Walkthrough of a Pre-Approval Manufacturing Site Inspection

FDA Small Business
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AGENDA

- ❑ PRE-APPROVAL PROCESS
- ❑ INSPECTION- OBJECTIVES
- ❑ INSEPCTION- PREPARATION

Pre-Approval Inspection

The FD&C Act provides that FDA may approve an NDA /ANDA/BLA only if the methods used in, and the facilities and controls used for the manufacture, processing, packing, and testing of the drug are found adequate to ensure and preserve its identity, strength, quality and purity.

Pre-Approval Process

- All sites listed in an application that will perform a commercial function must be evaluated for cGMP compliance.
- This does not mean that all sites require an inspection.
- There is a system for determining which sites require an inspection.

What triggers a PAI? (Old Model)

(CPGM 7642.832)

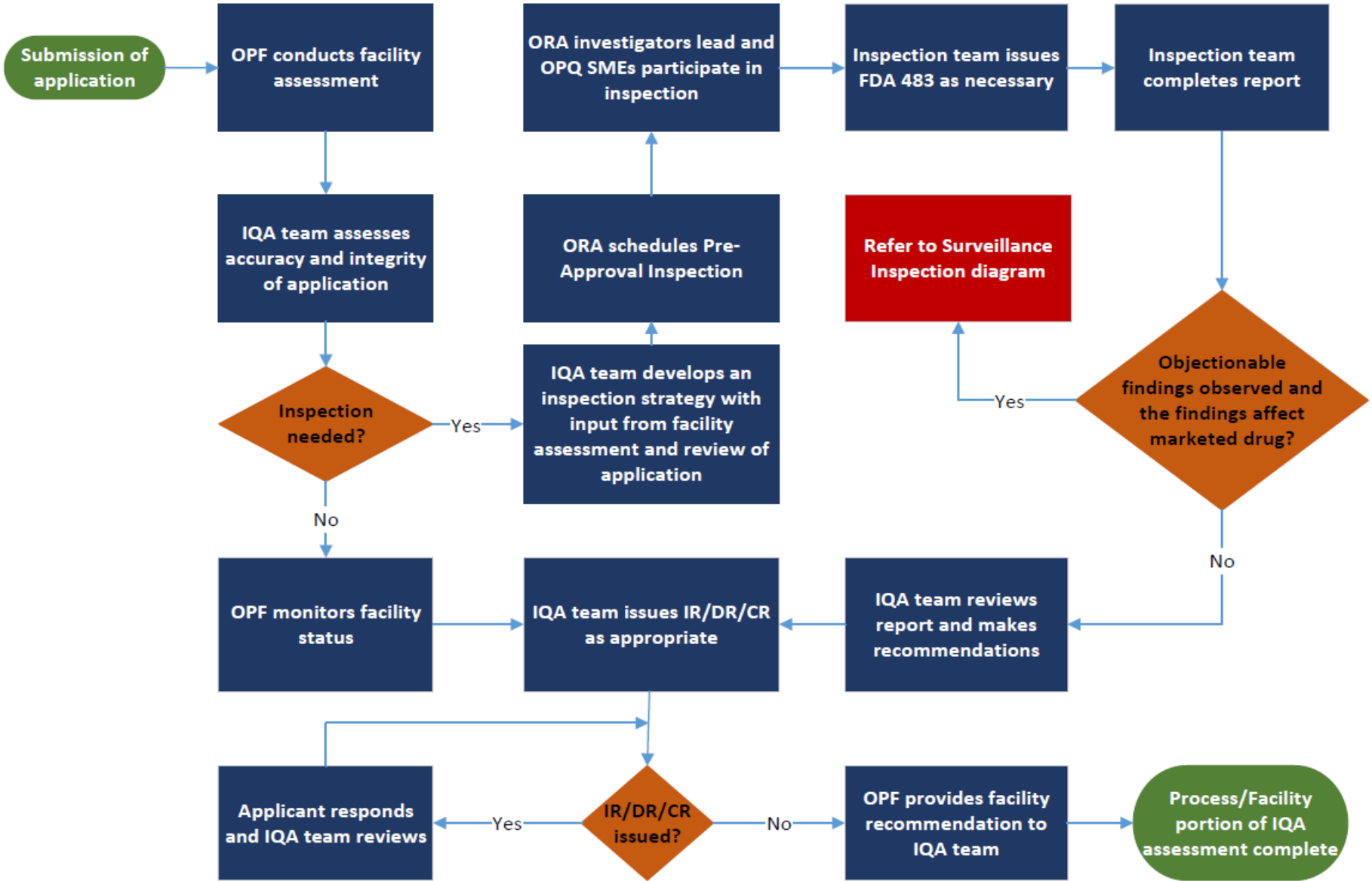
When one or more of the following criteria are met:

- First application filed by applicant
- First inspection for the establishment
- First generic
- New molecular entities
- Narrow therapeutic range (95%-105%)
- Substantially different manufacturing process or dosage form than previously covered at the establishment
- API derivation is high risk (derived from animal tissue)
- Site/product/process changes that are expected to pose a challenge to the state of control of the facility, for example new construction.

PAI determination- IQA Model

- Developed from experience with NDA and BLA review.
- PAI criteria and related profile/process are used differently
  - Not all priority criteria automatically trigger an inspection
  - Risk attributed used for a deeper facility risk evaluation
  - Captured as attributed in OPF facility risk assessment model
- Final determination for PAI is based on reviewers overall assessment
  - Related profile
  - Process complexity/known site capability
  - Previous inspection findings
  - Product specific attributes

Pre-Approval Facility Inspection Process



Review and Inspection Biotech products

Inspection –

Performed by CDER reviewer/investigators in OPF and OBP who have a focus on Product, Microbiology and CGMP aspects of manufacturing that product. Investigator is part of the review committee. ORA does participate based on availability. Sometimes, inspections performed only by ORA when CDER participants are not available.

When are PAIs not performed?

- If none of the above criteria are met, we may elect to “waive” the PAI.
  - Assuming the establishment has an acceptable profile.
- If a compliance action is in progress (WL, Injunction) we can recommend withholding approval without an inspection.
- If the firm is not ready we can recommend withholding approval without an inspection.

PAI vs. GMP Inspections

- Limited or no commercial manufacturing
- Product Development documentation/ Biobatch/clinical batch manufacturing
- More emphasis on authenticity of data and application commitments
- Analytical method development, Process validation commonly not completed
- Application actions are administrative; typical enforcement used for marketed products do not apply

Inspectional Guidance

Compliance Program Guidance Manuals (CPGMs) are public information and located on the FDA website.

Human Drugs:

CPGM 7346.832 - Pre-Approval Inspections

CPGM 7356.002 for CGMP inspections

- 7356.002A for sterile facilities
- 7356.002F and Q7 Good Manufacturing Practice Guidance of Active Pharmaceutical Ingredients for API CGMPs and 501(a)(2)(B) of the Act
- 7356.002M for BLAs

Inspection Objectives

Assure:

1. Readiness for Commercial Manufacturing
2. Conformance to Application and Commitments
3. Data Integrity Audit

PAI OBJECTIVES (SECTIONS 3.3-3.4)

Start of the Inspection

☐ Administrative Duties

Credentials, FDA-482 (domestic), and exchange of business cards

☐ Explanation

Purpose of visit

General plan on coverage during the inspection

☐ Schedules

Daily wrap up sessions

Facility Tour

- Storage Facilities (Raw Material, In-Process, Finished Product, Stability, and Retention)
- Release testing of Raw Materials,
- Material Flow, Personnel Flow
- Utilities (Water system, Process Gas, HVAC, HEPA
- Production Practices
  - Unit Operations (hood, isolators, etc.)
  - Aseptic Technique and Filling Operations, Lyophilization
  - Sterilization and Depyrogenation of Container closures, etc.
  - Terminal Sterilization
- Visual Inspection
- Packaging and Labeling
- Release Testing (i.e. chemical, physical, microbiological)

Facilities and Equipment

- ☐ Room Classification for sterile operations
- ☐ Microbial controls and Sterility Assurance
- ☐ Environmental and Personnel Monitoring
- ☐ Equipment Maintenance records
- ☐ Equipment Use Logs and Line Clearance
- ☐ Efficacy of cleaning methods.

Personnel Practices

- Observed practices vs. Expected/ validated practices
- Training Records
- Personnel (Sterile)- Gowning, training, aseptic technique, media fills or process simulations

Objective 1a: Readiness for Commercial Manufacturing

Determine whether the establishment(s) has a quality system that is designed to achieve sufficient control over the facility and commercial manufacturing operations

Objective 1(a): Manufacturing and laboratory changes, deviations, and trends relating to the development of new drug substance and product manufacturing have been adequately evaluated.

Objective 1b: Readiness for Commercial Manufacturing

Determine whether the establishment(s) has a quality system that is designed to achieve sufficient control over the facility and commercial manufacturing operations

Objective 1(b): A sound and appropriate program for sampling, testing, and evaluation of components, in-process materials, finished products, containers and closures for the purpose of releasing materials or products has been established, including a robust supplier qualification program.

Objective 1c: Readiness for Commercial Manufacturing

Determine whether the establishment(s) has a quality system that is designed to achieve sufficient control over the facility and commercial manufacturing operations

Objective 1(c): The establishment has sufficient facility and equipment controls in place to prevent contamination of and by the application product (or API).

Objective 1d: Readiness for Commercial Manufacturing

Determine whether the establishment(s) has a quality system that is designed to achieve sufficient control over the facility and commercial manufacturing operations

Objective 1(d): Adequate procedures exist for batch release, change control, investigating failures, deviations, complaints, and adverse events; and for reporting this information to FDA, such as field alert reporting.

Objective 1e: Readiness for Commercial Manufacturing

Determine whether the establishment(s) has a quality system that is designed to achieve sufficient control over the facility and commercial manufacturing operations

Objective 1(e): The feasibility of the proposed commercial process and manufacturing batch record, including instructions, processing parameters and process control measures, are scientifically and objectively justified. This objective is linked to the firm's process validation program.

Objective 1- Examples of Firms not capable of manufacturing products

- Renovation of facility, or equipment not installed
- No quality agreement between sponsor and establishment listed in application
- Lack of appropriate controls to ensure quality
- Multiple batch failures not reported in application

Objective 2: Conformance to Application

Verify the accuracy of the submission

- Observe processing lines and audit executed batch records.
- Review laboratory methods and compare with application
- Review biobatch and assess comparability with the commercial scale process
- Ensure API supplier is properly presented in the application
- Review raw data for biobatch and stability batch(es), including laboratory testing and manufacturing

Objective 3: Data Integrity Audit

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

- Retention of complete and accurate data is a CGMP requirement:
  - 211.180(d): “true copies” such as microfilm, photocopies or other “accurate reproductions” are OK in lieu of original records
  - “true copies” can still be considered raw data
- Submitting false data to the FDA is a criminal violation under
  - FD&C Act 501(a)2(B)(CGMP /adulteration provisions)
  - Title 18 U.S. Code - various sections

Examples of Data Integrity Issues

- Falsified data (complete fabrication of sterility testing, environmental monitoring, WFI testing, biological indicators for sterilization, bioburden samples, endotoxin testing, media fills)
- QA approval of incomplete and/or erroneous laboratory data
- Changes of specification (widening) not reported to 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

Objective 3: Data Integrity Audit

"Data Integrity" refers to the completeness, consistency, and accuracy of data. Data should be "**ALCOA**".

Attributable

Legible

Contemporaneously recorded

Original or true copy

Accurate

Electronic Data Integrity Manipulation

We have found 5 main types of fata integrity issues when reviewing electronic chromatography:

- Trial Sample Analysis
- Deletion of Data
- Testing Into Compliance
- Back-Door Manipulations
- Administrator Foul Play

What Documents Should the Firm Have Available for Review During the Course of the Inspection?

- ☐ Daily manufacturing schedules
- ☐ Complete Product List (including products in development)
- ☐ Correspondence with the Agency (e.g. Deficiency letters, any supplements and/or amendments filed concerning the application)
- ☐ List of all submissions, dates of approvals, pending submissions, refuse to file letters, and any other correspondence with the Agency.
- ☐ Chemistry Manufacturing Controls (CMC) section of the NDA/ANDA/BLA.
- ☐ A list of ALL batches, even those that were rejected.
- ☐ Master Batch Records and all executed batch records.

What Documents Should the Firm Have Available for Review During the Course of the Inspection?

- ☐ Facility Layout, Water System Diagram (PW and WFI), Air Handling Systems, Materials Flow Diagram, etc.
- ☐ Manufacturing Flow Charts including in-process control points
- ☐ Equipment Lists (Production and Laboratory); Sterilizers, lyophilizers, depyrogenation equipment
- ☐ Equipment Qualification Records (IQ/OQ/PQ)
- ☐ Equipment Maintenance Records

What Documents Should the Firm Have Available for Review During the Course of the Inspection?

- ☐ Product Development Reports and Summary
- ☐ Process Validation Plans, protocols, reports (if available – RAW DATA
- ☐ Specifications and Test methods for products covered

What Documents Should the Firm Have Available for Review During the Course of the Inspection?

- ☐ List of SOPs (index)
- ☐ List of all Out of Specifications Batches, Reason, and Status
- ☐ List of Deviations (planned and unplanned), Non-conformances, Incidents, Anomalies, etc.
- ☐ List of Reject, Reworked/Reprocessed Batches
- ☐ Change Controls
- ☐ Corrective and Preventive Actions
- ☐ Summary of Complaints (all complaints - including non-USA products if a foreign inspection)
- ☐ Annual Product Reports
- ☐ Annual Product Reviews

Recommendations

The inspection is one part of the approval process

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

<u>Recommend Approval</u>

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

<u>Recommend Withholding of Approval</u>

- 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***

- Recommendation are discussed during the close out.
- CDER has final authority on approval or withholding approval of all applications

Withhold Recommendations

When would a withhold be recommended? (examples)

- Significant data integrity problems including misrepresented data or other conditions related to the submission batch(s)
- Serious CGMP concerns with the manufacture of a biobatch or demonstration batch, such as a changes to formulation or processing that may cause FDA to question the integrity of the bioequivalence study
- Significant differences between the process used for pivotal clinical batches and the NDA submission batch
- Lack of complete manufacturing and control instructions or lack of data to support those instructions
- Lack of capacity to manufacture the drug product or the API (e.g. the firm is not ready for an inspection)

Withhold Recommendations

(More Examples)

- Full scale process validation studies were attempted prior to the PAI, demonstrate that the process is not under control and establishment is not making appropriate changes
- Incomplete or unsuccessful method validation or verification
- Records for pivotal clinical or submission batches do not clearly identify equipment or processing parameters used
- Significant failures related to the stability study that raise questions about the stability of the product or API
- Failure to report adverse findings or failing test data without appropriate justification

Inspection Close-out Meeting

1. Communicate Discussion Items
2. Issue FDA 483 to Top Management (if applicable)
3. Discuss Observations (If applicable)
4. Discuss Approval/Withhold Recommendation

QUESTIONS?

Please evaluate this session:

surveymonkey.com/r/DRG-D2S07

Call to Action

- Document Request System
  - Ensure that your firm has an established system for documenting FDA requests during inspection.
  - Ensure that documents are readily available.
  - Ensure that all requests are addressed in a timely fashion.
- Ensure that the appropriate personnel are available to provide explanation.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