GMP Trends

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

DATE OF ISSUE
July 15, 2018

C.I. ISSUE
Issue #996

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

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 J – RECORDS AND REPORTS AND 21 CFR 820 SUBPART M - REPORTS

GENERAL REQUIREMENTS – ANNUAL PRODUCT REVIEW {21 CFR 211.180(e)}

1. …..Records are not maintained so that data can be reviewed at least annually to evaluate the quality standards of each drug product to determine the need for changes in specifications or manufacturing or control procedures. {21 CFR 211.180(e)}

   Specifically, your firm's quality unit failed to conduct an annual review of the finished sterile drug ….. in order to evaluate the quality standards and determine the need for changes in specifications or control procedures. Your firm stated that your contract manufacturer performs the laboratory testing, records results and supplies these records upon request. At the time of this inspection, your firm's quality unit had not received records for the results of specific lots placed on annual stability testing in support of the two year labeled expiry date. Your firm failed to request these records from your contact manufacturer. Your firm's quality unit also reported receiving Annual Product Review Reports for ….. from your contract manufacturer during this inspection. None of the provided reports included the laboratory testing of the preservative ….., in order to monitor and measure the amount of microbial inhibitors. Your firm's quality unit reported no record review was conducted and documented for the annual stability studies and annual product reviews supplied by your contract manufacturer. Your firm's quality unit reported the requirements for annual product review records and annual stability studies were not established by your firm.

2. …..Written procedures are not followed for evaluations conducted at least annually to review records associated with a representative number of batches, whether approved or rejected. {21 CFR 211.180(e)(2)}

   Specifically, your Quality Unit failed to follow SOP ….., "Annual Product Review," in that reviews of all records associated with all of your drug products manufactured over the last six years have not been conducted.

3. …..Written procedures are not followed for evaluation done at least annually and including provisions for a review of complaints and investigations conducted for each drug product. {21 CFR 211.180(e)(2)}

   Specifically, your firm's deviation and CAPA procedures indicate senior management is responsible for conducting periodic reviews of deviation data and CAPA activity for adverse trends. Your firm's complaint procedure indicates reports and statistics will be generated to help discern any trends that may be occurring. Review of your firm's Management Review procedure and meeting minutes did not include an assessment of trends for deviations, complaints or CAPAs. Your firm stated that you do not track root cause codes for trends and that you do not have metrics for these activities.

4. …..Written procedures are not followed for evaluations done at least annually and including provisions for a review of complaints, recalls, returned or salvaged drug products, and investigations conducted for each drug product. {21 CFR 211.180(e)(2)}

   Specifically, the annual product review that was prepared by a third-party auditing company did not contain a review of any recalls, complaints, returned products, or salvaged products that occurred during the year preceding the report.

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PRODUCTION RECORD REVIEW {21 CFR 211.192}

1. …..The Quality Assurance Unit has approved and implemented documents that do not assure appropriate production, testing, and deviation review and release of commercial material.

   Specifically,

   a. The procedures for batch record review and batch release allow release of drug substance batches with open deviations or out of specification (OOS) results and for release of drug product made from such drug substance.

   i. SOP ….., "Review of Batch Records, Analytical Report, Relevant Records, Approval of Batch Release and Generation of CoA," for drug substance states: "if the deviation/OOS does not have any impact on the product/batch based on the completed impact assessment, but pending closure due to some other reasons, then batch can be released with appropriate justification." This is a "full" release, not a release under conditional quarantine status.

   ii. SOP ….., "Review of Batch Records, Analytical Report, Relevant Records, Approval of Batch Release and Generation of CoA," for drug product does not include a requirement to evaluate the deviation and OOS status of the drug substance used for the drug product manufacturing.

   b. The procedure for approving the test results for in-process samples and raw materials, SOP ….., "Testing and Approval/Rejection," allows the analyst performing the testing to also perform the review of the data and release the data to Quality Assurance or make a raw material usage decision in SAP.

   i. For in-process samples, SOP states that "after completion of analysis, results are entered in TI sheet/BMR sheet and signed by the analyst." Then, SOP states that "the TI/BMR sheet with meta data will be reviewed and released with signature and date (signature can be either self or by a second analyst)."

   ii. For raw materials, SOP states "once the analysis is completed by analyst, results review and usage decision in SAP can be completed by the same personnel whenever applicable.

2. …..Investigations of an unexplained discrepancy and a failure of a batch or any of its components to meet any of its specifications did not extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy.

   Specifically, despite performing an investigation with a root cause implicating an entire product line and finding widespread impact across the line during numerous retention sample reviews, you did not expand your investigation beyond individual lots to the whole line. For example, you received a complaint of multiple label defects (missing label, double labels, and peeling label) for ….., lot ….., and you determined the primary root cause of the defects was the use of label adhesive that was optimal for glass vial adhesion but not for plastic vials. This label adhesive was used for your six products, all of which use plastic vials. You did not consider and evaluate the impact on these other products, and, at the time of the investigation, approximately ….. still unexpired lots were on the market.

3. …..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, I found an atypical laboratory result reported during Non-Volatile Residue Limit Test for ….., lot ….. The results of this test were reviewed and approved by the firm's consultant, and this active ingredient was released to be used in your manufacturing process. Your firm failed to adequately review and implement the necessary controls to investigate the source of atypical results during the analytical testing.

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COMPLAINT FILES {21 CFR 211.198}

1. .....Procedures describing the handling of written and oral complaints related to drug products are deficiently written or followed. {21 CFR 211.198(a)}

   Specifically, the written procedure for handling complaints, SOP ....., "Complaint Handling and Evaluation," does not state to review the batch record associated with the complaint; to determine if there were other similar complaints for the same product; to determine if there were similar complaints for other products; to examine the retain sample if the lot number is known; to determine if the complaint represents a serious adverse drug experience, which is required to be reported to the FDA, and to perform trending of the complaints.

2. .....Written records of investigations into unexplained discrepancies and the failure of a batch or any of its components to meet specifications do not always include the conclusions and follow-up. {21 CFR 211.198(b)(2)}

   Specifically, investigation reports do not include a proper assessment and/or does not extend to other batches or samples related to the batch that was investigated. The investigation report for OOS ....., for the bulk finished product ..... Caplets, 100mg, batch ....., revealed that the OOS obtained during the assay results: Samples 1 and 2 were attributing the root cause to HPLC malfunction (i.e. injector malfunction or blocked tubing). The original results for sample 1 and 2 were invalidated and re-injected, using sample 1 as the control sample. However, the bulk finished product Uniformity of Dosage (i.e. ten samples) and the post pack finished sample Assay (i.e. two samples) of the same previous batch, tested concurrently by the same analyst and injected after the OOS assay result, were not re-injected because sample 1 (as control) confirmed the original results. The other samples were not re-injected to assure accuracy of the results because the results were within specification. Furthermore, the affected tubing was replaced and the injector accuracy and pump flow were tested. However, "Not Applicable" was stated under the corrective and/or preventive action section.

3. .....Written records of investigations into unexplained discrepancies do not include the conclusions and follow-up. {21 CFR 211.198(b)(2)}

   Specifically, 20 out of 20 Nonconformance Reports (NCRs) reviewed, as well as their associated Root Cause CAPA Investigation Reports, were inadequate based on the following:

   a. Investigations are not complete and potential root causes are not always identified. For example, NCRs ..... initiated for action level excursions for non-viable particle counts were attributed to the bottle and a bottle component without scientific justification. Review of the laboratory report revealed that metal particles were observed in the sample, however, there was no mention of the metal particles included in the investigation reports, nor was a root cause analysis conducted to determine the source of the metal particles, product impact and a corrective action.

   b. There was no scientific justification for the root cause assigned to action level excursion investigations for non-viable particle testing for aseptic filling lines. Specifically, sampling method technique and/or the ..... equipment was assigned as the root cause; however, there was no scientific justification or documentation provided to verify that the sampling techniques or equipment that was used caused the elevated non-viable particle reading. For example, NCR .... states that curtain movement during the time of sampling caused the out of specification non-viable particle count, thus the NCR was classified as sampling error. However, no scientific rationale could be provided for why this was a sampling error, since during this inspection, we observed, on Aseptic Fill Line ....., continuous curtain movement during the production of aseptic drug products.

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

COMPLAINT FILES {21 CFR 820.198}

1. .....Procedures for receiving, reviewing, and evaluating complaints by a formally designated unit have not been adequately established. {21 CFR 820.198(a)}

   Specifically, you have not established a complaint handling procedure. Section ....., of the Corrective and Preventive Action procedure, is the only procedure that addresses the management of complaints. The procedure does not state how all complaints received by the firm are processed in a uniform and timely manner, how oral complaints will be documented, or that complaints will be evaluated for investigation and that the evaluation will be documented.

2. .....Complaint files are not maintained. {21 CFR 820.198(a)}

   Specifically, SOP ....., "Customer Returns and/or Complaints," was established to handle and document customer complaints. The SOP was updated two years ago. The complaint procedure states that customer complaints are documented on Form ..... A supplier noted that a complaint was received from your company concerning a small screw that came off a latch head and was swallowed by the patient. The dentist tried to locate the screw, but it was never retrieved from the patient. Form ..... was not completed in accordance with the complaint procedure. No evaluation was documented to determine if this complaint was reportable under the Medical Device Reporting regulation.

3. .....Not all complaints have been reviewed and evaluated to determine whether an investigation is necessary. {21 CFR 820.198(b)}

   Specifically, five out of the nine complaints received since the last inspection document "erratic," "unsatisfactory," or "not satisfactory" test results using the ..... test kits you manufacture. However, no investigation was made for these complaints with respect to the ..... test kits, and the reason for not investigating the test kits was not documented.

4. .....Complaints involving the possible failure of a device, labeling and packaging to meet any of its specifications were not reviewed, evaluated and investigated where necessary. {21 CFR 820.198(c)}

   Specifically,

   a. The Error Log shows that your firm issued ..... Returned Good Authorizations for products that were returned for labeling errors, or incorrect items. No evidence was provided to demonstrate that these failures of the labeling and packaging to meet specifications were reviewed, evaluated, and investigated where necessary.

   b. Material Review Board (Nonconformance) record ..... was initiated for 17 ....., found to be oversized, allowing the non-locking screws to go through the .....; however, complaints were not initiated for these failures identified after distribution.

   c. Complaint ..... was closed prior to completion of all investigation activities. For example, the complaint record states: "The part will be sent out for ..... to determine if the part has defects on the surface which could be the cause of the breakage." The results of this testing were not received until after closure of the complaint. Furthermore, evaluation of the returned product was not documented.

5. .....Records of complaint investigations do not include required information. {21 CFR 820.198(e)}

   Specifically, "Customer Complaint" forms for the nine complaints received since the last inspection have not been completed, as required by your SOP ....., "Complaint Procedure." For example, all nine complaints have blank sections of the "Customer Complaint" form under "Date of this report," "Was the device used to diagnose or treat a patient?" and "Status of the patient." It is noted that even without these patient details each complaint was determined to not require an MDR report.

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