# Overview of USFDA Drug Regulatory Requirements Pharmaceutical Quality and Facility Inspections (GMP)

***Session II***

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# GMP – The Other Side of Chemistry, Manufacturing & Controls (CMC)


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# Topics of Discussion

- What is GMP?
- Who is responsible for GMP compliance?
- FDA's role in ensuring GMP
- Types of FDA facility inspections
- Typical FDA facility inspections
- Common GMP deficiencies during FDA facility inspections

# GMP (Good Manufacturing Practice)

- Required for all active pharmaceutical ingredients (API) and drug products (DP) subject to US Market Applications (including botanicals) with medical claims
- GMP requirements are detailed in
  - 21 CFR 210 and 21 CFR 211 for the Drug Product
  - ICH Q7A for the API

# Aspects of GMP Regulations

- Organization and Personnel
- Quality Systems
- Corrective and Preventive Action Program
- Documentation and Records
- Facilities and Equipment
- Quality Control (QC) Laboratories
- Validation/Qualification/Calibration

# GMP Responsibility

- Who is responsible for compliance?
  - All sponsors (US and non-US) of investigational and marketing applications to CDER for products that are intended for the US market
  - All US-registered pharmaceutical manufacturing, packaging and testing facilities (US and non-US locations) of APIs and drug products; these are subject to FDA inspections
  - Pharmaceutical starting materials, excipients, and reagents are not subject to GMP rules or to FDA inspection, but suppliers' CMC documentation is required from Sponsors of the regulatory applications

# Role of FDA's Office of Compliance (OC)

- Oversees GMP functions
- Receives site inspection requests from Center of Drug Evaluation & Research (CDER)
- Coordinates domestic Inspections with Field Officers located throughout the different District Area locations in the US
- Coordinates foreign inspections in India, China, Sub-Saharan African countries, Europe, Latin America with the FDA's designated permanent offices in these regions. All other inspections in countries with no permanent FDA presence are scheduled by OC headquarters
- Issues recommendations (allows/withholds drug approval)
- Communicates with the facilities involved
- Communicates with the sponsor of the drug application

# Role of FDA's Office of Compliance (OC)

- Coordinates with FDA's International Affairs Office in matters that relate to GMP
  - Oversees the international agreements and/or arrangements between FDA and other countries regarding the GMP aspects and collaboration efforts
  - To learn more about these agreements and memoranda of understanding, you can visit: http://www.fda.gov/InternationalPrograms/Agreements/MemorandaofUnderstanding/default.htm

# FDA Inspection Team

- Typically composed of one or two inspectors
- In the case of a Prior-Approval Inspection, the team may include one of the Quality reviewers responsible for the Sponsor's application

# Scope of an FDA Inspection

Will an FDA inspector audit all aspects of GMP at every inspection?

- Realistically, no!
- Inspectors will typically cover 3-4 aspects (listed on Slide 4)
- Inspectors will always audit the "Quality Systems"
  - Quality Systems (QS) assure overall compliance with GMP as well as internal procedures (SOPs) and specifications
  - QS include all product deviation evaluations and recalled or returned products

How long will an FDA Inspector spend per inspection assignment for a drug?

- Typically, 1-2 days per facility. The inspection event could range from 2-5 days depending on the number of alternate facilities for any given activity and whether or not the product requires microbiological evaluation (e.g., sterile product)

# Pre-Approval Inspection (PAI)

- A PAI is usually scheduled with a facility (announced)
- Reasons for PAI
  - NDA (Original or Supplementary application for a change)
  - ANDA (Original or Supplementary application for a change)
  - The ANDA dosage form is new on facility's profile
  - A facility has not undergone satisfactory inspection within 2 years
  - The drug is high-profile
  - First-time implementation of US GMP
- FDA will not conduct PAIs for ANDA facilities in good US GMP standing unless, as indicated above, the facility has no US GMP history or the ANDA is for a high-profile drug

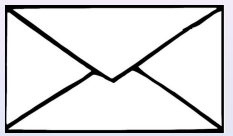
***Note:* Facility *refers to a manufacturing, packaging, analytical or stability testing site, or the sponsor's quality system location if not the manufacturer of the product***

# Post Approval Inspection

- Surveillance (routine) inspection
  - Comprehensive; inspection of a facility; frequency is based on suspected risk
  - FDA goal is to inspect all registered US & non-US facilities every 2 years
- For-cause (compliance) inspection
  - Follow up on past violations of a facility
  - Follow up on a complaint or allegation from an informant regarding a facility
- "Specific" Post-approval inspection
- Product-specific, soon after approval (process validation verification)
- "Surprise" inspection

***Note:* Facility *refers to a manufacturing, packaging, analytical or stability testing site, or the sponsor's quality system location if not the manufacturer of the product***

# Voluntary Inspections



FDA will accept invitations to audit any facility of special interest and will provide valuable feedback!

***Note:* Facility *refers to a manufacturing, packaging, analytical or stability testing site, or the sponsor's quality system location if not the manufacturer of the product***

# Publically Available Inspection Reports/Correspondence

- Form 483 (Inspectional Observations)
  - Generated by the Field Inspector and presented to OC
  - OC sends to
    - registered facility
    - sponsor of the product
    - CDER reviewing division
  - Includes deviations from current GMP regulations, application commitments, other regulations and the law
- Establishment Inspection Report (EIR)
  - Generated by the Field Inspector and presented to the OC
  - OC sends EIR to CDER reviewing division and facility
- Warning Letter
  - Issued by OC to sponsors and registered facilities ONLY for marketed products that deviate from GMP regulations, the law, or post approval commitments

# Private Inspection Forms

- Form 482 (Notice of Inspection)
  - Presented by the Field Inspector upon arrival at the facility to be inspected
- Form 484 (Sample Collection)
  - Used by the Field Inspector to collect samples, if needed

# Preparing for a Typical FDA Inspection

- Designate a spokesperson
  - Most knowledge of the Quality System
  - Can lead the GMP staff input
  - Understands roles of all key personnel
- Set an appropriate room with a conference table, and make available:
  - The organization chart of the facility
  - The building map with locations of the different operations
  - List of all Standard Operating Procedures (SOPs); be ready to pull any SOP at the request of the inspector and know where they are located
  - Roles and responsibilities of any contract manufacturers
- In the case of a PAI, a copy of the submission should be available so the inspector may verify the consistency of information in the application and the source documents on site
- Have all key personnel available to answer any questions that arise

# *Déroulement….*

- Inspectors arrive and meet the most senior person in the facility
- Identification and Form 482 (NOI) are presented
- Inspectors are escorted to the designated documentation conference room to meet the GMP spokesman and staff team
- Inspectors will decide on a strategy
  - Can the inspection be done in one day or will they need additional time?
  - Which aspects of GMP will they focus on (Quality System + 2-3 other aspects)?
- The Inspectors will take turns between inspection of facility operations and SOP verification
- Inspectors will coordinate with reviewing chemist (if present) regarding analytical methods and their validation documentation

# *Déroulement….*

- Inspectors visit the selected areas escorted by a facility's representative staff member, verify procedures, verify implementation of the standard operating procedures (SOP), ask questions to working staff and take notes
- At end of facility inspection, inspectors meet with the facility's spokesperson and staff team to wrap up the inspection, and commit to a time when an EIR will be available from the OC

# Examples of GMP Deficiencies During Inspection

**Manufacturing Deficiencies**

- Pivotal Bioequivalent (BE) batch in NDA/ANDA submission is not representative of the intended commercial batch
- Calculations for master formula are incorrect
- Raw material controls for API are deficient
- Acceptance controls for excipients (from vendors) are deficient
- Manufacturing equipment not accurately reported in batch record
- Suppliers of API reported in NDA/ANDA do not match those listed on drug product batch records
- Lack of investigation into complaints on product
- Lack of investigation into batch record deviations
- No PDR available for inspector review
- Failure to have a Sterility Assurance Plan for sterile products

# Examples of GMP Deficiencies During Inspection

**Analytical Methodology Deficiencies**

- Failure to comply with documented protocols (*e.g.,* stability protocol)
- Raw data in notebook incorrectly transcribed to reports (QC not done)
- Validation of API assay does not show stability-indicating capacity
- Failures (*e.g.*, in stability results) not addressed in NDA/ANDA application
- Stability chamber does not properly monitor temperature
- Dissolution testing done with tablet composite and not with individual tablets as regulations require
- Quality Assurance (QA) procedures not followed
- Instruments not properly calibrated or exceed their re-calibration schedule

# Examples of GMP Deficiencies During Inspection

**Documentation Deficiencies**

- No SOP for writing SOPs!
- Unplanned deviation related to implementation of SOP was reported as an planned deviation or *vice versa*
- Out-of-specification (OOS) analytical result not properly reported on the Corrective Actions and Preventive Actions (CAPA) form
- Water quality is not up to microbial limit standards for subject dosage form
- Lack of SOP for handling emergencies, such as fires or floods
- Inadequate account presented to inspectors regarding a past fire emergency and how it was handled (insufficient documentation of event and corrective actions)
- Warning instructions not clearly displayed

# Examples of GMP Deficiencies During Inspection

**Organizational/Personnel Deficiencies**

- Inadequate organizational chart. For example, too many roles for the same person (wears too many hats!)
- Not clear who is in charge of quality assurance
- Lack of clear position descriptions for GMP staff
- Lack of training requirements
- Training schedules not followed by personnel
- Laboratory analyst's training attendance not properly recorded or exhibited
- Gowning procedures not followed by some staff members
- No delegation procedure in place or inadequate procedure

# GMP Requires Continuous Upkeep!

- Conduct periodic internal audits to your facility
- Audit your contract manufacturer's facilities
- Audit your notebooks and always QC your reports
- Documentation, Documentation, Documentation! FDA wants you to document and report everything you do
- Make everyone in your firm responsible, not just the designated managers
- Keep staff informed and communicating across all areas
- Keep good communication with FDA's Office of Compliance: respond promptly to deficiencies with corrective actions
- Know your product and be confident of its quality
- Invite FDA to audit your facility – everyone likes to travel!

# GMP – C’est Fait!

Merci à Tous!