U.S. FOOD & DRUG ADMINISTRATION

The Dos and Don’ts of Pre-Approval Inspections: What to Expect When Being Inspected

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“This presentation reflects the views of the author and should not be construed to represent FDA’s views or policies.”

Learning Objective and Challenge

Learning Objective: To provide useful information to industry regarding the drug pre-approval inspection process

Challenge Question: What is one way your firm can prepare for a *successful* pre-approval inspection?

Agenda

- The Pre-Approval Process
- Inspection – Pre-Approval Inspection Objectives
- Inspection – Preparation (the dos)
- Inspection – Issues to avoid (the don’ts)

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- **The Pre-Approval Process**
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Purpose of a Pre-Approval Inspection

- A pre-approval inspection (PAI) is performed in order to ensure 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 Process

- All sites listed in an application that will perform a commercial function must be evaluated
- Not all sites require an inspection
- There is a system for determining which sites require an inspection based on risk

FORM FDA 356h

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
APPLICATION TO MARKET A NEW OR ABBREVIATED NEW DRUG OR BIOLOGIC FOR HUMAN USE
(Title 21, Code of Federal Regulations, Parts 314 & 601)

28. Establishment Information

Is the site ready for inspection? ☑ Yes ☐ No ☐ N/A

If No, when will site be ready? *(mm/dd/yyyy)* _____

What Triggers a PAI (Old Model)

Examples of PAI trigger criteria:

- First application filed by applicant
- First inspection for the establishment
- New molecular entities
- Substantially different manufacturing process or dosage form than previously covered at the establishment
- Site/product/process changes that are expected to pose a challenge to the state of control of the facility, for example new construction
- First generic to market

New Model - Integrated Quality Assessment (IQA)

Model developed from experience with drug application review process

PAI criteria and related profile/process are used differently

- Not all trigger criteria automatically trigger an inspection
- Risk attributed used for a deeper facility risk evaluation

Final determination for PAI is based on an overall assessment:

- Proposed operations and known site capability
- Process complexity and product specific risks
- Development and scale up risk
- Previous experience qualifying and maintaining processes
- Data Integrity concerns
- Control strategy implementation risk

Submission of Application

Office of Process and Facilities (OPF) & IQA team assesses application

Pre-Approval Inspection (PAI) Needed?

YES!

IQA/review team develops Inspection strategy from review of application

Office of Regulatory Affairs (ORA) Coordinates Pre-Approval Inspection

PAI Inspection

- ORA and CDER SMEs conduct PAI
  - 483 Issued as necessary
  - Recommendation made (approve/withhold)
  - Inspection Report Written

- OPF assesses 483 responses/ Inspection report
- Can request additional information
- Recommendation made to IQA team

- Facility assessment recommendation considered along with recommendation from other review areas
- Approve/withhold (complete response)

When are PAIs not performed?

- If none of the IQA/risk assessment criteria are met, PAI could be waived (assuming the establishment has an acceptable history) and application still be reviewed
- If a compliance action is in progress (WL, Injunction) FDA can recommend withholding approval without an inspection
- If the firm is not ready FDA can recommend withholding approval without an inspection

PAI Outcomes: Recommendations

The inspection is one part of the approval process

- Lead investigator will make a recommendation at the conclusion of the PAI (NAI, VAI, OAI)

<u>Recommend Approval (NAI/VAI)</u>

- Indicates that the inspection found no significant issues
- Response to FDA 483 observations is important

<u>Recommend Withholding of Approval (OAI)</u>

- Investigators observed that the site is not cGMP compliant, information in CMC is not consistent with site records, or information submitted is not accurate and complete
- Response to FDA 483 observations is ***critical***
- Recommendation should be discussed during the close out

***CDER/Center has final authority on approval or withholding approval of all applications

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PAI Objectives

1. Readiness for commercial manufacture
2. Conformance to the application
3. Data integrity

**Adherence to cGMP is also assessed during PAIs

Objective 1 – Readiness for Commercial Manufacture

Investigators 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 as it relates to the application product
- 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 R&D batches
  - ✓ Will review Product Development Reports
- Review master batch records and manufacturing instructions and SOPs
- Focus on change control, deviations and trends relating to the development and manufacturing experience to determine that there is adequate process understanding

Objective 1 – Readiness for Commercial Manufacture

- Will evaluate sampling plans; testing of components and product
- Adequate 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 validation / transfer studies and suitability for use

Objective 2: Conformance to Application

Investigators will verify the accuracy of the submission

- Observe processing lines and audit executed batch records
- Review laboratory methods and compare with application
- Ensure active pharmaceutical ingredient (API) suppliers/vendors are properly presented in the application
- Review biobatch and registration executed batch records, and assess comparability with the commercial scale process – should be the same
- Evaluate any unreported batches or test results for contextual data integrity

Objective 3: Data Integrity Audit

Investigators are to audit the raw data, hardcopy or electronic, to authenticate the data submitted in the drug application.

- Retention of complete and accurate data is a CGMP requirement
- "Data Integrity" refers to the completeness, consistency, and accuracy of data. Data should be "**ALCOA**"

Attributable
Legible
Contemporaneously recorded
Original or true copy
Accurate

Objective 3: Data Integrity Audit

Investigators review raw data used to generate results

- Control/security of raw data
- Employee accountability
- Audit for authenticity and accuracy
- Review raw data for biobatch and stability batch(es), including laboratory testing and manufacturing
- Inventory records/equipment logs
- Passing data submitted instead of failing data
- Improper invalidation of out of specification (OOS) results
- Exclusion of specific lots from the stability program to avoid submitting failing results

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***PAI Preparation (Dos)

- Be flexible and be prepared!
- Understand your manufacturing process
- Understand issues that arise during pharmaceutical development and manufacturing and address appropriately
- Have all required equipment and facilities
- Ensure equipment/facilities are clean, orderly and qualified
- Have required documents

Documents that should be ready for a PAI

<u>Product/process development documents</u>

- ✓ Product Development and technology transfer reports and summaries
- ✓ Process performance qualification protocols and reports; Validation Master Plan
- ✓ Specifications and test methods for products covered
- ✓ Manufacturing Flow Charts including in-process control points
- ✓ Raw data that supports product development
- ✓ Method validation plans, protocols, reports

Documents that should be ready for a PAI

<u>Quality function documents</u>

- ✓ Deviations (what ever they are called!)
- ✓ List of all batches manufactured (to include reject, reworked/reprocessed batches)
- ✓ Change Controls
- ✓ Corrective and Preventive Actions
- ✓ Complaints
- ✓ Out of specification results/investigations
- ✓ SOPs governing investigations, complaints, etc.

Documents that should be ready for a PAI

Other PAI document examples

- ✓ Facility layout and equipment diagrams
- ✓ Equipment Lists (production and laboratory)
- ✓ Equipment qualification records (IQ/OQ/PQ)
- ✓ Equipment maintenance records and schedules
- ✓ Master and executed batch records
- ✓ Cleaning records, procedures, and validation reports
- ✓ Manufacturing and laboratory schedule
- ✓ Complete product list

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Reasons for withhold recommendations

- Serious cGMP concerns (e.g. insanitary conditions, cross-contamination)
- Significant differences between the process used for pivotal clinical batches and the NDA submission batch
- Inadequate process control strategy
- Inadequate process understanding
- Failure to report adverse findings or failing test data without appropriate justification
- Significant failures related to the stability studies of APIs and drug products
- Incomplete method validation
- Missing equipment or insufficient qualification
- Significant data integrity problems
- Deviations from submitted application

Examples of Data Integrity Issues that could result in withhold recommendations

- Falsified data
- QA approval of incomplete and/or erroneous laboratory data
- Changes of specification (widening) not reported in application
- Testing into compliance; repeat testing until passing results, deletion of initial results
- Passing data submitted instead of failing data
- Exclusion of specific lots from the stability program to avoid submitting failing results

Case Study 1: Failure to report failing data

Scenario: Firm manufactured tablets that included wet granulation, tableting and enteric coating processes

- During inspection, review of the development batch records revealed several batches failed dissolution. Data was not reported in the filing submitted to FDA
- Investigations conducted into the failures stated that the assignable cause was the wet granulation process, compression of the core tablets, and/or the enteric coating of the core tablets, without further explanation
- During the inspection, the firm hypothesized that the root cause was the dew point during the enteric coating step. The firm did not have the capability of controlling the dew point in any of its coaters
- The firm does not have sufficient control of the tablet press. Firm could only operate press when vendor was present

Recommendation: Withhold for failure to report failing data and not understanding manufacturing process

Case Study 1: Failure to report failing data

What happened?

- Different batches would require different tablet press settings, and the firm had no idea why
- Investigators also found failing dissolution release testing without a root cause identified. This failing data was not reported
- Firm had now way of adequately controlling tableting or coating process – lack of process understanding
- There is no assurance that the finished product will consistently meet its finished product specifications

Case Study 1: Failure to report failing data

Takeaways

- Investigate deviations/issues prior to the PAI…Responsible person for issues identified and accountable
- Have SME ready to present significant issues during inspections
- Process design must be completed and adequate prior to the PAI inspection. Need evidence/data to support the manufacturing process
- Knowledge gained during development should be incorporated into process design/control strategy
  - ✓ Dissolution failure investigations may result in manufacturing changes depending on the root cause
  - ✓ Manufacturing changes may result in gaining sufficient control of the tableting process

Case Study 2: Know your commitments

Scenario: Firm storing drug substance in two different containers for stability and long-term storage. Only one container closure listed in application

- During PAI inspection it was revealed that the firm stored the drug substance in brown amber bottles for stability testing, and the finished drug substance in LDPE bags for permeant storage
- Stability studies were performed on drug substance samples packaged in amber glass bottles – incorrect container closure system
- Firm lacked data for the qualification of the proposed container closure system (LDPE bags) to store the drug substance

Recommendation: Withhold for failure to meet application commitments

Case Study 2: Know your commitments

What happened?

- The drug substance was packaged in LDPE bags; however, the stability studies were conducted in amber glass bottles
- Firm was unaware of commitments and requirements
- Firm responded that they will package the drug substance in amber glass bottles until they collect adequate stability data to support packaging in LDPE bags

Case Study 2: Know your commitments

Takeaway

- Know your commitments and be prepared for the inspection!!

PAI Resources for Industry

- Compliance Program Guidance Manual 7346.832 – Pre-Approval Inspections
- FDA Guidance for Industry – Quality System Approach to Pharmaceutical cGMP Regulations
- Respective product specific FDA and ICH guidance's

Special Thanks

- ORA Pharm1 OPQO Management
- REdI Boston Organizing Staff
- Christina Capacci-Daniel – CDER/OPF
- Slide adapted from Lucilia Nwatu & Denise DiGIulio – ORA

Questions?