CBER Inspections of Facilities for Biological Products

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Outlines

- FDA/CBER Inspections
  - Pre-license inspections and pre-approval inspections (PLIs and PAIs)
- Systems and Elements Covered during Inspections
  - Seven major Systems
    - Three Critical Elements
- Examples of FDA Form 483 Observations
  - Inspections of manufacturing facilities of biological products

Applicable Regulations

- Public Health Service Act (PHS), Section 351(a)(3)(c)
- Federal Food, Drug, and Cosmetic Act (FD&C Act), Section 704
- Title 21 Code of Federal Regulations (CFR)
  - 600-680: Biologics standards
  - 210, 211: Current good manufacturing practice (CGMP) regulations for finished pharmaceuticals
  - 820, CGMP regulations for medical devices
  - 1271: Human cells, tissues, and cellular and tissue-based products (HCT/Ps)

Role of Inspections in a Review Process

- PHS Act and CFR
  - A biologics license shall not be issued except upon determination that the product and establishment comply with standards established in the BLA and the requirements prescribed in applicable regulations
- FD&C Act
  - An inspection, if needed, is considered to be a part of the complete review of an application
    - A PLI supports the review of a biologics license application (BLA)
    - A PAI supports the review of a prior approval supplement (PAS)
    - All FDA Form 483 observations (if any) must be resolved before approval

FDA Compliance Inspections

- FDA/CBER Inspection (PLIs and PAIs)
  - Conducted by CBER/OCBQ/DMPQ
  - Performed around the mid-cycle review clock
  - Pre-announced (and product specific)
  - DMPQ performs facility review
    - High level review of investigational new drug (IND) meetings
    - In-depth review of BLA submissions
    - Verification of information during inspections (product specific)
- FDA/Office of Regulatory Affairs (ORA) Surveillance Inspections
  - Conducted by FDA/ORA, may include product specialist(s)
  - CGMP compliance of an entire manufacturing site

CBER Inspection Objectives

- Verify the manufacturer's compliance with CGMP
- Verify accuracy and completeness of information submitted in a specific submission (BLA or PAS)
- Review documentation that is not included in the submission but is part of the overall review of the product
- Evaluate manufacturing control
- Observe critical manufacturing processes, including aseptic processing and other sterility assurance or microbial quality steps

PLI and PAI

- Inspection Team
  - DMPQ lead Inspector
  - Product Specialist(s)
  - FDA/ORA inspector (invited)
- Waiver of an Inspection
  - CBER SOPP 8410, *Determining when Pre-License/Pre-Approval Inspections are Necessary*
  - Risk assessment
  - FDA inspectional history

Prior to CBER Inspections

- A Production Schedule
- A Teleconference to Discuss Logistics
- A List of Documents
  - Documents available prior to inspection per FD&C Act 704(a)(4) Records Request
    - List of deviations, Index of all SOPs
  - Documents available on site for inspectors
    - Specific SOPs, e.g., deviations, CAPA, change control, change-over, environmental monitoring (EM)
    - Records/reports, e.g., environmental performance qualification (EMPQ) reports, equipment qualification records, manufacturing batch records (MBRs)

Routine Inspection Activities

- Opening (1st day of an inspection)
  - FDA introduction (Inspectors' credentials, Form 482 for facilities in US)
  - Firm introduction/presentation
  - Inspection of facility
- Inspection daily activities
  - Review and discussion of various Standard Operating Procedures (SOPs) and records/reports with subject matter experts (SMEs)
  - Observation of manufacturing operations
  - Discussions of any concerns/issues
- Closing (the last day of an inspection)
  - Discussion of 483 observation items (if any), and discussion items
  - Issuing FDA From 483 observations (if any)

Major Systems Covered during Inspections

- Seven Major Systems Covered during PLIs and PAIs
  - Quality
  - Facility and Equipment
  - Production
  - Materials
  - Packaging and Labeling
  - Laboratory Control
  - Donor Eligibility (only for some HCT products)
- Three Critical Elements (of each major system)
  - Standard operating procedures (SOPs)
  - Training
  - Records

Quality System

- Quality Oversight to All Systems and Assurance of Overall CGMP
  - Quality assurance (QA)
  - Quality control (QC)
- Approved Written Procedures and Documentation
  - Site master file and quality manual
  - Quality agreements
  - Training and qualification
  - Deviation management and corrective and preventive action (CAPA)
  - Change control
  - Document control procedures (batch records, labeling)

Facility and Equipment System

- Facility Design to Prevent Contamination/Cross-contamination
  - To provide adequate space for orderly manufacturing
  - Segregation of manufacturing steps
  - Unidirectional flows (preferred)
  - Temporal segregation and procedural controls
- Facility to Provide a Controlled Environment
  - Suitable building materials for cleanroom interior surfaces (smooth, impervious, unbroken and cleanable, resistant to deterioration)
  - Sealed joints, coved corners

Facility and Equipment System cont.

- Heating, Ventilation, and Air Conditioning (HVAC) System and Utilities
- Major Equipment Qualifications
  - Process performance qualification
  - Preventive maintenance and calibration
    - PM protocol, schedule, PM logs, calibration status (verification in MBR)
- Facility and Equipment Cleaning
  - Cleaning agents efficacy study
  - Cleaning procedures
  - Routine cleaning schedule and logs/records
  - Routine monitoring

HVAC System

- Using HEPA or ULPA Filtration to Provide Clean Air to Cleanroom Areas
- Considerations of Appropriate Cleanroom Classifications
  - Single or multi-product facility
  - Concurrent vs campaign manufacturing
  - Closed system vs open operations
- Air Handling Units (AHU)
  - Dedicated vs shared by different cleanrooms
  - Single-pass air vs recirculated air
- Airflow and Pressures Differentials (Monitored with a Warning System and Recorded)
- HEPA Filter Certification, Repair and Replacement
  - Filter recertification intervals: every 6 months for Grade A/B, and 12 months for Grade C & D cleanroom areas

Utilities and Computerized Systems

- Utilities
  - Qualifications of water systems and gases
  - Routine monitoring (chemical and microbial)
- Building Monitoring System
  - Recordings
  - Alarms, notifications and calibrations
- Additional Automated Computer Systems
  - Validation

Environmental Monitoring

- Environmental Monitoring (EM)
  - Environmental monitoring performance qualification (EMPQ) should be differentiated from routine operational EM
    - After the initial EMPQ, cleanroom requalification is performed after a shut-down or a major modification to cleanroom areas
    - Routine operational EM (viable and non-viable) should be performed in cleanroom areas
  - EM SOPs
  - EM Sampling Plan (supported by a risk assessment)
  - Qualified EM personnel performs EM sampling
  - Acceptance criteria (recommendations in ISO 14644, Annex 1, USP 1116, and FDA Guidance, *Sterile Drug Products Produced by Aseptic Processing* – CGMP, 2004)

Environmental Monitoring cont.

- Environmental Monitoring (EM) Records/Trending
  - Cleanroom temperature, humidity and differential pressure trending (routine EM data)
  - EM Air sampling
    - Non-viable air particulates
    - Viable air (active, passive)
  - EM Surface Sampling (viables)
    - Facility surface (walls, doors, etc.)
    - Equipment (e.g., BSC, incubators)
    - Personnel monitoring (aseptic operations)
- EM Deviation, Investigation and CAPA

Contamination and Containment Control

- Facility Design
  - HVAC system
  - Segregation
  - Flows (Personnel, material, product, equipment, and waste)
- Procedural Controls
  - Training
  - Gowning
- Facility and Equipment Cleaning
  - Cleaning validations
  - Line clearance and changeover
- Routine EM
- Pest Control

Production System

- Observation of Critical Manufacturing Processing Steps
- Manufacturing Process Validation
  - Batch records for conformance lots (or PPQ lots)
  - Sampling and testing
  - Small equipment calibration status
  - Pre- and post-use cleaning
  - Deviations
- Aseptic Processing
  - Operator gowning qualification and personnel monitoring records
  - The most recent smoke study for Grade A areas (BSC or isolator)
  - The most recent aseptic processing simulation (APS) study report
- Reprocessing, Rework Steps (if any)

Material System

- Warehouse/Inventory System
  - Storage and distribution SOPs
  - Segregated areas for quarantine and reject materials
  - Records
- Components/Raw Materials
  - Incoming material testing and releasing
    - Risk assessment
  - Identity test for critical incoming materials
- Shipping Validation
- Shipping Documentation
  - Chain of identity (COI) and chain of custody (COC)

Laboratory Control System

- QC Lab Is Separate from Manufacturing Areas
  - Physical separation with a separate entrance
  - Clean, controlled environment
  - Grade A BSC or isolator for any open and aseptic operations
- SOPs and Records
  - QC lab equipment qualification and calibration
  - Analytical method validation and acceptance criteria
  - Testing of in-process, drug product, and EM samples
  - Out of specifications (OOSs) and investigations

Labeling and Packaging

- Approved Written Procedures and Documentation
  - Labels storage, printing, usage and reconciliation
  - Line clearance
  - Controls to prevent label mix-ups
- Equipment Qualification
- Process Validation
  - Temperatures during labeling and packaging
  - Label adherence

Most Common Observations

- More Observations for Quality, Facility and Equipment, and Production systems
  - Observations were identified by inspectors (not representing a final determination of compliance)
  - Discussion of observations with inspectors during an inspection and in the responses to FDA Form 483

Common Inspection Issues

- Procedures
  - There are no written procedures for…
  - Written procedures for … are incomplete/deficient
  - Written procedures for … are not followed
- Documentation
  - Good documentation practices are not followed
  - Data are not adequately secured, maintained, and managed

Quality System Observations

Type of Observation	Examples
Deviation Management	• Deviations were not initiated. • Lack of a complete root cause analysis. • Investigation of out-of- specification (OOS) of one batch was not extended to other batches of the same product. • Timeline for closure of non-conformance is not justified.
CAPA	• CAPAs are not effective. • Lack of timeframes for CAPA implementation, evaluation of CAPA effectiveness, and closing of CAPA.
Training	• Aseptic technique training is inadequate.
Document Control	• Data are not adequately secured, maintained, and managed.
Quality Oversight	• Lack of quality oversight over...
Change Control	• Change of xxx (equipment, e.g., TFF) without a change control.

Facility and Equipment System Observations

Type of Observation	Examples
EM and EMPQ	• Lack of air monitoring (viable and non-viable) of cleanroom areas. • Lack of surface viable sampling of Grade C pass-throughs or Grade A BSC post-operations. • Sampling sites did not represent the sites where most critical operation took place.
Equipment Cleaning and Facility Cleaning	• Cleaning procedures for equipment and facilities were not specific enough to allow for consistent execution.
Equipment Qualification	• Qualification of equipment (e.g., Grade A BSC) has not been performed or is deficient.
Calibration/Maintenance	• Unplanned maintenance was performed without the quality oversight.
Disinfectant Effectiveness	• Disinfectant effectiveness study was not performed or is deficient.

Production System Observation

Type of Observation	Examples
Batch Record (BR)	• The BR does not document the completion of each significant step. • The BR does not document that all critical in-process parameters were met.
Aseptic Process Simulation (APS)	• APS does not simulate all of the critical aseptic processes executed during the production. • Growth promotion testing was not performed.
Process Validation	• The process performance qualification (PPQ) study was based on clinical batches prior to defining the commercial process. • Changes made to the commercial manufacturing process were not evaluated during PPQ study.
Reprocessing/Rework	• Reprocessing was performed without a written procedure.

Material System Observations

Type of Observation	Examples
Incoming Material Testing and Specification	• Failure to reject lots of components that did not meet the appropriate written specifications . • Suppliers' certificate of analysis for components or consumables used during production of X are not periodically verified through testing of incoming lots.
Inventory Control and Storage	• Materials are not being properly segregated. • Receiving/incoming materials area is overflowing with received materials. • Storage areas are not adequately labelled.

Laboratory Control System Observations

Type of Observation	Examples
Testing Method	• The suitability of all testing methods is not verified under actual conditions of use.
Sample Storage and Tracking	• No documented system is in place to track and manage the flow of the samples.
In-process and Release Specification/OOS Investigation	• Testing into compliance: Retests of bulk and final products were performed prior to initiation of manufacturing investigation of OOS for cell count and viability. The sample was retested in triplicate with passing results and the lot was released.

Labeling and Packaging System Observations

Type of Observation	Examples
Final Packaging Inspection	• Visual inspection (VI) parameters have not been fully defined. • VI reject rate is not based on suitable statistical procedures. • When VI failed and reinspection of temperature-sensitive product could not be performed, no alternative strategy or remediation plan was developed.

Shipping	• Shipping validation is inadequate in that:
	  ○ The temperature during the shipment does not represent a worst case temperature challenge.
	  ○ Shipper temperature and container closure integrity are not verified appropriately upon receipt.
	• Shipped plasmids were labeled incorrectly. Material failed identity test upon receipt.

Labeling	• Lack of control of the label templates and excess printed labels. • Excess printed labels returned from production are stored in an unlocked cabinet.

Summary

- CBER Inspections (PLIs and PAIs)
  - Conducted by CBER/DMPQ around mid-cycle review clock
  - All FDA Form 483 observations (if any) must be resolved before approval
- All Major Systems Inspected during PLI and PAI
  - SOPs, training and records
- Examples of Common Observations Identified during Inspections

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Thank You!

Any Questions?