GMP Trends

DISTRICT ADDRESS
GMP Trends LLC
P.O. Box 1111
Firestone, Colorado 80520

DATE OF ISSUE
May 15, 2018

C.I. ISSUE
Issue #992

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED
To: Responsible Person, Director of Quality Assurance

FIRM NAME	STREET ADDRESS
Pharmaceutical and Related Industries	5600 Regulation Lane
CITY, STATE AND COUNTRY	**TYPE OF ESTABLISHMENT INSPECTED**
United States of America and Worldwide	Pharmaceutical and Medical Device

DURING A REVIEW OF INSPECTION REPORTS OF U.S. FIRMS (I) (WE) OBSERVED:

EDITED EXCERPTS FROM ACTUAL 483 OBSERVATION REPORTS BY FOOD AND DRUG ADMINISTRATION INVESTIGATORS

********** **SPECIAL ISSUE** **********

483 observations pertaining to deficiencies regarding 21 CFR 211 Subpart C – Building and Facility

DESIGN AND CONSTRUCTION FEATURES {21 CFR 211.42}

1. .....Buildings used in the manufacture, processing, packing, or holding of a drug product do not have the suitable construction to facilitate cleaning, maintenance, and proper operations. {21 CFR 211.42(a)}

   Specifically, the manufacturing area for ….. products contains ceiling tiles made of a compressed fibrous material. During the inspection, an open drum of in-process material being used to manufacture ….., lot ….., was observed positioned directly below damaged and soiled sections of this ceiling material.

2. .....Buildings used in the manufacture, processing, packing, or holding of a drug product do not have the suitable size, construction, and location to facilitate cleaning, maintenance, and proper operations. {21 CFR 211.42(a)}

   Specifically, buildings and facilities used to manufacture ….., an Active Pharmaceutical Ingredient (API), and its intermediates shall be designed and constructed to facilitate cleaning, maintenance and operations to minimize potential contamination. For example, I observed deficiencies related specifically, but not limited to the following:

   a. An uncovered top of Tank ….. used to prepare ….. provided direct contact with the manufacturing environment. The ….. emptying into this tank was insulated, wrapped with packing tape and appeared to be rusted. The hole also appeared rusted.

   b. Use of packing tape on the hopper auger feeding the …..

   c. Use of packing tape on the vacuum line between the ….. Tank …..

3. .....The control systems necessary to prevent contamination or mix-ups are deficient. {21 CFR 211.42(b)}

   Specifically,

   a. A process is not established to prevent product mix-ups between expired and in-date anticipatory compounded products; several examples of expired products were observed co-mingled with in-date product anticipatory compounded products were noted.

   b. A clear solution with no identifiable contents or expiration date was observed and in an unlabeled spray bottle located in the ISO-7 anteroom: the pharmacy manager said it was non-sterile …..

   c. A discolored cloth towel was the only hand-drying towel located at the hand washing sink used for preparation of non-sterile products …..

4. .....The flow of drug products through the building is not designed to prevent contamination. {21 CFR 211.42(b)}

   Specifically, there is potential risk for contamination during the compounding of bulk powdered drugs.

   a. Non-dedicated equipment such as the ….., tablet press, and the ….. used in the production of your firm's implantable ….. pellets is not adequately cleaned between each batch to prevent cross-contamination.

   b. The ….. balance, used in the mixing of your firm's bulk powdered drugs for implantable ….. pellet compounding, was observed to have a crack in the glass that ran diagonally from the top to the bottom of the glass, which has a potential for cross-contamination and foreign objects in your bulk powdered drugs.

   c. The ….. used in your firm's ….. and ….. does not meet the manufactures specifications, which has a potential for cross-contamination when mixing your bulk powdered drugs.

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DURING A REVIEW OF INSPECTION REPORTS OF U.S. FIRMS (I) (WE) OBSERVED:

DESIGN AND CONSTRUCTION FEATURES {21 CFR 211.42 (c)}

1. …..Separate or defined areas to prevent contamination or mix-ups are deficient regarding operations related to the storage of in-process materials. {211.42(c)(4)}

   Specifically, during inspection of the pharmacy area during the weighing of ….. Tablets, Lot ….., multiple in-process raw materials are placed all in the pharmacy rooms during weighing. Out of ….. drums stored in the pharmacy room during weighing, we observed several drums opened and unsealed.

2. …..Separate or defined areas to prevent contamination or mix-ups are deficient regarding operations related to the quarantine storage of drug products prior to release. {211.42(c)(4)}

   Specifically, your firm lacks separate or defined areas to segregate release and quarantined drug product to prevent mix-up. I observed that finished drug product skids containing ….. cases of ….., lot ….., approved for commercial release were sorted along with quarantined drug product ….., lot …..

3. …..Separate or defined areas to prevent contamination or mix-ups are deficient regarding operations related to aseptic processing of drug products. {211.42(c)(4)}

   Specifically, you did not produce sterile drugs under ISO 5 conditions. All manipulations performed in the production of drug products ….., which are required to be sterile, are conducted in an unclassified enclosure located in an ISO 8 production laboratory. The interior top underside of this enclosure contained residue build-up and yellow stains. There are no controls to prevent microbial contamination, bacterial endotoxin and unintended chemical and physical contaminants for producing sterile drug products.

4. …..Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the room to produce aseptic conditions. {211.42(c)(10)}

   Specifically,

   a. Non-sterile wipes are used to clean the ISO-5 LAF hood where aseptic filling occurs.

   b. Non-sterile and non-lint free mop-heads are used to clean the ISO-7 anteroom and buffer room areas that are adjacent to the ISO-5 LAF hood where aseptic filling occurs.

   c. The cleaning procedure provides minimal detail regarding the technique for cleaning the ISO-5 LAF hood where aseptic filling occurs.

   d. No records were available demonstrating the disinfectant solution of ….. used to clean the ISO-5 LAF hood is effective against spores throughout the solution's use period.

   e. Although the formula worksheet for ….. solution states ….., there is no prior cleaning step performed to remove soil and debris prior to disinfection.

   f. Although cleaning procedure ….., "Maintenance of the Aseptic Compounding Area," states the walls and floor in the ISO-7 anteroom and buffer areas are cleaned with ….., no records were available demonstrating this cleaning agent is effective against spores.

5. …..Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas. {211.42(c)(10)(iv)}

   Specifically, when collecting finger dab samples of the ..... gloves, your EM sampling operator failed to ensure that each finger touched the surface of the ..... sampling plate.

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DURING A REVIEW OF INSPECTION REPORTS OF U.S. FIRMS (I) (WE) OBSERVED:

VENTILATION {21 CFR 211.46}, PLUMBING {21 CFR 211.48} AND WASHING AND TOILET FACILITIES {21 CFR 211.52}

1. .....There is no environmental design, control, or monitoring for the product packaging room. {21 CFR 211.46(a)}

   Specifically, there is no facility or equipment control or monitoring for elements such as humidity or temperature in the product packaging room. The ..... product is susceptible to clumping in the presence of humidity as stated by your Quality Assurance Manager.

2. .....Equipment for adequate control over air pressure, humidity and temperature is not provided when appropriate for the manufacture, processing, packing or holding of a drug product. {21 CFR 211.46(b)}

   Specifically,

   a. Your firm's air pressure differential monitoring system has no set ranges for alarm settings. This system monitors the air pressure differential between the warehouse area and the repacking rooms.

   b. Your firm does not monitor the temperature or the humidity levels in the repacking rooms.

   c. Your firm does not have any written procedures that address the air pressure differential monitoring system and temperature/humidity monitoring in the repacking rooms.

3. .....Equipment for adequate control over humidity and temperature is not provided when appropriate for the manufacture, processing, packing or holding of a drug product. {21 CFR 211.46(b)}

   Specifically, Procedure ....., "Stability Evaluation of Marketed Products at Room Temperature Environmental Conditions," states that all ICH guideline products must be stored at ..... temperature and ..... relative humidity. During a review of temperature and humidity recording charts over the last 12 months, a total of 23 charts showed temperature and humidity readings which exceeded the permissible limits. None of these excursion events were investigated to determine root cause or assess sample impact. Additionally, there is no justification supporting representative nature of the placement of ..... temperature and humidity monitoring in the stability storage room.

4. .....Adequate exhaust systems or other systems to control contaminants are lacking in areas where air contamination occurs during production. {21 CFR 211.46(c)}

   Specifically, particle counter ....., that is connected to the syringe filling line in Room ....., had a communication error for one month. SOP ....., "Room Conditions: Monitoring and Recording," states that a maintenance work order must be initiated to correct the excursion. No work order has been initiated to correct this excursion; therefore, no airborne particles were collected within this unit during this period.

5. .....The plumbing system contains defects that could contribute to the contamination of drug products. {21 CFR 211.48}

   Specifically, we observed three dead leg areas in the piping of your water system. Two dead legs were located between the well water feed and the water softener tanks. A third dead leg was located between the high pressure ..... pump and the ..... tubes.

6. .....Adequate, clean washing and toilet facilities are not provided for personnel. {21 CFR 211.52}

   Specifically, soap or detergent and air driers or single service towels are not provided at hand or foot washing facilities used by manufacturing personnel immediately prior to gowning and entry into production areas with open, exposed toe sandals.

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MAINTENANCE {21 CFR 211.58}

1. …..Buildings used in the manufacturing, processing, packing and holding of a drug product are not maintained in a good state of repair.

   Specifically, the facility where manufacturing, processing, packing and holding of drug product ….. is not maintained in good state of repair, the ceiling and floors are made of painted wood, where paint is worn out, the doors have gaps to open environment, and windows in the facility are not accessible to clean.

2. …..Buildings used in the manufacturing and processing of a drug product are not maintained in a good state of repair.

   Specifically, a piece of non-contact surface cabinetry with peeling paint and exposed particle board was observed directly above dishwasher racks holding glassware and utensils that were cleaned with soap and water from the production of ….. Suspension and ….. Capsule. The area of exposed particle board is not an easily cleanable surface, and the moisture from the dishwasher may lead to the potential for microbial growth and degradation.

3. …..Buildings used in the manufacture, processing, packing or holding of drug products are not maintained in a clean and sanitary condition.

   Specifically, during the walk-through inspection, it was noted that prior to aseptic processing, spatters of material were observed on the ceiling of the ISO-51 LAF hood where aseptic filling occurs: according to the cleaning log, the hood was in a clean status.

4. …..Buildings used in the manufacturing, processing and packing of a drug product are not maintained in a good state of repair.

   Specifically, there is inadequate coordination between engineering/maintenance and production unit with regards to planned preventative maintenance on the HVAC units and permitted concurrent manufacturing activities. A preplanned maintenance on an Air Handling Unit for Room ….. was performed concurrently while operators performed cleaning operations. Room Cleaning Logbook for ….. documents the room was cleaned after production of ….., Batch ….., was processed. There was no assessment of impact to ….. or production activities in the manufacturing area during air handling unit maintenance work, as maintenance was not aware production was on-going in Room …..

5. …..Building, facilities and equipment are not maintained to ensure the API's identity, strength, quality and purity.

   Specifically, an approximately 46 inch crack running in the East to West direction was present along the ceiling of the "Room …..," directly above the ….., used to manufacture ….. According to your Director of Quality Assurance, this crack occurred in the paint and bedding compound of the ceiling, thus was exposing the underlying sheetrock. Your firm's Vice President of Quality Assurance and Quality Control stated that this crack had not been observed or documented prior to the commencement of the FDA Inspection. Subsequently, your firm opened nonconformance ….. to address this deficiency, in which no root cause was identified. Subsequently, during the inspection, we identified the sight glass of reactor ….. "failed" and ruptured through the ceiling of the room where the crack was observed. Your Director of Quality Assurance indicated that this incident was such that "the ceiling was a mess." We requested documentation pertaining to corrective measures to replace the ceiling. Your firm's Director of Quality Assurance indicated that no quality report was available, and the firm did not provide documentation of the ceiling repairs.

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