DISCUSSION TOOL
PRESENTED TO THE AABB CT REGULATORY AFFAIRS SUBSECTION

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Introduction

This case study is intended to extract portions of information from an actual US Food and Drug Administration (FDA) Form 483 that was published by the FDA. It is based on an inspection of a Compounding Pharmacy Inc. Herein, this presentation, referred to as the “firm”.

While the firm may or may not be held to Current Good Manufacturing Practice (cGMP), the purpose of this PowerPoint presentation is to demonstrate how the finding may be applicable to a 351 product HCT/P manufacturing facility that is held to cGMP requirements.
FDA Finding

The firm’s sterility sample consisting of one vial of bulk product from lot#081….was sterile.

The FDA tested 50 vials from the same lot. Fifty (50) of the 50 tested vials had viable growth. One (1) vial showed microscopically fungal morphological features

Parallel HCT/P GMP Requirement

Subpart E-Control of Components and Drug Product Containers

211.82 Receipt and storage of untested components, drug product containers, and closures.

(a) Upon receipt and before acceptance, each container or grouping of containers of components, drug product containers, and closures shall be examined visually for appropriate …, and contamination

211.84 Testing and approval or rejection of components, drug product containers, and closures

(a) Each lot of components, drug product containers, and closures shall be withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit.

(1) The containers of components selected shall be cleaned where necessary, by appropriate means

(6) Each lot of a component, drug product container, or closure that is liable to microbiological contamination that is objectionable in view of its intended use shall be subjected to microbiological tests before use.
Non-Sterile Product- Continued

FDA Finding-Repeated
The firm’s sterility sample consisting of one vial of bulk product from lot#081...was sterile.

The FDA tested 50 vials from the same lot. Fifty (50) of the 50 tested vials had viable growth. One (1) vial showed microscopically fungal morphological features

Parallel HCT/P GMP Requirement-Continued
Subpart F-Production and Process Controls
211.100 Written procedures; deviations
(a) There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. ...
FDA Finding-Repeated
The firm’s sterility sample consisting of one vial of bulk product from lot#081...was sterile.

The FDA tested 50 vials from the same lot. Fifty (50) of the 50 tested vials had viable growth. One (1) vial showed microscopically fungal morphological features.

Parallel HCT/P GMP Requirement-Continued
Subpart F-Production and Process Controls
211.110 Sampling and testing of in-process materials and drug products.
(a) To assure batch uniformity and integrity of products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch.
FDA Finding-Repeated
The firm’s sterility sample consisting of one vial of bulk product from lot#081…was sterile.

The FDA tested 50 vials from the same lot. Fifty (50) of the 50 tested vials had viable growth. One (1) vial showed microscopically fungal morphological features

Parallel HCT/P GMP Requirement-Continued
Subpart I-Laboratory Controls
211.165 Testing and release for distribution
(b) There shall be appropriate laboratory testing, as necessary, of each batch of drug product required to be free of objectionable organisms
(d) Acceptance criteria for the sampling and testing conducted by the quality control unit shall be adequate to assure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release. The statistical quality control criteria shall include appropriate acceptance levels and/or appropriate rejection levels.

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FDA Finding-Repeated
The firm’s sterility sample consisting of one vial of bulk product from lot#081…was sterile.

The FDA tested 50 vials from the same lot. Fifty (50) of the 50 tested vials had viable growth. One (1) vial showed microscopically fungal morphological features

Parallel HCT/P FDA Requirement-Continued
610.12-Sterility
(a) The test. Except as provided in paragraph (h) of this section, manufacturers of biological products must perform sterility testing of each lot of each biological product’s final container material or other material, as appropriate and as approved in the biologics license application.
A GMP Manufacturing Facility Should Have:

Standard Operating Procedures:

- Testing and sampling of components
- Testing and sampling of bulk product
- Testing and sampling of final product
- Validation of culture methods
- Review and release of incoming containers and closures. (Certificate of Analysis, Certificate of Compliance)
- Sanitation of manufacturing areas. The sanitation by both manufacturing staff and general custodial staff shall be documented.
- Validation of cleaning agents utilized
- Validation to demonstrate cleaning agents do not interfere with environmental monitoring (e.g. touch plates)
- Environmental monitoring alert and action levels. Reporting and review of these levels by Quality Assurance (QA) and appropriate supervisors. Impact on scheduled manufacturing
FDA 483 Finding
83 of 321 vials from lot #081…(lot distributed to hospitals/clinics) contain what appeared to be greenish black foreign matter.

17 vials from lot #081… contain what appeared to be white filamentous material

Parallel HCT/P GMP Requirement
Subpart E-Control of Components and Drug Product Containers
211.82 Receipt and storage of untested components, drug product containers, and closures.
(a) Upon receipt and before acceptance, each container or grouping of containers of components, drug product containers, and closures shall be examined visually for appropriate …., and contamination
FDA 483 Finding-Repeated
83 of 321 vials from lot #081…(lot distributed to hospitals/clinics) contain what appeared to be greenish black foreign matter.

17 vials from lot #081… contain what appeared to be white filamentous material

Parallel HCT/P GMP Requirement-Continued
Subpart F-Production and Process Controls
211.100 Written procedures; deviations
(a) There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. …
A GMP Manufacturing Facility Should Have:

Standard Operating Procedures:

• Review and release of incoming containers and closures (Certificate of Analysis, Certificate of Compliance)
• Sanitation of manufacturing areas. The sanitation by both manufacturing staff and general custodial staff shall be documented.
• Environmental monitoring alert and action limits
• Heating, Ventilation and Air Conditioning (HVAC) system maintenance
FDA Finding
Production worksheets state raw materials are sterile. Staff stated that the firm uses some non-sterile active pharmaceutical (API) ingredients and raw materials. During the inspection we observed that labeling for API and raw materials did not indicate they were sterile.

Parallel HCT/P GMP Requirement
Subpart E-Control of Components and Drug Product Containers
(a) There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures; such written procedures shall be followed
211.84 Testing and approval or rejection of components, drug product containers, and closures.
(a) Each lot of components, drug product containers, and closures shall be withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit.
(6) Each lot of a component, drug product container, or closure that is liable to microbiological contamination that is objectionable in view of its intended use shall be subjected to microbiological tests before use.
FDA Finding-Repeated
Production worksheets state raw materials are sterile. Staff stated that the firm uses some non-sterile active pharmaceutical ingredients (API) and raw materials. During the inspection we observed that labeling for API and raw materials did not indicate they were sterile.

Parallel HCT/P GMP Requirement-Continued
Subpart I-Laboratory Controls
211.165 Testing and release for distribution
(b) There shall be appropriate laboratory testing, as necessary, of each batch of drug product required to be free of objectionable microorganisms
A GMP Manufacturing Facility Should Have:

Standard Operating Procedures:

- Specifications (specs) for materials used in production should be established and used in the materials review and release process. The specs should require the ingredients/materials to be sterile.
- Testing and release of components
FDA Finding
Firm personnel stated that the firm shuts off the air conditioning from 8:00 pm to 5:30 am nightly in the Clean Room.

Parallel HCT/P GMP Requirement
Subpart C-Buildings and Facilities
211.46 Ventilation, air filtration, air heating and cooling

(a) Adequate ventilation shall be provided

(b) Equipment for adequate control over air pressure, microorganisms, dust, humidity, and temperature shall be provided when appropriate for the manufacture, processing, packaging, or holding of a drug product.

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FDA Finding-Repeated
Firm personnel stated that the firm shuts off the air conditioning from 8:00 pm to 5:30 am nightly in the Clean Room.

Parallel HCT/P GMP Requirement-Continued
Subpart F-Production and Process Controls
211.100 Written procedures; deviations
(a) There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. …
A GMP Manufacturing Facility Should Have:

Standard Operating Procedures:
- Management of facility policies on air control
- Continuous monitoring/alarms related to air handling status
FDA Finding
The firm provided no documentation or evidence to support that the steam autoclave cycle used to sterilize suspensions formulated using non-sterile API and raw materials is effective.

Subpart F-Production and Process Controls
211.13 Control of microbiological contamination
(b) Appropriated written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of any sterilization process.
A GMP Manufacturing Facility Should Have:

Process Qualification (PQ)/Operational Qualification (OP): Equipment shall be subject to qualification prior to use

Validation: A protocol that demonstrates the desired outcome on a consistent basis

Verification: Each cycle shall be verified for effectiveness (e.g., indicator tape, biological indicator, run print-out). The verification shall be reviewed.

Standard Operating Procedures
FDA Finding
The firm is abutted to the rear and along a parking area by a recycling facility that handles such materials as mattresses and plastics. On one of the dates of inspection the area was observed to include large equipment (e.g. excavators and freight trucks) producing airborne particulates (e.g. dust). Rooftop units serving the firm’s HVAC system were estimated to be located approximately 100 feet from the recycling facility.

Subpart C-Buildings and Facilities
211.42 Design and construction features
(a) Any building or buildings used in the manufacture, processing, packing, or holding of a drug product shall be of suitable size, construction and location to facilitate cleaning, maintenance, and proper operations.
A GMP Manufacturing Facility Should Have:

Standard Operating Procedures:
- Environmental monitoring of airborne and non-airborne viable and non-viable particles shall be described. This includes alert and action levels
- HVAC management: How the air supply system is managed and maintained
FDA Finding
A boiler installed within approximately 30 feet of the entrance to a ISO 8 prep room was observed to be leaking water into puddles. Moreover, wet floor surfaces around the boiler appeared to be soiled with thick white debris and thick black granular material.

Parallel HCT/P GMP Requirement
Subpart C-Buildings and Facilities
211.56 Sanitation
(a) Any building used in the manufacture, processing, packing, or holding of a drug product shall be maintained in a clean and sanitary condition.

211.58 Maintenance
Any building used in the manufacture, processing, packing, or holding of a drug product shall be maintained in a good state of repair.
A GMP Manufacturing Facility Should Have:

Standard Operating Procedures:

- Maintenance of equipment should include a program of not only equipment used in clinical production, but also facility related equipment.

- Sanitation of manufacturing areas and non-manufacturing areas should be defined. The sanitation by both manufacturing staff and general custodial staff shall be documented.
FDA Finding
Gaps were observed between sliding doors located at the transition between the Prep Room (ISO 8) and the warehouse, despite being fully closed. This room is used for the preparation of equipment and includes the xxxx.

Parallel HCT/P GMP Requirement
Subpart C-Buildings and Facilities
211.58 Maintenance
Any building used in the manufacture, processing, packing, or holding of a drug product shall be maintained in a good state of repair.
A GMP Manufacturing Facility Should Have:
Standard Operating Procedures:

• Approval of newly constructed or remodeled manufacturing areas
• Facility maintenance
• Facility failure
• Inspection of the facility (walk-throughs)
FDA Finding
The tacky mat located within the entrance of the Prep Room ISO 8 at the transition to the warehouse was observed to be brown and soiled. This room is used for the preparation of equipment.

Parallel HCT/P GMP Requirement
Subpart C-Buildings and Facilities
211.56 Sanitation
(a) Any building used in the manufacture, processing, packing, or holding of a drug product shall be maintained in a clean and sanitary condition.
A GMP Manufacturing Facility Should Have:
Standard Operating Procedures:

- Requirements for sanitation and maintenance of the facility
- Inspection of the manufacturing areas