GENERAL OVERVIEW API Inspection Program Applying ICH Q7, Inspectional Outcome

PDA-PIC/S
ICH Q7 Training
Hyderabad/Ahmedabad, India
September 2015

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Objectives

- Brief Introduction and Purpose of API Inspections
- Types of Inspections of Inspections
- Difference between an Inspection and an Internal Audit
- Applying ICH Q7 Principals During and Inspection
- Compliance Outcomes

Legal Bases for CGMP

Section 501(a)(2)(B):

"A *drug*... shall be *deemed* to be *adulterated* if the *methods* used in, or the *facilities* or *controls* used for, its *manufacture*, *processing*, *packing*, or *holding* do not conform to or are not operated or administered in conformity with *current good manufacturing practice* to assure that such drug meets the requirements of this Act as to *safety* and has the *identity* and *strength*, and meets the *quality* and *purity* characteristics, which it *purports* or is *represented* to *possess*."

What is a drug?

The term "**drug**" means[1] …

A) An article ***recognized*** in the US Pharmacopeia (USP) or Homeopathic Pharmacopeia of the US (HPUS) or National Formulary (NF).

B) Articles ***intended*** for use in the ***diagnosis, cure, mitigation, treatment, or prevention*** of disease in man or other animal.

C) Articles *(other than food)* ***intended*** to affect the structure or function of the body of man or other animal.

D) Articles ***intended*** for use as ***a component*** of any article specified in **A, B, or C**.

[1] As defined in section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act

Legal Bases for CGMP

FDASIA 2012 amendment to section 501:

CGMP "includes the implementation of *oversight* and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the *safety of raw materials*, materials used in the manufacturing of drugs, and finished drug products."

Four Major CGMP Inspections

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

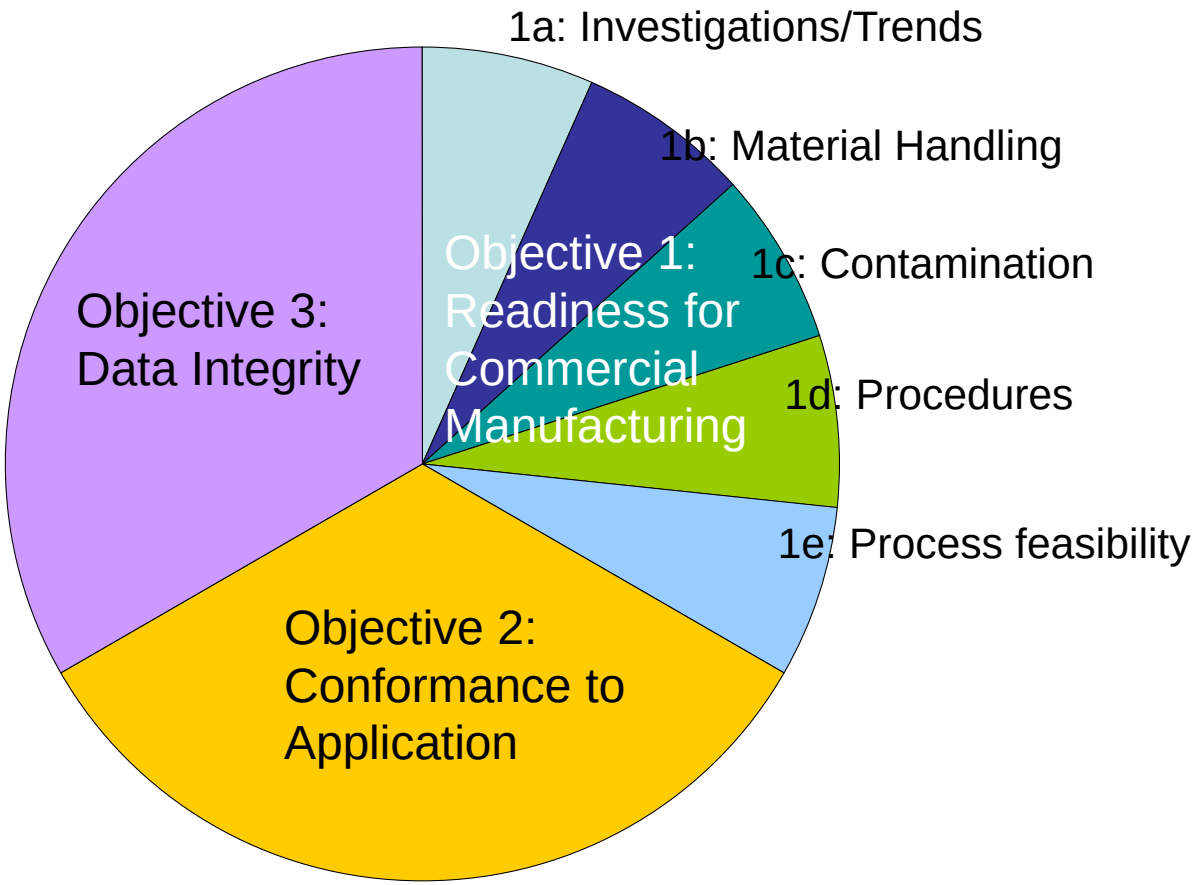
*1-3 have compliance programs and FDA's procedures are available on the web

**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

Pre-Approval Inspection Program (7346.832)

A pre-approval inspection (PAI) is performed to assure 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)



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…)

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
- Facility and equipment
- Production
- Laboratory
- Materials
- Packaging and Labeling

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
  - Complaint or Recall
  - Adverse event cluster (i.e. heparin)
  - or other "event"
  - Informant
  - Information from other Regulatory Authority
  - Questionable information obtained during the application/DMF review process or agency surveillance review
- 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

Polling Question #2 (pick 1)

What was the reason for your last inspection?

A. Pre-approval inspection; your firm was named in the CMC section of A/NDA or BLA
B. Post-approval inspection
C. Surveillance inspection
D. For-cause; i.e. your firm had a recall or submitted an increased number FARs to the FDA recently
E. Not sure
F. Have not been inspected by the FDA, yet!

"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

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)

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

Applying ICH Q7

- The ICH Q7 document is not an FDA regulation

- We inspect API manufacturers against the ICH Q7 Guidance Document, but we enforce the Food Drug and Cosmetic Act when we inspect API

But what really happens ….

What Happens During Inspections

- Verify the commitment made (what did the firm say they would do?)
- What did the company do?
- When did you do it?
- Who did it?
- How was it done ?
- What did you do, when things did not go as you had planned or expected?

What Happens During Inspections ?

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

Key GMP Areas

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

Investigators watch the manufacturing process and employee practices

What Happens During Inspections

- Can the firm produce documented evidence of past events?
- Where are documents and who reviewed them?
- 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?

What Happens During Inspections

- Are activities recorded contemporaneously ?
- Is data being fabricating data to create acceptable test results or copying existing data as new data ?
- Is data discarded/disregarded ?
- Is the documentation for samples retested appropriate ?
- Data looks to good to be true!!!!!!
- Failing stability studies or unexpected results not submitted in the filing
- Did the firm investigate the unexpected result?
- No raw data (i.e. sample weights, standard prep, sample solution prep)

Readiness for Commercial Manufacture

The investigative team will determine whether your firm has a quality system that is designed to achieve sufficient control over the facility and commercial manufacturing operations.

- Evaluate overall CGMP compliance
- Evaluate the specific PAI product and process
  - ✓ Is the facility adequate/qualified-building; equipment; water systems?
  - ✓ Is there evidence/data to support the manufacturing process and specifications?
  - ✓ Will review development data for all R&D batches
  - ✓ Will review Product Development Report
- Will review batch records for submission batches (pivotal, qualification and/or biobatches)
- Focus on change control, deviations and trends relating to the development process to determine that there is adequate evaluation

Readiness for Commercial Manufacture

- Will evaluate sampling plans; testing of components and product
- High focus on your supplier qualification program
- Evaluate facility and equipment procedures with a focus on contamination controls
- Evaluate the quality system specifically for batch release, discrepancy management, investigation completeness, complaint and ADE handling.
- Focus on laboratory system (SOPs; Personnel; Training) and stability data
- Evaluate test methods (validated?) and impurity profile

Conformance to Application

The investigators will verify that the formulation, manufacturing and/or processing methods, and analytical methods are consistent with descriptions contained in the CMC section of the application.

As part of the inspection, they will audit records and procedures and the batch records submitted in the application to assure:

That the proposed production process is the same process that was used for the manufacture of the bio/stability batches (and other pivotal clinical batches).

Data Integrity

The investigators will audit the raw data

To authenticate and verify that all relevant data (e.g., stability, biobatch data) were submitted in the CMC section of the application such that CDER product reviewers can rely on the submitted data as complete and accurate.

Data Integrity

- FDA will take action against companies that commit data fraud or provide false information to the agency.

- "Companies must provide truthful and accurate information in their marketing applications…. The American public expects and deserves no less."

Janet Woodcock, M.D., Director, CDER

February 25, 2009 FDA News Release

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

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, prosecut
  - □ Invoke AIP

http://www.fda.gov/downloads/ICECI/Inspections/FieldManagementDirectives/UCM382035.pdf

- Positive behaviors recognized

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!!!

Be Prepared For the Inspection

- Once an application is submitted to the agency, the firm and all facilities mentioned are considered to be ready for inspection.

- Make records readily available during the pre-approval inspection
  - ✓ Development Report
  - ✓ Batch Records
  - ✓ Laboratory Records
  - ✓ Protocols/SOPs

Reactive Compliance

Issues generally identified after major discrepancy or during the FDA inspection

- Issues identified after project completed/batch released
- FDA investigators seen as adversaries
- Inspection involves defending and arguing
- Rely on inspection findings to identify problems…may not address the most non-compliant areas
  - ✓ Snapshot in time
  - ✓ Limited audit time

Proactive Compliance

- Firm is aware of significant issues before inspection; CAPAs in place; if needed
- Senior management is aware of compliance / inspection issues at site so there are no surprises during the inspection
- Sponsor conducts due diligence before they name contractors/suppliers in applications and prepares all sites for PAIs
- Quality and Operations work together to investigate deviations/issues…Responsible person for issues identified and accountable
- Quality and Operations work together to best present significant issues during inspections (identify Subject Matter Experts)

PAI Outcomes

The inspection is one part of the approval process

- Lead investigator will make a recommendation at the conclusion of the inspection.

Recommend Approval

- Indicates that the inspection found no significant issues
- Response to observations is important

Recommend Withholding of Approval

- Investigators observed that the site is not GMP compliant, information in CMC is not consistent with site records, or information submitted is not accurate and complete.
- **Response to observations is critical**

CDER reviewer makes the ultimate decision on whether to approve or withhold.

Primary Reasons for a PAI Withhold

- Pending enforcement action (Warning Letter, Seizure, Injunction)
  - including uncorrected violations (previous deviations persist)
- Site is not ready or withdrawn
  - including drug not made here
- Insufficient development data/ production/ process controls
- Inadequate lab controls
- Inadequate QA functions

Case : Nonconformance to Application

The firm lacks data for the qualification of the proposed container closure system (LDPE bags) to store the finished API ABC. For example, the firm lacks storage stability data. The current stability studies were performed on samples packaged in amber glass bottles. However, the drug substance is packaged in LDPE bags.

Recommendation: Withhold for failure to meet application commitments

Case : Nonconformance to Application

Takeaway

Know your commitments and be prepared for the inspection!!

Case : API Intended Use Issue

Background

Finished Product Manufacturer had >200 Adverse Events for pyrogenic events in parenteral drug product. …with at least two critical outcomes

Investigation found that there was a high endotoxin content in parenteral-grade API used in manufacturing

- ✓ Composite samples did not reveal intra-batch variability in endotoxin.
- ✓ Tested each drum as part of the investigation and found some drums failed for endotoxin limits and some did not.

Warning Letter issued - withhold of applications

Case : API Intended Use Issue

What happened

- API was previously sold for use in tablets
- API manufacturer received customer complaints for failed endotoxin limits for over 2 years. No corrective measures were implemented by API firm.
- Inappropriate water quality was used for processing of active ingredients and cleaning associated equipment

Case 5: API Intended Use Issue

Takeaways:

- Knowing and qualifying your suppliers prevents future problems.
- APIs meeting specifications are not necessarily suited for use in manufacturing your product.
- Limit exposure to supply chain risks by qualifying multiple sources of APIs

Questions?

Acknowledgements

LT. CDR. **Denise DiGuglio**

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