GMP Trends

DISTRICT ADDRESS	DATE OF ISSUE
GMP Trends LLC P.O. Box 1111 Firestone, Colorado 80520	April 1, 2019
	C.I. ISSUE: Issue #1013

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: United States of America and Worldwide	TYPE OF ESTABLISHMENT INSPECTED: 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

MANUFACTURING CONTROLS

1. …..Complaint procedures are deficient in that they do not include provisions that allow for the review to determine if the complaints represent serious and unexpected adverse drug experiences which are required to be reported to FDA.

   Specifically, the Director of Consumer Affairs & Legal Relations at your firm stated that she was not aware of a procedure for reporting unexpected adverse drug experiences to the FDA. Furthermore, the Director of Consumer Affairs and Legal Relations could not define what constituted an adverse drug experience. Currently, no employee at your firm is qualified to determine what constitutes an adverse drug event.

2. …..Batch production and control records do not include complete information relating to the production and control of each batch.

   Specifically, I observed the following deficiencies in the ….. batch record:

   a. Misdated Batch Record issuance.

   b. Lack of raw material lot numbers of ingredients used.

   c. Statement of actual yield and statement of percentage of theoretical yield at appropriate phases of processing.

   d. Lacks use of hand-held pH meters at Crystallizer.

   e. Lacks documentation of periodic weight checks for finished bags of ….. in the bagging area.

   f. In-process and laboratory control results.

   g. Sampling performed.

   h. Complete labeling, including specimens or copies of all labeling used.

3. …..The procedures for the annual quality standards record evaluation are deficient in that they do not address a review of complaint, recall, returned drug product, salvaged drug product and investigation records for each drug product.

   Specifically, your firm's "Annual Product Review Procedure" describes only a review of packaging components. This procedure does not include a review of batch records, complaints, recalls, returns, drug product specifications, or manufacturing control procedures. A review of your firm's last two annual product reviews shows a labeling checklist with approval and two labels. These Annual Product Reviews did not document a review of batch records, complaints, recalls, returns, drug product specifications, or manufacturing control procedures.

4. …..Deviations from production time limits are not documented.

   Specifically, excursions in hold time are not investigated, trended or otherwise evaluated for product impact. There have been multiple hold time excursions for multiple drug products. Your firm's Annual Product Quality Review was silent regarding manufacturing hold time excursions. Your firm's Quality Manager qualified this practice by referencing an SOP which states "In case during commercial manufacturing if the product-exceeds the established hold time period at any stage, sample shall be collected and shall be submitted to Quality Control for re-testing."

5. ….Employees are not given training in written procedures required by current good manufacturing practice regulations.

   Specifically, the training records reviewed for ….. employees lacked complete documentation of training on GMPs. Additionally, the SOPs provided for GMP training: SOP ….., "Training Policy," and SOP ….., "GMP Principles and Basic Hygiene for Employees," and SOP ….., "Employee Sanitary Practice," cover hygiene and sanitation and do not adequately describe the GMP responsibilities for staff based on job function.

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

LABORATORY CONTROLS

1. .....The establishment of standards and laboratory control mechanisms including any changes thereto, are not drafted by the appropriate organizational unit and reviewed and approved by the quality control unit.

   Specifically,

   a. The firm maintains reference standard spectra on the computer accessible by all. The reference standard files lack controls to prevent deletion, modification, or the ability to save over original files.

   b. The firm does not have a laboratory instrument logbook to track the use of the Fourier Transform Infrared (FTIR) Spectrometer, to include the dates of use, identity of users, and samples analyzed on the instrument.

   c. The firm does not ensure the contract laboratory performing active ingredient assay testing, on finished drug products is using validated or verified compendia methods per the firm's SOP ....., "Outside Contractor/ Vendor Qualification." The procedure states that contractor/vendor audits are to be performed ..... by quality control personnel, however, the firm's most recent vendor audit of the laboratory occurred four years ago. The firm did indicate validated and verified compendia methods were used at the time of the audit.

2. .....Laboratory records are deficient in that they do not include a complete record of all data obtained during testing.

   Specifically,

   a. Records of laboratory analyses are documented on pre-printed, unbound pages, and the results are transferred to product specification sheets without a second person review of the data obtained during in-process and finished product testing. During in-process microbiological testing for ....., Lot ....., ... cfu/ml was the total plate count (TPC) result observed; however, ... cfu/ml was the result reported on the Product Specification Sheet for this analysis.

   b. SOP ....., "Plate Count Test and Procedure," requires performing quantitative plate counts in which dilutions are performed when large numbers of colonies are observed on a plate. During raw material testing of ....., lot ....., ... colony forming units (cfu) were reported. There was no record showing the quantity of powder weighed and dilution steps taken to achieve a readable plate.

   c. Laboratory records do not include a record of all calculations performed in connection with the test. For example, liquid density in-process test results do not include the calculation or verification of the calculation.

   d. In-house prepared media plates were observed in the laboratory without the lot number of the material being tested, the identity of the media, the date the media was prepared, and the expiration date of the media.

3. .....Reserve samples from representative sample lots or batches of drug products selected by acceptable statistical procedures are not examined visually at least once a year for evidence of deterioration.

   Specifically, your firm failed to visually examine the following representative samples of drug products for evidence of deterioration: for the year ....., approximately 26 representative samples were not visually examined, and for the year ....., approximately 50 representative samples were not visually examined. In addition, lots that were visually examined lacked documentation as to who conducted the visual exam, when the visual exam was performed, and acceptable criteria for passing the visual exam. Your Quality Assurance Chemist stated written documentation for visual exams are provided in the Annual Product Review reports. An example of this documentation consists of the statement "Complies" under 13.0 "Control samples review" within the Annual Product Review report, and there is no additional written information in regard to the visual examinations conducted.

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

PACKAGING & LABELING CONTROLS

1. .....Master production and control records lack a description of the drug product containers, closures and packaging materials, a specimen or copy of each label and all other labeling, and the signatures and dates entered by the person or persons responsible for the approval of labeling.

   Specifically,

   a. Your firm does not have an approved Master Label for the ..... ointment. Last year, your customer made a significant change to the label and you are currently using two (2) different versions of the label for some package sizes (8oz and 16oz). The Master Batch Record also does not state that the labeling for the product is pre-printed on the jar.

   b. Your firm does not have a description of the containers and closures to be used for the ..... ointment other than the size.

2. .....Establishment of the reliability of the container supplier's report of analyses is deficient in that the test results are not appropriately validated at appropriate intervals.

   Specifically, the firm's vendor qualification program is inadequate in that the Quality Unit failed to establish the reliability of the component supplier's report analysis by performing periodic analytical evaluations. The quality management accepts consumables such as primary packaging for their final drug substances by performing a ..... inspection and reviewing the supplier's Certificate of Analysis. For example, the Quality Unit accepted ..... liter bags from ..... on two separate occasions. The Certificate of Analysis for each of the aforementioned containers purports that they are sterile and endotoxin free, however, the Quality Unit failed to validate the reported testing at any periodic basis. The aforementioned drug substances are utilized in the manufacturing of the sterile injectable final drug products.

3. .....There is a lack of written procedures describing in sufficient detail the receipt, identification, sampling, and examination of labeling and packaging materials.

   Specifically, your firm does not have any written procedures for the receipt, identification and release of pre-labeled drug packaging components (polypropylene jars) used for packaging of the ..... ointment. SOP ....., "Receipt, Identification and Storage of Components, Raw Materials, & Bulk Product," discusses comparing each batch of labels received against a Master Label before releasing to production, but the procedure does not discuss pre-printed packaging components. Several years ago, your firm changed from using a stick-on label to using pre-printed (silk-screened) jars. There is no documentation showing that the pre-labeled jars are sampled, examined, and the labeling compared to a Master Label before release into production. Your documentation of the receipt of the containers does not identify that the jars are pre-labeled or the version of the label. Your firm also does not describe the type of Certificate of Conformance to accompany each lot of pre-printed jars received. SOP ..... discusses Certificates of Analysis for components but does not specifically discuss packaging materials. Your firm is not always receiving a Certificate of Conformance/Certificate of Compliance with each shipment of jars.

4. .....Batch production and control records do not include complete labeling control records, including specimens or copies of all labeling used for each batch of drug product produced.

   Specifically, copies of the labeling placed on the ..... ointment are not always maintained. Your customer made a significant labeling change to the ..... ointment sometime last year. Your firm is still using some of the pre-printed jars with the old version of the label. Your firm is not always maintaining a copy of the labeling used and does not indicate in the batch record how many jars are filled with each label.

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

MEDICAL DEVICE-MANUFACTURING CONTROLS

1. .....Procedures for receiving, reviewing, and evaluating complaints by a formally designated unit have not been established.

   Specifically, your Vice President of Business Development and Regulatory Affairs indicated that your firm ..... does not have a complaint procedure because your firm's parent company ..... keeps and maintains your firm's quality system procedures which are written in a Chinese language at their facility in China.

   a. I observed that your firm has not documented complaints in a uniform and timely manner. Your President indicated that your firm is responsible for receiving and communicating all customer complaints to your manufacturing facilities. None of the nine complaints that the Vice President of Business Development and Regulatory Affairs provided me with indicate who at your firm initially received the complaints, or the date the complaints were initially received by your firm. I requested to see your firm's documentation of complaint .....; when they were each received and by whom. Your president provided the email document for only two. Complaint ..... shows that it was initially and solely received by your Vice President of your firm's West Coast Sales team via email, but the formal complaint record that your firm communicated to your manufacturing site indicates that the complaint was received a month later. The complaint was not processed for 34 days after the initial receipt date.

   b. I observed that your firm is not evaluating complaints to determine whether they represent an event which is required to be reported to FDA. For example, your Vice President of Business Development and Regulatory Affairs indicated that your firm does not have a complaint procedure for the activities conducted at this firm. Subsequently, your firm does not have a procedure that specifically identifies how an MDR evaluation will be conducted upon receipt of a complaint or by whom. Your Vice President of Business Development and Regulatory Affairs provided me with 9 complaint records to demonstrate that your firm's complaints are being documented. None of the nine records include documentation to demonstrate that an MDR evaluation was conducted.

2. .....Procedures for acceptance of incoming product have not been established.

   Specifically, General Inspection Work Instructions for ....., describes the incoming inspection activities to be performed for ..... silicone tray inserts/mats which include ..... Receiving inspection records of the ..... tray for lot numbers ..... and ..... document the ..... results as passing for the samples ..... but actual results were not documented. In addition, lot number ..... of the .....Tray, was received and inspected 6 days later. All ..... mats sampled failed ..... and a nonconformance was initiated, dispositioned and closed with ..... of the mats returned to the vendor. However, this lot of mats was used in the production/assembly of finished ..... Systems, lot number ..... one day prior to the incoming inspectional completion date and nonconforming material report initiation and disposition date which was during this FDA inspection.

3. .....The evaluation-of potential suppliers was not documented.

   Specifically, your employees did not produce documentation that demonstrated that your firm assessed your vendors in accordance with your Vendor Selection and Vendor Oversight procedures.

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