How to Successfully Prepare for and Host a Regulatory Inspection

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Agenda

I. The Purpose and Scope of Inspections
II. FDA Inspection Authority in the U.S. and Foreign Inspections
III. Key FDA Inspection References and What You Can Get From Them
IV. Important Site Logistics for Managing Inspections
V. The FDA-483
VI. What Causes FDA to Escalate Enforcement
Purpose of FDA Inspections

• Determine whether or not violations of law exist at the inspected entity

• If so,
  • Obtain voluntary correction if possible, if not…
  • Collect evidence to support FDA regulatory action to force compliance or remove violative products from channels of commerce. Evidence to be obtained includes:
    – Evidence of FDA jurisdiction (usually obvious, not always)
    – Evidence that a violation/violations exist
    – Evidence of corporate and individual (personal) responsibility for violations
    – Evidence to demonstrate that interstate commerce is involved (again usually obvious)

• The evidence collection process is complex and differentiates FDA inspections from company audits and even audits or inspections by other health regulatory authorities

• Inspections may also be used to maintain surveillance of current industry practices and gather information the agency needs in order to properly target its regulatory policies and enforcement efforts.
Scope of FDA Inspections is Set by Law

• The Federal Food, Drug and Cosmetic Act, Chapter 7, Section 704 contains most of the relevant inspection authority – most of it dating to 1953

• Section 704 states in part: “For purposes of enforcement of this chapter, 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, 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 vehicle being used to transport or hold such food, drugs, devices, tobacco products, or cosmetics in interstate commerce; and (B) to inspect, at reasonable times and within reasonable limits and in a reasonable manner, such factory, warehouse, establishment, or vehicle and all pertinent equipment, finished and unfinished materials, containers, and labeling therein…”
Scope of FDA Inspections is Set by Law

- 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, the 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 chapter, or which may not be manufactured, introduced into interstate commerce, or sold, or offered for sale by reason of any provision of this chapter, have been or are being manufactured, processed, packed, transported, or held in any such place, or otherwise bearing on violation of this chapter.

- No inspection authorized by the preceding sentence …shall extend to financial data, sales data other than shipment data, pricing data, personnel data (other than data as to qualification of technical and professional personnel performing functions subject to this chapter), and research data (other than data relating to new drugs, antibiotic drugs, devices, and tobacco products and subject to reporting and inspection under regulations lawfully issued …"
Wait – Do We Really Need to Know All That?

YES!

FDA is under no obligation to inform you what you must do, what the agency is prohibited from doing, and what is optional. It is your responsibility to know your rights, what FDA has the right to do, and what they are not permitted to do.

It’s not like being detained or arrested by the police – there is no practical equivalent of the “Miranda Warning”.

Company SOPs have to be developed and implemented to ensure that the company obeys the law and understands what must be done and what is discretionary. This is not always crystal clear.
Practical Impact

- **Reasonable time** means any time regulated operations are being conducted at the premises, even 2 AM on Christmas Day!

- Reasonable time is NOT determined by the clock or the calendar, but by what is going on on the premises – ANY time regulated activity is going on, FDA may enter and inspect. (Theoretically even 2:00 AM on a legal holiday, if the location is operating.)

- This is supported by case law in several regulatory venues

- **Reasonable limits** generally means FDA must focus on things relevant to its regulatory mission. The law provides for things that are off limits, such as sales data (other than shipping data), personal data about employees (other than their qualifications) and other similar limitations.

- **Reasonable manner** is less well defined, but usually means such things as being accompanied on the premises, registering like any visitor, obeying safety rules, not endangering product quality or interfering with patient care, and so forth.

- FDA has developed policies to comply with all this and rigorously trains its employees to follow the law when conducting inspections
Foreign Inspections

- When operating outside of the US, FDA has no legal inspection authority as it does in the US*

- However, the exact same procedures are followed, with the exception that a Notice of Inspection (FDA-482) is not issued to foreign sites

- FDA may lack direct authority outside the US but does have significant leverage and can still base approval decisions and regulatory action (Warning Letters, import detentions and refusals, approval delays and refusals, product seizures in the US, and so forth) based on foreign inspection findings.

- If a foreign company refuses, delays or obstructs an FDA inspection, the law empowers FDA to find the products from the site where the refusal was made to be adulterated and liable to be proceeded against (refusal of entry into the US or seizure if in US commerce)

* In this context, “In the US” includes the 50 States, the District of Columbia and US Territories such as Puerto Rico, Guam, and American Samoa
Basic FDA Inspection Procedures

- Unannounced inspections: Asking for the most responsible individual at the company (the law specifies the “owner, operator or agent in charge”) - applies mainly to domestic US sites

- Most GCP inspections are an exception and are preannounced, as are foreign inspections (with rare exceptions)

- Credentials shown and the Notice of Inspection (FDA form 482) is issued to US sites (not at foreign sites)

- Observation of facilities, equipment environmental conditions, employee practices, etc.

- Inquiry/interviews with employees

- Contemporaneous note taking

- Document collection

- Development of evidence of individual (personal) responsibility for violations

- Interstate commerce and affidavits

- Sample collection
FDA Web Site Resources

KEY RESOURCES YOU CAN ACCESS AT WWW.FDA.GOV TO HELP WITH YOUR INSPECTION PREPARATION AND MANAGEMENT EFFORTS
Investigations Operations Manual (IOM)

• **What it is:** The FDA Investigator’s “Bible”. Describes general operating procedures for all aspects of the investigator’s job.

• **Where to find it:** [http://www.fda.gov/ICECI/Inspections/IOM/default.htm](http://www.fda.gov/ICECI/Inspections/IOM/default.htm)

• **How to use it:** Assistance in preparing for FDA inspections and understanding inspection related policies and operational instructions

• **Key Sections:**
  - Chapter 2, Regulatory
  - Chapter 5, Establishment Inspection
  - Chapter 7, Recall Activities
Compliance Program Guidance Manual (CPGM)

• **What it is:** A series of programmatic “SOPs” that describe the process for conducting different types of inspections and sampling programs, and deciding what course of action to take when violations are found

• **Where to find it:**
  [http://www.fda.gov/iceci/compliancemanuals/complianceprogrammanual/default.htm](http://www.fda.gov/iceci/compliancemanuals/complianceprogrammanual/default.htm)

• **How to use it:** Key to preparing for FDA inspections. In all CPGMs, see especially “Part III – Inspectional” and “Part V – Regulatory/Administrative Strategy” sections

• **Key Programs (there are several others also):**
  - CPGM 7356.002, Drug Manufacturing Inspections
  - CPGM 7346.832, Pre-Approval Inspections
  - CPGM 7348.810, Sponsors, Monitors and CROs
  - CPGM 7348.811, Clinical Investigators (site level inspections)
Compliance Policy Guides (CPG)

• **What it is:** An internal FDA document (or collection of documents) that describes precedents for FDA decision making in several key areas

• **Where to find it:**
  [http://www.fda.gov/iceci/compliancemanuals/compliancepolicyguidancemanual/default.htm](http://www.fda.gov/iceci/compliancemanuals/compliancepolicyguidancemanual/default.htm)

• **How to use it:** Help understand FDA position on common issues that arise and require consistent regulatory response by FDA

• **Key Sections:**
  • CPG Sec. 130.300 FDA Access to Results of Quality Assurance Program Audits and Inspections
  • CPG Sec. 490.100 Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval
Regulatory Procedures Manual (RPM)

• **What it is:** The District Office Compliance Officer’s “Bible”. Describes the standards and processes by which all FDA regulatory actions come about

• **Where to find it:**  
  [http://www.fda.gov/iceci/compliancemanuals/regulatoryproceduresmanual/default.htm](http://www.fda.gov/iceci/compliancemanuals/regulatoryproceduresmanual/default.htm)

• **How to use it:** Gain a better understanding of the FDA regulatory action process and how decisions are made (such as around Warning Letters, product seizures and consent decrees of injunction)

• **Key Sections:**
  - Chapter 2, FDAAuthority
  - Chapter 4, Advisory Actions (includes Warning Letters)
  - Chapter 6, Judicial Actions (seizures, injunctions, prosecutions)
Field Management Directives (FMD)

• **What it is:** Guidance to FDA Field Offices about several areas of District Office management

• **Where to find it:** [http://www.fda.gov/iceci/inspections/fieldmanagementdirectives/default.htm](http://www.fda.gov/iceci/inspections/fieldmanagementdirectives/default.htm)

• **How to use it:** Help understand how FDA makes decisions about inspection report classification and miscellaneous other issues

• **Key Sections:**
  - FMD 13A, Foreign Inspection Program
  - FMD 86, Establishment Inspection Report Conclusions and Decisions
  - FMD 120, FDA-483, Inspectional Observations
Site Logistics

MANAGING THE INSPECTION
EFFECTIVE COMMUNICATION TECHNIQUES
Usual Sequence of Events

• Arrival – whether announced or unannounced

• Introductory discussion and issuance of FDA-482 (Notice of Inspection*)

• Next – often but not always – general facility tour

• Conduct of the inspection in accordance with guidance documents and assignment memorandum (if any)

• Collection of samples (sometimes) and issuance of the FDA-484 (Receipt for Samples)

• Preparation and issuance of the FDA-483

*A Notice of Inspection is only issued within the US and territories such as Puerto Rico, not at foreign locations
FDA Inspection Procedures And Techniques Common To All Inspections

- Observation
- Inquiry
- Contemporaneous notes
- Individual responsibility
- Some controversial issues include:
  - Photography
  - Affidavits
  - Requests for information outside scope of FDA authority
Notice of Inspection, FDA-482

• Required under Section 704(a) of the FD&C Act (but only used domestically, not foreign)

• Cites sections of the law that give the FDA authority to inspect

• Per law, must be given to the “owner, operator or agent in charge”

• FDA will attempt to see the highest level official who will see them, but will accept anyone the company delegates authority to receive the 482

• FDA personnel must present their credentials at the time the 482 is issued

• The only thing you need to do with the 482 is file it
FDA Investigator’s Preliminary Questions

• Who is in overall charge?

• Names, duties of key staff

• Activities conducted at the inspected location

• Location of files, data

• General logistics for inspection
What to Ask the FDA Investigator

• Purpose of the inspection
  • General or “directed” (for cause) inspection?

• Who from FDA will participate?

• Scope of the inspection (products, areas to be covered)?

• Expected duration of inspection?

• Any special records needed?

• Request daily debriefing on issues
What to **Tell** the FDA Investigator

- Company policy regarding:
  - Hours of operation
  - Security issues and procedures
  - Special risks or hazards in facility
  - Procedure for restricted area access
  - Appropriate attire
  - Photography policy
  - Requests for records
  - Requests for interviews
Key Company Roles During the Inspection

- First point of contact (receptionist, security guard, etc.)
- Senior Management
- Primary Inspection Host
- Scribe
- Runners
- Ready room support
- Subject matter experts
- Other employees
- Legal counsel or consultant retained to assist with the process
Problems And Pitfalls To Avoid

• Thinking you are in charge of what happens (you aren’t; FDA is)

• Using “Secret” signals, codes, hand gestures, etc designed to control people’s answers

• Shifting blame:
  • “We’ve been inspected before and no one ever mentioned this issue”
  • “Everyone in the industry does it this way”

• Complaining about the government, taxes, or FDA procedures

• Asking personal questions of FDA personnel
Dos and Don’ts

• **DO** Know your job responsibilities (job description, SOPs, contract, protocol, etc.)

• **DO** Review pertinent documentation, if possible

• **DO** Ensure you understand the questions;
  - Listen carefully to the question
  - Ask for clarification if necessary

• **DO** Answer ONLY the question that is asked

• **DON’T** volunteer information (except when pre-agreed upon)

• **DO** Answer truthfully and completely, within the scope of the question
Dos and Don’ts

• DO ONLY answer questions related to your duties
• DO Guide FDA to the right person if it is not you
• DO Refer to documentation (SOPs, etc) if needed
• DO Avoid “hallway talk”
• DO Be polite, non-defensive, non-argumentative
• DO Correct any erroneous information provided
• DO Follow company policy regarding FDA affidavits
• DO Ask for help if you need it
• DO Stay within the scope of your direct, personal knowledge
Dos and Don’ts

• Don’t leave sensitive documents in plain sight

• Don’t be offended if FDA “checks out” your answers

• Don’t directly provide copies of any documents
  • go through escort / inspection manager

• Don’t respond to questions unless escort / inspection manager is present

• Don’t offer anything of substantial monetary value (meals, gifts, etc.)
  • coffee, tea, water, etc are OK however
Refusing, Delaying or Obstructing FDA Inspection

• NEVER refuse without knowledge and advice of counsel

• Prohibited act - criminal violation

• Recent Change: Under FDASIA law passed July 6, 2012, refusal can cause your products to be deemed adulterated, subject to legal action

• Warrants
  • Administrative inspection warrant
  • Search warrant

• FDA procedure for refusals & response to stalling tactics
Avoiding Refusals

• If you are asked by an FDA Investigator “Are you refusing me…?” you should respond as follows:

• “No, I am not refusing you [whatever] but before I comply with your request I need to follow our company policy which requires me to consult with our legal counsel and senior management. Please be patient while I do this.”

• Immediately involve legal counsel whenever the question of a refusal is raised by FDA personnel
Daily Wrap Up Meetings

• The Investigations Operations Manual (IOM) now requires the Investigator to accommodate requests for daily wrap up

• Keep meetings short, to the point

• Make corrections to issues if possible

• Keep careful records, follow through on concerns expressed

• Meet as a company after FDA departs and debrief from the day; plan next day
ANSWERING INTERVIEW QUESTIONS
Interviews During FDA Inspections

- An inspection is primarily a fact-gathering activity
- FDA is interested in getting the facts right
- Truthfulness is critical. It is a Federal crime to lie to the FDA during an inspection
Interviews During FDA Inspections

• FDA will usually want to interview the person(s) with the best first hand knowledge of the matter of interest, not necessarily your top subject matter expert, Director, VP or even your CEO

• If you are the one who was directly involved and has first hand personal knowledge of the issues, then you are the one FDA will want to interview – in fact, you are the one they should want to interview!
General Rules For Answering Questions During Inspections

1. Be sure you understand the question correctly. Ask for clarification if you do not.

2. ALWAYS be honest and truthful.

3. DO NOT guess at what you think the answer is or should be.

4. If you do not know the answer, or are not sure, say so.

5. If referring to an SOP will help you answer, that is ok.

6. Answer only what you are asked about. Do not provide information that is not asked for by the FDA Investigator.

7. STOP when you have finished providing your answer.

8. Wait for the next question.
Kinds of Questions and How to Answer Each

• **Direct Questions:**

  • Example: “What is this?”

  • Example: “Do you have an SOP for that activity?”

  • Example: “Is this your signature?”

  • These are easy to answer, many can be answered yes or no.
Kinds of Questions and How to Answer Each

• **Leading Questions**

  • Example: “Why didn’t you clean this equipment before use?”

  • Example: “What is your procedure for using raw materials before they are released by QA?”

  • These questions are based on assumptions that may or may not be correct.

  • If the assumption is **not correct**, challenge the question.

  • If the assumption is **correct**, answer the same as a direct question – just the facts.
Kinds of Questions and How to Answer Each

- **Hypothetical Questions**
  - Example: “What would you do if there was a power failure?”
  - Hypothetical questions present some event or situation and ask how you would respond if it happened.

- If there is an established procedure (SOP) for the event, refer to that.
- If not, **do not guess** how you would handle it. Say you are not sure but it would be up to management and QA to decide how to proceed.
Kinds of Questions and How to Answer Each

- **Open-Ended Questions**
  - Example: “Can you tell me some more about that?”
  - Example: “What happened next?”
  - Example: “What is your opinion about that?”
  - Ask the questioner to be more specific, or
  - Answer with one additional fact or detail, then stop and wait to be asked for more.
Kinds of Questions and How to Answer Each

- **Challenging or Confrontational Questions:**
  
  Every area or operation has some problems. If FDA finds one of your problems, you may be asked a challenging question.

  - **Example:** “Why hasn’t this been fixed?”
  
  - **Example:** “Do you think it is ok to use this equipment in this condition?”
  
  - **Example:** “Why didn’t you examine your retain samples as part of this investigation?”
Kinds of Questions and How to Answer Each

- **Challenging or Confrontational Questions:**
  
  - If possible (and if true), explain these issues by saying “Yes, we understand. Here is our justification (or, here is what we are doing about that…”
  
  - If you were not aware of the problem, say “I was not aware of this. We will look into it right away and respond to you with our assessment (later, tomorrow, or at some near future date)
FDA INSPECTION FINDINGS

• The FDA-483, The Exit Discussion, and Post-Inspection Correspondence
The FDA-483

- List of factual observations
- Significant, product-related
- Worst first
- Quality system format
- “Turbo EIR”
The FDA-483

• Legal basis of the 483 – Section 704(a) FDCA

• The 483 is supposed to be objective, factual, legible and significant, and generally, listed “worst first” (within applicable systems)

• **Significance** is dependent upon a number of factors, including, but not limited to:
  • **Context** in which the observation occurred
  • **How frequently** the observation occurred
  • **How long ago** the observation last occurred
  • The **impact** (or lack thereof) on **product quality**
  • The **health hazard** posed by the observation
  • Whether the **risk** posed by the observation is theoretical or actual
How 483 Item Significance Is Determined

• Relationship to product quality, patient safety, clinical performance of the product

• Impact: Extensive or isolated

• Health hazard aspects

• Frequency of occurrence ("pattern")

• How recently something happened

• Did review system detect the problem?

• Investigated? Conclusions & follow up?
The Exit Discussion

• Have the “right people” present

• Agree on discussion strategy

• Control the environment

• Do not make commitments you cannot keep; keep time lines reasonable

• Present any disagreement calmly, logically, back up with facts
The Exit Discussion

• **Simple four-step strategy:**
  • Step 1: Verify that the 483 is factually correct
  • Step 2: Ensure that the wording is not misleading
  • Step 3: Understand FDA’s reason for each citation
  • Step 4: Request deletion of item(s) you believe are improperly cited, and provide your rationale; back up with documentation
The Written 483 Response

• In the *Federal Register* of August 11, 2009 FDA posted a new policy regarding timeliness of the written response to a 483.

• Key point:

  • If you want your response to be considered by FDA as part of their overall decision whether to issue a Warning Letter, you **must** get your written response to the agency within 15 business days.

• The law does not require that you respond to a 483 at all, either orally or in writing. But **everyone** does, almost without exception, and if you do not, it will be seen as very anomalous and quite negative.
The Written 483 Response

An effective outline for response to each item...

1. In response to this observation, we are taking the following actions: [list what you are doing]

2. We believe this approach is reasonable because [state]:
   a) Your assessment of the reason(s) why the observation occurred; “root cause”
   b) Your assessment of the impact on product quality
   c) Your assessment of the scope of impact (other batches, other products) and how you determined the scope

3. We will complete these actions by [date]

4. We will take the following steps to ensure these actions had the intended effect [list; generally, this will be audit or monitoring]
Enforcement Options

• For FDA inspections within the Untied States, there are many options. The most common are:

• Advisory Actions:
  • FDA-483
  • Warning Letter
  • “Regulatory Meeting”

• Administrative Actions:
  • Withhold or deny approval of submission (NDA, ANDA, BLA, etc)
  • …continued…
Enforcement Options

• Administrative Actions (continued)
  • Suspend or revoke biologics license (biologics only)
  • Exclude clinical data from consideration
  • Disqualify a clinical investigator
  • Application Integrity Policy
  • Others
Enforcement Options

• Judicial actions: Civil and criminal

  • Civil actions:

    - Seizure of products
    - Injunctions

  Either can be resolved via a “consent decree”; sometimes both seizure and injunction in the same decree

• Criminal prosecution

  • Under the Food, Drug and Cosmetic Act
  • Under other statutes

• Exclusion from Federal procurement – a side effect of prosecution

  • The Department of Health and Human Services, Office of Inspector General (OIG) has the authority to exclude individuals and entities from Federally funded health care programs and maintains the List of Excluded Individuals and Entities (LEIE). Anyone who hires an individual or entity on the LEIE may be subject to civil monetary penalties.

  • Companies and individuals convicted of FDCA violations may face exclusion, which could be devastating to the company and to effected individuals.
Consent Decrees

• A *consent decree* is actually a negotiated settlement of a civil action, either a product seizure or an injunction

• An *injunction* is a lawsuit by FDA against a company seeking a court order that forces the company to comply. Injunctions are ordinarily resolved via consent decrees, and when you hear the term “consent decree” this is usually what it is referring to.

• What happens under a consent decree
Summary

• **A regulatory inspection is a predictable, and to an extent, controllable event if you:**

  • Know your rights (and the regulator’s) under the law
  • Understand the agency’s inspection procedures
  • Plan and document your procedure in advance, anticipating what is likely to occur
  • Train your staff so they understand the process and know what is expected of them
  • Provide adequate space, comfort and support to the inspection team and your personnel for the duration of the inspection
  • Communicate clearly and thoroughly, sticking to the facts and the data
  • Respond promptly and effectively to observations, following through to make sure your actions worked as intended