GMP Trends

DISTRICT ADDRESS	DATE OF ISSUE
GMP Trends LLC P.O. Box 1111 Firestone, Colorado 80520	January 15, 2017
	C.I. ISSUE Issue #960

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 Quality issues, such as deficiencies in management review, internal audits, annual product reviews, employee training and reserve samples.

MANAGEMENT REVIEW AND INTERNAL AUDITS

1. .....Management with executive responsibility has not reviewed the suitability and effectiveness of the quality system.

   Specifically,

   a. Management reviews do not ensure that the quality system satisfies the requirements. The Quality Manual defines the scheduling and holding a formal annual Management Review meeting where the quality metric data is presented and reviewed by Senior Management. The management review conducted last year did not cover topics related to the Quality System, e.g. Business topics listed included invoicing orders and third party shipping codes.

   b. The firm's Quality System Manual describes establishment, maintenance and monitoring of the Quality System procedures. These procedures are not adequately established. Examples: Internal audits, CAPA, Document Control, Complaint Handling and Management review procedures are not adequately established and implemented. The firm does not have records of internal audits, CAPA data and records of current procedures.

2. .....Procedures for management review have not been adequately established.

   Specifically, your firm failed to implement your firm's SOP ..... "Management Review Procedure," requiring management reviews to be conducted annually. For example, over the last five years, your firm's management reported and provided documentation of two Management Reviews being conducted. No documented management reviews were conducted for the other three years.

3. .....The results and/or dates of management reviews are not documented.

   Specifically, your firm's Management Review procedure, SOP ....., states that management review will be performed ..... Over the last three years, your firm has not performed or documented any management reviews to assess the effectiveness of the quality system.

4. .....Quality audits were not performed at defined intervals to determine whether the quality system activities and results comply with quality system procedures.

   Specifically, you have indicated on SOP ....., "Quality Audit Procedure," that quality audits will be conducted every ..... months. You are conducting quality audits annually, rather than the defined interval written in your quality audit procedure.

5. .....Procedures for quality audits have not been adequately established.

   Specifically, your firm failed to implement your firm's SOP ....., "Internal Audits Procedure," requiring internal quality audits to be completed by qualified auditors being independent of the areas/activities being audited. For example,

   a. Your firm's "Internal Quality Audit Plan and Report" states your firm's Plant and Quality Manager performed audits in areas which they are directly responsible.

6. .....Quality Audits and re-audits have not been performed.

   Specifically, your firm's Internal Audit procedure SOP ....., required you to develop an Internal Audit Plan and to perform internal audits of your firm's quality system. Over the last three years, your firm has not established any Internal Audit Plans or performed any internal audits for your firm.

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

ANNUAL PRODUCT REVIEWS

1. …..Records are not maintained so that data therein can be reviewed at least annually to evaluate the quality standard of each drug product to determine the need for changes in specification or manufacturing or control procedures.

   Specifically, your firm does not conduct an adequate review, at least annually, on each product and/or formula your firm manufactures. Review of your firm's "Annual Product Review Minutes," demonstrated that your firm: 1) does not list the products you reviewed during this meeting; 2) does not document the batch records reviewed to determine if a representative number have been reviewed and which ones were rejected or approved; 3) does not list the Out of Specifications, Nonconformance or investigations conducted, and 4) does not provide information on complaints of Corrective Actions/ Preventative Actions that were reviewed during this meeting, including the drugs associated with complaints and CAPAs. These meeting minutes do not provide the data required to determine if there was a need for changes in the manufacturing, control procedure or specification of your drug products.

2. …..Records are not maintained so that data therein can be reviewed at least annually to evaluate the quality standard of each drug product to determine the need for changes in specification or manufacturing or control procedures.

   Specifically, your firm has no procedure in place describing the requirement to perform Annual Product Reviews (APR) in which quality standards such as the following will be assessed: Trends, Change control, product improvement projects, reprocess/rework, complaints, rejects, deviations, out of specification, stability failures, etc. Your Director stated your firm has never performed an APR for any of the drug products distributed by your firm. In addition, your firm has not requested or reviewed your contract manufacturer's APR to ensure that they conducted the APRs related to their areas of coverage (i.e. manufacturing process) for your drug products to determine the need for changes in drug product specifications, manufacturing or control procedure.

3. …..Annual product reviews do not include a review of all appropriate data to evaluate quality characteristics indicative of potential trends.

   Specifically, the Annual Product Review for ….. did not include an evaluation of content uniformity data as part of the Trend Review Summary section to ensure the detection of potential adverse trends.

4. …..Written procedures are not established for evaluations conducted at least annually to review records associated with a representative number of batches, whether approved or rejected.

   Specifically, your procedure SOP ….., "Annual Product Review," does not define a timeline for completing Annual Product Reviews. Your most recent Annual Product Review of ….. covered a two year time period. It has been three years since your last Annual Product Review of this product.

5. …..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.

   Specifically, your firm failed to follow SOP ….., "Annual Drug Review," to review all drug products annually. Your firm has not performed annual drug review for at least three drug products that have been manufactured and distributed for the last three years.

6. …..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.

   Specifically, your Quality Unit failed to follow SOP ……, "Annual Product Quality Review," in that the complaints captured in the Annual Product Review for ….. were not adequately evaluated to identify trends such as ….. that may indicate a need to change product specifications or controls.

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

TRAINING

1. …..Individuals responsible for supervising the manufacture and holding of a drug product lack the training and experience to perform their assigned functions in such a manner as to assure the drug product has the safety, identity, strength, quality and purity that it purports or is represented to possess.

   Specifically, your firm failed to ensure both the Vice President of Quality and Quality Manager have adequate training and experience to assure commercially distributed product has the safety, identity, strength, quality and purity that it is represented to possess. Your firm's employees assumed these roles in October of last year. Prior to assuming these roles, your firm stated neither employee had necessary training and experience to perform these functions. Your firm also stated currently you are working on establishing the responsibilities, duties, and training requirements for these positions. There has been no relevant cGMP training received by the Vice President of Quality and Quality Manager. These employees are responsible for reviewing, approving, releasing, and distributing finished sterile drugs.

2. …..Employees engaged in the processing and packing of a drug product lack the training required to perform their assigned functions.

   Specifically, personnel involved in independent processing and packaging operations do not have all required On-The-Job training which is commensurate with their intended job duties. For example, training records for Process Tech ….., documenting his On-The-Job training received, were not available upon request. Furthermore, during a walkthrough of the facility, I observed a Product Operator performing independent duties on a packaging line currently running. A review of the employee's training records showed the employee had not yet received the appropriate job specific OJT training to conduct packaging operations independently.

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

   Specifically, SOP ….., "Training," is not being fully followed. This SOP states: "Individual training logs for each employee will detail his/her various certifications, when obtained, who administered the test, expiration dates (in all cases no longer than ….. past last certification), and any recertification." There is no record of any job-specific training ever being conducted for employees hired by the firm that conduct quality and production operations.

4. ….Your firm lacks adequate production and process controls to ensure the consistent production of a drug that meets the applicable standards of identity, strength, quality and purity.

   Specifically, your personnel lack the training to perform their assigned functions. Your firm's training for counting microbial growth in plates is not clear. Your technician counted ….. CFU for a plate of environmental viable air monitoring for the location which was above the action limit. After the high result, the plate was counted by several other technicians and reviewed by QA. The root cause of the high level was identified as incorrect counting by the first technician. Nonconformance Record NCR ….. was opened. The investigation concluded that the correct amount of colonies for the sample was below the maximum action limit. After we reviewed this NCR and discrepancies with the counted colonies, your firm reviewed the report and concluded that the technicians and/or QA were not properly trained and that the root cause for the NCR was invalid. The original result obtained was correct and location ….. did exceed the action limits for viable air monitoring.

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

RESERVE SAMPLES

1. …..The reserve sample of drug product does not consist of at least twice the quantity necessary to perform all the required tests of drug product.

   Specifically,

   a. Retain (i.e. reserve, retention) samples observed to be stored in your in-house laboratory were observed to not be representative of each lot or batch of drug product. The retain samples do not consist of at least twice the quantity in order to perform required testing. In addition, the storage temperature conditions could not be determined.

   b. Your firm does not have documentation that a visual analysis of retain samples manufactured by your firm is being performed in order to determine if deterioration has occurred.

2. …..Reserve drug product samples are not representative of each lot or batch of drug product.

   Specifically, during inspection of reserve samples of ….., lots ….., from the representative lots the firm randomly places bottles of reserve samples in carton boxes. The reserve samples are not stored in the proper orientation as it would be when the drug product is marketed and as stated in SOP ….., "Reserve Samples." In addition, reserve samples of drug products were stored in QA room with no temperature and humidity monitoring. Employee ….. stated this is a temporary holding spot before products are placed in the warehouse.

3. …..Drug product reserve samples are not stored in an immediate container-closure system that has essentially the same characteristics as the marketed product.

   Specifically, according to SOP ….., "Reserve Samples of Bulk Finished Product," your firm ships bulk finished products in ….. bags and corrugated cardboard boxes with or without the use of desiccants; however, the reserve samples collected from bulk finished products are stored in bottles at your firm.

4. …..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, the firm has not established written procedures to inspect retain drug product samples at least annually for evidence of deterioration.

5. …..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, SOP ….., "Retain Program," was not followed in that retain samples were not inspected for signs of deterioration. The QC Manager was not aware of this requirement but as per the SOP, he is responsible for the review of the inspections.

6. …..Reserve samples for active ingredients and drug products are not retained for one year after the expiration date of the drug product.

   Specifically, your firm does not have any written procedures for sampling, identifying, storage and retention of reserve samples that are collected of active pharmaceutical ingredients and finished drug products. Your current unwritten policy is to retain reserve samples for ….. after production.

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