Preparing for an FDA Pre-Approval Inspection (PAI)

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- Understanding the PAI Experience: What to Expect
- Inspection Management Plan
- Preparing for the Inspection

Introduction

Why a Pre-Approval Inspection?

The purpose of a pre-approval inspection (PAI) is to ensure that your facility is in compliance with FDA rules and regulations.

Investigators want to know that product development was done appropriately and the current good manufacturing practices (cGMP) are up to FDA standards.

An inspection can be very **intimidating** to all involved, but is vital if you want to obtain **FDA approval**.

What if I have a negative report?

Major delays before you can market your product can arise from a negative report such as:

- Contract problems – You might have problems with **Government, contracting partners,** or other **companies**
- Legal problems
- Loss of reputation – Information from 483's is routinely **published**
- Stockholder-Market issues – Negatively affects **stock prices**
- Consumer safety issues – **Loss of trust** by consumers

What's the impact?

At best, an FDA inspection can be disruptive to your operations.

At worst, it can mean lost revenue and damage to your reputation. You can even be shut down!

Managing the Inspection

One of the primary goals is to **MANAGE** the inspection from start to finish by:

- Understanding the FDA's expectations
- Preparing your site
- Generating documented evidence of compliance with FDA regulations
- Interacting appropriately with FDA inspectors
- Managing the inspection on the day of the audit

Understanding the PAI Experience: What to Expect

What to Expect

When pharmaceutical (drug) or device manufacturers apply for pre-market approval of a new product, the FDA must conduct a pre-approval inspection (PAI).

FDA sends a team of individuals to conduct the pre-approval investigation. The team may include:

- Lead investigator
- Microbiologist
- Chemist
- Computer Specialist
- Reviewer from Headquarters (e.g. Drugs or Devices)

What to Expect

Investigators will review your application before ever visiting your site. When they arrive, they will compare the information in the application to what they find.

What investigators look for:

- How you handle Quality Assurance
- Proper training of employees
- Formulation development (for drugs)
- Deviation and failure investigations

FDA Inspection Trends

Quality Assurance (QA) system is the number one issue for inspectors (in recent years).

The PAI has been one area in which they have developed a risk-based approach. Rather than trying to cover everything, inspectors will look at how your facility manages and monitors anything that has risk.

Important: Special attention is being given to the new Quality Systems programs that have been introduced under FDA's "GMPs for the 21st Century" Initiative

Closing Meeting

Form 483 – “Notice of Inspectional Observations” may be issued at the conclusion of the inspection if violations are found.

- If you do not receive a 483, do not assume that the FDA has approved of everything you are doing. It is probably just means that you were in compliance in the areas they had time to inspect on this visit.

An Establishment Inspection Report (EIR) is prepared after the inspection regardless of whether violations were found.

Inspection Management Plan

Think about this!

When the FDA comes to conduct a PAI, they expect to find some problems.

If their investigation of your facility revealed no problems, they would likely turn your company upside down, trying to find out what you are hiding.

What are your issues?

All companies have some issues – that is a given. What FDA investigators really want to see is how you address those problems:

- Do you honestly investigate your problems?
- Do you try to control the problems?
- Do you look for the root cause of a problem?

Companies that try to control problems are viewed by the FDA as companies with a high standard of quality.

Inspection Management Plan

In a PAI, you will have some advance notice of when the inspection will take place. Therefore, a Inspection Management Plan should be in place.

The **Inspection Management Plan** should provide for:

- Response to arrival of investigators
- Guidance of inspectors' activities
- Procedure for working with investigators
- Documentation of inspection

The management plan or SOP should spell out all of the procedures that you will follow during an investigation.

Preparing for the Inspection

Conduct Internal Audits

Internal Audits are a key element of the quality system.

- Required per §21CFR Part 820.22
- Objective is to evaluate activities and documentation to ensure compliance to regulations and internal procedures.
- Ideal for preparing organization for external audits.
- Internal audit reports are not normally viewed by FDA inspectors.

Personnel Training

Educate personnel about the inspection process so they can be prepared

Train individuals to interface with FDA investigators

- Do’s & Don’ts

Verify that training has been provided for personnel on their current job functions and that supporting records are on file

The goal is to minimize the opportunity for incorrect answers provided to the inspectors or providing too much information

Review External Documents

Be familiar with:

- FDA Regulations as applicable
  - 21CFR Parts 210/211 (Drugs), Part 820 (Devices)
- FDA Guidance Documents
- FDA Guidance Manuals for Inspectors

Review:

- Warning Letters (www.fda.gov)
- Prior FDA 483's
- Prior Establishment Inspection Reports (EIR)

Review Internal Documents

Relevant documents and records should be reviewed prior to the inspection.

- Ensure that all relevant records exist and are readily available.
- Ensure that all records are accurate.
  - Note: Do not change records after the fact; rather add the correction and an explanation, sign and date it!

The FDA inspector will be comparing the details of the application to the records you have in house.

Identify records that you will pre-stage for ease.

Examples:

- Large volume validations
- Design History Records

Review Internal Documents

Some of the documentation to consider for pre-review:

- Clinical trials/studies
- Operating procedures
- Batch reports
- Laboratory records (associated with batch test)
- Non-conforming materials reports
- Out-of-specification reports
- Training records – past records and GMP training
- Development reports
- Validation/qualification documents
  - Process validation
  - Cleaning validation
  - Computer validation
  - Environmental evaluation

Prepare an Inspection Team

An inspection team to manage the inspection should be prepared and roles identified prior to the inspection.

Rooms should be identified to ease the inspection:

- An Audit room will be where the inspector will interview personnel.
- A Staging “War” room will be where documents will be set up and processing of inspector requests will take place.

Inspection Team – Audit Room

In the audit room personnel **SHOULD** include:

- Escort: Key personnel to accompany investigators. They should know how to develop a rapport with the investigator. They will answer most questions about quality systems.
- Scribe: Keeps detailed notes about the audit including topics discussed, questions asked, inspector mood, etc.
- Runner: Sends requests to staging room (walks or electronic) for processing.
- Subject Matter Expert (SME): Answers technical questions that Escort cannot answer.

Inspection Team – Staging Room

In the staging room personnel **MAY** include:

- Room Head: Leads room, meet & greet SME's
- Coordinator: Obtains requests from Audit room runner. Contacts appropriate SME. Tracks all requests to ensure they are filled.
- Reviewer: Reviews any documentation that will be sent to the inspector.
- Prep person: Prepares SME's prior to going to Audit Room
- Runner/Helper: Handles administrative duties (copying, stapling, sorting, etc.). Backup to coordinator when things get hectic.

Conduct Mock Audits

Mock audits are conducted to evaluate the status of compliance of the firm and how employees respond to questioning. If possible use an external consultant.

Items to consider during a mock audit include:

- Focus on the laboratory – an FDA “hot spot”
- Review of key internal documents
- Cleanliness of the workplace
- Employee responses to questioning
- How efficiently can you fill inspector requests

Remediate

Use the lessons learned from all the activities to be ready for the FDA Inspection.

- Fix the problems
- Close the gaps

Practice, practice, practice…

Conclusion

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- You need not dread an FDA inspection if you are adequately prepared.
- FDA inspections have revealed some trends in recent years. The agency is taking a tougher posture on new applications and using a risk based approach.
- Inspectors usually look at two systems in depth. QA is their number one concern in recent years.
- They may also look at another system, such as facilities and equipment; materials; production; packaging and labeling; or laboratory controls.

Conclusion

- FDA does not expect your facility to be perfect. They expect all companies to have some issues. What they really want to see is how you address those problems.
- The FDA tends to view companies that try to control these problems to have a high standard of quality.
- Use the FDA inspection as a learning tool, not as a negative or adversarial experience.

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Contact Information

Stay tuned for Part 2 of FDA Inspections:
"Managing the Inspection"

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