

TEAM BIOLOGICS INSPECTION APPROACH

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Objective

- Provide a brief overview of the Team Biologics program
- Outline the Team Biologics inspection approach under Compliance Program 7345.848

Team Biologics - Who Are We?

- Team Biologics is a partnership between ORA and CBER
 - Established in 1997
 - Focus on ensuring the quality and safety of biologic products
 - Assure consistent comprehensive inspections of biologics manufacturers

- Core Team Includes specially trained field investigators:

Rose Ashley	Omotunde Osunsanmi
Jacqueline Diaz-Albertini	Prabhu Raju
Cynthia Jim	Helen Ricalde
Mihaly Ligmond	Paula Trost
Christian Lynch	Supervisor: Ann Marie Montemurro

- Also includes: CBER product specialists, ORA and CBER compliance officers, and respective management

What Do We Do?

- Responsible for conducting post-market inspections of licensed biologic drugs and devices including:
 - Vaccines
 - Allergenic extracts products
 - Antitoxins, antivenins, and venoms
 - Plasma derived products, including their recombinant analogues
 - Licensed IVD products
 - Gene / Cellular Therapy Products

Note: In 10/2007 the inspection responsibility for CDER regulated licensed therapeutic products was transferred from Team Biologics to the District Offices

Inventory of Firms

- 28 Vaccines and Related Products
- 42 Plasma derived products and their recombinant analogues
- 15 Allergenic Extracts
- 26 IVD
- 1 Cell Therapy

Includes both domestic and foreign sites

Team Biologics Inspections

- TB post-approval inspections led by ORA
 - biennial GMP
 - Directed / Compliance Follow-up inspections – may be more frequent

- Inspection Team
 - ORA CT Investigator(s)
 - Center Product Specialists
 - Participation on-site or via telephone
 - May Include district participation
 - Can be conducted jointly with CBER/DMPQ pre-approval inspection

Systems Based Inspections

- Utilize a **risk-based approach** to conducting inspections which identifies **six key systems** and **three critical elements** within each system that are common to establishments that produce biological drug products.
- This approach is outlined in Compliance Program Guidance Manual (CPGM) 7345.848, Inspection of Biologic Drug Products.

Note: Licensed IVD inspections are not conducted using the system based approach.

Systems Approach

➤ Six Key Systems

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

➤ Three Critical Elements

- Standard Operating Procedures (SOPs)
- Training
- Records

Quality Product

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graph TD; QP[Quality Product]; QS[Quality System  
Directed by Quality Unit]; LCS[Laboratory Control System]; PS[Production System]; PLS[Packaging and Labeling System]; FES[Facilities and Equipment System]; MS[Materials System]; QS --> QP; QS --> LCS; QS --> PS; QS --> PLS; QS --> FES; QS --> MS; LCS --> QP; PS --> QP; PLS --> QP; FES --> QP; MS --> QP;
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Quality System
Directed by Quality Unit

**Laboratory Control
System**

**Production
System**

**Packaging and Labeling
System**

**Facilities and Equipment
System**

**Materials
System**

Quality System

This system assures overall compliance with CGMPs, internal procedures, and specifications which includes, but is not limited to the quality control unit (QC) responsibilities such as:

- release of components and in-process materials
- change control
- reprocessing
- batch release
- annual record review
- validation protocols and reports
- product defect evaluations
- complaint handling
- evaluation of returned and salvaged products

Assessment of the Quality System

- **Phase I** – evaluate whether the QC unit has fulfilled its responsibility to review and approve all procedures related to production, quality control and quality assurance and to ensure the procedures are adequate for their intended use. This assessment should also include review of the associated record keeping systems.
- **Phase II** – assess data collected in order to identify quality problems that might be linked to other systems

Quality System – 483 / Warning Letter Examples

- Failures were not fully investigated and documented, nor were they extended to other batches as appropriate. For example:
 - a. You failed to quarantine numerous process intermediates associated with the use of [redacted] filter membranes that were identified to cause foaming during filtration. This foaming was found to be associated with leaching of [redacted] into process intermediates. These process intermediates were used to further manufacture finished vaccine product lots.
- Failure to report any event and relevant information associated with the manufacturing of a licensed biological product that represents a deviation from current good manufacturing practice, applicable regulation, applicable standards, or established specifications that may affect the safety, purity, or potency of a distributed biological product as required by 21 CFR 600.14(b). For example, you failed to report to FDA that:
 - a. product complaints were received concerning glass in the product, which your investigation concluded were missed during the 100% inspection of the product;

Quality System – 483 / Warning Letter Examples

- You failed to establish adequate written procedures describing the handling of all written and oral complaints regarding a drug product [21 CFR 211.198]. For example, Standard Operating Procedure (SOP) 123-456, **[redacted]** directs that a lot history be performed. This lot history is performed for the final finish lot number, which is the packaging/labeling lot number. However, complaints such as leaking vials/syringes and various container/closure defects would be associated with a fill lot number, and a fill lot number may be associated with several final finish lot numbers.

Facilities and Equipment System

- This system includes the measures and activities that provide an appropriate physical environment, along with the equipment and resources that are used in the production of the biological drug product.
- Assessment of this system may include:
 - Verification of the appropriateness and maintenance of buildings and facilities
 - Equipment qualification, calibration, maintenance and cleaning (validation and routine)
 - Facility utilities (HVAC, water, steam, and compressed air) qualification, routine monitoring and maintenance

Facilities and Equipment System – 483 / Warning Letter issues

- Your disinfectant effectiveness study # FR000-01 dated 01/01/2008, is incomplete.
The study did not evaluate the effectiveness of the disinfectants in use on fungi and spore forming microorganisms. Spore forming microorganisms have been routinely isolated in your manufacturing facility and accounted for 17% of total isolates identified in 2008 and 2009; 14% in 2007 and 7% in 2006.
- Your firm failed to establish an adequate system for cleaning and disinfecting the room and equipment to produce aseptic conditions. For example your firm's cleaning validation studies demonstrate the selected cleaning agent is not effective on spore forming microorganisms. However, spore forming microorganisms have been detected in the environmental monitoring samples, personnel monitoring samples, and sterility test samples of final product.

Facilities and Equipment System – 483 / Warning Letter issues

- Failure to keep equipment and supplies used in work on or otherwise exposed to any potentially pathogenic agent separated from equipment and supplies used in the manufacture of products to the extent necessary to prevent cross-contamination [21 CFR 600.11(e)(5)]. Hallway 111 in building H, which connects directly to the sterile gowning suite used for sterile processing and to the equipment airlock for passing equipment in and out of the sterile filtration room, does not provide for adequate segregation of early production materials from materials used in sterile processing. During sterile filtration of vaccine A concentrate lot 00000, this common hallway was utilized to transport already-sterilized equipment into the equipment airlock as well as to transport soiled equipment and carts containing inoculated eggs, for personnel traffic, and to transfer reagents between rooms.
- You failed to assure that equipment used in the manufacture, processing, packing and holding of a drug product is calibrated, inspected, or checked according to a written program designed to assure proper performance [21CFR 211.68(a)]. Specifically, a set of control samples representing defect types are examined by the automated inspection equipment prior to beginning each inspection process. The reject set testing allows high rates of known rejects to be accepted by the equipment. In addition, the first time non-accepts are sent back through the equipment and only those rejected a second time are discarded.

Materials System

- This system includes the measures and activities to control finished products, such as components, source materials, water or gases that are incorporated into the product, and container and closures.
- Assessment of this system may include:
 - Validation of computerized inventory control processes
 - Product storage
 - Distribution controls
 - Records for detection of counterfeiting
 - Control of facilities used for storage (warehouse, cold rooms, freezers, etc)

Materials System – 483 / Warning Letter issues

- **Written procedures are not followed for the storage and handling of drug product containers.**

Specifically, SAP inventory for Glass syringe lot 999999 did not match the physical inventory in the warehouse reject cage on 7/3/07. One box from this sprayer lot was found damaged on 6/18/07, and was placed in the reject cage. However, this transaction was not entered into SAP as required by written procedures.

- **The segregation of products to prevent products mix-up is deficient, for example:**

- 1) Staging areas for receiving and shipping of products are conducted from the same location and there are no identifications of the areas for the storage of incoming and outgoing products.
- 2) Freezer #371B (-40°C) for the storage of received products and Freezer (Cold Room #371) for the storage of work in progress (WIP) were not identified.
- 3) Caged area for Controlled Drug Substances is not identified.

Materials System – 483 / Warning Letter issues

- You failed to assure that container closure systems provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of bulk drug substances and sterile solutions used in production. For example:
 - a. Study FR #99-000, [redacted] did not include an assessment of the effect of storage conditions. This container/closure is used for bulk drug substances.
 - b. [Redacted] sterile filtered solutions used in the manufacture of vaccines are stored in containers for [redacted]. Validation studies have not been conducted to assure container/closure integrity.
- There is no assurance that the 1000 mL bottles with screw cap closures used to store frozen bulk product are non-reactive, additive or adsorptive.

Production System

- This system includes the measures and activities to control the manufacture of biological drug products including following and documenting performance of approved manufacturing procedures.
- Inspection of this system may include evaluation of:
 - Batch formulation
 - Dosage form production
 - Sterile filtration
 - Aseptic processing
 - In-process testing
 - Lot release
 - Process validation

Production System – 483 / Warning Letter issues

- Your firm failed to establish an adequate system for monitoring environmental conditions of aseptic processing areas [21 CFR 211.42(c)(10)(iv)]. For example:
 - a. There is no documentation that monitoring covers all production shifts and is performed during active operations.
 - b. There is no assurance that monitoring is at the locations where critical operations are performed.
- Failure to follow appropriate written procedures designed to prevent microbial contamination of drug products purporting to be sterile [21 CFR 211.113(b)]. For example, during aseptic filling operations for vaccine X, an operator was observed with head and torso over partially stoppered vials while loading vials onto lyophilization trays.

Production System – 483 / Warning Letter issues

- At least three [redacted] manufactured in 2006 exceeded your endotoxin action limit of [redacted] EU/ml. Three [redacted] that exceeded the endotoxin action limit were blended with [redacted] that did not exceed your action limit and were used in the formulation of final product lots T3 and T4 that were shipped to and distributed in the United States.
- Your firm failed to assure that there are written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess [21 CFR 211.100(a)]. For example:
 - a. The validation performed in December 2006 for [redacted] machines 2, 3, and 4 is not representative of the actual automated inspection process for detection of [redacted] defects, in that there was no assessment of acceptably filled vials. This equipment is used to inspect multiple vaccine products from filling lines 131 and 138.
 - b. Process control limits were not evaluated and re-established for filling line defects for vaccine final product as required by SOP 321X. The SOP states that the Process Control Limits (PCL) should be evaluated after the first [redacted] lots and again after [redacted] lots or sooner if changes were made to the process. [Redacted] lots were inspected by the [redacted] from February 2006 to September 2007, yet the limits have not been evaluated.

Production System – 483 / Warning Letter issues

- Visual inspection operators and QC personnel lack the necessary training or qualifications to perform their assigned functions. Specifically:
 - a. Operator 2 passed the filled syringe screening certification on 9/2/08; however, failed to pass the 10/13/08 medical surveillance for visual acuity. There is no documented medical rationale as to why the failing visual acuity results would not interfere with job performance.
 - b. Visual inspection procedures for QC inspectors are not reflective of qualification. Specifically, QC inspectors are qualified using white/black background and magnifying glass; however, routine procedures are not specific and QC Inspectors do not inspect vials under these conditions.
- You failed to ensure that operators performing setup, sterile filtration and/or aseptic dispensing use proper aseptic techniques to prevent microbial contamination of monovalent lots. Specifically:
 - a) Operators were observed wearing safety glasses allowing for skin to be exposed and, therefore, increasing the opportunity for contamination.
 - b) On March 28, 2007, an operator was observed removing his/her safety glasses, then removing and cleaning his/her prescription type glasses, thus allowing for skin to be exposed.
 - c) Also, an operator was observed sampling his/her fingers onto an agar touch plate and without sanitizing or changing his/her gloves, mixing the sterile filtered monovalent.

Packaging and Labeling System

- This system encompasses the measures and activities that control packaging of biological drug product.
- Inspection of this system may include evaluation of:
 - procedures and documentation of label control to prevent mix ups
 - facilities, equipment, and support systems to maintain proper environmental and processing controls during operations

Packaging & Labeling System – 483 / Warning Letter issues

- Examination of labeled product for suitability and correctness is not documented in the batch record. Specifically, during labeling & packaging operations, final product syringes can be rejected by the automated equipment at several stations. The syringes rejected by the automated equipment are manually inspected by production operators and reintroduced to the packaging operations if deemed acceptable. However, this visual inspection and reintroduction into the line is not documented in the batch record.

Laboratory Control System

- This system measures the activities related to laboratory procedures, analytical methods development, validation or verification, and the product stability program
- Inspection of this system includes the evaluation of:
 - SOPs for control of microbiological contamination and environmental monitoring
 - Records for source materials
 - In-process and finished process testing
 - Methods for sampling and testing
 - Validation of test methods

Laboratory Control System – 483 / Warning Letter issues

- Failure to establish the accuracy, sensitivity, specificity, and reproducibility of test methods, in that analytical methods have not been validated [21 CFR 211.165(e)]. For example:
 - a) Sterility test method STR-MTM-0006 has not been validated for sterility testing of [redacted] liquid bulk.
 - b) bioburden test method S004 has not been validated for bioburden testing of [redacted] pre-filtration bulk.
- Laboratory raw data is recorded onto data sheets. These sheets may be printed at will by analysts from a computerized document management system without tracking as to the number of data sheets printed or used.
- Data was not available to support expiration dates assigned to in-house prepared reagent solutions used in the testing of final bulk product.

Level I and Level II Inspections

The inspection will be conducted under either a **Level I** or **Level II** inspection option.



Level I

- In-depth audit of the three critical elements in each of the six systems and provides a comprehensive evaluation of the establishment's compliance with CGMPs
- Always apply in the following conditions:

Level I

- Initial inspection of a firm
- Firms that have a history of fluctuating compliance problems
- Compliance follow-up inspections (ex. Inspection following warning letter)
- Firms under a Consent Decree of Permanent Injunction
- Firms under NOIR and/or other administrative actions
- Significant changes since last inspection
- After two previous inspections conducted have been at Level II

Level II

Streamlined evaluation of an establishment's compliance with CGMPs, and provides coverage of the **three critical elements in two mandatory systems (Quality and Production), plus at least one additional system** on a rotating basis during successive biennial inspections. Level II is used for the following options:

Level II

- The establishment has a satisfactory history of compliance.
- One of the two previous Biennial inspections was a Level I inspection.
- The inspection preparation revealed no specific trends that may have significant impact on product safety or quality (review of BPDRs, product recalls, etc)

Note: If significant objectionable conditions are noted during a Level II inspection, the inspection could change to a Level I while in progress.

Additionally

- Since 2005, TB has been conducting “off-year” inspections of manufacturers of Influenza Virus Vaccine
- Flu vaccine manufactures are scheduled every year with the off-year inspection occurring in-between routine biennial inspections
- Off-year inspections include coverage of flu vaccines only (Quality, Production and other systems as needed)

Top 10 Drug Observations Cited in Turbo EIR

- 21 CFR 211.22(d)The responsibilities and procedures applicable to the quality control unit are not [in writing] [fully followed]. Specifically, ***
- 21 CFR 211.100(b)Written production and process control procedures are not [followed in the execution of production and process control functions] [documented at the time of performance]. Specifically, ***
- 21 CFR 211.110(a)Control procedures are not established which [monitor the output] [validate the performance] of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Specifically, ***
- 21 CFR 211.160(b)Laboratory controls do not include the establishment of scientifically sound and appropriate [specifications] [standards] [sampling plans] [test procedures] designed to assure that [components] [drug product containers] [closures] [in-process materials] [labeling] [drug products] conform to appropriate standards of identity, strength, quality and purity. Specifically, ***
- 21 CFR 211.100(a)There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Specifically, ***

Top 10 Drug Observations Cited in Turbo EIR continued

- 21 CFR 211.192 There is a failure to thoroughly review [any unexplained discrepancy] [the failure of a batch or any of its components to meet any of its specifications] whether or not the batch has been already distributed. Specifically, ***
- 21 CFR 211.165(a) Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the [final specifications] [identity and strength of each active ingredient] prior to release. Specifically, ***
- 21 CFR 211.25(a) Employees are not given training in [the particular operations they perform as part of their function] [current good manufacturing practices] [written procedures required by current good manufacturing practice regulations]. Specifically, ***
- 21 CFR 211.188 Batch production and control records [are not prepared for each batch of drug product produced] [do not include complete information relating to the production and control of each batch]. Specifically, ***
- 21 CFR 211.67(b) Written procedures are not [established] [followed] for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product. Specifically, ***

Summary

- Team Biologics is a partnership between ORA and CBER
- TB is responsible for conducting post-market inspections of licensed biologic drugs and devices
- Utilize a systems-based approach to conducting inspections as outlined in Compliance Program Guidance Manual (CPGM) 7345.848, Inspection of Biologic Drug Products.
 - Six systems
 - 3 critical elements

?? QUESTIONS ??

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