An Overview of Pre-License Inspections for Biotech Products

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Outline

- Regulatory Definition of Biological Products
- Regulatory Requirements for Biological Products Submitted under Biologics License Applications (BLAs)
- CDER Biotech Pre-license and Pre-approval Inspections
- Common Deficiencies

What is a Biological Product?

- Biological products are licensed under Section 351 of the Public Health Service (PHS) Act

- The term "biological product" is defined as “a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings” (Section 351 of the PHS Act)

- PHS Act amendments:
  - Updated definition of a “biological product” (2/21/2020)
    - Protein: Any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size.
  - Inclusion of the biological products under the “deemed to be a license” provision in section 7002(e)(4) of the BPCI Act (3/23/2020)

Biological Products Regulated by CDER

- Monoclonal antibodies for in vivo use.
- Most therapeutic proteins, including cytokines (e.g., interferons), enzymes (e.g. thrombolytics), and other novel proteins,
- Immunomodulators (non-vaccine and non-allergenic products intended to treat disease by inhibiting or down-regulating a pre-existing, pathological immune response)
- Growth factors, cytokines, and monoclonal antibodies intended to mobilize, stimulate, decrease or otherwise alter the production of hematopoietic cells in vivo.

Pharmaceutical Quality Considerations for BLAs

- The product, the manufacturing process, and the manufacturing facilities must meet standards prior to license issuance (21 CFR 601.4)
- Complete commercial scale Process Performance Qualification (PPQ) studies and submit data in the application (2011 PV Guidance)
- Facility ready for inspection and is manufacturing the complete product for which a biologics license is desired
- Not permit in BLAs to reference drug substance, drug substance intermediate, or drug product (DS/DSI/DP) DMFs

*Note: Allow biological products deemed to be licensed under the PHS Act on March 23, 2020 to continue to reference a MF for drug substance, drug substance intermediates or drug products information

Guidances on Sterile Drug Products Produced by Aseptic Processing

- Guidance for Industry, 2004
  - Current good manufacturing practice regulations (21 CFR parts 210 and 211) when manufacturing sterile drug and biological products using aseptic processing

- Guidance for Industry, 1994
  - Information should be submitted in support of sterility assurance for products manufactured by aseptic processing
    - Identification of the manufacturing areas and type of fill line
    - The sterilization and depyrogenation processes used for containers, closures, equipment, and components
    - Information for media fills
    - the integrity of the container-closure system
    - Bacterial Endotoxins and Sterility Testing Methods and Release Criteria

Assessment of Manufacturing Facility during a Pre-License Inspection

Regulatory Authority

- 21 CFR 600.21 –Time of Inspection
  - Inspection conducted while the establishment is in operation and is manufacturing the complete product for which a biologics license is desired

- 21 CFR 601.20 – Biologics licenses; issuance and conditions
  - Product examination - compliance with requirements
  - Availability of product for examination and inspection during all phases of manufacture
  - Inspection - compliance with requirements (establishment)

A Risk Based Criteria for Biotech Inspection Decision

- Prior inspection history
  - new facility/building/filling line without inspection history
  - Prior experience with similar manufacturing process
  - Information shared by other Regulatory Authorities
- CGMP issues relevant to application product
- Product risks
- Novel technologies
- Process complexity
- Application specific concerns
- Significant process changes

Alternative Approaches to Inspections

- Records Request under § 704(a)(4) of the FD&C Act
  - In advance or in lieu of an inspection
- Inspection Waiver
  - Based on record review
  - Prior inspection history
  - Experience with similar manufacturing process

How to Prepare for PLIs?

- Early and frequent communication/meetings with FDA to discuss manufacturing facilities and timelines for inspection
  - Provide production schedules for the complete product
  - Ensure timely responses to Agency's Requests

- Conducting mock inspections
  - The information submitted is complete, accurate, and consistent with site records

- The site is ready for inspection upon submission

Examples of Application Deficiencies
&
During PLIs/PAIs

Common Submission Deficiencies

- Complete PPQ not conducted to support submission
- Product will not be manufactured within review cycle and/or during inspection
- Sterilization validation data is insufficient
- Failures to submit equipment qualification, process simulation, sterility testing methods
- Discrepancies between the information submitted in an application and the manufacturing process performed at a site

PLI/PAI Deficiencies: Quality Oversight

- Contract Manufacturing Arrangement does not clearly define and establish each party's manufacturing activities
- Inadequate oversight of the testing and record review
- Deviations, OOS investigations and CAPA implementation

PLI/PAI Deficiencies: Data Reliability

- Manipulation of sample preparation and test procedures to obtain favorable results
- Deletion of electronic data including audit trial
- Operators were assigned administrative privileges, able to access data file and delete date/files

Aseptic Processing Deficiencies

- Inadequate smoke studies
  - Missing set-up activities, dynamic conditions, interventions
- Inadequate media fill procedures
  - Failure to simulate the entire aseptic operations, product contact equipment
- Inadequate environmental monitoring
- Inadequate aseptic practices
  - Excessive movements
  - Inadequate glove disinfection
- Inadequate design and constriction of facility and equipment
  - HEPA filter failures
  - Inadequate validation of sterile hold time for product contact equipment

Summary

- Regulatory Requirements for BLAs
  - Submit commercial scale process validation data in the application
  - Availability of product for examination and inspection during all phases of manufacture

- Pre-License/Pre-Approval inspections are required for BLAs and supplements (for new facilities)
  - Evaluate product quality and observe manufacturing operations
  - Verify compliance with commitments made in the BLA or supplement
  - Adherence to CGMPs

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