Overview of Pre-Approval Inspections

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NWJ-DO Pre-Approval Manager
Pre-Approval Drug Inspections
What are Pre-Approval Inspections?

One of the last reviews of the drug approval process, which may effect the availability to the consumer.
Objective-

Assure that establishments involved in the manufacturing, testing, or other manipulation of new drug dosage forms and new drug substances are audited.

(pg. 5 of CP)
Compliance Program 7346.832

Audited for:

1) compliance with CGMPs
2) for conformance with application commitments
3) authentic and accurate data
4) laboratory testing of products, including evaluations of the adequacy of analytical methodology
Other Compliance Programs

- 7356.002- Drug Manufacturing Inspections- as most of the time PAI will also incorporate GMP coverage of facility
- Center for Veterinary Medicine- CVM
History of Pre-Approval Inspections

- Generic Drug Scandal of 1980’s
- 1990, when the agency instituted product-specific, pre-approval inspections of manufacturing sites listed in a sponsor's application.
Pre-Approval Acronyms

- **PAM** - Pre-Approval Manager
- **PAI** - Pre-Approval Inspection
- **NDA** - New Drug Application
- **ANDA** - Abbreviated New Drug Application
- **IND** - Investigational New Drug
- **NADA** - New Animal Drug Application – (Issued through Centers Veterinary Medicine or CVM).
Pre-Approval Acronyms

- **PDUFA**: Prescription Drug User Fee Act

- **User Fee Date**: The date by which an agency decision on an application is due

**Why is this so important to the Agency?**
PDUFA

- Prescription Drug User Fee Act of 1992
- Allows FDA to charge for reviewing applications- in return, FDA commits to taking quicker actions in applications
- Provides FDA with increasing levels of resources
PDUFA II

As a result of success, PDUFA was reauthorized extended through September 20, 2002

By 2002, PDUFA fees permitted FDA to spend an additional $161.8 million/year for the drug evaluation process

Resources spent to hire personnel to review applications; update IT infrastructure
PDUFA

Congress re-evaluates and considers renewal of PDUFA every 5 years
Pre-Approval Acronyms

CMC - Chemistry, Manufacturing, and Controls – (reviewed by investigator during inspection)

Contained within CMC sections information about API; excipients; manufacturing process; reprocessing; analytical/micro testing; packaging/labeling; components; stability
Pre-Approval Acronyms

- Bioequivalence Study- A Bioavailability Study in which a comparison is made between two or more products.

A generic drug (filed under an ANDA) must prove bioequivalence to the brand drug (NDA) for which it is compared. Comparison must be noted in application.
Generics are not required to replicate the extensive clinical trials that have already been used in the development of the original, brand-name drug. Instead, they must show they are bioequivalent to the pioneer/innovator drug and fall into acceptable parameters set for bioavailability, which is the extent and the rate at which the body absorbs the drug.
Pre-Approval Acronyms

*Biobatch* for generic product (ANDA) - The batch of dosage form in which the bioequivalency study was conducted to demonstrate equivalence to the innovator product (NDA).
Pre-Approval Acronyms

*Biobatch for brand product (NDA)*- the batch tested in the clinic in which the pivotal studies were conducted or the batch used in a bioequivalency study that was compared against the pivotal clinical batch.
Role of the PAI Manager
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- Liaison between Centers, Field & Applicants
- Physically manages 3rd copy CMC & Correspondence
- Review of 3rd copy to highlight inspectional concerns
- Issues PAI Inspections to District for assignment to CSOs
Role of the PAI Manager

- Receives Assignments from CDER/CVM
- Reviews firm’s GMP history
- Contacts firm for clarification on operations related to application/general GMP
- Responds to Centers
- Responds to firms
- Schedules Post-Approval Inspections, if necessary (under CP 7346.843)
Role of the PAI Manager

- Is the application for a new chemical entity?
- Is the application for the first generic drug?
- Was a GMP inspection conducted within the last year?
- Does the firm have an acceptable status?
Role of the PAI Manager

What do we inspect?

NDA’s, ANDA’s, NADA’s & IND’s which are manufactured, tested or packaged at either a Domestic or International Facility

Inspectional coverage will include supplements (prior approval, CBE and SUPAC)

All establishments listed within an application may be inspected
Role of the PAI Manager

- EES - Establishment Evaluation System:
  Computer system used for tracking the status of drug applications; assignments and associated firms; accessible only by the Pre-Approval Manager. (PDUFA dates and special comments for applications are noted within EES system).
Role of the PAI Manager

- Receives all third copies of applications.
- Issues pre-approval assignments.
- Tracks all district pre-approval activities.
- Enters District recommendations/information into EES.
- Reviews inspection information (483, EIRs) for PAI, NAI-VAI inspections.
- Reviews inspection information (483, EIRs,) with Compliance Officer for OAI inspections which included PAI coverage.
- Communicates application status information to the inspected firms (District Status Notification letters).
Role of Firm-(manufacturing establishment)
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- Make records available to conduct the pre-approval inspection—
  - Development Report
  - Batch Records
  - Laboratory Records
  - Protocols/SOPs
Role of Firm- *(manufacturing establishment)*

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

- Once an application is submitted to Center, firm and all facilities should be considered ready for inspection.
FDA Investigator’s Role
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- Evaluate overall cGMP compliance
- Evaluate specific product and process
  - Is the facility adequate-building; equipment; water systems?
  - Is there data to justify the process?
  - Is there evidence/data to support the manufacturing process?
- Review R&D information
- Product Development Report
The data generated during product development which defines the drug product and targets the steps in the manufacturing process where variation is critical to quality and thereby focus the subsequent process validation effort.
Product Development Report

- API - Impurity Profile
- How is 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

- 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 Report *may not be a formal document*
FDA Investigator’s Role

- Development Data - look at all R&D batches
- Impurity Profile - *note specifications*
- Specifications (Data to support)
- Production Trends
- Change Control
- FDA Correspondence/ Deficiency Letters
- Stability Data
Equipment Qualification

During the inspection the following areas should be covered:

- Installation Qualification
- Operational Qualification
- Performance Qualification
FDA Investigator’s Role

- Sampling Plan-(SOPs outlining; techniques training of personnel)
- Laboratory-(SOPs; Personnel; Training)
- Test Methods-(Validated)
- Target Drug Product Specifications
- Reprocessing/Reworking
- Standard Operating Procedures
- Batch Records-submission batches
FDA Investigator’s Role

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

Review all Batch Records - submission batches ; master batch records
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.
In summary the FDA Investigator’s Role

- Conduct assigned pre-approval inspections in accordance with the compliance program and DO SOP.
- Conduct the pre-approval inspections by the due date listed in the assignment (or communicates the delay to the Pre-Approval Manager).
- Notifies Pre-Approval Manager with an “Approve” or “Withhold” recommendation.
- Collects profile samples per compliance program 7346.832; District policy/IOM; and Profile Sample Memo issued in 2002.
- Completes all PDUFA assignments and gives recommendation by due date (**no exceptions!!!**).
In summary the FDA Investigator’s Role

- Investigator should inform firm of the outcome of the inspection.
- Inspected firm will receive a Post Inspectional Letter from the inspecting district informing them of recommendation made to CDER.
- Firm should receive a copy of the establishment inspection report (FMD-145)
Examples of 483 Observations

Analysts had access to all data which was stored on the hard drive. With no security measures taken, including no procedures for backup, no procedures for password usage, and no procedures for data file handling, analysts could overwrite, alter and delete original data.
Examples of 483 Observations

Segregation of particles in a new hopper over the encapsulation operation resulted in a failure of the validation bulk capsule assay criteria. Validation personnel failed to notify Quality Assurance of the failure. The product was recalled from the market on __________.
Examples of 483 Observations

- Other examples have been related to:
  - No raw data or missing data to support the application
  - No investigation of batch failures or out-of-specification (OOS) results
  - Lack of validation for essential equipment
  - Lack of validated analytical methods
Communicate

- Communicate findings with firm
- Discuss your recommendation with your supervisor; with PAM
- Within 2 days send recommendation to PAM (CDER EES Report- page 2)
NWJ-DO- Past examples for reasons to “Withhold”

- Ill defined API quality-particle size, potency failure, quality attributes
- No processing equipment qualification
- Inadequate manufacturing environment
- Manufacturing and Laboratory OOS and Deviation Investigations
- Ill defined processing procedures
- Laboratory Data & Results Reporting
40 Withhold Recommendation Categories

- Drug not made here
- Facility withdrawn from application
- Firm not ready
- Inadequate firm response
- Previous deviations persist
40 Withhold Recommendation

Categories

- Insufficient development data
- Building & Facilities
- Contamination
- Pending regulatory actions
  - Warning Letter
  - Seizure
  - Injunction
40 Withhold Recommendation Categories

- Inadequate change control procedure
- Component or intermediate controls
- Deviation from DMF/NDA/ANDA
- Deviation from monograph
- Environmental controls
40 Withhold Recommendation Categories

- Holding & distribution
- Lab controls
- Master record non-specific or deficient
- Packaging and labeling controls
- Production and process controls
- QA Functions
40 Withhold Recommendation Categories

- Organization
- Records/reports
- Reprocessing
- Specifications
- Stability program
- SOP’s lacking or inadequate
- Training
- System Qualification (IQ/OQ)
40 Withhold Recommendation Categories

Validation Issues

- API process validation
- Computer validation
- HVAC validation
- Media Fills
- Water system validation
- Scale-up validation failure
- Validation protocol inadequate
- Equipment Qualification
- Equipment cleaning validation