

Overview of Biological Drug Inspections

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Purpose of the Presentation

- To provide an overview of the Center for Biologics Evaluation and Research (CBER), the products we regulate and how we regulate the products through application reviews and inspections.
- To discuss possible outcomes of violative findings.

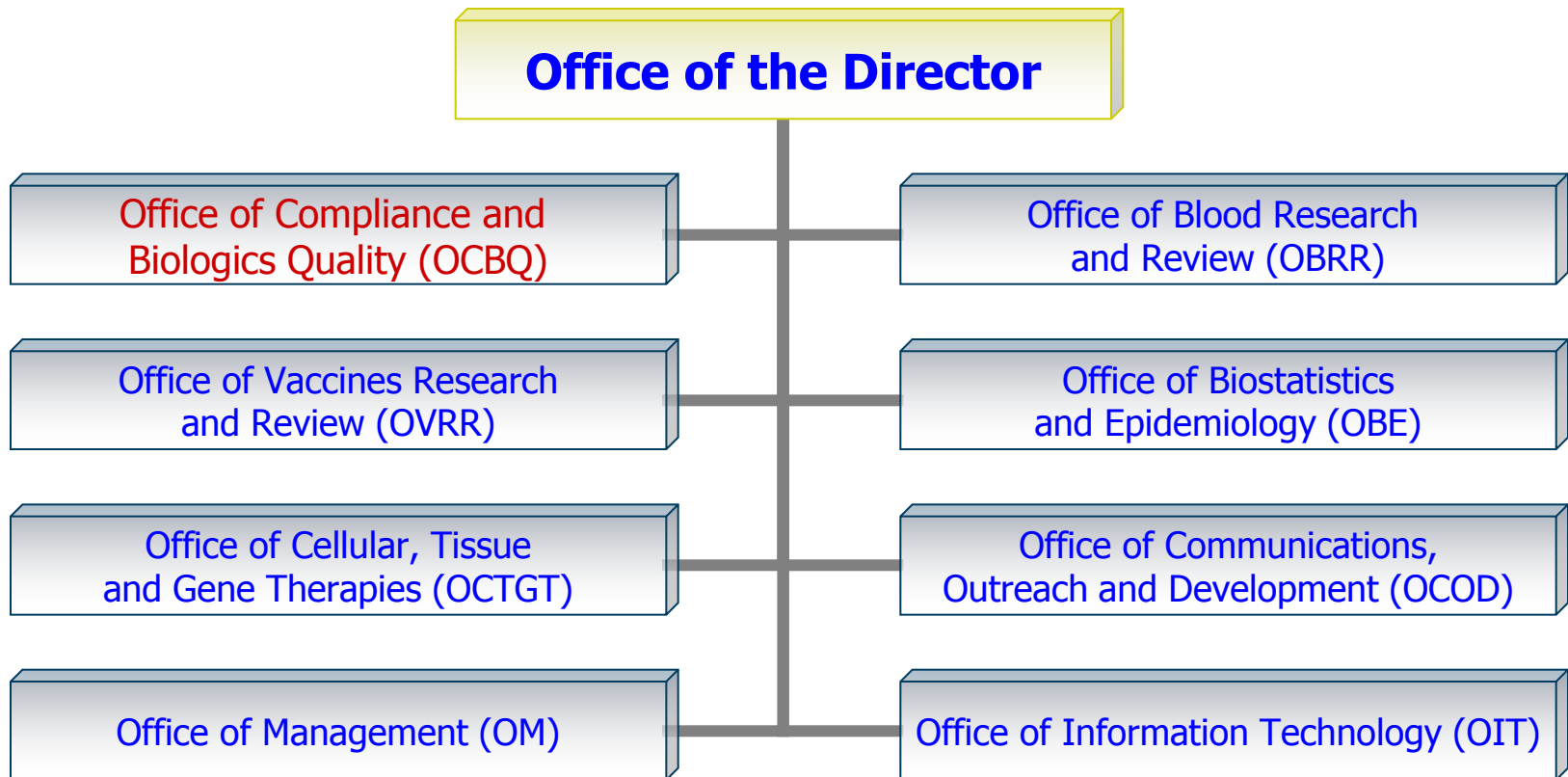
Presentation Outline

- Introduction of CBER regulated products
- Overview of biological drug inspections
- Observations found during inspections
- Post-market regulatory actions

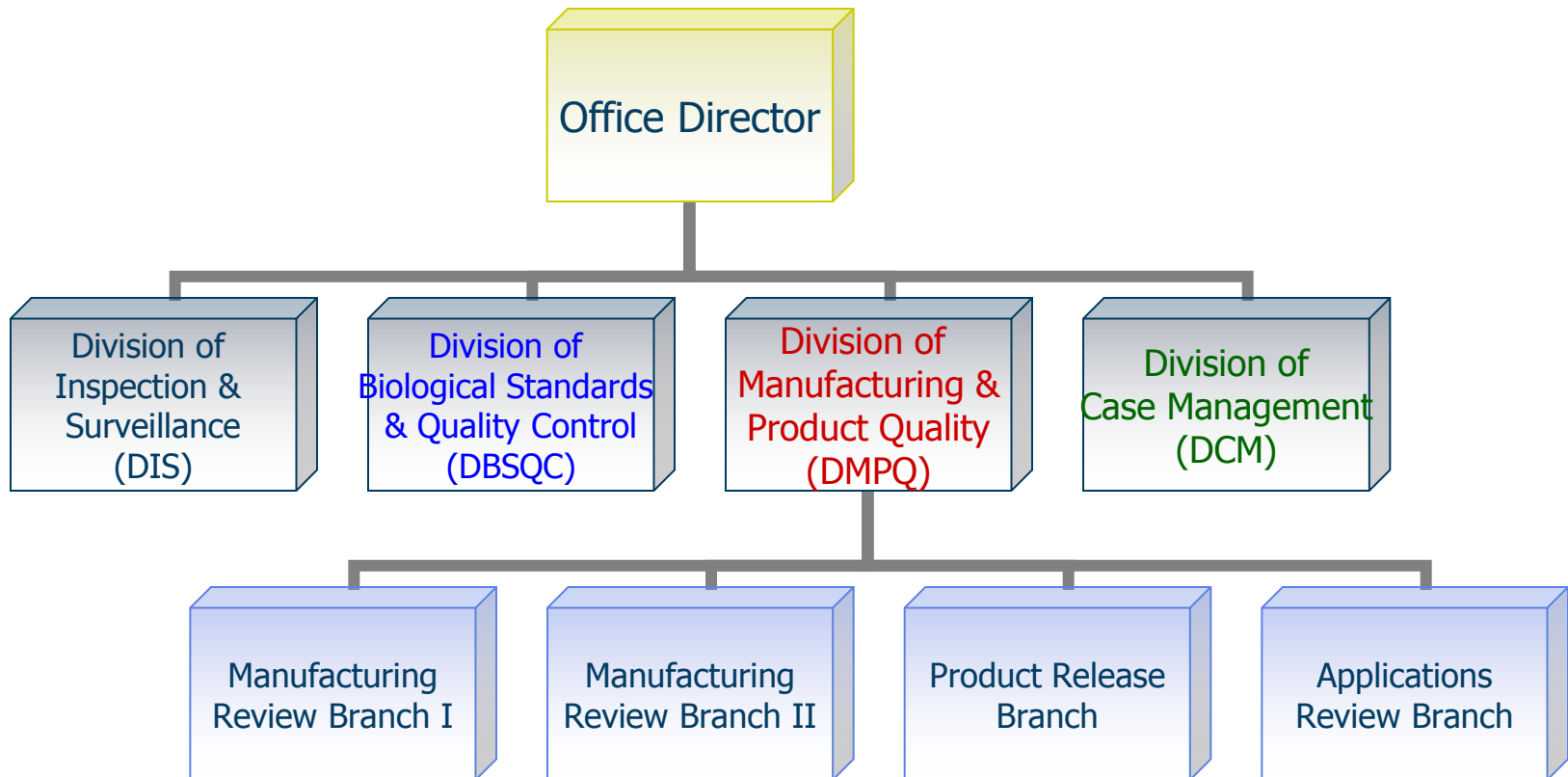
CBER Mission

To ensure the safety, purity, potency, and effectiveness of biological products including vaccines, blood and blood products, and cells, tissues, and gene therapies for the prevention, diagnosis, and treatment of human diseases, conditions, or injury. Through our mission, we also help to defend the public against the threats of emerging infectious diseases and bioterrorism.

Center for Biologics Evaluation & Research (CBER)



Office of Compliance & Biologics Quality (OCBQ)



Products Regulated by CBER

- Allergens – allergen patch tests, allergenic extracts
- Blood & blood products – blood derivatives, whole blood, blood components
- Selected devices – IVDs for blood screening, cell separation devices, blood collection containers
- Vaccines – preventive and therapeutic
- Cellular & gene therapy products
- Human cell, tissue, and cellular and tissue-based products (HCT/Ps)
- Xenotransplantation products
- Biosimilars

Unique Challenges for Biologics

- Most biologics are derived from cells, tissues, or living organisms
- Most biologics are complex mixtures that are not easily characterized
- Tend to be heat sensitive and susceptible to microbial contamination
- Complexity of manufacturing facilities, materials, processes and products

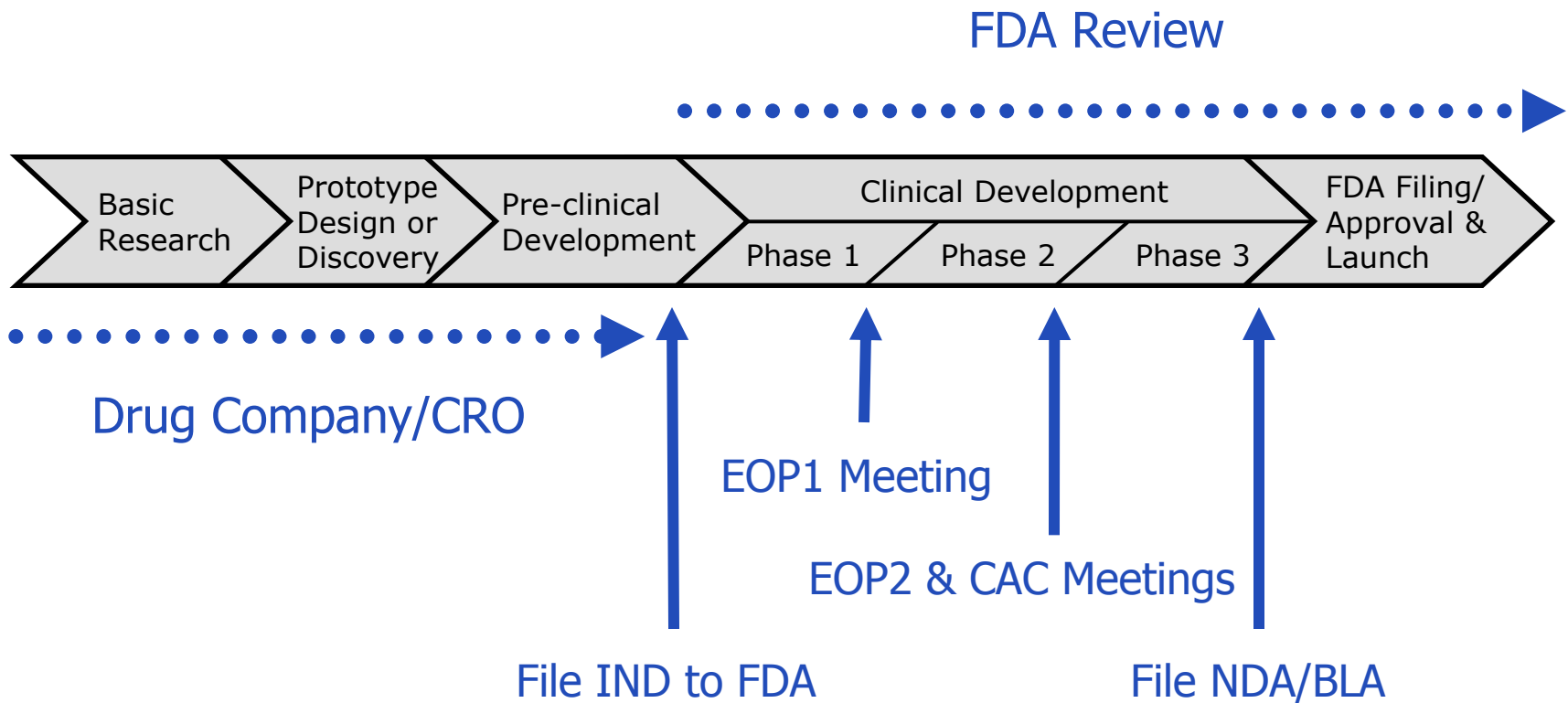
Unique Challenges for Biologics

- Many biological products cannot be terminally sterilized and aseptic techniques must be used from start to finish during manufacture
- Complex mechanisms of drug actions
- Highest public concern for safety of critical products given to healthy individuals
- Unique roles in healthcare and national preparedness (pandemic, war/disaster, counterterrorism)

Different Regulatory Pathways for Products Regulated by CBER

- **Biologics License Application (BLA)**
- Investigational New Drug Application (IND)
- Investigational Device Exemption (IDE)
- Premarket Notification 510(k)
- Premarket Approval Application (PMA)
- Post-market Supplement – Prior Approval Supplement (PAS), Change Before Effective (CBE/CBE-30), Annual Report (AR)
- NDA, ANDA, Drug Master Files (DMF)

Overview of Drug Development



Information to Be Submitted in BLA for Approval

- Applicant information
- Product, methods, establishment and manufacturing information – chemistry, manufacturing and controls (CMC)
- Non-clinical studies
- Clinical studies
- Statistics / Epidemiology
- Pharmacology / Toxicology
- Labeling
- Other information as required by statutes and regulations

Legal Basis for Conducting Inspections

Public Health Service Act (PHS Act), Sec. 351(c) – Any officer, agent, or employee of the Department of Health and Human Services, authorized by the Secretary for the purpose, **may during all reasonable hours enter and inspect any establishment for the propagation or manufacture and preparation of any biological product.**

Legal Basis for Conducting Inspections

Federal Food, Drug, and Cosmetic Act (FD&C Act), Sec. 704(a)(1) – Officers or employees duly designated by the Secretary upon presenting appropriate **credentials** and a **written notice** to the owner, operator, or agent in charge, are authorized:

Legal Basis for Conducting Inspections

(A) to **enter, at reasonable times, any factory, warehouse, or establishment** in which food, drugs, devices, or cosmetics are manufactured, processed, packed, or held, for introduction into interstate commerce or after such introduction, or to enter any vehicle, being used to transport or hold such food, drugs, device, or cosmetics in interstate commerce; and

(B) to **inspect, at reasonable times, and within reasonable limits and in a reasonable manner, such factory, warehouse, establishment, or vehicle and all pertinent equipment, finished and unfinished materials, container, and labeling** therein.

Legal Basis for Conducting Inspections

21 CFR Part 601.20(d) – A biologics license shall be issued or a biologics license application approved **only after inspection of the establishment(s)** listed in the biologics license application and **upon a determination that the establishment(s) complies with the standards established** in the biologics license application and the requirements prescribed in applicable regulations.

Legal Basis for Conducting Inspections

21 CFR 601.2(d) – Approval of a biologics license application or issuance of a biologics license shall constitute a determination that the establishment(s) and the product meet applicable requirements to ensure the **continued safety, purity, and potency** of such products. Applicable requirements for the maintenance of establishments for the manufacture of a product ... shall include but not be limited to the **good manufacturing practice requirements** ...

Legal Basis for Conducting Inspections

21 CFR Part 600.21 – The inspection of an establishment for which a biologics license application is pending need not be made until **the establishment is in operation and is manufacturing the complete product** for which a biologics license is desired. In case the license is denied following inspection for the original license, no reinspection need be made until assurance has been received that the faulty conditions which were the basis of the denial have been corrected.

Type of Inspections

- Pre-License Inspection (PLI) – for a new applicant or a new product under a BLA that has not been previously approved
- Pre-Approval Inspection (PAI) – for major changes made to an existing BLA
- Bioresearch Monitoring Inspection (BIMO) – for products under IND (e.g., GLP, GCP)
- CGMP Inspection – for post-approval or biennial CGMP surveillance
- Directed Inspection – for cause

Pre-License Inspection (PLI)

- An inspection of a firm that has not been licensed by the FDA for a new product under BLA review
- May be a US or non-US licensed firm with a new product
- May involve several manufacturing or testing sites
- Part of BLA review process, normally conducted at the mid-cycle of BLA review
- Pre-announced

Pre-License Inspection (PLI)

- Conducted when the establishment is in operation and is manufacturing the biological drug products
- Led by inspectors from DMPQ in OCBQ with participation of product specialists. Investigators from ORA District Office and Team Biologics may also participate
- Is a **system-based, risk management approach** to conducting inspections of manufacturing facility and production process

Inspection Objectives

- **Verify:**
 - The firm's compliance with FDA applicable laws and regulations including CGMP
 - Accuracy and completeness of the contents and information submitted in the BLA
- **Evaluate:**
 - The consistency of manufacturing operations as supported by process validations and controls

What Will Inspectors Do during the Inspection?

- Present credentials and Issue Form FDA 482 – Notice of Inspection (issued to domestic firms only)
- Interview personnel and review and/or verify documents and records
- Collect evidence/exhibits to support the observations (e.g., SOPs, validations and investigations)
- Bring to the attention of the manufacturer any significant deficiency observed during the inspection

What Will Inspectors Do during the Inspection?

- Walk through the facilities and visually observe the manufacturing processes of the product, including:
 - Facilities, utilities and equipment
 - Gowning
 - Aseptic processing
 - Changeover / line clearance
 - Cleaning and sanitization
 - QC testing
 - Receiving, storage, distribution & shipping
 - Data entry, data tracking
 - Batch records

What Will Inspectors Do during the Inspection?

- Document objectionable conditions by issuing **Form FDA 483 – Inspectional Observations**
- Bring to the attention of the manufacturer any significant deficiency observed during the inspection

System-based, Risk Management Approach

➤ **The Seven Key Systems**

- Quality System
- Facilities & Equipment System
- Materials System
- Production System
- Packaging & Labeling System
- Laboratory Control System
- Donor Eligibility (for cord blood)

➤ **The Three Critical Elements**

- Standard Operating Procedures (SOPs)
- Training
- Records

Six Key Systems Generally Covered during the PLI

- Quality System
- Facilities & Equipment System
- Materials System
- Production System
- Packaging & Labeling System
- Laboratory Control System

Quality System

Assures overall compliance with CGMP, applicable regulations, internal procedures, and specifications.

Quality System

- Responsibilities of Quality Control Unit (QCU) include:
 - Release and/or reject all components, in-process materials, containers and closures, packaging, labeling, and finished products
 - Approve and/or reject procedures and specifications
 - Change controls
 - Deviations, OOS
 - Investigations, CAPA
 - Product recalls, rejects
 - Reporting of complaints, AE, BPDR

Quality System

- Responsibilities of QCU include (cont'd):
 - Batch records review
 - Annual product review
 - Validation protocols and reports
 - Evaluation of returned and salvaged products
 - Training program
 - Document controls, record keeping
 - Vendor audit/qualification

Quality System

Both the license holder (manufacturer) and the contractor share the responsibility for the product quality; however, the license holder remains ultimately responsible for compliance with established product standards, specifications, CGMP and applicable regulations. The contractor is only responsible for complying with the applicable regulations specific for the manufacturing steps that they perform.

Facilities & Equipment System

Includes the measures and activities that provide an appropriate physical environment, equipment and resources that are used in the production of the drug substances and drug products.

Facilities & Equipment System

- Facility and Utility – Verify:
 - Facility qualifications
 - Utility system qualifications such as water, air, gas and steam
 - Heating, ventilation, and air conditioning (HVAC) system qualifications
 - Cleaning, sanitization, sterilization
 - Routine inspection, and maintenance program(s)

Facilities & Equipment System

- Equipment – Verify:
 - Equipment qualifications such as autoclave, lyophilizer, filling machine and fermentor, etc.
 - Equipment cleaning/sanitization
 - Routine inspection, calibration and preventive maintenance
 - Effectiveness of cleaning/sanitization agents
 - Computer system validation/qualification

Facilities & Equipment System

- Environmental monitoring (EM) program –
Verify:
 - Cleanroom qualification – room classification, alert and action levels
 - EM sampling location, size, frequency and timing
 - Monitoring of viable and non-viable airborne particles, surface, and personnel
 - Identification of facility microbial isolates
 - Periodic review, trending and analysis of EM data, as well as corrective and preventive actions

Materials System

Includes the measures and activities to control the drug substances and drug products as well as the components, source materials, water or reagents that are incorporated into the finished drug products, and containers and closures.

Materials System

- Review and verify:
 - Validation/qualification of inventory & tracking systems
 - Receiving
 - Product storage, quarantine, security
 - Predistribution and distribution controls
 - Shipping validation
 - Control of facilities used for storage, quarantine & distribution
 - Container & closure system

Production System

Includes the measures and activities to control the manufacturing processes and testing of the drug substances and drug products, including following and documenting performance of approved manufacturing procedures.

Production System

- Review and/or observe:
 - Process validation
 - Aseptic processing validation
 - Sterile filtration
 - In-process controls and testing
 - Establishment of the time limits for completion of each phase of critical process
 - Lot release
 - Batch records

Production System

- Request a demonstration of process controls and validations (where necessary) for:
 - Maximum production throughput
 - Aseptic processing
 - Prevention of mix-ups, contamination and cross-contamination
 - Changeover and line clearance

Packaging & Labeling System

Includes the measures and activities that control packaging and labeling of the drug products.

Packaging & Labeling System

- Review and verify:
 - Control of packaging and labeling materials
 - Procedures for storage, issuance, removal, and destruction of labels
 - Maintenance of chain of identity throughout the entire manufacturing processes
 - Procedures and documentation of control of labeling issuance to prevent label mix-ups
 - Changeover and room clearance

Laboratory Control System

Includes various measures and activities related to laboratory procedures, analytical methods development, validation or verification, and the stability program.

Laboratory Control System

- Review the procedures for control of microbiological contamination and EM test
- Review the records for source materials, in-process and finished drug product release specifications
- Evaluate the methods for sampling and testing products for safety, purity, potency, identity, and stability, etc.
- Ensure the analytical testing methods are validated or qualified

Laboratory Control System

- Review and verify:
 - QC equipment qualification
 - Records for QC equipment inspection, calibration and maintenance
 - Validation and results of:
 - Sterility testing
 - Microbiological testing
 - Stability testing
 - Analytical testing

Three Critical Elements to Be Covered for Each System

- Standard Operating Procedures (SOPs)
- Training
- Records

Standard Operating Procedures

- Determine if the firm has approved written SOPs and associated records for each of the six systems
- Verify, through walk-through and actual observation, if the firm follows the approved written SOPs and adheres to the applicable regulations
- Determine if the SOPs include all critical steps and these steps are followed during the manufacturing and control of the biological drug substances and drug products

Standard Operating Procedures

- Verify if:
 - The most current version of approved SOPs are used by operators
 - SOPs are periodically updated to reflect any process change
 - All personnel are trained on most current version of SOPs

Training / Personnel

- For each manufacturing operation or QC function, personnel should be trained for their specified tasks
 - Determine if the firm has an adequate number of trained personnel to perform the assigned functions and specific operations
 - Verify if all personnel have appropriate education and training to perform specific duties
 - Verify if operators have been re-trained on a regular basis for CGMP, gowning, and aseptic processing, etc.

Records

- Records must be maintained concurrently with the performance of each step of manufacture
- If records are maintained in an electronic format in place of paper format, the record tracking / keeping system should comply with 21 CFR Part 11

Records

- All records must:
 - Be accurate, legible
 - Identify the individual performing the work
 - Include dates of the various entries
 - Show test results and interpretation of the results
 - Show the expiration date assigned to specific lot
 - Have sufficient details to provide a traceable and complete history of the work performed

Records

- Record review by the investigator may include:
 - Review of a sampling of records for operations performed in each of the systems
 - Verification that records are complete and maintained as required
 - Verification that the firm reviews records pertinent to the manufacture of the lots or units prior to release and distribution
 - Review of all records related to product retention, deviations, out of specifications, complaints, rejects, and failure investigations

Records

- Record review by the investigator may include (cont'd):
 - SOPs
 - Process Validation
 - Facility and equipment qualification
 - Computer system validation
 - Master batch records and executed batch records
 - User logs
 - Inventory
 - Vendor audits
 - Training
 - Laboratory testing

Outcome of Inspections

- No Action Indicated (NAI)
- Voluntary Action Indicated (VAI)
- Official Action Indicated (OAI)
- Complete Response (CR) Letter or Non-concurrence Letter

FY11 GMP Inspection Citations – Biological Drugs

Citation	Citation Language
211.192	“You failed to thoroughly investigate any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications.”
211.113(b)	“Your firm failed to establish and follow appropriate written procedures designed to prevent microbial contamination of drug products purporting to be sterile and to assure that such procedures include validation of sterilization processes.”

FY11 GMP Inspection Citations – Biological Drugs

Citation	Citation Language
211.94(a)	“You failed to assure that drug product containers or closures are not reactive and additive so as to alter the safety, identity strength, quality and purity of the drug beyond the official or established requirements.”
600.14	“You failed to report biological product deviations for lots of bulk and final drug product that represent marketed product and have failed stability at various time points.”
601.12	“You failed to inform FDA about each change in the production process established in your approved license application(s).”

FY11 GMP Inspection Citations – Biological Drug Intermediates & Substances

- Failure investigations
- Production and process controls
- Control of microbiological contamination
- Equipment cleaning and maintenance
- Laboratory controls
- Control of components

Post Approval Surveillance

- Post marketing commitments (PMC)
- Surveillance / Adverse Event (AE) reporting
- Biological Product Deviation Report (BPDR)
- Lot Release (for most BLA)
- Reporting post-approval changes as supplement to BLA (e.g., PAS, CBE/CBE-30)
- Annual Report
- GMP inspections

Objectives of Regulatory Actions

- Provide prior warning
- Prevent distribution
- Correction

Types of Regulatory Actions

- Regulatory meetings
 - Requested by FDA to inform responsible individuals or firms about how their products, practices, processes, or other activities are considered to be in violation of the law
 - Can be an effective enforcement tool to obtain prompt voluntary compliance

Types of Regulatory Actions

- Advisory actions
 - Warning Letters – issued for significant violations that may lead to enforcement actions if not promptly and adequately corrected
 - Untitled Letters – cite violations that do not meet the threshold of regulatory significance for a Warning Letter

Types of Regulatory Actions

- Administrative actions
 - License revocation or suspension
 - Orders of retention, recall, destruction and cessation of manufacturing related to human cell, tissue and cellular and tissue-based products (HCT/Ps)
- Judicial actions – seizure, injunction, consent decree, prosecution

Judicial Actions

- Seizure – Attachment of goods through Court order by a U.S. Marshal
- Injunction – An order issued by the Court requiring a defendant to perform an act, or forbidding him from doing a specified act
 - Grants FDA power to inspect facilities at the firm's expense, shut down operations, and dispose goods
 - Violation of terms can result in civil or criminal charges

Judicial Actions

- Consent decree – A settlement of a lawsuit or criminal case in which a person or company agrees to take specific actions without admitting fault or guilt for the situation that led to the lawsuit
- Prosecution – allows FDA to hold those responsible legally liable for their acts
 - Civil penalties
 - Criminal investigation/prosecution

Examples of Violations that May Result in Enforcement Actions

- History of repeated or continual violations
- Intentional or flagrant violations
- Violations present a reasonable possibility of injury or death
- Despite issuance of Form FDA 483 and/or Warning Letter, the violations have not been corrected, or are continuing

Examples of Violations that May Result in Enforcement Actions

- CGMP violations
- Contaminated products – microorganisms, pesticide residues
- The product shows short contents, sub-potency, or super-potency

Summary

- Biological drug products are subject to the applicable regulations promulgated under FD&C Act and PHS Act, including CGMP
- FDA uses a system-based, risk management approach to conduct inspections of biological drug manufacturers – **seven key systems and three critical elements**
- Regulatory actions may be taken for violations of FDA laws and regulations

References

- 21 CFR Parts 210, 211 – Current Good Manufacturing Practice for finished Pharmaceuticals
- 21 CFR Parts 600, 601, 610 – Biological Products
- 21 CFR Part 11 – Electronic Records
- Compliance Program Guidance Manual – Inspection of Biological Drug Product (CBER) 7345.848
- Investigations Operations Manual (IOM), Chapter 5 – Establishment Inspections
- Regulatory Procedures Manual

Acknowledgement

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