U.S. FOOD & DRUG ADMINISTRATION

FDA Drug Manufacturing Inspections

Russell K. Riley
Compliance Officer
Office of Pharmaceutical Quality Operations, Div. III
ORA | US FDA

REdI 2020 – August 26, 2020

Learning Objectives

- Learn about the purposes, conduct, and expectations of FDA drug manufacturing inspections
- Learn how to prepare for, host, and respond to FDA drug manufacturing inspections
- Learn about the potential consequences of FDA inspections

Scope

- The term “manufacturing” includes:
  - Production, packaging, labeling, storage, receiving, shipping
  - Testing and material handling at all stages
  - Quality oversight at all stages
- Drugs intended for commercial distribution, clinical trial use, or the preparation for such
- Mainly finished drug products and active ingredients, but can include inactive ingredients and container/closures too

Purposes

- Broadly, to evaluate the controls in place to assure drug quality and prevent violations (CGMPs, application commitments)
- Can be:
  - Surveillance, pre-approval, post-approval, compliance follow-up
  - In response to recalls, complaints, adverse events, samples, etc.
  - Comprehensive or limited, but rarely covers every area

Conduct

- Observation of operations
- Record review and collection
- Employee interviews
- Field exams
- Sample collection, environmental swabbing
- Photography and videography

Conduct

- All operations, records, employees, etc. within scope of CGMPs and applications are within scope of inspection
- The direction of the inspection is driven by the Investigator(s)
- Will begin with the Investigator(s) issuing FDA Form 482 (domestic only) and showing Federal credentials
- May end with issuance of FDA Form 483

Conduct

- Investigators will look at what has been done (e.g. batch records) and how (e.g. procedures)…
- But also the scientific justification:
  - Why do you do it the way you do?
  - What evidence do you have to show adequacy?
  - How do you continually verify adequacy?

Conduct

- Usually unannounced, but there can be exceptions
- Length can vary depending on focus, findings, and evasiveness of the firm
- False statements and falsified records can be federal crimes

FDA Expectations

- Timely, open access to all operations, records, and employees within scope
  - Definition of operations
  - Definition of records
- Answer questions truthfully
- Assure safety of Investigator(s)

Firm Expectations

- Inspections occur at reasonable times and in a reasonable manner
  - Any time the firm is in operation
  - Investigator(s) cannot make firm conduct operations
- The Investigator(s) should state the purpose of the inspection and should discuss findings on a daily basis
- Financial and private personnel info is off-limits

Preparation

- Understand who knows each part of the operation the best
- Train employees to answer questions truthfully
  - If they do not understand a question, say so
  - If they do not know the answer, say so
- Be prepared to obtain records and make copies

Hosting

- Designate a primary host/point of contact
  - Coordinates walk-throughs, observing operations
  - Coordinates employee interviews
  - Coordinates requests for records and copies
  - Takes notes, or designates someone to do so

Hosting

- Investigators often have a daily summary of findings at the end or beginning of each day
  - Also may discuss plans for next day
  - Good opportunity to ask questions, provide further information on concerns voiced
  - Useful to have senior management at these

Response

- If violations are found (whether issued an FDA Form 483 or not), firms are encouraged to respond in writing
  - Corrective and preventive actions should seek to be wide-ranging, not limited
  - Evidence of actions taken should be provided
  - If future actions are proposed, give timeline of future updates
- FDA policy: for a response to be considered during the evaluation of a potential action, it should be submitted within 15 business days of the close of the inspection

Inspection classification

- Inspections typically receive one of three classifications:
  - No Action Indicated (NAI): no objectionable conditions or practices were found.
  - Voluntary Action Indicated (VAI): objectionable conditions were found but do not meet the threshold for regulatory action.
  - Official Action Indicated (OAI): objectionable conditions were found and regulatory action is warranted.

FDA Regulatory Actions

- Most inspections do not result in FDA taking action against regulated firms
- Inspections that do result in action are typically based on
  - Significance of findings, threat to public health
  - Inadequacy of firm response
  - History of non-compliance

FDA Regulatory Actions

- Non-judicial actions are most common, including:
  - Regulatory meeting
  - Untitled or Warning Letter (latter is posted online)
  - Withholding approval of applications (pre-approval inspections)
  - Import Alert (foreign facilities)

FDA Regulatory Actions

- Judicial actions, including:
  - Seizure: Judge orders Federal Marshals to take possession of violative products
  - Injunction: Judge orders a firm to take and/or cease activities until specific requirements are met
  - Prosecution: typically reserved for the most egregious cases

Other Inspection Outcomes

- Firms classified OAI may not get applications approved, government contracts
- Recalls
- FDA Press Releases
- Voluntary cessation of production and/or distribution

Challenge Question #1

Drug Manufacturing Inspections don't typically cover:

A. Production

B. Testing

C. Adverse event procedures

D. Quality controls

Challenge Question #2

Regulatory actions stemming from Drug Manufacturing Inspections may not include:

A. Suspending a firm's drug license

B. Seizure of drug products

C. Warning Letter

D. Withholding approval of applications

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Questions?

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Russell.riley@fda.hhs.gov


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