What To Expect When Being Inspected

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Overview

• Types of inspections
• How investigators prepare for the inspection
• The FDA inspection begins…
• The FDA inspection ends…
• Questions
Poll Question

What are your biggest concerns about a FDA Inspection? (select top 3)

<table>
<thead>
<tr>
<th>Concern</th>
<th>Percentage</th>
<th>Votes</th>
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</thead>
<tbody>
<tr>
<td>Non-compliance with CGMPs</td>
<td>0%</td>
<td>0</td>
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<tr>
<td>Won’t know the answers to the investigator’s questions</td>
<td>0%</td>
<td>0</td>
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<tr>
<td>Won’t have complete documentation</td>
<td>0%</td>
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<tr>
<td>Which investigator will conduct the inspection (i.e. lack of consistency of inspecational approach between investigators)</td>
<td>0%</td>
<td>0</td>
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<tr>
<td>Will not be prepared when FDA comes to inspect</td>
<td>0%</td>
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Four Major CGMP Inspections

1. Pre-approval*
2. Post-approval*
3. Surveillance (CGMP, routine)*
4. For-cause or directed**

*1-3 have compliance programs and FDA’s procedures are available on the web

**For cause/directed are the most unscripted ...is harder to prepare for and the investigator may have a specific assignment that is not publicly available
A pre-approval inspection (PAI) is performed to contribute to FDA’s assurance that a manufacturing establishment named in a drug application is capable of manufacturing a drug, and that submitted data are accurate and complete.
Pre-Approval Inspection Program (7346.832)

Objective 3: Data Integrity

Objective 2: Conformance to Application

Objective 1: Readiness for Commercial Manufacturing

1a: Investigations/Trends

1b: Material Handling

1c: Contamination

1d: Procedures

1e: Process feasibility
Post-Approval Inspection Program (7346.843)

- Inspection of products marketed under a recently approved application
- Monitor for changes in the production and control practices that occur after approval (6-24 months)
- Assignments issued by CDER based on recommendations and risk
- Coverage is based on reason for inspection (pre-approval inspection, past history...
CP7356.002 “Drug Manufacturing Inspections”

Covers both domestic and international inspections

Increased use of question-based inspection programs to focus and ensure consistent coverage regardless of location
New Inspection Protocol Project (NIPP)

• New paradigm for inspections and reports that will advance pharmaceutical quality
• Standardized approach to inspection
• Data gathering to inform “quality intelligence” of sites and products: both positive and negative behaviors
• Risk-based and rule-based process using expert questions
• Semi-quantitative scoring to allow for comparisons within and between sites
• More common inspection report structure
Surveillance Inspections: Strategy

- Activities in drug firms can be organized into **systems** that are sets of operations and related activities.

- Control of all **systems** helps to ensure production of drugs that meet intended safety, identity, strength, quality and purity characteristics.
What are the systems?

- Quality
- Production
- Laboratory
- Materials
- Facilities & Equipment
- Packaging & Labeling
What are the Systems?

Six systems:
- Quality
- Facilities and Equipment
- Materials
- Production
- Packaging and Labeling
- Laboratory Controls

21 CFR 211:
- Subpart B - Organization and Personnel
- Subpart C - Buildings and Facilities
- Subpart D - Equipment
- Subpart E - Components and Container/Closures
- Subpart F – Production and Process Controls
- Subpart G - Packaging and Labeling
- Subpart I - Laboratory
The inspection is defined as audit coverage of 2 or more systems, with mandatory coverage of the Quality System. Different numbers of systems may be covered depending on the purpose of the inspection.
Inspection Options

• Full inspection
  • Quality system plus three other systems

• Abbreviated inspection
  • Quality system plus one other system
Full versus Abbreviated

**Full:**
- Initial inspection
- History of noncompliance
- Significant changes
  - New technologies, equipment, facilities
- Follow-up to a W/L
- Revert to an Abbreviated Option with District Concurrence

**Abbreviated:**
- When not using the Full Inspection Option
- Surveillance inspections
- Adequate for routine coverage
- Rotate systems with the Abbreviated Option – District will monitor
Abbreviated Inspection Option is meant to provide an efficient update evaluation of a firm's CGMP compliance.

Generally done when:

- a firm has a record of satisfactory CGMP compliance
- with no significant recalls or product defects or field alert incidents
- with little shift in the manufacturing profiles of the firm within the previous two years
For-cause and Directed inspections

- Anything other than a routine inspection*
- Investigate a specific problem that has come to FDA’s attention:
  - NDA Field Alert report
  - Recall
  - Adverse event cluster (i.e. heparin)
  - or other “event”
- Generally the focus is on the specific event and the company response
- Determine state of control in a specific area of processing (i.e. verify correction of previous deficiencies)

*Routine inspections are PAIs, post approval and surveillance
Poll Question #2

What was the reason for your last FDA inspection?

- Pre-approval inspection; your firm was named in the CMC section of A/NDA or BLA: 0% (0)
- Post-approval inspection: 0% (0)
- Surveillance inspection: 0% (0)
- For-cause; i.e. your firm had a recall or submitted an increased number FARs to the FDA recently: 0% (0)
- Not sure: 0% (0)
- Have not been inspected by the FDA, yet!: 0% (0)
- No Vote: 0% (0)

Broadcast Results
But what really happens ....
FDA Inspections

• An official examination of a facility to determine its compliance with laws and regulations administered by the FDA

• Are FACT finding

• Obtain EVIDENCE

• Are REGULATORY
Authority to Enter and Inspect

- Section 704(a) of the FD&C Act provides authority for FDA to conduct inspections.

“upon presenting appropriate credentials and a written notice to the owner, operator, or agent in charge.”

Be reasonable (Time, Limits, Manner) in order to achieve the objective of the inspection.
Common FDA Inspection Forms

- FDA-482 Notice of Inspection
- FDA-484 Receipt for Samples
- FDA-483 Inspectional Observations
The inspection team

• Investigators

• Other Specialists
  • Chemistry Expert
  • Microbiology Expert
  • Process/Facility Expert
  • Formulation Expert
Preparing for an Inspection

Investigator(s) create an inspection plan based on the following information:

- Previous establishment inspection reports (EIRs)
- Previous FDA Form 483 observations
- Responses to FDA-483s and/or Warning Letters and related firm commitments
- Firm’s website (including product literature, products manufactured, recent press releases, etc.)
- Consumer complaints, ADE’s, Recalls, FARs since the last inspection
Preparing for an Inspection

• Review application or Drug Master File (DMF)
• Review guidance documents
• CGMPs and the FFDCA
• FDA compliance programs
• Investigations Operations Manual (IOM) Chapter 5 ESTABLISHMENT INSPECTIONS

(http://intranet.ora.fda.gov/directives/cpgm/master_list.htm)
Compliance Program Guidance Manuals

Pre-approval:

• 7346.832/7352.832, Pre-Approval Inspections/Investigations

Post-Approval/Surveillance:

• 7346.843, Post-Approval Audit Inspections

• 7356.002, Drug Process Inspections (sub-programs follow…)
  • 7356.002A, Sterile Drug Process Inspections
  • 7356.002B, Drug Repackers and Relabelers
  • 7356.002C, Radioactive Drugs
  • 7356.002E, Compressed Medical Gases
  • 7356.002F, Active Pharmaceutical Ingredients Process Inspections
  • 7356.002M, Inspections of Licensed Biological Therapeutic Drug Products
  • 7356.002P, Positron Emission Tomography

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm252671.htm
“FDA Guide to Inspections of…”

- Topical Drug Products
- Pharmaceutical Quality Control Laboratories
- Validation of Cleaning Processes
- High Purity Water Systems
- Lyophilization of Parenterals
- Microbiological Pharmaceutical Quality Control Labs
- Dosage Form Drug Manufacturers – CGMPs
- Solid Oral Dosage Forms Pre/Post Approval Issues
- Oral Solutions and Suspensions

http://www.fda.gov/ICECI/Inspections/default.htm
“FDA Guidance for Industry”

- International Conference on Harmonization (ICH) Guidance
  - ICH Q7, Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients
  - ICH Q8, Pharmaceutical Development
  - ICH Q9, Quality Risk Management
  - ICH Q10, Pharmaceutical Quality System
  - ICH Q11, Development and Manufacture of Drug Substances

- Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice (September 2004)

- Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production (October 2006)

- Process Validation: General Principles and Practices (Jan 2011)
Investigations Operations Manual

• Primary source of information regarding Agency administrative and general procedural rules for FDA employees who perform field investigational activities

• Assures quality, consistency, and efficiency in field operations

• Extends to all individuals who perform field investigational activities

• Available on-line at

  http://www.fda.gov/ICECI/Inspections/IOM/default.htm
Contents

- Administration
- Regulatory
- Sampling
- Establishment Inspections
- Imports
- Recall Activities
- ORA Directory
  - incl. field program monitors
Credentials

• Required by law to be shown upon starting an inspection

• Investigator displays credentials to the top management official ("owner, operator, or agent in charge")

• Management may examine the investigator’s credentials and record the number and name

• Credentials are not to be photocopied
Delegated Authority

When investigators are issued Credentials, certain parts of the Commissioner's enforcement authority, as specified in Staff Manual Guide 1410.32, is re-delegated to them. (i.e. conduct examinations, inspections, and investigations; to collect and obtain samples; to have access to and to copy and verify records as authorized by law)

http://www.fda.gov/AboutFDA/ReportsManualsForms/StaffManualGuides/ucm049578.htm
Notice of Inspection

• Must be issued to start the inspection*

• All team members must sign

• Original given to firm and copy included in EIR

• Also known as the FDA-482

*A notice of inspection is not required to be issued during foreign inspections; however credentials should be presented to the top management official.
Notice of Inspection

FDA-482 Notice of Inspection

Notice of Inspection is hereby given pursuant to Section 704(a)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 374(a)) and/or Part F or G, Title III of the Public Health Service Act (42 U.S.C. 262-264)

As a small business that is subject to FDA regulation, you have the right to seek assistance from the U.S. Small Business Administration (SBA). This assistance includes a mechanism to address the enforcement actions of Federal agencies. SBA has an Office of Ombudsman's Office that receives complaints from small businesses about Federal agency enforcement actions. If you wish to comment on the enforcement actions of FDA, CALL (888) 734-3247. The website address is www.sba.gov/ombudsman.

For industry information, go to www.fda.gov/industry.

Signature(s) (Food and Drug Administration Employee(s))

Sidney H. Rogers

Signature(s) (FDA Employee(s))

Sidney H. Rogers, Investigator

Applicable portions of Section 704 and other Sections of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 374) are quoted below:

Sec. 704(a)(1) For purposes of enforcement of this Act, officers or employees duly designated by the Secretary, upon presenting appropriate credentials and a written notice to the owner, operator, or agent in charge, are authorized (A) to enter, at reasonable times, any factory, warehouse, establishment, or establishment in which food, drugs, devices, tobacco products, or cosmetics are manufactured, processed, packed, or held, for introduction into interstate commerce or after such introduction, or to enter any factory, warehouse, establishment, or establishment in which food, drugs, devices, tobacco products, or cosmetics are manufactured, processed, packed, or held, for introduction into interstate commerce or after such introduction, and to inspect such factory, warehouse, establishment, or establishment in a reasonable manner, such factory, warehouse, establishment, or vehicle and all pertinent equipment, finished and unfinished materials, and labeling therein. In the case of any person (including farms and restaurants) who manufactures, processes, packages, transports, distributes, holds, or imports foods, the inspection shall extend to all records and other information described in section 414, when the standard for records inspection under paragraph (1) or (2) of section 414(a) applies to any record required to be maintained by the limitations established in section 414(c). In the case of any factory, warehouse, establishment, or consulting laboratory in which prescription drugs, nonprescription drugs intended for human use, restricted devices, or tobacco products are manufactured, processed, packed, or held, inspection shall extend to all things therein (including records, files, papers, processes, controls, and facilities) bearing on whether prescription drugs, nonprescription drugs intended for human use, restricted devices, or tobacco products which are adulterated or misbranded within the meaning of this Act, or which may not be manufactured, introduced into interstate commerce, or sold, or offered for sale by reason of any provision of this Act, have been or are being manufactured, processed, packed, transported, or otherwise held in any such place, or any action on the reverse of this Act. No inspection authorized by the preceding sentence or by paragraph (3) shall extend to financial data, sales data other than shipment data, pricing data, personnel data (other than data as to qualifications of technical and professional personnel performing functions subject to this

(Continued on Reverse)
The FDA Inspection Begins...

• Issue Notice of Inspection
• Display Credentials
• Lead investigator states purpose of inspection
• Lead investigator provides general agenda
• Tour facility
• Get into details
• Daily wrap up meetings
What are Investigators Looking For?

Verification that a manufacturer is operating in a sufficient state of control by reference to the GMP regulations and policies; if not, the investigator must document accordingly to support necessary action.

CGMP violations include:

- Poorly trained employees
- Poorly maintained or contaminated equipment and facilities
- Lack of process control
- Failure to conduct investigations and resolve discrepancies/failures/deviations/complaints
Investigators look at facility and operations

- Equipment and Facility
- Production
- Packaging and Labeling
- Laboratory
- Warehouse…reject cage

Investigators watch the manufacturing process and employee practices
Investigators look at documentation

• Can the firm produce documented evidence of past events?

• Is there scientific evidence to support conclusions made in reports?

• Do investigations or trending reports demonstrate issues that could effect the quality or safety of marketed product?
Key Post Market Information

• Recall [21CFR 7]

• Complaints → FDA, firm, MedWatch

• Field Alert Reports and Biological Product Deviation Reports
  • NDA and ANDA holders are responsible for filing FARs [21CFR314.81(b)(1)]
  • BLA holders are responsible for filing BPDRs [21CFR601.12]

• Rejects
Investigators look for data integrity issues

- Not recording activities contemporaneously
- Fabricating data to create acceptable test results or copying existing data as new data
- Discarding data or re-running samples without appropriate documentation
- Data looks to good to be true
- Failing stability studies not submitted in the filing
- No raw data (i.e. sample weights, standard prep, sample solution prep)
Documentation of inspectional findings

Inspection findings that demonstrate that a firm is not operating in a state of control may be used as evidence for taking appropriate advisory, administrative and/or judicial actions.

Examples of Evidence:

- Direct observation of CGMP deviations
- Procedures
  - Observe not following or lack of a written procedure
- Verbal communications
  - Admission that a violation occurred
- Written records and documents
- Investigator’s regulatory notes
  - Written record created during inspection
Regulatory Notes

• Are the contemporaneous, sequential record of daily investigatory efforts

• They record observations relevant to violations

• They document positive findings and corrective actions

• Should be accurate, objective, factual and free of personal feelings or conclusions

• Are the property of the government and are releasable under the Freedom Of Information Act

• Are used to refresh the investigator’s memory when reporting certain important details of the inspection and serves as the basis for reports
The FDA inspection ends…

- Formal Close Out
- May include:
  - Sample Collections
  - Affidavits (domestic)
  - Issuance of FDA 483, Inspectional Observations
The FDA inspection ends...

- Inspections are generally classified into one of three categories
  - NAI-No Action Indicated
  - VAI-Voluntary Action Indicated
  - OAI-Official Action Indicated

- Initial outcome:
  - PAI: Investigator informs firm management at the conclusion of the inspection of his/her initial recommendation
  - Post-Approval: Investigator will not provide recommendation at the conclusion of inspection
  - Expect a copy of FDA inspection report
Back at the FDA office investigators…

- Write the Establishment Inspection Report
  - Must be done in a timely manner
  - Incorporate all inspectional findings from each team member

- Communicate with District personnel
  - Investigations Branch
  - Compliance Branch

- Communicate with laboratory
  - Prepare sample collection reports

- Submit District recommendation
GMP Findings

• FMD-86 Establishment Inspection Report Conclusions and Decisions
  • Voluntary Action
  • Advisory Action (i.e. Warning Letter, Untitled Letter)
  • Legal Sanctions (i.e. seizure, injunction, prosecution)


• Positive behaviors recognized
Poll Question #3

What would be most difficult in preparing for an FDA inspection?

- Ensuring complete and accurate documentation
- Training all the staff to follow and know the CGMPs and related FDA guidance
- Defining roles and delegating responsibility for specific issues and topics
- Anticipating what FDA is planning to do before they arrive
- No Vote

Broadcast Results
Summary

To ensure a successful FDA inspection:

• Know and comply with FDA regulations and policies
• Ensure an effective quality system.
• Say what you do, and do what you say… have written SOPs and train your staff to follow them
• Ask the investigator for clarification if you don’t understand or agree with an observation
• Be proactive and have a good attitude
• Display a willingness to correct problems…but don’t promise to make a correction if you don’t agree or are not positive you will be able to follow through

…and be prepared for the FDA inspection!!!
Take Home Message

Be Prepared For the FDA Inspection

• Assure you and your staff are following and know the cGMP regulations and related FDA guidance
• Assure management is aware of significant issues before inspection
• Define roles and have responsible person for issues identified and accountable
• Constantly improve systems and processes

If you are committed to making a high quality drug you will not have a problem!!!
Questions?

Evaluation: surveymonkey.com/r/CGMP-D2S3