Biopharmaceutical Policy Division sends a letter detailing the purpose of its visit to the applicant.

The preapproval inspection takes an average of 2-3 days at a local site and 3 days at a foreign site, with 2-3 inspectors inspecting each firm. If a firm fails to meet the requirement of any item on the evaluation form, KFDA inspectors assess whether it is a critical, major or minor noncompliance. When critical deviations are uncovered that pose a potential risk on the impact of the quality of the product, the application will be returned to the applicant.

The application, which only allows for major or minor observations, can be approved after any deficiencies are

Table 1 KGMP Timeline

1974	1977	1982	1984
WHO recommend members to apply GMP	Established Korean Good Manufacturing Practices	Published the evaluation checklist for the KGMP certification	Established KGMP Evaluation Council
1985	**1990**	**1994**	**2000**
Began an evaluation of a manufacturer for the KGMP certification	Established Bulk GMP and Cosmetic GMP	Legalized KGMP as a obligatory regulations;	Combined BGMP with KGMP
2000	**2002**	**2008**	
Established the annex for Biotechnology products	KGMP became an obligation to API manufacturers.	Revised KGMP; introduced validation, deviation management, and change control etc	

corrected. Generally, the KFDA inspectors give firms two months to correct any issues. The Pharmaceutical Quality Division (or the Biopharmaceutical Policy Division) hands its opinion to the division which takes responsibility to approve the application.

Periodic Inspections

Periodic inspections take place as a part of KFDA's annual safety surveillance plan. The Pharmaceutical Quality and Biopharmaceutical Policy Divisions respectively set up an annual work plan, which states the primary goal, the criteria for specific selection and the inspection candidate lists and so on. (The KFDA currently does not perform periodic inspections on foreign manufacturing sites because of labor and budget restrictions.)

In 2005, the KFDA began implementing intensive inspections toward all of KGMP manufacturers with its revised evaluation form that is posted on the KFDA website in order to obtain transparency. If a firm fails to meet KGMP compliance during an inspection, the KFDA's inspectors assess the observation which they have found. If the deviation has the potential risk to threaten the public health via the marketed products, the KFDA will enforce an administrative measure on the firm with the violation.

Post-inspection, the evaluation form, which assesses the firm's quality history, future plans to upgrade quality systems and KGMP requirements, are marked with a "grade" from A to E and results are posted on KFDA's website. Manufacturers that receive a "bad grade" or are in violation of the KGMPs are subject to more frequent inspections.

The Pharmaceutical Quality or the Biopharmaceutical Policy Divisions will report the request of an administrative measure (the equivalent of an FDA enforcement action) to the KFDA's regional offices, which has jurisdiction over the inspected site. The Regional Office tells the firm which articles they have violated within the Pharmaceutical Affairs Act.

Next, a firm has time to counter any observation it receives. When the firm presents their objections, the Regional Office can hold an official hearing with the firm in order to listen to its opinions carefully and examine the proof provided. If the company's argument is valid, it will be accepted. Otherwise, the KFDA's regional office imposes administrative measures that can vary from ceasing the manufacture/distribution of a product for a specific period, seizing the product from the market, withdrawing either the manufacturers or importers license or imposing a monetary penalty. However, KFDA has only the authority to enforce the Pharmaceutical Affairs Act. If the firm violates other Korean laws, such as environmental laws, KFDA has to transfer the case to the prosecution.

Harmonization: The Direction of the Future

Harmonization might be a key word to understand recent KFDA's actions. In the 2010 work plan, KFDA was preparing to join PIC/S and to translate and publish the entire KGMPs regulations into English, effectively to communicate the details of KFDA's expectations.

In the latest effort to analyze preapproval inspections, KFDA manufactures are required to adopt the new KGMP revisions fully. This should lead to better compliance and higher quality products. It has also been reported that the KFDA will give more attention to follow up the corrections of observations and consider initiating periodic inspections in foreign sites.

Moving Tow@rds eCTD Submissions, continued from page 32

Despite being technically harmonized by an ICH-agreed upon eCTD specification (ICH M2 EWG), there are regional differences in eCTD requirements like the need for "Study Tagging Files" in the United States and regionally different submission procedures like a web-based portal in the United States versus an eCTD submitted on some sort of electronic media device (e.g., cd-rom or flash drive) as required in Europe.

For submissions within the EU/EEA, the applicant is even faced with the differing "eCTD-readiness" of the competent authorities involved in the relevant application procedure. On January 1, 2010, the European Medicines Agency required that electronic-only submissions

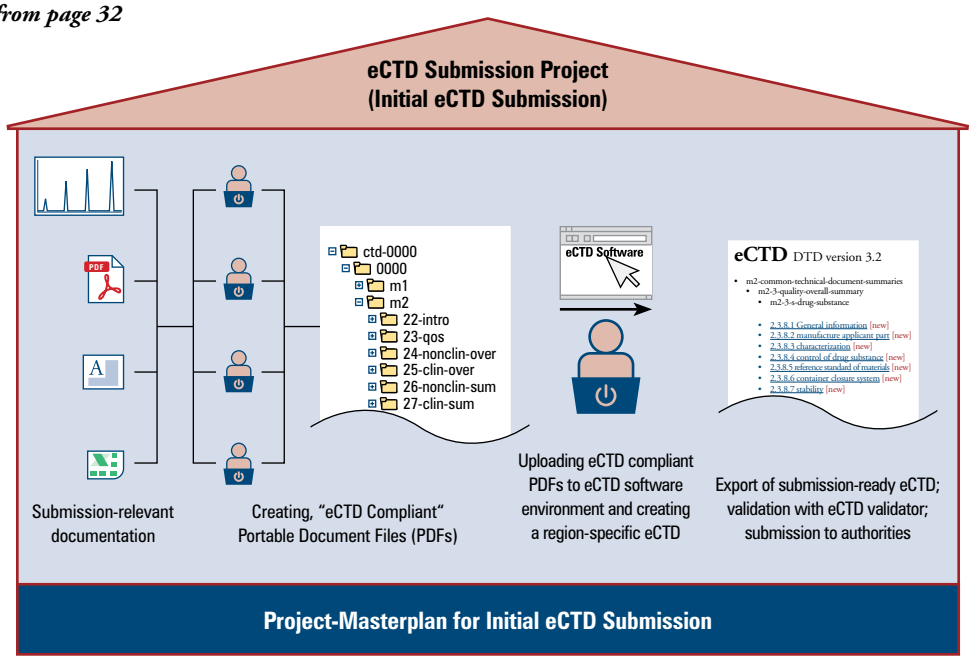

Figure 1: From File to eCTD – A document must go through numerous formatting steps until it is ready for submission under the eCTD

in eCTD-format would go into effect for applications following the centralized procedure. As for applications following the mutual recognition procedures (mutual recognition and decentralized procedure), the eCTD readiness differs among the national competent authorities, with about 44% of the NCAs still not being "eCTD ready" **(5)** resulting in "mixed" submissions of paper- and eCTD- formats depending on which of the the NCAs are involved. **(6)**

While competent authorities and applicants, especially within the EU/EEA, are still struggling with the "eCTD implementation process," technology is progressing rapidly. The ICH M2 has initiated the development of the next major version of the eCTD. **(7)**

An eCTD submission is a complex project requiring more than a suitable IT infrastructure; project management and (document) workflow processes need to be adapted, the collaboration within all parties involved within and outside the enterprises need to be optimized and the "e-skills" of employees need to be increased. **Figure 1** (see previous page) outlines the step a document goes through to form a submission-ready eCTD.

Is this the right time for a paradigm shift towards "Good eSubmission Pr@ctice" in view of optimized utilization of "information and communication technologies" and "e-skills" of regulatory affairs professionals? This question will be discussed in the November/December issue of the *PDA Letter*.

About the Author

Barbara is based in Switzerland. She is the Managing Director of PhACT GmbH; a company that provides advice and service in drug regulatory affairs, with a specialty in EU regulatory submissions including biotechnology. Barbara has more than 20 years of experience in regulatory affairs and previously worked with the Federal Institute for Drugs and Medicinal Devices (BfArM)-the German Health Authorities.

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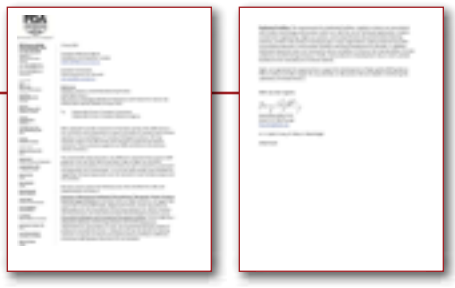
continued on page 39

PDA Praises, Criticizes EU Revision of Annex 2



For the comments grid, visit www.pda.org/regulatorycomments

19 July 2010
European Medicines Agency
Compliance and Inspection, London
ADM-GMP@ema.europa.eu
European Commission
Pharmaceuticals Unit, Brussels
entr-gmp@ec.europa.eu

Reference: Eudralex, Volume 4, Good Manufacturing Practice
Draft GMP Annex 2
Manufacture of Biological Medicinal Substances and Products for Human Use
ENTR/C/8/SF D(2010) 380334, 09 April 2010

To: Responsible Person: European Commission
Responsible Person: European Medicines Agency

PDA is pleased to provide comments on the latest revision of EU GMP Annex 2. Our comments were prepared by an expert committee of members with practical expertise in the manufacture of a variety of biological products. We have attached a table in the EMA format that lists both our general and specific comments. These comments augment our 2008 comments on the previous revision of Annex 2.

The revised draft reads well and is very different in approach than previous GMP guidances. We note that efforts have been made to apply not only PDA's technical recommendations on the first draft, but also to include the overall spirit and approaches we recommended. As such the draft provides more flexibility by suggesting risk based approaches and risk rationale for each facility/company and circumstance.

We have concerns about the following issues that will affect the utility and implementation of Annex 2.

Exclusion of Monoclonal Antibody & Recombinant Therapeutic Protein Products from the Scope of Annex 2: Consistent with our 2008 comments, we suggest that current Part II of the GMP Guide, aligned with ICH Q7, remains the reference GMP guidance for the manufacture of the drug substance (i.e. API) for classical, well characterized, cell culture/fermentation based biological products such as monoclonal antibodies and recombinant therapeutic proteins. Current GMP Part I adequately addresses sterile drug substance and sterile drug product requirements for such products. As such, we recommend that those classes of products be excluded the Annex 2. Doing this will have the benefit of reducing confusion on the part of industry and inspectorates by avoiding an additional, unnecessary GMP guidance document for such products.

Dedicated Facilities: The requirements for dedicated facilities, implied or stated, are inconsistent with modern technology and practices which can, with the use of risk based approaches, modern containment engineering, single-use systems, and comprehensive decontamination/cleaning practices, enable multi-product manufacturing in many organizations. Many products have been successfully produced in multi-product facilities and shared equipment for decades. In addition, dedicated equipment does not necessarily reduce variability or enhance the reproducibility of active substance manufacturing processes. Finally, most products in development rely on multi-product facilities for the manufacture of clinical material.

Again, we appreciate the opportunity to support the development of high quality GMP guidance. PDA is ready to provide support for any activities or discussions that are helpful in furthering the usefulness of revised Annex 2.

With very best regards,
Georg Roessling, Ph.D.
Senior VP, PDA Europe

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 www.pda.org/regulatorynews.

ICH

ICH Amends Daily Limits for Solvent Cumene

ICH has amended *Q3C: Impurities: Residual Solvents*, recommending that the permitted daily exposure of the solvent cumene should be revised. The expert working group deemed cumene as more toxic thus changing its designation to Class 2 instead of Class 3.

Comments should be submitted by September 20, 2010.

Europe

MHRA Clarifies Guidance on Supply Chain Obligations

Clarifying a November 2009 guidance, entitled, *Trading medicines for Human Use: Shortages and Supply Chain Obligations*, the MHRA says that a registered pharmacy, which also holds a wholesale dealer's license, should ensure that its "retail" and "wholesale" transactions are clearly separated and fully documented. This ensures that:

- Medicinal products for wholesale supply are kept in the licensed distribution chain at all times, under a full quality system that is expected to be operated by licensed wholesale dealers and Good Distribution Practice controlled conditions before they are distributed for retail supply
- The obligation in Article 81 of European Directive 2001/83/EC, for the maintenance of an appropriate and continued supply of medicinal products is being met by licensed distributors. This is because those in the supply chain can be clearer as to which medicines are going to meet the needs of patients in the UK.

The guidance requests that the various parties in the supply chain to bear in mind their obligations in respect of supply of medicines and to be aware of the consequences of exporting medicines for the supply of medicines to UK patients.

European Medicines Agency Organization Guide Published

The European Medicines Agency has published a guide to its various units, sectors and sections. The guide gives the names of the heads of units, sectors and section heads, as well as a general description of what each unit does within the European Medicines Agency.

Europe

EMA Requests Comments on Advanced Therapy Medicinal Products Document

The European Medicines Agency has published a document containing procedural advice about the interactions between its Committee for Advanced Therapies (CAT) and notified bodies for medical devices. The document provides details of possible scenarios and timelines for the assessment of combined advanced therapy medicinal products by the CAT..

The deadline for comments is October 29.

North America

Four-Part MOU to Strengthen Collaborations among FDA, NIH, NTP and EPA

A four-part Memorandum of Understanding (MOU) has been signed by the U.S. FDA; the National Toxicology Program (NTP); the Environmental Protection Agency (EPA), Office of Research and Development; and the National Institutes of Health (NIH): National Institutes of Environmental Health Sciences, National Human Genome Research Institute and NIH Chemical Genomics Center.

This MOU will strengthen the existing collaborations that utilize the complementary expertise and capabilities of the parties in the research, development, validation and translation of new and innovative methods that characterize key steps in toxicity pathways.

The MOU became effective June 4, 2010.

House Bill to Provide U.S. FDA with Recall Powers for Adulterated, Misbranded Drugs

A bill, HR 5740, introduced in the House of Representatives by Chairman Edolphus Towns (D-NY), amends the Food, Drug and Cosmetic act and gives the U.S. FDA the authority to demand a recall when there are signs that a drug has been adulterated, misbranded, or exposure to a drug may cause serious adverse health consequences or death.

Referred to the House Committee on Energy and Commerce, the bill also requires that anyone that the believes a drug is adulterated or misbranded or thinks that there is a reasonable probability that the use, consumption of or exposure to the drug will cause a threat of serious adverse health consequences or death should notify the FDA.

Agency Draft Guidance on ICH Annex 14 Available for Comment

An Agency draft guidance on bacterial endotoxin testing is now available for comment. The draft guidance, entitled, *Q4B Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions; Annex 14: Bacterial Endotoxins Test General Chapter* is available for comment until September 14.

Agency Draft Guidance on ICH Annex 13 Available for Comment

An Agency draft guidance on Bulk Density and Tapped Density of Powders is now available for comment. The draft guidance, entitled, *Q4B Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions; Annex 13: Bulk Density and Tapped Density of Powders General Chapter* is available for comment until September 13.

Agency Guidance Helps Manufactures Develop, Conduct IVD Studies

A guidance designed to assist manufacturers in developing and conducting studies

for In Vitro Diagnostic (IVD) devices, particularly for those exempt from most of the Investigational Device Exemption regulations is now available. The guidance, *In Vitro Diagnostic Device Studies – Frequently Asked Questions* explains data considerations that ultimately will affect the quality of the premarket submission.

Draft Guidance Recommends Changes to Information Included in Annual Reports to Agency

A draft guidance that provides recommendations to holders of NDAs and ANDAs regarding the types of changes that may be reported in annual reports is now available.

Entitled, *CMC Postapproval Manufacturing Changes Reportable in Annual Reports*, the draft guidance describes CMC postapproval manufacturing changes that the U.S. FDA has determined will likely present minimal potential to have adverse effects on product quality and may be reported by applicants in an annual report.

The draft guidance excludes PET drug products.

Comments are due to FDA by September 23.

Agency Seeks Comment on Medical Device Reg.'s Requirements

The Agency is collecting information about recordkeeping requirements related to the medical devices CGMP quality system regulation.

Comments can be submitted on the collection of information until August 23.

Agency Updates Submission Address

The U.S. FDA is updating the address for applicants to submit abbreviated new drug applications (ANDAs) and ANDA amendments, supplements, and resubmissions in the CFRs. This will also affect investigational new drug applications (INDs) for in vivo bioavailability and bioequivalence studies in humans that are intended to support ANDAs.

U.S. FDA Guidance Helps Applicants Submit CMC Drug Substance Information in CTD Format

A Center for Veterinary Medicine guidance providing recommendations on the chemistry, manufacturing and controls (CMC) information for drug substances that should be submitted to support original new animal drug applications and abbreviated new animal drug applications is now available.

The Agency guidance, *Drug Substance Chemistry, Manufacturing, and Controls Information* is structured to facilitate the preparation of applications submitted in Common Technical Document format.

Key Regulatory Dates

Comments Due:

September 13
U.S. FDA Draft guidance on ICH Annex 13, Bulk Density and Tapped Density of Powders General Chapter comments due

September 14
Agency draft guidance on ICH Annex 14, Bacterial Endotoxins Test for General Chapter comments due

September 20
Comments due for amended ICH guidance, Q3C: Impurities: Residual Solvents

September 23
Agency draft guidance CMC Postapproval Manufacturing Changes Reportable in Annual Reports comments are due

FDA Collection of information due on Medical Device Regulation Requirements

Send us your news briefs. If you follow the regulatory news in your country or region, send your briefs to hough@pda.org; we might post them online, in the *PDA Connector* and/or in the *PDA Letter*.

Moving Tow@rds eCTD Submissions, continued from page 35

5. "eCTD Implementation Survey Report by the Swedish Presidency of the EU – 2009 (covering the period from July 2008 to June 2009)," March 2010, Heads of Medicines Agencies, www.hma.eu/uploads/media/eCTD_SurveyJuly_2008_to_June_2009.pdf
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7. ICH M2 ESTRI, ICH M2, estri.ich.org

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Create More Transparency

Quint Studer

1 Make sure senior leadership is aligned. Does everyone see the external environment the same way? Does everyone understand organizational goals and plans? Does everyone agree on what success looks like? If not, it's time to remedy the situation.

Alignment is most important at the senior level because all information cascades downward from it. If one senior leader is out-of-sync with the others, then everyone under her is going to be out-of-sync. In a big organization, that could be hundreds of people.

2 Close the perception gap between senior leadership and middle managers. Senior leaders generally have a pretty clear grasp of the real issues facing the organization. They are steeped in these issues every day. Mid-level managers—who, after all, are busy managing—don't always see things the same way. The only solution is for senior leaders to relentlessly communicate the issues to them.

You can address these issues in supervisory sessions. You can hold regular meetings with mid-level managers. You can send out email alerts that link to news items driving high-level decisions. If you're a senior leader, it's critical to make sure the people under you understand the big-picture issues and their implications. It's one of the most important parts of your job.

3 Help people understand the true financial impact of decisions. Get comfortable framing all major decisions in economic terms. If a manager wants to spend money on something—a new piece of equipment, a new employee, a salary increase—she needs to be prepared to explain in financial terms how it will

pay off for the company. Employees, too, need to understand the real cost of mistakes or lapses in productivity, as well as the potential positive impact of doing things in a new way.

Many of the healthcare leaders I work with use a financial impact grid to educate employees on how certain issues translate to dollars. The idea is to teach everyone to think like the CFO. Educating people in this way can be very powerful in changing their behavior.

4 Put mechanisms in place for communicating vital issues to frontline employees. People aren't going to pick up on what leaders want them to know by osmosis. You need to tell them clearly, succinctly and often. That means putting in place a system, or a series of systems, to ensure that the transparency value gets translated into action.

5 Prepare managers to answer tough questions. If a manager tells his employees the company is cutting back on overtime, he'll almost certainly hear questions like, "If money's so tight, how can the company afford the new construction project?" Or, "I depend on my overtime hours as part of my salary. Will everyone's salary be cut?" The manager needs to know ahead of time exactly how to answer so that he won't blurt out a we/they perpetuator like, "Sorry, that's the orders from the top."

In a transparent company, there's no reason to hide financial realities from anyone, but that doesn't mean managers naturally know the best way to phrase their answers. Some are just better communicators than others. Anticipating tough questions, formulating the right key words and sharing them with leaders at all levels allows everyone to answer them consistently.

6 When you have bad news, treat employees like adults. Once a tough decision has been made, share it with everyone immediately. Don't sneak around behind closed doors and certainly don't lie.

Knowing what's happening, and what it means, is always better than not knowing. And often, what people are imagining is worse than what's really happening.

7 Keep people posted. When something changes, let them know. This builds trust between leaders and employees and keeps them connected to the big picture.

Be sure to share any good news you get. Transparency doesn't mean "all bad news, all the time." When you disseminate positive developments as quickly as you do negative ones, you boost employee morale and reinforce any progress that's being made.

About the Author

Quint Studer formed Studer Group®, an outcomes firm that implements evidence-based leadership systems that help clients attain and sustain outstanding results. He is the author of *Hardwiring Excellence: Purpose, Worthwhile Work, Making a Difference; 101 Answers to Questions Leaders Ask* and *Results That Last: Hardwiring Behaviors That Will Take Your Company to the Top*. For more information, visit www.studergroup.com.

Volunteer Spotlights

www.pda.org/spotlight

Robert Caunce, Quality Project Manager, Hospira

PDA Join Date: 2001

Areas of PDA Volunteerism: Australia Chapter President (2008-2010); Australia Chapter member (2008–present); Regulatory Affairs and Quality Committee member (2009–present)

Interesting Fact about Yourself: I must like to volunteer, as I am also a Cub Scout Leader in Australia

Why did you join PDA and start to volunteer? I was previously with another industry association, but found PDA more useful for the industry, and I like being involved with the latest information and networking opportunities.

Of your PDA volunteer experiences, which stand out the most? Getting my award recently at the PDA annual meeting; unfortunately, I was unable to attend in person.

How has volunteering through PDA benefited you professionally? It has allowed me to meet many talented people across the world that share a passion for our industry and more importantly the people that our products assist. This resource network and information is a priceless.

Which PDA event/training course is your favorite? I would have to say the Australian chapter meetings, but I guess I am a little biased. Other than these, the Annual Meeting is up there.

What would you say to somebody considering PDA membership? You will never regret joining the organization. The technical reports by themselves provide you with countless hours of specific information gathered from the industry experts. These together with the networking opportunities at a local and global level will stay with you throughout your career. So sign that dotted line.

Saeed Tafreshi, President, Intelitec Corporation

PDA Join Date: 1998

Areas of PDA Volunteerism: Southern California Chapter (2006-present); Membership Advisory Board (2008-present); Chapter Council (2008-present)

Interesting Fact about Yourself: Unless the current laws change, I will not be eligible to run for President of the United States of America!

Why did you join PDA and start to volunteer? I joined PDA to gain a broader view of the industry's science, regulations, current thinking and future perspectives. Starting to volunteer was a result of gaining knowledge through membership and the desire to advance the benefits of membership for others. It is simply a way to put something back into the industry that has provided so much for me.

Of your PDA volunteer experiences, which stand out the most? Our first board meeting in Southern California Chapter, when we were laying out our initiatives. At the time, the feeling was that we might have set the bar a bit too high, but we now realize that aiming high is the ultimate stimulate for a committed team. Winning is always fun and much sweeter as the underdog!

How has volunteering through PDA benefited you professionally? Volunteering will provide many opportunities to share knowledge and ideas, and if you choose, it will enable you to work with others. This experience will certainly result in a much faster rate of growth in your areas of interest, and eventually you will notice the advantages.

Which PDA event/training course is your favorite? The PDA/FDA joint conference has always been one of my favorites. Of course, our Southern California events are very special too!

What would you say to somebody considering PDA membership? Just do it! It would be the best professional investment on yourself. My gains are truly priceless.

Recipients of the 2009 Honor Awards

www.pda.org/2009honorawards

The honor awards have been presented to esteemed PDA members since the first award was given in 1958. It is our intention to highlight each of the 2009 Honor Award Winners in each upcoming issue of the Letter until the 2011 Annual Meeting. This month we have chosen to spotlight the individuals who were awarded the Frederick D. Simon Award.

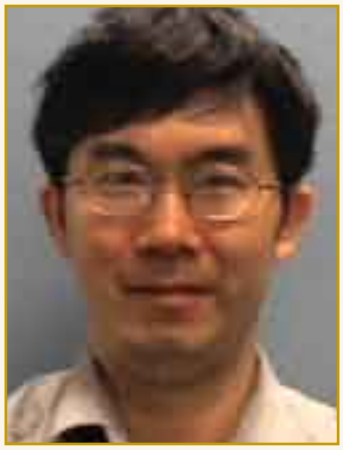
Frederick D. Simon Award

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.

The paper, *Distribution of Silicone Oil in Prefilled Glass Syringes Probed with Optical and Spectroscopic Methods*, was published in the March/April 2009 issue of the *PDA Journal of Pharmaceutical Science and Technology*. This author's of the paper are:

Zai-Qing Wen

Xiaolin Cao

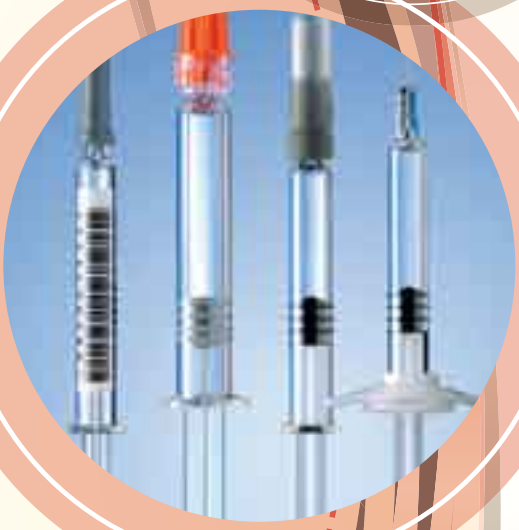


Bruce Eu

Aylin Vance

Fabian Vega

Robert Schulthesis
(Picture unavailable)



The Parenteral Drug Association presents:

The Universe of Pre-filled Syringes and Injection Devices

The Advanced Needs of Pre-filled Syringes and Autoinjectors

OCTOBER 18-21, 2010

JW MARRIOTT LAS VEGAS RESORT & SPA
LAS VEGAS, NEVADA

Discover successful strategies to **improve manufacturing, packaging, safety, accuracy of drug delivery, administration and compliance while reducing costs** during this conference!

Overcome the challenges of new product introduction and support of existing products by becoming aware of scientific and technological advancements. The PDA Training and Research Institute (PDA TRI) will offer two courses to accompany this conference:

- Technical Development of Pre-filled Syringes, Autoinjectors and Injection Pens - *New Course*
- Syringes and Elastomers: Understanding the Effects on Quality and Demonstrating the Production Process, Influences and Needs - *New Course*

CONFERENCE OCTOBER 18-19

EXHIBITION OCTOBER 18-19

COURSES OCTOBER 20-21

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Learn to Manage and Mitigate Microbial Risks

Washington, D.C. • October 25-28 • www.pda.org/microbiology2010

Edward C. Tidswell, PhD, Baxter Healthcare Corporation

How do we creatively plot and steer a course of improvement in microbial control and product quality? In an era where economy, efficiency and expediency in "all things microbiological" is an expectation, we must look toward an increasing understanding of fundamental microbiology, microbial physiology, new innovations and the commercial realization of new technology both inside and outside our field. In an age where seeing only through the lens of a microscope just won't cut it, the opening keynote address at *PDA's 5th Annual Global Conference on Pharmaceutical Microbiology* by **C. Mark Ott**, PhD, Chief Microbiologist, Habitability and Environmental Factors Division, NASA Johnson Space Center, offers a microbiological perspective through a different kind of lens. His presentation is focused on how to manage and meet microbial risks in the context of aerospace. Understanding this in an environment and schedule far more alien and limiting than our own may help us innovate and implement superior microbial risk assessment, mitigation and control strategies in our own specific context.

In contrast, the second keynote address by **Thomas J. Arista**, Investigator, National Expert, Pharmaceutical/Biotechnology, ORA/ORO, Division of Field Investigations, U.S. FDA, similarly provides a perspective of distinct and unique value. Arista will elaborate on applying risk-based approaches to microbial control strategies in pharmaceutical/biopharmaceutical manufacturing and related areas, emphasizing practical guidance on how to apply these principles and addressing the benefits of such an approach to patient safety.

A very special luncheon address will be delivered by **Rita R. Colwell**, PhD, Distinguished University Professor, Center for Bioinformatics, Computational Biology, University of Maryland and USP Board of Trustees, concerning the future direction of analytical microbiology. Colwell is one of microbiology's most recognized, accomplished and insightful researchers with notable and pertinent contributions in the field of microbial dormancy, viability and vitality. Yet again, the PDA's Annual Global Conference on Pharmaceutical Microbiology proves to be a truly unique event, likely the only environment and setting which connects world-renown experts in both fundamentals and practical aspects of microbiology to its delegates.

This year's conference provides another distinctly appealing and value-adding agenda, a session detailing the assessment, evaluation and control of objectionable microorganisms during the manufacture of non-sterile drug products. In parallel, a session will cover topics salient to terminally sterilized products. The effectiveness of moist heat sterilization monitoring, controlling and measuring processes will also be addressed.

Investigations remain an important aspect of laboratory work and are likely to remain so. At this conference, one session is dedicated to this subject matter and includes case studies of microbial contamination in biologic product manufacturing presented by **Kalavati Suvarna**, PhD, Microbiologist, CDER, U.S. FDA. A concurrent session will cover product sterility assurance for parenteral products and certain medical devices. FDA representatives will give presentations on medical device mass seizures where microbiological evidence was found in production and laboratory observations (**Dennis E. Guilfoyle**, PhD, Pharmaceutical Microbiologist International Expert, U.S. FDA) and product/labeling attributes potentially impacting sterility assurance (**Neal J. Sweeney**, PhD, Supervisory Microbiologist, Office of Generic Drugs, CDER, U.S. FDA).

One regular session exclusive to PDA's Annual Global Conference on Pharmaceutical Microbiology is "Urban Myths." "Science-based regulation" begs the question of how much of our common microbiological wisdom in the pharmaceutical industry is actually based on fact. This session examines aspects of pharmaceutical microbiology from this perspective to explore our current understanding and "best practice" with an eye to determining whether what we believe in reality is in fact rooted in "good science." The "Ask the Expert Panel" is an unrivaled session which brings an international panel of experts including several personnel from regulatory agencies together to directly answer your questions.

Biopharmaceutical manufacture continues to see growth and is inevitably accompanied by the uncertainty and variability associated with biological systems. A session is dedicated to control strategies and designs in reducing risk of microbial contamination during open and closed biopharmaceutical operations. In tandem, a session of expert presentations will describe approaches to viral safety and control including recent advances in PCR technology.

Six further podium presentations by industrial experts are dedicated to rapid microbial methods, implementation, validation, and case studies. These are followed by three separate sessions concerning global compendial (USP, EP, JP) challenges associated with rapid microbial methods. International representation from global agencies (EP, FDA/CDER, FDA/CBER, TGA and PMDA) will present at these sessions. This represents an ideal and unique opportunity to gain a clear understanding of how to implement rapid microbial methods.

Clearly PDA's Annual Global Conference on Pharmaceutical Microbiology remains the industry's premier event for microbiologists. This event is rich with data, information and guidance and has a selection of international experts and regulatory agency personnel found nowhere else. Visit www.pda.org/microbiology2010 for more information.

Innovative Training Strategies Taught at the Biennial Conference

Baltimore, Md. • October 11-15 • www.pda.org/biennial2010

Conference Chair Joyce Winters, JWinters Consulting

On behalf of the Program Planning Committee and PDA, I would like to invite you and your staff to attend the *2010 PDA Biennial Training Conference*, October 11-13 in Baltimore, Md. This conference is one you won't want to miss.

Following the 2008 conference, the Program Planning Committee immediately began to plan for the 2010 conference. We examined what worked best, where improvements were needed and analyzed current needs. This year, we will have more than 20 different concurrent sessions featuring topics that are designed for all levels of training for individuals. These sessions, plus networking opportunities, will provide you with a forum to learn from the experiences and successes of your fellow trainers.

The 2010 conference theme is *Training and Performance in a Changing Environment*. As trainers, our goal is always to ensure performance meets the organization's expectations. We also recognize the environment and priorities are always changing, so we invited the best and most innovative presenters to share their ideas on training and performance.

Aligning with the theme, **Allison Rossett**, PhD, Professor of Educational Technology, San Diego State University, will present a plenary workshop, entitled "Job Aids and Supporting Performance." This workshop will focus on moving knowledge from the classroom to knowledge everywhere. We also will offer a valuable take-away during "The Trainer's Toolbox – A Roundtable of Current Topics" led by conference committee members. It will be an opportunity to gain knowledge and ideas from your experienced colleagues on issues facing all trainers.

In addition, **Rebeca Rodriguez**, National Expert Investigator, U.S. FDA, will be on hand to provide a presentation, entitled "An Overview of Personnel Qualification Issues Found During FDA Inspections." A topic of great interest to us all. The conference will also feature an exhibition where you can see what is available to enhance your training objectives.

Also complementing the conference are four PDA TRI courses on October 14-15:

- "Designing and Presenting Effective GXP Training Programs to Meet New FDA Training Requirements" *(October 14)*
- "Developing and Using Virtual Learning Opportunities" *(October 14)*
- "Introduction to Competency-Based Training" *(October 14-15)*
- "FDA Inspection Readiness for a Training Systems Audit" *(October 15)*

[Editor's Note: See related article about TRI's courses for the Biennial Conference on page 50.**]**

With a location just a few blocks away from the Inner Harbor in Baltimore, a dynamic program by outstanding training professionals and networking opportunities galore, you don't want to miss this event!

Global Experts to Present at Prefilled Syringe & Device Meeting

Las Vegas, Nev. • October 18-21 • www.pda.org/prefilled2010

Graham Reynolds, West Pharmaceuticals

As we approach this year's *Universe of Pre-Filled Syringes and Injection Devices* meeting we look forward to welcoming you to Las Vegas, Nev. October 18-21.

Since the introduction of this annual PDA meeting, which focuses on pre-filled syringes and associated injection devices, we have seen a significant growth in this type of packaging and delivery system. It has long been acknowledged that pre-filled syringes offer significant benefits to both the user and drug manufacturer. According to an April 2010 Greystone Associates Report, last year, 2.23 billion pre-filled syringes were manufactured, which is up 14.4% compared to 2008. With the growth of therapies aimed at chronic conditions such as rheumatoid arthritis, multiple sclerosis and other autoimmune diseases, the preferred packaging and delivery system has become the pre-filled syringe in combination with an autoinjector. This trend is set to continue and drive future innovation.

It is rare to see a segment of the industry where so many factors have an influence, and create challenges/opportunities for all involved.

These include:

- Growth in specific market segments, increasing competitive pressures and the ongoing need for life cycle management
- Regulatory trends, increasing scrutiny by regulatory agencies and drive towards improved quality
- Continuing innovation from packaging and delivery system suppliers
- Increasing requirements for pharmaceutical and biotech companies and a market which is often sensitive to change
- Patients, family members and caregivers are assuming more responsibility for treatment, including more injectable therapies

This year we have been delighted with the support from presenters, exhibitors and participants and have been able to put together a comprehensive program to cover many key topics around these issues.

Plenary sessions during the two-day conference will include topics such as:

- A keynote speech by **Debra R. Lappin**, President, Council for American Medical Innovation, who will address the intimate relationship among national health policy, medical needs and the role of injection devices and innovation
- End user needs, human factors and regulatory challenges in the development of devices and combination products
- Syringe selection, characterization, manufacturing best practices and regulatory challenges
- New primary containers with an emphasis on plastic syringes

Two parallel tracks of sessions, led by global experts, enable participants to choose from a variety of current and compelling topics. Some other exciting offerings include:

- Two breakfast sessions covering new developments in safety devices and invasive drug deliveries, respectively
- Four poster sessions and networking opportunities with industry experts
- Exhibit hall of current and future products or technologies
- Two new PDA Training and Research Institute courses on the development and manufacture of prefilled systems

This is an excellent opportunity to interact with peers and industry experts in this growing field, and we look forward to welcoming you to Las Vegas! Whether you are new to the field or an industry veteran, you will take away practical knowledge to put immediately into use, as well as to meet new colleagues and contacts. We invite you to participate in the *2010 PDA Universe of Pre-Filled Syringes and Injection Devices*, October 18-21, in Las Vegas, Nev. We hope to see you soon! Please visit the website at www.pda.org/prefilled2010 for more information and to register.

Ex-Regulator to Share Moist Heat Sterilization Concepts

Chicago, Ill. • December 6-7 • www.pda.org/moistheatworkshop

Mike Sadowski, Baxter Healthcare

Please remember to mark December 6-7 on your calendar so you can remember to attend the *PDA Technical Report Workshop: Moist Heat Sterilizer Systems, Steam in Place and Parametric Release of Pharmaceutical and Medical Device Products Terminally Sterilized by Moist Heat* in Chicago. In addition to participating in this highly interactive workshop, attendees also will discover that this is one of the best times of the year to experience Chicago and its famed Magnificent Mile—all garnished with lights and decorations to welcome shoppers.

PDA's flagship sterilization reference, Technical Report No. 1 was revised in 2007 to provide updated and best demonstrated practices for the cycle design, development and ongoing control of moist heat sterilization processes. Since the issuance of this popular technical report, three additional task forces have been hard at work on the development of a series of companion documents designed to leverage and complement the content of Technical Report No. 1. The product of these task forces are the following technical reports:

Technical Report No. 48 (New in 2010), *Moist Heat Sterilizer Systems*

Technical Report Draft (New in 2010), *Steam-in-Place*

Technical Report No. 30 (2010 Revision), *Parametric Release of Pharmaceutical and Medical Devices Terminally Sterilized by Moist Heat*

The planning committee has designed this comprehensive sterilization workshop to provide attendees with the unique opportunity to interact in technical discussion with the sterilization experts that contributed to the development of these documents. In addition to the technical report leaders from each of the task forces, **Terry Munson** (retired FDA Chief, Sterile Drug Branch and currently Vice President for Parexel Consulting) will provide practical insight and guidance on moist heat sterilization concepts from a regulator's point of view.

The following sessions in this workshop are focused on presenting moist heat sterilization concepts and the foundation of science that supports the moist heat sterilization approaches summarized in the previously mentioned technical reports:

- Fundamentals of Moist Heat Sterilization: Sterilization Microbiology and Engineering
- Parametric Release for Moist Heat Sterilized Products
- Development of User Requirements for Sterilization Systems
- Verification and Validation
- Sterilization of Filter Configurations
- Maintenance of the Validated State
- Post Aseptic Fill Lethal Treatment
- Panel Discussion – Ask the Experts

On behalf of the Planning Committee, we invite you to attend this workshop in Chicago. This is your opportunity to gain first-hand and up-to-date knowledge of moist heat sterilization from the experts while networking with industry sterilization, quality, and regulatory professionals.

PDA's 5th Annual Global Conference on Pharmaceutical Microbiology

Advances in Microbial Control and Product Quality

October 25-28, 2010 • Capital Hilton • Washington, D.C.

The agenda will include discussions on topics such as objectionable microorganisms, investigations of microbial data deviations, manufacturing and product attributes impacting sterility assurance, new technologies and more!

The keynote addresses are:

Mitigating Microbial Risk during Spaceflight Missions
C. Mark Ott, PhD, Chief Microbiologist, Habitability and Environmental Factors Division, *NASA Johnson Space Center*

Practical Regulatory Guidance on Risk Assessment for Microbial Controlled Issues
Thomas Arista, Investigator and National Expert Pharmaceutical/Biotechnology, ORA/ORO, Division of Field Investigations, *FDA*

New this year! A third half day featuring a partnership with US Pharmacopeia (USP) with sessions related to Rapid Microbiological Methods.

Popular sessions to attend include the:

- **Ask the Experts Panel Discussion** where representatives fromglobal regulatory agencies, standards-setting authorities and thepharmaceutical industry present their latest perspectives on themicrobiological challenges that are faced related to aspectof drug manufacturing.
- **Urban Myths** session where industry experts dispel commonlyheld myths in pharmaceutical microbiology.

What is PDA?

The Parenteral Drug Association (PDA) is a global non-profit organization of over 9,500 members. Our focus and emphasis is in the areas of **sterile product technology, biotechnology and quality and regulatory compliance concepts and systems** – become a part of our community, join PDA today!

www.pda.org/join

For details and to register, visit
www.pda.org/microbiology2010

Register by **September 14** and save up to **$200!**

CONFERENCE OCTOBER 26-27 EXHIBITION OCTOBER 25-26 COURSES OCTOBER 28

Lyophilization Technology Updates Discussed at Workshop

San Diego, Calif. • November 15-18 • www.pda.org/freezedry2010

Sidney Wolfe, DPD Consulting

Lyophilization technology has permitted the development of many drugs and diagnostic reagents that cannot be commercially produced and distributed in aqueous solutions because of required quality standards for performance, safety and shelf life. This need has driven the health care industry to develop and implement lyophilization to produce quality and user-friendly products with robust and efficient process in a rapid and dependable manner. To carry out this type of development, practitioners of lyophilization development and implementation must be skilled in the adaptation of a wide range of scientific, engineering and quality principles.

Even though the scientific principals used by the drug and diagnostic industries to lyophilize materials is the same, the final product format of lyophilized diagnostic and therapeutic products may be quite different and have different requirements. Most therapeutic products must be produced sterile, have a stringent purity and potency requirement. The therapeutics industry has mainly relied upon using glass vials and rubber stoppers for the final product format. Diagnostic products have specific requirements for performance in an assay, cost and compatibility with test procedures. Though vials are used for some diagnostic products, advances in sophistication and miniaturization has driven product packaging that includes the use of specialized devices, cassettes, microtiter plates and even chips to insert directly into a diagnostic instrument. Despite these differences, both industries utilize lyophilization for product stabilization and must use many of the same scientific, engineering and quality principles. Thus, both industries have developed similar and complimentary practices that can be shared to improve cost, quality and process robustness.

The healthcare industry has been advancing in the quality data in regulatory submissions, indicative of their knowledge and understanding of their products and methods of manufacturing. As a consequence, more and better quality data that is passed on when a new product is integrated into manufacturing results in greater success in getting the new product to market with a robust and dependable process. This can also be reflected in the observations noted by a knowledgeable assessment of the development, manufacturing and control in manufacturing a health care product. Knowledgeable assessments are invaluable feedback in preparing to bring a new product to market and assuring that manufacturing operations are providing the highest quality product to the patient. Insight to critical considerations along with a unique perspective into the current status of the industry is critical for success. Lyophilization practitioners must understand and apply the benchmark level of contemporary industry expectations for development, science applied and approaches for manufacturing.

The intent of the *2010 Pharmaceutical Freeze Drying Workshop* is to bring together people from both the diagnostics and therapeutics industry who are involved with lyophilization and understand its basic principles, to further develop skills and understanding of the wide range of activities required to develop a lyophilized product. The presentations at the meeting will cover not only the current state-of-the-art for formulation, cycle design, container options, process implementation and transfer and quality assessment but will also discuss integration of these factors using Quality by Design (QbD) principals and fitting them into the current and possible future regulatory framework. Speakers will discuss the implementation of current practices and provide case studies of the application of these principles in a wide range of activities including development, operations and quality assessment. Presentations will be delivered by experts in their field, a poster session will cover the latest developments and exhibits will be provided by prominent industry vendors with the latest innovations. U.S. FDA representatives will give presentations on what is expected in submissions and what should be known and in place for manufacturing. The workshop will provide networking opportunities with the participants involved in a broad range of activities associated with lyophilization technology.

We look forward to seeing you in November at this unique industry event which will bridge the diagnostic and therapeutic sectors of the industry using lyophilization technology and provide a forum for sharing the expertise developed in each discipline. The pre-workshop PDA TRI course, "Fundamentals of Lyophilization," will take place on November 15-16. The *2010 Pharmaceutical Freeze Drying Workshop* will take place on November 17-18. To learn more, please visit www.pda.org/freezedry2010.

***PDA Journal* Fact: Since 1998, over 40 articles mention or address lyophilization**

"Train the Trainer" Courses Offered at Biennial Conference

Baltimore, Md. • October 14-15 • www.pdatraining.org/training

Stephanie Ko, PDA

Good educators refine their skills periodically to stay up-to-date on the newest technologies, acquire new skills and become more knowledgeable of available resources. If training is a part of your job function, you don't want to miss our "Train the Trainer" courses, immediately following the *2010 PDA Biennial Training Conference*.

In "Designing and Presenting Effective GXP Training Programs," taught by **Elaine Lehecka Pratt**, President, Lehecka Pratt Associates, participants will learn a practical, stepwise approach to creating and presenting interesting and effective GXP training programs for their facilities. Additionally, participants will identify ways to audit-proof training documentation, evaluate training effectiveness and relate potential course topics to facility quality objectives and U.S. FDA quality requirements.

Next, we offer "FDA Inspection Readiness for a Training Systems Audit," taught by **Barbara van der Schalie**, Clinical Training Manager, SAIC-Frederick. This course also uses a step-by-step approach that will teach participants to critically evaluate the elements of FDA inspection readiness for a training system audit and construct a plan that meets their company's regulatory requirements. At the end of the course, students will be able to list the critical elements of an FDA Training System Audit and describe how to achieve inspection-ready status.

"Introduction to Competency Based Training," taught jointly by **Dave Gallup**, President, Training and Communications Group, and **Richard Sands**, Project Manager, RTS Training Services, will provide trainers the ability to design a competency-based technical skill training program.

"Developing Using Virtual Learning Opportunities," a new course, is taught by **James Vesper**, President, LearningPlus. In an age of advancing technology, virtual learning becomes greater in demand when the source of instruction and the learner are separated by time and/or space. Participants will identify the tools and technologies used to develop and deliver virtual learning and where they can be most effectively used. At the conclusion, participants will have designed a virtual learning opportunity given a topic and specific technology.

Trainers need training too. Don't let this opportunity pas you by!

PARENTERAL DRUG ASSOCIATION TRAINING AND RESEARCH INSTITUTE (PDA TRI)

Upcoming 2010 Laboratory and Classroom Training for Pharmaceutical and Biopharmaceutical Professionals

Save **10%** by registering early!

Become a PDA member and save even more on your course registration!

October 2010

19-20: Fundamentals of D, F and z Value Analysis
Bethesda, Maryland | www.pdatraining.org/DFandZ

Register for both courses and save $500

21-22: Validating a Steam Sterilizer
Bethesda, Maryland | www.pdatraining.org/VSS

20-21: PDA's Universe of Pre-filled Syringes and Injection Devices Course Series
Las Vegas, Nevada | www.pda.org/Pre-filled2010

26-29: Contamination Control
Bethesda, Maryland | www.pdatraining.org/Contamination

28: PDA's 5th Annual Global Conference on Pharmaceutical Microbiology Course Series
Washington, D.C. | www.pda.org/Microbiology2010

November 2010

3-4: Bioassay Development and Validation
Bethesda, Maryland | www.pdatraining.org/BioassayVal

4: Developing a Robust Supplier Management Process
Bethesda, Maryland | www.pdatraining.org/SupplierManagement

15-16: Fundamentals of Lyophilization
San Diego, California | www.pdatraining.org/Lyophilization

16-18: 2010 New Brunswick Course Series
New Brunswick, New Jersey | www.pdatraining.org/NewBrunswick

Course held at the PDA TRI facility in Bethesda, Maryland.

The PDA Training and Research Institute is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education.

For more information on these and other upcoming PDA TRI courses please visit **www.pdatraining.org**

Cold Chain Challenges Discussed at Conference

Berlin, Germany • October 7-8 • www.pda.org/pccm2010

Conference Co-chairs Erik J. van Asselt, PhD, PCCIG, Europe and Rafik H. Bishara, PhD, PCCIG, USA

Today's supply chain for pharmaceuticals is complex. Many activities are globally outsourced and/or split including manufacturing, packaging, storage and distribution. As a result, multiple stakeholders with different business strategies distribute pharmaceuticals in various presentations and temperature sensitivity ranges from manufacturing sites via packaging sites and warehouses to the end user: the patient. With the appearance of more and more GDP regulations from regulatory agencies worldwide, as well as guidances from various organizations, institutes and industry and a lack of harmonization, the pharmaceutical industry faces many challenges to find the appropriate distribution solutions to remain in compliance to ensure patient safety and to meet the business needs in relation to product quality, delivery and cost.

Members of the PDA's Pharmaceutical Cold Chain Interest Group (PCCIG) at the PDA Europe Conference and Training on Pharmaceutical Cold Chain Management will be reporting for the first time on guidances for excursion management and stability testing to support the distribution of temperature–controlled pharmaceuticals. Round table discussion will examine the origin of 2–8°C and how stability data may support shipping beyond the label claim. Additional topics being addressed by the European and American PCCIG groups will be discussed, and the opportunity to participate on these task forces will be reviewed.

Storage solutions, transportation routes via road, air and ocean, packout systems, a case study on the qualification of shipping routes, temperature monitoring, risk management and quality agreements with suppliers and logistical service providers will be presented at the conference. In addition, time has been allocated for service providers to show and discuss their new cold chain visibility solutions.

A newly designed training course, "PDA Good Temperature-Controlled Management Practices" will be offered on October 5–6.

Participants will learn about:

- Global regulations, pharmacopeial standards, WHO requirements and industry best practices
- Developing and qualifying shipping containers
- Cold chain risk management, assessment, reduction and tools for trend analysis
- Temperature monitoring and analyzing time/temperature data

Because product security is becoming another key area, proper planning, monitoring and good execution is required. The regulatory requirements continue to increase to ensure proper handling , storing and distribution of the temperature-controlled products until they reach the end user: the patient. Risk assessments and risk mitigation plans are key to support the areas of concern for product security challenges, including counterfeiting, diversion, tampering and product theft. *The 2010 PDA Europe Conference on Pharmaceutical Cold Chain Management* will address these concerns.

The new training course and PDA Pharmaceutical Cold Chain Management Conference in Berlin promise to be very exciting and a must join. We look forward to meeting you!

Learn about Recent Developments at Parenteral Conference

Berlin, Germany • October 26-28 • www.pda.org/parenterals2010

Conference Co-chairs Friedrich Haefele, PhD, Boehringer–Ingelheim and Nik Seidenader, Seidenader Maschinenbau

On behalf of the Program Planning Committee and PDA, we are pleased to invite you to attend the *Parenterals 2010* conference. Our target is to integrate the most recent developments concerning process, technology and regulatory trends in manufacturing of parenterals into the meeting.

The *Parenterals 2010* Conference will be held in Berlin, Germany on October 26-28. From around the world, this conference will bring together regulators, production and validation professionals from our industry, as well as component suppliers and equipment vendors. You will have the opportunity to get an update on current and emerging technology and regulations to help you cope with your daily professional challenges.

The agenda is designed to encourage discussion and networking with colleagues in our industry on a wide range of crucial issues and vital questions. The conference will provide you with practical information you can apply immediately upon returning to the workplace.

The program will cover:

- Technology updates, innovations in equipment and process technology
- Production environments and their control
- Facilities design and production planning
- Impact of recent regulatory guidances
- Component related quality impacts, testing and inspection ➤

The Parenteral Drug Association presents...

2010 PDA Conference on Pharmaceutical Cold Chain Management

Temperature Controlled Pharmaceutical Supply Chain – From Manufacturer to the End User

October 7-8, 2010 | Hotel Hilton Berlin | Berlin, Germany

Conference | Exhibition | Course

www.pda.org/pccm2010

Many activities today are globally outsourced and/or split – including manufacturing, packaging, storage and distribution. As a result, multiple stakeholders with different business strategies distribute pharmaceuticals in various ways and temperature sensitivity ranges from manufacturing sites via packaging sites and warehouses to the end user: **the patient**.

The vast regulations from agencies, guidance from organizations and lack of harmonization all create challenges to find the appropriate distribution solutions **to remain in compliance and ensure patient safety – as well as meet the business needs of product quality**, delivery and cost! Not to mention having to combat the serious problems of counterfeiting, diversion, tampering and product theft.

The *2010 PDA Conference on Pharmaceutical Cold Chain Management* is a forum for interactive discussion and debate to provide strategies and pragmatic solutions in the landscape for temperature-controlled warehousing and logistics.

The program includes:

- ☑ EMA, WHO and USP representatives giving updates on regulations and public standards
- ☑ Detailed Review of Industry Performance Specifications of Refrigerator Equipment Used in Storage and Distribution
- ☑ Round Table Discussion: Beyond the 2-8 deg C
- ☑ Air Cargo Capacity – The Future of Transporting Vaccines to Developing Countries: A World of Change and Challenge
- ☑ The Challenges of Ocean Freight for the Transportation of High Value Temperature Controlled Pharmaceuticals
- ☑ New Technology Development in Passive Delivery Systems as they Relate to Design and Qualification
- ☑ 2D Barcode System in Turkey for Product Track and Trace: First Experiences from a Wholesaler's/Distribution Center's Perspective
- ☑ And more!

Exhibition and sponsorship opportunities are available!
Please contact Katharina Keisers-Engstfeld at keisers@pda.org for more information.

What is PDA?

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www.pda.org

To register, visit www.pda.org/pccm2010

- Regulatory expectations and trends

In addition, the program features a poster session that will display the most recent scientific studies and new technologies. All posters will be introduced by a short oral presentation during the plenary sessions.

The conference will illustrate how manufacturing parenterals has developed, what has been achieved, what is known to still be an issue, as well as future solutions and technologies that will be implemented and applied. Finally, regulatory expectations and experiences are the focus, giving the audience a chance to learn, discuss and receive updates on these issues. It is essential to understand GMP trends in order to prevent unpleasant surprises when inspected, so being informed about current observations during inspections concerning manufacturing will be of additional benefit.

Breaks, on-site luncheons and evening receptions will provide opportunities to meet new and old friends as well as colleagues. We are looking forward to meeting you in Berlin.

Visual Inspection Forum to Address Regulatory Developments

Berlin, Germany • October 5-6 • www.pda.org/vif2010

Program Co-Chairs John Shabushnig, PhD, Pfizer, and Markus Lankers, PhD, rap.ID GmbH

Several years ago, big Pharma started a wave of restructuring in preparation for the companies losing patent protection on blockbuster drugs. The layoffs at these companies include thousands of research and development positions, which may be surprising in light of their need for new drugs. Comparable losses in manufacturing followed. The necessary financial savings are being achieved; however, one of the downsides of these job cuts is the loss of experience for the company. Fewer people remain who understand the increasingly complex technical areas required for successful discovery, development and manufacturing operations. At the other end of the spectrum are the many start-up companies that do not have the resources typically found in larger companies. They have never had such expertise and don't know what they don't know. They also may face unique challenges with new and novel formulations and packaging systems. They too need an efficient means to gain critical quality and manufacturing expertise.

At the same time, companies of all sizes must be able to find their way through the stringent quality requirements for such areas as particulate matter control. Their success will be determined by their ability to navigate the many regulatory hurdles, harmonize inspection practices and successfully adopt the newly emerging technologies. A focused exchange on specialized topics, as well as efficient training for those people replacing departing colleagues, might be essential for the success of these companies.

Visual inspection continues to be an important element of the manufacturing process and the quality assurance of injectable products. Product inspection provides necessary information for lot release and coupled with defect identification, contributes to a strategy of continuous process improvement. Since 2000, PDA has organized the Visual Inspection Forum to discuss new technical and regulatory developments in this field. The meeting provides a forum to present and discuss new developments in the field of visual inspection, including a basic understanding of the sampling and inspection process, practical aspects of manual and automated methods and the regulatory and compendial requirements that govern them.

The PDA Visual Inspection Forum is a continuing series of meetings presented annually and alternating between Europe and the United States. Last year it was held in the United States and continues to be a superior event focusing on this important topic. If these challenges are impacting you and your business, then the *2010 PDA Visual Inspection Forum* is a must for you and October 5-6 should be marked on your calendar.

This is an excellent opportunity to learn more about visual inspection and to discuss inspection challenges with the experts, as well as to train those in companies who have had to reduce their staff in the areas of manufacturing, R&D, Validation and Quality. We have provided time in the program for networking with the speakers and for discussion of your specific inspection challenges. As in past years, the meeting will feature an exhibition where attendees can see the latest in commercial inspection hardware and discuss production needs with key suppliers of inspection systems and services. Special attention will be given to packaging component quality requirements and validation case studies for visual inspection processes. For more information on the Visual Inspection Forum and related training course, visit www.pda.org/vif2010. We look forward to seeing you at this exciting and informative meeting.

We are also pleased to again add an optional two-day training course. This course covers the basics of the inspection process and its application to injectable products. It will be a combination of lecture/discussion and hands-on laboratory exercises used to develop and practice practical inspection skills. The skills developed through this course may be applied to both manual human inspection and automated machine inspection. This course will be held immediately following the Visual Inspection Forum on October 7-8 in the same location.

PDA
Connecting People, Science and Regulation®

PDA Europe Upcoming Conferences October 2010

Visual Inspection Forum

Visual inspection continues to be an important element of the manufacturing process and the quality assurance of injectable products. Product inspection provides necessary information for lot release, and, coupled with defect identification, contributes to a strategy of continuous process improvement. The meeting will provide a forum to present and discuss new developments in the field of visual inspection, including a basic understanding of the sampling and inspection process, validation of manual and automated methods and the regulatory and compendial requirements that govern them. Special attention will be given to specific inspection challenges of biopharmaceutical drugs e.g. turbid media as well as the differentiation between protein aggregates and foreign particles.

5-6 October 2010
Berlin/Germany

Pharmaceutical Cold Chain Management

Temperature Controlled Pharmaceutical Supply Chain - From Manufacturing to the End User

The 2010 PDA two day event will focus on the supply chain of temperature controlled pharmaceuticals from the manufacturer to the end user. Aspects of temperature controlled qualification and validation using new technologies will be presented. Distribution stability studies and shipping outside of label claim will be debated. A special session is planned on storage and transportation solutions for ambient, refrigerated and frozen products. Wholesalers and pharmacists will be invited to present their plans and systems for Quality Agreements, temperature alarms and distribution traceability. The attendees will hear from regulators, industry experts, and cold chain solution partners about risk management for temperature controlled supply chain.

The 2010 **NEW** two day Cold Chain Training will consist of 4 modules covering (1) Global regulatory requirements including an overview of the recently published PDA Technical Report No. 46, Last Mile: Guidance for Good Distribution Practices for Pharmaceutical Products to the End User, (2) Packaging Development, (3) Temperature Monitoring and Data Analysis, (4) Cold Chain Risk Management. All concepts will be clarified by round table discussions and case studies.

7-8 October 2010
Berlin/Germany

Conference, Exhibition: 7-8 October
New Training Course: 5-6 October

For other events see:
www.pda.org/europe

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on the Media Fill Test

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