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Guess Who's Knocking at Your Door: Assuring Inspection Success!

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Steven Niedelman

- Currently Lead Quality Systems and Compliance Consultant to the FDA & Life Sciences practice team at King & Spalding
- Retired from the Food and Drug Administration in 2006 after a 34-year distinguished career
- Deputy Associate Commissioner for Regulatory Affairs
- Chief Operating Officer of the Office of Regulatory affairs
    - Served as the principal liaison to the Center for Devices and Radiological Health
    - Was a member of: The Global Harmonization Task Force (GHTF) Steering Committee, FDA/Medical Device Industry Grassroots Initiative Steering Committee, and CDRH Post Market Initiative Steering Committee
- Director and Deputy Director of FDA's Office of Enforcement
- Various management positions throughout the Office of Compliance at the Center for Devices and Radiological Health (CDRH)
- He began his FDA career in 1972 as an Investigator in FDA's New York District Office.

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Today's Agenda

Overview of FDA's Inspection Program

FDA's Authority to Inspect

What to Expect During an Inspection

The "Do's and Don'ts" During an Inspection

Overview of FDA's Inspection Program

FDA and its Inspections

- FDA is a public health, law enforcement agency whose mission is bringing safe and effective products to market as quickly as possible while assuring they are manufactured, sold and labeled correctly.
- FDA inspections assess the firm's conformance with FDA regulations by:
  - examining the company's written policies and procedures
  - observing resulting outputs the policies and procedures require (such as…following a procedure, documenting a record, maintaining a file, or testing product etc.)

The Purpose of an FDA Inspection

A careful, critical, official examination of a facility to determine its *compliance with laws*.

Inspections may be used to *obtain evidence* to support *legal actions* when violations are found.

(Source: FDA Investigations Operations Manual)

FDA Authority

- Upon presentation of credentials and Notice of Inspection (FDA-482) - FDA has authority to:
  - Conduct inspections without an inspection warrant.
  - Inspect, *at reasonable times* (this would include any time the facility is in operation), and *within reasonable limits*, *and in a reasonable manner* any factory, warehouse, or establishment in which devices are manufactured, processed, packed, or held for introduction into interstate commerce or after introduction into interstate commerce
  - Issue a List of Observations (FDA-483) if needed at the conclusion of the inspection

Note: the term 'reasonable' is not defined by FDA

Types of Inspections

- Current Good Manufacturing Practices (cGMP)/Quality Systems Inspections
  - Check conformance with cGMP/Quality Systems
    - FDA inspections are a “snapshot in time” based upon what was observed
      - You are responsible for, and are expected to be in full compliance with all applicable portions
- Pre-Approval Inspections: NDA’s, PMA’s, Licensing
  - Bioresearch Monitoring (“BIMO”)
- “For Cause” Inspections
  - Adverse Event (AE)/MDR
  - Recalls
  - Customer and Trade Complaints
  - Whistleblower Reports
- BIMO Inspections

FDA and its Inspections

- FDA inspections and investigations focus on multiple themes:
  - Sterility Assurance
  - Avoidance of chemical or microbial cross-contamination
  - Process Validation
  - Documentation Practices: Application Integrity Policy
  - Investigation of Nonconformances (Complaints, Deviations, Incidents, Product Returns)
  - Corrective and Preventive Action ("CAPA")
  - Required Reporting (MDR, Adverse Events, Recalls, Field Alerts, Corrections and Removals, among others…)

FDA's View on Basic Quality Assurance Principles

- Quality, safety and effectiveness must be designed and built into the product
- Quality cannot be inspected or tested into the finished product
- Each step of the manufacturing process must be controlled to maximize probability that the finished product meets all quality and design specifications

FDA's View of cGMPs/QSR Inspection

- FDA will focus on how the product is manufactured.
  - *Actual quality of the finished product is relatively unimportant in terms of QSR compliance!*
- If a product is not manufactured in compliance with cGMPs/QSR, it is deemed adulterated and subject to regulatory action *(even if it meets specifications and is safe and effective).*

FDA’s Authority to Inspect

FDA's Inspection Authority

- Consent is not the basis on which an FDA inspection is conducted.
- Permission or authorization by the company to inspect is not required
  - Refusal to permit an inspection is in violation of the FD & C Act, subjects the company and the responsible person to penalties
  - FDA can obtain an inspection warrant, if needed
    - May seek a search warrant if fraudulent activity is suspected

FDA's Inspection Authority

- Section 704(a) of the Federal Food, Drug, and Cosmetic Act ("FDC Act") grants FDA the broad authority to enter and inspect regulated facilities:
  - Inspections must be conducted at reasonable times,
  - within reasonable limits, and
  - in a reasonable manner.

    NOTE: FDA broadly interprets "reasonable" as it is undefined!
- Section 704(e) authorizes FDA to inspect and/or copy records, reports, files, papers, processes, controls, and facilities pertaining to:
  - Adverse Event reports

Factors That May Increase Likelihood/Frequency of Inspection

- Risk Based Approach:
  - Prior inspectional history (Establishment Inspection Reports)
  - Newly registered facility (baseline inspection)
  - History of failure to fulfill promised corrections
  - Follow-up to significant FDA-483s (List of Observations)
  - Follow up to Warning Letters
  - Sudden changes to AE/MDR reporting
  - Ongoing or increasing number of Recalls, esp. Class I
  - Pending NDA submission
  - Recidivism (repeat violations)
  - Level of Risk of Products Involved
  - Challenging or novel manufacturing processes

Statutory Requirements:

- A (drug or) device shall be deemed adulterated - [21 U.S.C. 352]
  - [(h)]: If it is a device and the methods used in, or the facilities or the controls used for, *its manufacture, packing, storage, or installation are not in conformity with applicable requirements under Section 520(f)(1)* or an applicable condition prescribed by any order under Section 520(f)(2)
- The following acts and the causing thereof are hereby prohibited: [21 U.S.C. 331]
  - [(a)]: The introduction or delivery for introduction into interstate commerce of any food, drug, device, cosmetic or tobacco product that is adulterated or misbranded

Scope of FDA's Inspection Authority

- FDA has the authority to inspect the following:
  - Facilities used to design, manufacture, or distribute FDA-regulated products
  - Vehicles used to hold or transport pharmaceuticals
  - Raw materials and components
  - Pertinent equipment
  - Finished and unfinished pharmaceuticals
  - Containers used to manufacture, store, or distribute pharmaceuticals
  - Labeling (including promotional materials)
  - Records showing the movement of raw materials, components, and finished devices in interstate commerce
  - All records relating to Adverse Event Reports ("AEs") and recalls; and
  - All records required by the cGMP, including Drug Master Files, Batch records, Product Reviews, and Complaint Files.

Scope of FDA's Inspection Authority

FDA does *not* have the authority to inspect:

- Financial data
- Sales data (other than shipping data)
- Pricing information
- Information regarding personnel (other than information regarding the qualifications of technical and professional personnel performing functions subject to FDA regulation)
- Reports or records resulting from internal audits, management reviews, and supplier audits.
  - *However,* FDA does have the authority to examine written procedures established for
    - internal audits
    - management reviews,
    - supplier audits, *and*
    - written certification that these activities have been performed and documented and any required corrective action and preventive action (CA/PA) has been undertaken. (See 21 CFR § 820.180(c))

What to Expect During an Inspection

FDA Inspections - What must **FDA** do?

- Upon initial arrival for an inspection, FDA must show credentials and issue a form FDA-482 "Notice of Inspection" to the "to the owner, operator, or agent in charge"
- Provide a form FDA-484 Receipt for Samples, for any samples collected
- On completion of an inspection, FDA may provide to the owner, operator, or agent in charge an FDA-483 "List of Observations"
- Attempt to obtain a signed affidavit to document distribution of a specific products(s) and/or interstate commerce to establish jurisdiction
  - It is *not* recommended that they be signed, read or listened to

FDA Inspections – What Must **You** Do

Front Room

Where FDA Investigators spend most of their time

Where you will be if you are called to speak to an FDA Investigator

What's going on in there?

- FDA Investigators are asking questions and reviewing documents
- Designated staff and SMEs are responding to FDA requests and managing the flow and atmosphere of the conversation
- Someone from the firm is taking notes
- Someone from the firm is sending requests for documents or people to the back room
- Someone is tracking receipt of requested documents
- There is paper everywhere

Back Room

Where staff responds to requests from the front room (people or documents)

Where you will go first if you are called to speak to an FDA Investigator

What's going on in there?

- Screens show notes, chats, requests, etc.
- Documents are being pulled, copied, and reviewed in response to requests
- Document requests are being time-tracked upon receipt and fulfillment
- SMEs are being prepared to be in the front room
- Runners are in and out like lightning
- Always several ongoing requests and things being addressed at once

Ensure adequate office supplies are available

Color code multiple audit streams and maintain copy of everything provided

What Can You Do To Prepare?

- Develop audit procedures and conduct mock audits to ensure everyone knows their role and is “audit ready” at all times!
- Ensure current tables of organization are up-to-date
- Have an up-to-date opening presentation
- Know scope of inspection (if pre-announced)
- Have copies of all procedures available for review
- Understand the profile of an FDA Investigator
- Listen carefully to questions
- Respond only to those questions within your knowledge and responsibility
- Follow company procedures

Investigator techniques

"Different Strokes for Different Folks!"

Every investigator is an individual – and each has his/her own way of conducting inspections!

- Slow, methodical
- "Columbo" like
- Rapid fire

- No matter what style, *all* investigators share the same goal of determining compliance with the laws and regulations – and are expected to be professional and courteous at all times!
- Anticipate same or similar questions to be asked several ways to determine commitment to and accuracy of an earlier responses
- Expects some questioning to appear circular – it is to confuse you
- Don't be lured into a false sense of friendship – and share info you should not!

FDA Inspections - What will **FDA** do?

- FDA asks questions –
  - Often probing
  - Some obvious
  - Often the same question several ways or to several people to see if they get a consistent response.
- FDA requests and reviews documents: "all things therein (including records, files, papers, processes, controls, and facilities)"
  - Receipt and testing of materials
  - Production records
  - Testing records
  - Equipment and maintenance records
  - Procedures
  - Many others

FDA Inspections - What will **FDA** do? (cont'd)

Observe ongoing operations during tours and "walk-throughs"

- May verify documentation by revisiting operation

Compare:

- answers to documents
- answers to answers
- documents to documents
- answers and documents to what they observe
- answers, documents, and observations to previous submissions, past commitments and firm responses

Interview personnel

FDA Inspections - What Can You Expect?

Do Investigators provide any feedback?

- Most investigators are fairly open, and will discuss concerns and issues as they are identified
- Most investigators conduct daily wrap-up meetings:
  - unfinished and open issues
  - "issues of concern" that may be possible FDA-483 items
  - definite FDA-483 observations
- These discussions provide an opportunity to identify issues for which it may be beneficial to provide additional information/explanation, or implement immediate corrections
  - If possible, Investigators may verify correction were made

Closeout Meeting with Management

- List of Observations are typically presented at the conclusion of the inspection at a closeout meeting
  - Those in attendance should include
    - Investigators involved in the inspection
    - Most responsible individual at the firm
    - A cross functional team from the firm to address questions that may arise
- This meeting provides the opportunity to question or clarify findings and understand the investigators concerns
- Findings that are incorrect or in error should be discussed with the investigator for correction/deletion
- Device firms have opportunity annotate findings
  - Promise to correct - Corrected, not verified
  - Corrected and verified - Under consideration

FDA Inspections - What Can We Expect?

Does everything go on an FDA-483?

- NO!
  - Limited to what is required by law, and deviations from certain regulations
  - There are many topics that do not go on FDA-483s, such as labeling violations, Registration and Listing, generally product approval issues, significance of AEs, etc.
    - *unless, the investigator had discussions with the Center and a decision was made the finding was supportable and to include the finding*

Company Response to FDA-483

- Firms must respond within fifteen working days for response to be considered by FDA. May request an extension in certain situations
- Response should address systemic issues as well as specific findings identified on the FDA 483, provide substantive description of actions taken and planned, establish timeframe for promised actions with milestones, and provide objective evidence of corrections made
- Corrective actions and preventive actions (CA/PA) may be required
- Retrospective reviews may be needed
- Firm should keep FDA apprised of progress of commitments by providing timely updates and providing objective evidence

FDA Reaction to FDA-483 Response

- Assess findings; review for repeat observations
- Assess adequacy of timely response
  - Provide feedback as appropriate
- Will review company's progress
- Monitor progress of CA/PA through updates
- May choose to re-inspect
- Will classify inspection outcome as OAI, Official Action Indicated, VAI, Voluntary Action Indicated or NAI, No Action Indicated
- If response is inadequate, further action may be taken
  - Warning Letter - Recidivist Warning Letter
  - Regulatory Meeting - Seizure
  - Injunction - Prosecution
  - Import Alert
  - Detention without physical examination

The “Do’s and Don’ts” During an Inspection

Appropriate Interview Behavior

Do:

- Be courteous, respectful and non-confrontational
- Develop trust
- Be objective and factual
- Demonstrate a willingness to listen – understand FDA's concern(s)
- Remember the investigator's goal: evidence gathering
- Exercise care in promising corrections
- Resist "informal" casual discussions

Appropriate Interview Behavior

Do:

- Listen to the question
- Seek clarification if necessary
- If you do not know, say, “I do not know,” and offer to seek the answer
- Answer questions concisely, directly and honestly
- Answer “yes” or “no” to “yes” or “no” questions
- Stop talking when you have answered the question

Inappropriate Interview Behavior

Do not:

- Use firm's jargon or acronyms – may contribute to confusion
- Comment on the quality of the inspection
- Answer questions you don't know the answer to
- Argue amongst yourselves
  - Seek a 'caucus' break if necessary to iron out differences
- Convey arrogance or impatience
- Make "off the record" statements
  - *Remember – Nothing is off the record!*

Inappropriate Interview Behavior

Do Not:

- Be intimidated by “pregnant pauses”
- Be dismissive of FDA’s concerns
- Make admissions
- Volunteer information not requested

Conclusions

- Inspections are useful compliance mechanisms of FDA – they serve as the *"Eyes and ears of FDA"*
- Inspections are detailed and comprehensive and provide a "snapshot in time" of what the current ongoing activities are taking place at a firm.
  - They are not intended to be used as the tool by industry to measure compliance.
- Can impact a firm's ability to get products approved, Certificates for Foreign Governments issued, and government contracts cleared.
- Noncompliance with the regulations has serious implications

Questions?

Thank You!