NEW ENGLAND PDA NEWSLETTER

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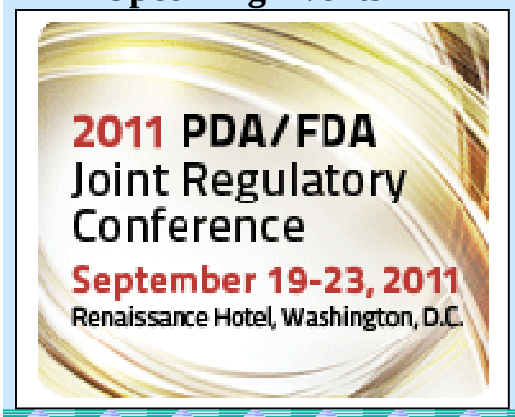
Connecting People, Science and Regulation

Upcoming Events



PDA June Workshops

PDA Pharmaceutical Ingredient Supply Chain Workshop June 6-8th

PDA Analytical Methods Development & Validation Workshop June 20-21st

Single Use Systems Workshop June 22-23rd

FDA Inspection Readiness

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Introduction

In the U.S. the Food and Drug Administration (FDA) is charged with ensuring that healthcare products are safe, effective, and of a requisite quality. One of the ways that they meet this mandate is through the periodic inspections of healthcare company facilities and records. An unfavorable FDA inspection can result in various regulatory actions, which can negatively impact a company's business and revenues. Since these inspections are generally unannounced, healthcare companies need to maintain a basic level of inspection readiness at all times.

The focus of most general GMP Compliance inspections is to ensure that the healthcare company can provide evidence, in the form of procedures and documentation, that they have their products and processes under control.

Results of Non-Compliance

FDA-483 (Inspectional Observations) – At the conclusion of the inspection the FDA inspector will generally issue an FDA-483 listing objectionable observations. A written response should be sent to FDA within 15 business days to avoid further compliance action.

Warning Letter – If after reviewing the inspection results, the FDA determines that the facility is in violation of the Federal Food, Drug, and Cosmetic Act a warning letter may be issued. Warning letters are issued only for significant violations that may lead to enforcement action if they are not promptly and adequately corrected. Failure to adequately respond in writing to the FDA-483 within 15 business days can result in issuance of a Warning Letter. Warning Letters are publicly available, free of charge, and can

result in unfavorable media attention thus affecting stock prices and consumer confidence.

Consent Decree Injunction – If the FDA determines that an observation(s) is serious enough or if a firm repeatedly violates cGMPs, the FDA may pursue action through a Federal Court. Often these consent decrees include fines, requirements for specific actions including use of 3rd party resources, defined due dates for specific actions and penalties for noncompliance. Costs associated with a consent decree can range into millions of dollars paid in fines, additional costs associated with payment of 3rd parties, and indirect costs associated with impact on stocks and public image.

Current FDA Inspection Methods

Current FDA inspection methods rely on evaluating systems. Pharmaceutical inspections follow the six system approach. The Six System Inspection technique uses a top-down approach to evaluate the requirements within the following six systems:

- Quality Systems
- Materials
- Facilities and Equipment
- Production
- Packaging and Labeling
- Laboratories

Companies can minimize or eliminate potential problems that might be observed by a regulatory inspector by conducting periodic internal audits of each of the systems and subsystems identified by the FDA. An internal audit schedule should be established and followed that ensures that all systems are audited at least annually.

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http://www.pda.org/MainMenuCategory/Chapters/New-England/Chapter-Resources_1.aspx

The newsletter has the following reach:

- **Our direct e-mail distribution reaches over 1,800 contacts throughout New England.**
- **Our membership includes people from manufacturing, research, QA, QC, engineering, contract manufacturers, consultants, and regulatory.**
- **We promote the newsletter at New England PDA's bi-monthly dinner meetings, often with company tours, which regularly attract 50-100 attendees.**
- **We post the newsletter on our chapter's website at Global PDA (www.pda.org), an organization that has over 10,000 members.**

Deadline	Publication Date
March 01, 2011	April 2011
July 01, 2011	August 2011
October 01, 2011	November 2011

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Key Documentation

Procedure on regulatory inspections. Such a procedure should define key responsibilities during and after an inspection, including who will serve as the company primary contact and spokesperson and who will serve as the scribe responsible for maintaining notes and records of the inspection. The procedure should also address such issues as logistics, use of cameras by a regulatory inspector, initial meeting and introductions, off-hour inspections, dealing with affidavits, documentation of inspections, sharing of confidential information, close-out meeting, and responding to inspectional observations. All personnel should be trained in the proper way to interact with regulatory inspectors

Organization chart. This provides an overview of the company's management structure and also provides evidence of an independent quality unit. The organization chart should be kept current and readily available.

Readily available documents. An FDA inspection is a snapshot in time of the operations observed during the inspection. Therefore to get a better perspective on the controls and systems in place the FDA relies on reviewing documentation. To expedite the inspection process, documents such as validation protocols and reports, change control records, batch records, annual record review results, investigations, training records, equipment logs, and environmental monitoring records and sterilization records for sterile product manufacturing facilities should be readily available. A system should be established to ensure that such records are quickly scanned for any significant problems prior to providing the requested documents to the FDA.

Problem Indicators. The FDA will generally want to inspect records that indicate potential problems such as complaints, product quality returns, rejected materials, investigations, Out-Of-Specifications (OOS), Corrective Action-Preventive Action (CAPA), Field Alert Reports, and recalls. Such records should be periodically reviewed to ensure that they are being completed in a timely manner and in compliance with SOPs. Particular attention should be paid to any complaints received through the FDA complaint reporting system, as the inspector will likely follow-up on such complaints.

Validation Documentation. If the inspection is being conducted within the first year following approval of a new drug, the inspector will likely want to review the process validation documentation to ensure that validation was performed as required. The validation documentation should be readily available for inspection. A review of the process and associated procedures and batch records should be performed to ensure that they are consistent with the process that was validated and that all regulatory commitments are being met.

SOPs. The GMPs require a number of written and approved SOPs to be followed. Lacking an SOP that is required by the GMPs will likely lead to an observation. Internal audits should verify that SOPs are followed.

Personnel Training. Personnel should be trained in the SOPs that are applicable to the functions they perform and should be retrained when there are changes to the SOPs. All training should be documented. There should be a method of assessing the effectiveness of the training.

Facilities and Equipment

A key part of a successful inspection is to ensure that the facilities and equipment are in good condition and always inspection-ready.

- Facilities and equipment should be clean and organized.
- Dirty equipment, leaking pipes, loose insulation, holes in walls, flaking paint, and gaps around doors are easy items to spot that indicate quality is not a priority.
- Cleaning equipment and tools should be stored.
- Equipment should be calibrated and the calibration status easily determined.
- Equipment status (in process, clean, dirty) should be easily determined.
- Pest control devices should be periodically inspected to ensure that captured or dead pests are not inside traps.

Periodically touring production, warehouse, and laboratory areas is a simple way to ensure that the facilities and equipment are maintained in a compliant manner.

Expediting the Inspection

The quicker that an inspection can be completed the sooner those involved in the inspection can return to performing their routine jobs. Lengthy inspections tend to indicate potential problems.

- Knowledge of the inspection process. The inspection can be expedited if those involved with the inspection understand the inspection process including the reason for the inspection, the specific systems and subsystems included, and the rights and authority of the FDA inspector. Personnel should understand that an FDA inspection does not necessarily mean that there is a problem and that the FDA Inspector is only doing their job. Responses should address the specific question asked, and not elaborate. Answers should be factual.

- Knowledge of internal processes. The company representative accompanying the inspector should have a good knowledge of the internal company operations and processes and be able to answer most of the questions quickly without the need to contact other company personnel. Detailed questions on a specific topic may require a subject matter expert, but when possible the FDA contact person should be able to answer simple questions. The company representative should be knowledgeable in the company's policies regarding regulatory inspections and with regulatory requirements.

- Documented Rationale. Documented rationale, including risk assessments where necessary should be available for key decisions.

- Stay Current. The company should stay current with FDA regulations, guidance documents, and compendia and should ensure that any changes that impact operations are reviewed and considered. Periodic reviews of Warning Letters can provide signals regarding the current areas of interest. Care should be taken to not adjust operations based on review of Warning Letters unless there is really a potential problem.

Inspection Follow-up

Respond in writing to any observations within 15 business days of the end of the inspection. Responses should include details and schedules for addressing the observations noted on the FDA-483. If actions have been completed provide evidence that they were completed. Delayed responses or inadequate responses can lead to a Warning Letter or other regulatory actions.

Conclusion

Drug product manufacturing requires a commitment to comply with stringent requirements, and to allow the FDA to inspect operations. Inspections can be disruptive to operations and if unprepared can lead to potential regulatory actions or unfavorable media attention that can affect revenues. Understanding the inspection process and remaining ready for inspections can minimize the potential for an unfavorable outcome.