GMP Trends

DISTRICT ADDRESS	DATE OF ISSUE
GMP Trends LLC P.O. Box 1111 Firestone, Colorado 80520	March 15, 2018
	C.I. ISSUE: Issue #988

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 B – Organization and Personnel

RESPONSIBILITIES OF QUALITY CONTROL UNIT {21 CFR 211.22(a)}

1. …..The Quality Control Unit is not adequately involved in all quality related matters.

   Specifically, the test parameter of ….., USP Lot ….., was changed without the approval of the quality assurance department. The firm's Quality Assurance unit specified that all APIs received from the ….., USP vendor must be fully tested before being released, due to the number of material failures received. However, the laboratory unit released material based on the vendor's certificate of analysis.

2. …..The Quality Control Unit lacks authority to fully investigate errors that have occurred.

   Specifically, your quality unit does not always ensure all investigations are scientifically sound and complete. For example, your OOS investigation for ….. Tablets, Batch ….., for Assay did not identify the root cause and recommended the investigation to your Manufacturing and Science Technology team (MSAT) to identify the root cause. Your OOS investigation assigned a corrective action and preventive action to reject the batch. MSAT proposed to change from reporting the assay test results to reporting the average blend uniformity as the assay result. A root cause was not identified in the investigation conducted by MSAT and a corrective and preventive action was not provided other than changing the way the assay results are reported and rejecting the batch.

3. …..The Quality Control Unit lacks authority to fully investigate errors that have occurred.

   Specifically,

   a. Your firm received ….. product quality complaints for ….. Spray, including leak problems, missing spray pumps and spray pump issues. However, your investigation and trend analysis did not extend to ….. Spray, which has similar packaging components.

   b. Your investigation of Production Deviation ….. revealed the contamination originated from the wash room spray nozzle. However, your investigation did not extend to other products to demonstrate that they are not impacted by the contamination.

4. …..The Quality Control Unit lacks the authority to review production records to assure that no errors have occurred.

   Specifically, during a walk-through of the manufacturing and packaging area, we observed stacks of blank and pre-printed logbooks being retained by the production department. In addition, the stamps used for the issuance of these logbooks, that are used to record manufacturing data, were also retained by the production department. The Quality Unit did not have oversight for the issuance and reconciliation of these logbooks used in the manufacturing area because the issuance and reconciliation of these logbooks were being performed independent of the Quality Unit by each respective production area department head.

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

RESPONSIBILITIES OF QUALITY CONTROL UNIT {21 CFR 211.22 (d)}

1. …..The responsibilities and procedures applicable to the Quality Control Unit are not fully followed.

   Specifically, review of firm's quality system written procedures and associated records revealed there is a lack of assurance that the procedures have been adequately implemented or established. For example, a review of your firm's Lab Equipment's Parts Replacement Log Book have resulted in at least ..... incidents last year in which unscheduled maintenance had to be performed on the HPLCs due to leak, clogging, lamp error message and pressure variation, etc. Any chromatographs generated (if any) containing erroneous data due to HPLC failure are not maintained, and all the HPLCs on site have no audit trial capability. Analysts were not instructed to record these events in their laboratory notebooks, and only subsequent successful testing data were written in the notebooks.

2. …..The responsibilities and procedures applicable to the Quality Control Unit are not fully followed.

   Specifically, review of firm's quality system written procedures and associated records revealed there is a lack of assurance that the procedures have been adequately implemented or established. For example, Firm's QA/QC department failed to review laboratory ambient stability temperature chart records used for monitoring stability samples, as per SOP ….., "Ambient Stability Chambers Performance Qualification/Calibration."

3. …..The responsibilities and procedures applicable to the Quality Control Unit are not in writing and fully followed.

   Specifically, the Quality Control Unit was not performing the following activities:

   a. **The GC system is not proven as suitable prior to the running of residual solvents samples. System suitability is run after the samples are injected. This holds true for the residual solvents analysis for all API products for the U.S. market.**
   b. **The HPLC system is not proven as suitable prior to the running of ….. Purity of API.**
   c. **Cleaning logs for production equipment or for the sampling/dispensing room are not controlled, issued or tracked by Quality. Logbook pages can be copied from the procedures by production personnel as needed.**
   d. **Electronic chromatograms are not reviewed during the release of analytical data. In addition, not all analytical data sheets used by QC analysts during the testing of APIs are documented as reviewed.**

4. …..The responsibilities and procedures applicable to the Quality Control Unit are not in writing and fully followed.

   Specifically, your quality unit failed to follow SOP ….. "Production Master Records - Production Events Log," in that production events/deviations reported by email or phone to QA by the night and weekend production shifts were not adequately tracked, documented, and investigated to determine the root cause and take appropriate corrective and preventive action.

5. …..The responsibilities and procedures applicable to the Quality Control Unit are not fully followed.

   Specifically,

   a. **SOP….. requires the Quality Department to ensure Process Discrepancy Reports (PDR) are generated, processed, and that the final disposition of the product is determined. PDRs were not generated when they should have been for several lots reviewed.**
   b. **SOP….. states that Collective and Preventative Actions may originate from PDRs. When investigations for the above issues were requested, management advised that because no PDRs were initiated, no investigation into the root cause of these issues related to drug products occurred.**

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

PERSONNEL QUALIFICATIONS {21 CFR 211.25(a)}

1. …..GMP training was not conducted on a continuing basis and with sufficient frequency to assure that employees remain familiar with cGMP requirements.

   Specifically, the firm did not document any cGMP training given with regards to the receipt, quarantine, approval and release, repacking, labeling, storage, distribution, written procedures, etc. for the API drug ingredients repacked by the firm. The firm did not maintain employee training files. In addition, the firm was not following their SOP ….. titled "cGMP Quality Manual," section "Training," which reads in part: "Documented procedures for identifying training needs, including training in specific job skills, procedure training and continuous training in regulatory requirements, have been established. Personnel who perform assigned tasks within the operation are required to be qualified on the basis of education, training and/or experience. Personnel qualification files are maintained for each employee and included at a minimum, a written and approved job description, CV, records of training attended and procedure reviewed."

2. …..Employees are not given training in the particular operations they perform as part of their function.

   Specifically, you have no documentation on file to show that your three Quality Assurance Managers have the relevant education, training, qualifications or received adequate training or otherwise acquired the requisite skills to perform their assigned duties, including but not limited to approving batch records, preparing and revising procedures, and approving protocols and records.

3. …..Employees are not given training in the particular operations they perform as part of their function and written procedures required by current good manufacturing practice regulations.

   Specifically, your firm's SOP ….., "Change Control System," fails to provide instructions for training when major changes within a master batch manufacturing record occurs. Instead, your firm allows for area management and the quality unit to determine when training should or should not be conducted. The following examples illustrate major changes within a master batch manufacturing record where training was not conducted.

   a. Change Control Number ….., to include new equipment stations ….. for the manufacturing of ….. tablets.

   b. Change Control Number ….., to create a new Master Packaging Batch Record for ….., USP with the packaging configuration of 25g/bottle.

4. …..Employees are not given training in the particular operations they perform as part of their function and current good manufacturing practices and written procedures required by current good manufacturing practice regulations.

   Specifically, training files do not contain details to ensure personnel are trained on the particular operations performed. For example, finishing department operators were documented on being trained in the cleaning of equipment without detailing what equipment was covered. There are ….. types of equipment in the finishing department. Documentation could not be provided that ….. and ….. were trained on the cleaning of ….., even though they performed the cleaning of ….. earlier this year. The version of the procedure being trained on is not documented, and training is not provided to operators on revisions to master production batch records and master cleaning records.

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

PERSONNEL RESPONSIBILITIES {21 CFR 211.28 }

1. …..Clothing of personnel engaged in the processing of drug products is not appropriate for the duties they perform.

   Specifically,

   a. Sterile drug products are aseptically manipulated by the clean room operators who were observed wearing non-sterile eyeglasses, a non-sterile hair net, and non-sterile under garments that were worn outdoors prior to entry to the clean room.

   b. The clean room operator was observed re-using coveralls that were hanging on a hook in the anteroom.

   c. The operator's forehead was not covered, allowing exposed facial skin over the critical ISO 5 laminar flow areas where sterile injectable drug products are processed.

   d. We observed the gowning practices of the pharmacist prior to the production of ….. Injection. He entered the sterile production area wearing a single pair of non-sterile gloves. Within the clean room he donned a second pair of gloves, sterile latex, powder free. When he extended his arms to ensure that fingers filled the appropriate position, the pharmacist's bare wrist and forearm were exposed to the ISO 7 clean room environment.

2. …..Production personnel were not practicing good sanitation and health habits.

   Specifically, during the review of your disinfectant efficacy study, I found one of your microbiologists, whose name was listed as one of the qualified personnel allowed to enter the aseptic vial filling room had a mustache. According to your SOP, all persons working in aseptic manufacturing areas are to keep their hair short and shave regularly in order to minimize the hazards of contamination through hair.

3. …..Protective apparel is not worn as necessary to protect drug products from contamination.

   Specifically, protective apparel is not worn as necessary to protect drug products from contamination. Specifically, personnel do not wear sterile gowns, hoods, or sterile sleeve covers during aseptic processing. In addition, preparation of sterile product is performed by personnel with exposed skin on their face and neck.

4. …..Clothing of personnel engaged in the manufacturing and processing of drug products is not appropriate for the duties they perform.

   Specifically,

   a. The general gowning attire for entry into IOS 5/ISO 7 classified areas consists of the following: a gown (bunny suit) that has foot covers attached, a single hair net, safety glasses and a single ear loop face mask. The operators also use a single pair of sterile gloves. During the walkthrough, we observed employee ….. don the gloves inside the ISO 5 laminar flow hood. The general gowning requirements leave exposed skin around the eye, forehead and neck of the person preparing the sterile drug.

   b. Your firm is sterilizing the gowns (bunny suits) worn in the ISO 5 hood and the ISO 7 clean room via ….. Your firm does not have any written procedures for the sterilization of the gowns and does not have documentation to show that the sterilization process has been verified.

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