Pre-Approval Inspections for Drug Products

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Presentation Overview

- Disclaimer
- Organization
- Pre-Approval Inspections
  - Inspection process
  - Inspection program objectives
- Role of the firm
- Role of the investigator
- Post inspection activities
- 483 Trends

Disclaimer

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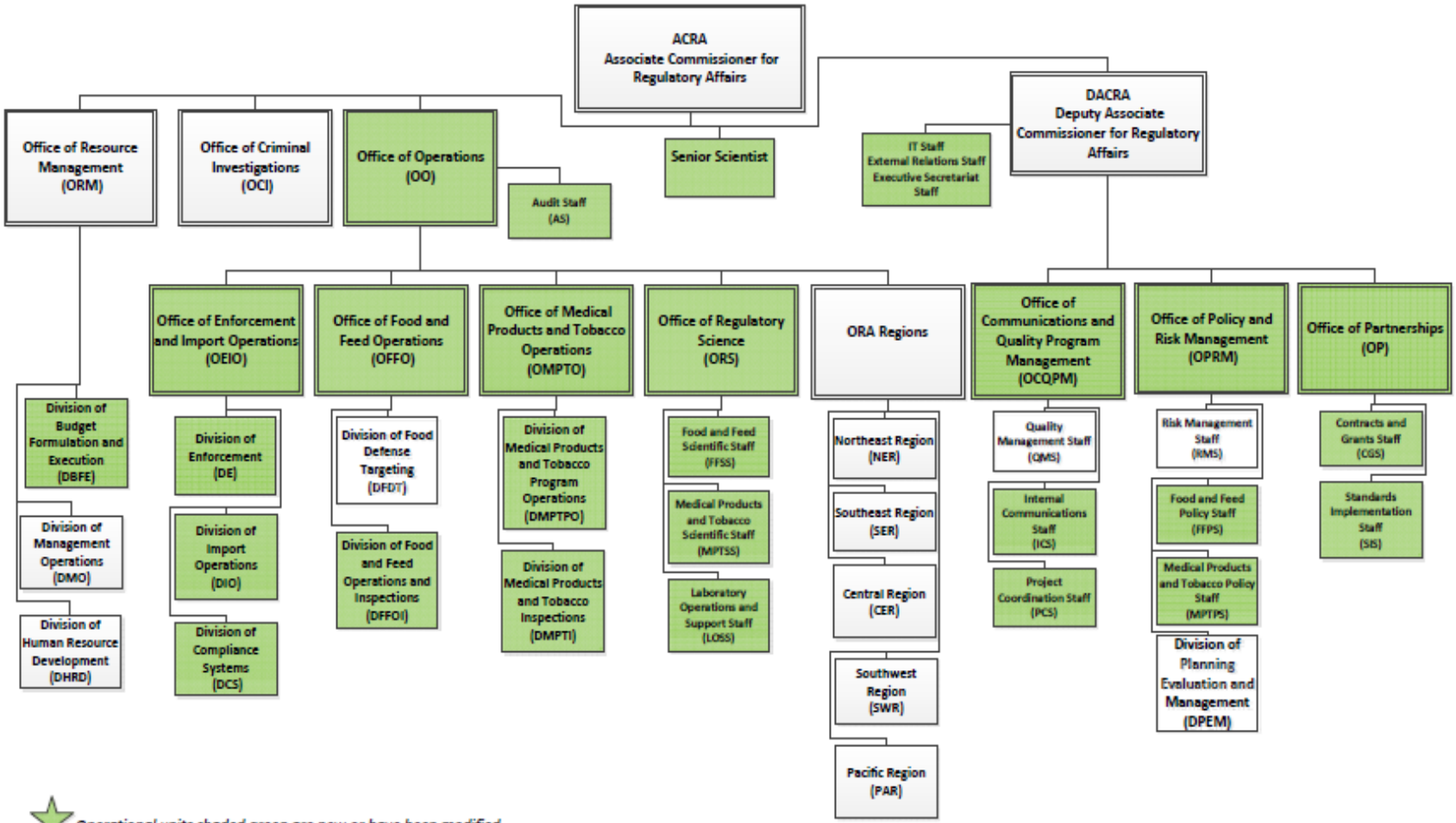
Office of Regulatory Affairs Effective October 1, 2012



Operational units shaded green are new or have been modified

ORA Office of Regulatory Affairs

CDER Offices

Office of Compliance (OC)

- Office of Manufacturing and Product Quality (OMPQ)
  - Division of Good Manufacturing Practice Assessment (DGMPA)
    - New Drug Manufacturing Assessment Branch
    - Generic Drug Manufacturing Assessment Branch
    - Biotech Manufacturing Assessment Branch
  - Division of International Drug Quality (DIDQ)

- **Office of Pharmaceutical Science (OPS)**
- Office of Biotechnology Products (OBP)
- Office of New Drug Quality Assessment (ONDQA)
- Office of Generic Drugs (OGD)
- Office of Testing and Research (OTR)
- Office of New Drugs
- Office of Drug Evaluation (ODE) I through IV
- Office of Antimicrobial Products
- Office of Hematology and Oncology Products

http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ContactCDER/UCM070722.pdf

Pre-Approval Inspection Process

- One of the last reviews of the drug approval process, which may effect the availability to the consumer
- A systematic review of the application and the manufacturing process
- Not every application may result in a PAI

Pre-Approval Inspection Programs

- **Human (CPGM 7346.832)**
  - New Drug Applications (NDA)
  - Abbreviated New Drug Applications (ANDA)
  - Investigational New Drugs (IND)
  - Antibiotic New Drug Applications (AADA)
  - Supplements (i.e. PAS, CBE-0, CBE-30, etc.)
  - Active Pharmaceutical Ingredients (API)

- **Animal (CPGM 7368.001)**
  - New Animal Drug Applications (NADA)
  - Abbreviated New Animal Drug Applications (ANADA)
  - Investigational New Animal Drug Applications (INADA)
  - Supplements
  - APIs
  - Type A medicated articles

What is the goal of a Pre-Approval Inspection?

To assure that establishments involved in the manufacturing, testing, or other manipulation of new drug dosage forms and drug substances are evaluated for

- conformance with commitments in the application
- site cGMP compliance
- data authenticity, reliability and accuracy
- adequacy of analytical methodologies

Initiation of the Inspection

- No pre-announcement
- Investigator will arrive on site and typically ask for the most responsible person
- Issuance of 482, Notice of Inspection to the most responsible person on site.
- Start of the inspection

Compliance Program 7346.832, Pre-Approval Inspections

- Three primary objectives:
  - **Objective 1:** Readiness for Commercial Manufacturing
  - **Objective 2:** Conformance to Application
  - **Objective 3:** Data Integrity Audit

PAI Program Coverage

- All manufacturing sites listed in the application, foreign or domestic
  - API manufacturers
  - Control testing laboratories
  - Packaging facilities
  - Finished dosage form manufacturers
  - Others – container/closure system manufacturers, specialty laboratories, etc.

Objective 1: Readiness for Commercial Manufacturing

Determine whether the establishment has a quality system designed to achieve sufficient control over the facility and commercial manufacturing operations

- Categorized into 5 sub-objectives

Objective 1: Readiness for Commercial Manufacturing

Objective 1a

- manufacturing and laboratory changes, investigations and trends.
- product manufacturing demonstrates the establishment has appropriately assessed related issues.

Objective 1: Readiness for Commercial Manufacturing

Objective 1b

- sound and appropriate program for sampling, testing and evaluation of components, in-process materials, finished products, container closures.

Objective 1: Readiness for Commercial Manufacturing

Objective 1c

- Sufficient facility and equipment controls to prevent cross-contamination.

Objective 1: Readiness for Commercial Manufacturing

Objective 1d

- Adequate procedures for controlling changes, investigating failures/deviations, complaints/adverse events, conducting recalls, and reporting this information to FDA.

Objective 1: Readiness for Commercial Manufacturing

Objective 1e

- Evaluate the feasibility of the proposed commercial process and manufacturing batch record, which would include instructions, processing parameters, and process control measures.

Objective 2: Conformance to Application

Verify that the formulation, manufacturing or processing methods, and analytical methods are consistent with information contained in the CMC section of the application for the biobatch, proposed commercial batch, and API

- This would include:
  - Observing processing and/or testing operations
  - Compare the biobatch manufacturing process against the proposed commercial batch record

Objective 3:
Data Integrity Audit

Audit hardcopy and/or electronic *raw data* to authenticate the data submitted in the CMC section of the application

- For example:
  - Laboratory notebooks and associated chromatograms generated during release testing of biobatch
  - Failure to include aberrant test results in CMC section
  - Improper invalidation of OOS results

Other Compliance Program Links

- Center for Drug Evaluation and Research (CDER)
  - 7356.002- Drug Manufacturing Inspections- PAI will usually incorporate cGMP coverage of post-market products.
- Center for Veterinary Medicine (CVM)
  - 7371.001 Drug Process and New Animal Drug Inspections
  - 7368.001 Pre-Approval Inspections NADA

Product Development Report

- A very useful document for both the firm and the Agency
- The data generated during product development which defines the drug product, targets the steps in the manufacturing process where variation is critical to quality and thereby focuses the subsequent process validation effort.

Product Development Report

- API
  - Impurity Profile
  - How is the API characterized
- Excipients
- Formulation
  - Wet or Dry Granulation
  - Solution or Suspension
  - Sterile - Terminal/aseptic conditions
  - Tablet/Capsule - Immediate/Modified Release/Extended Release

Product Development Report

- Describes the development of Processing: Equipment, order of addition of ingredients to the formulation, mixing times and speeds, drying time and temperature, nitrogen blankets, blending, hold times, compression, slugging, filling, polishing, imprinting, labeling and packaging.

- Product Development Report ***may not*** be a formal document

Batch Records

- The batch records submitted in the application must be audited as part of the inspection to assure:
  - *That the proposed production process is the same process that was used for the manufacture of the bio/stability batches.*

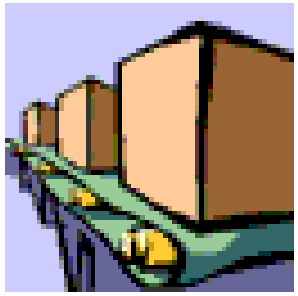
Reprocessing /Rework

Reprocessing/Reworking

- GMP regulations require reprocessing procedures to be in writing. If firm makes provisions for reprocessing drug product, details must be submitted as part of the application.
  - Standard Operating Procedures
  - QA review and approval

Role and Responsibilities

Manufacturers, Labelers, Packagers, Contract Testing Labs, Sterilizers, etc.



The firm's role

- The manufacturing and all associated facilities must be listed within the application (contract labs, packagers, etc.)

- Once an application is submitted to Center, the firm and all facilities should be considered **ready for inspection**.

The firm's role

- Make records available (as appropriate) to conduct the pre-approval inspection
  - Product Development Report
  - Batch Records
  - Laboratory Records
  - Protocols/SOPs
- Assure facility is cGMP compliant and ready for an FDA inspection.

Investigator Role

- Conducts PAI in accordance with CPGM and other guidance and direction.
- Promptly notifies Pre Approval Manager (PAM) of application issues so that the PAM can contact the reviewer (e.g. problems with specifications)
  - **It is not the investigator's job to advise the firm regarding what specifications are appropriate for drug products during the PAI. This is the reviewer's function.**

Investigator Role

- Notifies PAM of significant GMP and/or data integrity issues that may likely result in a withhold recommendation
- Informs firm management at the conclusion of the inspection of his/her recommendation to PAM
- Provides PAM with pertinent information needed for District recommendation (e.g. FDA 483, EI dates, proposed classification) upon completion of inspection

Investigator's Role

Assess the following:

- Quality Systems
- Manufacturing Operations
- Sampling Plans
- Laboratory
- Test Methods Validation
- Drug Product Specifications
- Reprocessing/Reworking
- Standard Operating Procedures
- Batch Records

Investigator's Role

- Investigator should inform the management at the conclusion of the inspection of his/her recommendation to the Pre-Approval Manager.
  - Recommendations: Approval or Withhold
- Collects profile samples per compliance program 7346.832 when requested by the assignment.

District Office Role

- Respond to inspection requests
- Inspect sites in accordance with the PAI program
- Report findings and provide a recommendation on site acceptability to the Center
- District Director is the most responsible person
- District must meet PDUFA dates
- District must meet District goal dates
- May analyze the drug product
- May evaluate the analytical method validation before approval

Inspection Close-Out

- There will be a close-out meeting
  - No Surprises
  - FDA-483 (Inspectional Observations)
    - **may or may not be issued**
- Firms have the opportunity to respond in writing to the Investigator's Observations or Discussion Points
    - verbal (during the inspection) and in writing (to the District Director)
    - **15 days to respond for consideration of further action**
- If physical samples were collected, FDA-484 (Receipt for Samples) will be issued.

After the Inspection

- An Establishment Inspection Report (EIR) is written.
  - Submitted to Supervisory Investigator for review
  - If further action warranted, it is forwarded to the Compliance Branch Director

Post PAI Inspection Activities

- The investigator will provide the Pre-Approval Manager with the information needed for District recommendation upon completion of the inspection
- Inspected firm may receive a Post Inspectional Letter from the inspecting district informing them of **recommendation** made to CDER
- Firm will receive a copy of the EIR
  - (FMD-145)

After the Inspection

- Inspections are generally classified into one of three categories
  - **NAI**-No Action Indicated
  - **VAI**-Voluntary Action Indicated
  - **OAI**-Official Action Indicated

- Regulatory action may come from VAI and will come from OAI inspections. In some instances, regulatory actions may come from NAI inspections.

Post PAI Inspection Activities

- After the PAI is completed the information is transmitted to CDER/CVM and a final decision is made and communicated with the application holder.

Post-Approval

- Post-Market inspectional cycle
- Firms usually inspected on a biennial basis
  - Can be more often based on compliance history, complaints, etc.

State of Control

- An important term to keep in mind
- Operating under a **State of Control** produces finished drug products for which there is an adequate level of assurance of quality, strength, identity and purity
- If any **one system** out of control, the firm is out of control and thus all profile classes are unacceptable.

TOP TEN PHARMACEUTICAL OBSERVATIONS

1. **21 CFR 211.22(d)** The responsibilities and procedures applicable to the quality control unit are not [in writing] [fully followed].

2. **21 CFR 211.192** There is a failure to thoroughly review [any unexplained discrepancy] [the failure of a batch or any of its components to meet any of its specifications] whether or not the batch has been already distributed.

3. **21 CFR 211.100(a)** There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

TOP TEN PHARMACEUTICAL OBSERVATIONS cont'd

4. **21 CFR 211.160(b)** Laboratory controls do not include the establishment of scientifically sound and appropriate [specifications] [standards] [sampling plans] [test procedures] designed to assure that [components] [drug product containers] [closures] [in-process materials] [labeling] [drug products] conform to appropriate standards of identity, strength, quality and purity.

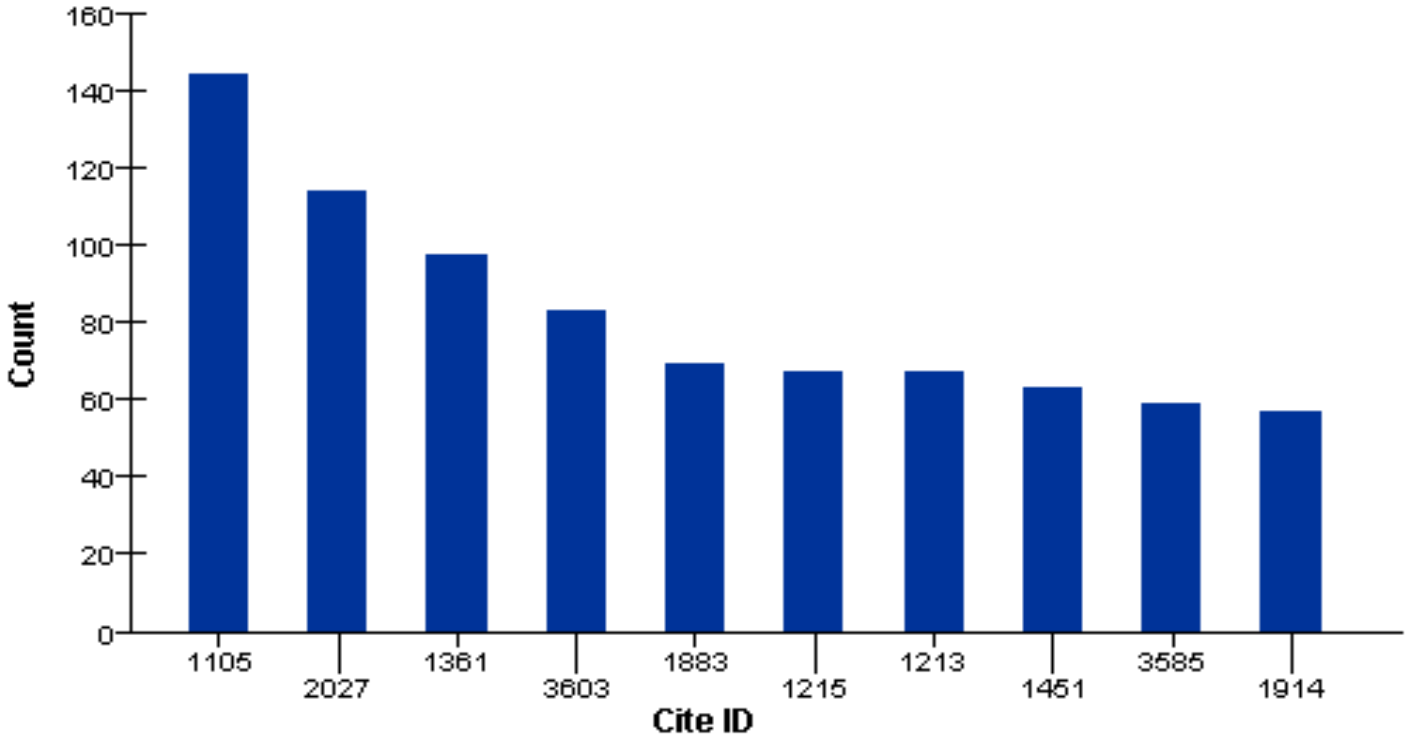
5. **21 CFR 211.165(a)** Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the [final specifications] [identity and strength of each active ingredient] prior to release.

6. **21 CFR 211.67(b)** Written procedures are not [established] [followed] for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product.

TOP TEN PHARMACEUTICAL OBSERVATIONS cont'd

7. **21 CFR 211.67(a)** Equipment and utensils are not [cleaned] [maintained] [sanitized] at appropriate intervals to prevent [malfunctions] [contamination] that would alter the safety, identity, strength, quality or purity of the drug product.
8. **21 CFR 211.113(b)** Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not [established] [written] [followed].
9. **21 CFR 211.110(a)** Control procedures are not established which [monitor the output] [validate the performance] of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.
10. **21 CFR 211.166(a)** There is no written testing program designed to assess the stability characteristics of drug products.

Top 10 Drugs Observations Used in Turbo EIR Between June 2012 and June 2013



Summary

- The PAI program has a long and successful history.
- The PAI program remains a critical part in the review of new products submitted to the Agency.
- FDA expectations during the PAI have been and will remain constant. With the passage of GDUFA, we expect PAI assignments will greatly increase, especially foreign assignments.
- FDA's expectations are clearly defined in agency compliance programs and in other guidance documents.

Thank you.

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