Center of Excellence Overview of Outsourcing Facility Inspections

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Outsourcing Facilities

Drugs compounded in accordance with all conditions of section 503B are **exempt** from:

- Section 502(f)(1) (labeling with adequate directions for use),
- Section 505 (new drug approval requirements), and
- Section 582 (drug supply chain security requirements)

CGMPs for Outsourcing Facilities

- Outsourcing facilities are not exempt and must comply with CGMP requirements.

  – See draft guidance, "Current Good Manufacturing Practice — Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act," which, when finalized, will reflect FDA's current thinking on compliance with CGMP requirements for 503B facilities.

CGMPs for Outsourcing Facilities

- FDA recognizes the differences between compounding outsourcing facilities and conventional drug manufacturers, and the need, to some extent, to appropriately tailor CGMP requirements for outsourcing facilities while maintaining the minimum standards necessary to protect patients from the risks of contaminated or otherwise substandard compounded drug products.

Insanitary Conditions

- Outsourcing facilities are subject to the prohibition on insanitary conditions.
- FD&C Act 501(a)(2)(A) – A drug is deemed to be adulterated "if it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health."

Inspectional Coverage

- Aseptic Operators and Operations
- Process and Facility Design
- Environmental &
  Personnel Monitoring
- Product Inspection & Component Control
- Packaging and Labeling Control

FDA-483 Examples

Helpful Link: Compounding: Inspections, Recalls, and other Actions | FDA

Example 1

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

There is a failure to thoroughly review any unexplained discrepancy and 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,

a) Your firm has not conducted investigations into the majority of environmental monitoring and personnel monitoring excursions (recovery of organisms) identified as occurring in the ISO 5 environment. From January 1, 2021 to March 31, 2022, your firm had approximately 1686 instances of excursions related to work performed in the ISO 5 area to include personnel monitoring, viable air and viable surface samples.

Your firm stated that approximately 240 excursions related to monitoring of personnel who performed filling/capping and sanitizer functions, which are critical roles during the aseptic filling of sterile drug products, were not investigated.

There were approximately 51 excursions related to viable air or surface samples within the ISO 5 hood. No investigation was conducted for 48 of the 51 excursions.

Example 2

OBSERVATION 5

Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the room and equipment to produce aseptic conditions.

Specifically,

A. HEPA filters located in Clean Rooms (b) (4) and in the ISO 5 LAFW and BSC hoods are sprayed directly with cleaning agents during cleaning procedures. In addition, surfaces other than the hoods and tables, are not wiped after being sprayed.
B. On 08/01/19, I observed an operator use one sterile wipe to clean an ISO 5 LAFW, then wipe down a stainless-steel table (upper and lower shelves), and then clean another ISO 5 hood.
C. Your firm lacks antimicrobial effectiveness testing of cleaning agents used in the ISO 5 areas.
D. (b) (4) water used in the dilution of the firm's cleaning agents, (b) (4) and (b) (4) are not sterile. These products are used in the ISO 5 rooms and hoods.
E. Spray bottles used to store (b) (4) and (b) (4) are non-sterile. These bottles are maintained in the ISO 5 and ISO 7 Clean Rooms during production.

Example 3

OBSERVATION 4

Aseptic processing areas are deficient regarding air supply that is filtered through high-efficiency particulate air filters under positive pressure.

Specifically, your firm failed to conduct a smoke study under dynamic conditions within the ISO-5 (b) (4) Flow Hood (b) (4)). This hood was utilized for the production of Nalbuphine HCL, 10mg/1mL, lot #20200108.

Example 4

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

Drug products failing to meet established specifications are not rejected.

Specifically, we identified approximately fifty-nine (59) lots that were out-of-specification (OOS) for potency/reconstitution time and were released by your firm from January 1, 2021 through February 16, 2022. The table below illustrates the eleven (11) lots currently on the market and within expiration date.

Warning Letter Examples

Helpful Link: Compounding: Inspections, Recalls, and other Actions | FDA

Example 1: Adulterated Drug Products

The FDA investigators noted that drug products compounded in your facility that were intended or expected to be sterile were prepared, packed, or held under insanitary conditions, whereby they may have become contaminated with filth or rendered injurious to health, causing your drug products to be adulterated under section 501(a)(2)(A) of the FDCA [21 U.S.C. § 351(a)(2)(A)].

For example, the investigators observed that the ceiling tiles of your ISO 7 cleanrooms were not fully sealed, allowing ingress of unfiltered air from the surrounding non-classified area.

Example 2: Adulterated Drug Products

The FDA investigators also noted CGMP violations at your facility, causing your drug products to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA [21 U.S.C. § 351(a)(2)(B)]. The violations include, for example:

- Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42(c)(10)(iv)).

For example, the investigators observed that the firm lacks meaningful data for EM. The firm was performing viable air and surface sampling after cleaning was conducted. In addition, the firm has not established alert and action limits for EM of surface and viable air within the ISO-5 aseptic processing area therefore numerous excursions have not been properly investigated.

Example 3: Adulterated Drug Products

- Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

For example, the investigators observed that the firm had 4 sterility failures in the past 2-months. The firm's investigation failed to include all potential root causes that may have contributed to the failure including the fact that the sterilization cycle had not been validated or that the final qualification report noted that growth was observed for the specified parameters used.

Example 4: Adulterated Drug Products

- Your firm failed to establish 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 (21 CFR 211.100(a)).

For example, the investigators observed that the firm had not validated their process for Testosterone or Estradiol Pellets. In addition, numerous potency failures have been observed but the drug products were released to the market.

U.S. FOOD & DRUG ADMINISTRATION

THANK YOU!!!

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