GMP Trends

DISTRICT ADDRESS	DATE OF ISSUE
GMP Trends LLC P.O. Box 1111 Firestone, Colorado 80520	February 15, 2017
	C.I. ISSUE: Issue #962

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. …..Procedures applicable to the quality unit are not fully followed.

   Specifically, according to SOP ….., "Corrective and Preventative Action (CAPA)," Quality Assurance (QA) is required to decide if an effectiveness check is needed, and if not, enter a justification. However, QA personnel did not justify why an effectiveness check was not required regarding CAPA ….. after excessive API material was found on a ….. during processing. Although CAPA ….. stated the justification was captured in change control record ….., regarding revalidation of the ….. process, no effectiveness check was required in this change control record, and there was no justification why an effectiveness check was not required.

2. …..Time limits are not established when appropriate for the completion of each production phase to assure the quality of the drug product.

   Specifically, the firm's bulk hold time (BHT) extension study for ….. tablets is inadequate in that:

   a. The bulk hold time extension study failed to take into consideration the potential effects of routine transport of the firm's semi-finished oral solid ….. products between different sites during production and testing activities. There was no shipping study conducted as part of the bulk hold time extension studies to assess the impact of transport conditions of the physical attributes of the products. For example, several customer complaints were on the conditions on the physical attributes of the products. The complaints regarding broken tablets were received for ….. batches within the last twelve months by the firm.

   b. Although the finished bulk dosage forms were stored in bulk containers for ….., real-time stability data under the interim storage conditions were not generated to demonstrate comparable stability to the final dosage from in the marketed package. The bulk products are typically held for longer than ….., but they are not monitored for stability under controlled, long-term storage condition for the length of the holding period.

   c. There is a lack of established tests including description, hardness, thickness, friability, and disintegration to monitor the physical characteristics of the bulk products in the extended interim storage.

3. …..Complaint records are deficient in that they do not include the findings of the investigation and follow-up.

   Specifically, according to SOP ….., "Complaint Handling," your firm will initiate a CAPA as defined in SOP ….. whenever the same type of complaint is received ….. times. Your firm has received approximately ….. complaints over the last 11 months for ….. capsules reporting different tablets found in the bottle. However, no CAPA has been initiated.

4. …..Procedures describing the warehousing of drug products are not followed.

   Specifically, during a tour of the facility a rejected batch of ….. tablets, lot ….., was found stored in the warehouse near the incoming receiving area instead of in the rejection cage or in a trailer, as per SOP ….., "Removal of Rejected Material From the System and Destruction of Rejected and Waste Material." In addition, the deviation from this SOP did not initiate a Notice of Event or investigation to justify improper storage of the rejected batch.

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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 test procedures and laboratory control mechanisms including any changes thereto, are not reviewed and approved by the quality control unit.

   Specifically, the Quality Control Unit (QCU) has not reviewed or approved test methods used by their contract testing facility to test their finished drugs products. According to the Technical Manager, the firm does not know and has never seen the finished product test methods utilized by the contract laboratory to test the firm's drug products.

2. .....Established laboratory control mechanisms are not followed.

   Specifically, during the inspection of the quality control laboratory, we noted widespread non-cGMP employee documentation practices as follows:

   a. Missing laboratory notebook review signatures and date.

   b. The placement of shredders inside the laboratory, as well as the laboratory manager's office.

   c. The practice of making entries in a single laboratory notebook by separate analysts, although the book was assigned to another personnel.

   d. Storage of raw chromatograph and UV test results in open cabinets.

   e. Quality Control Analyst discarded live test record in trash bin.

   f. Analyst stored original laboratory and calculation data from HPLC and CU analyses on her personal network drive.

   g. Several laboratory analytical equipment remained non-networked as stand-alone equipment used to generate test data within the laboratory.

3. .....Laboratory controls do not include the establishment of scientifically sound and appropriate specifications, and standards, designed to assure that components conform to appropriate standards of identity, strength, quality and purity.

   Specifically, your firm lacks laboratory controls for sample handling and testing. For example, your firm's Quality Control Laboratory lacks a procedure and documentation for samples received for testing by the Quality Control laboratory. Samples collected for raw material, in process, finished product and stability testing are not logged in when received by the lab to identify the material sampled, person sampling, lot number and date of delivery to ensure chain of custody.

4. .....Appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel.

   Specifically, your firm has not validated the computer software program that is used to perform HPLC and GC analysis on ….. in-process and finished drug product samples. The Laboratory Supervisor stated that data has been deleted in the past, and your firm has not retained any HPLC or GC raw data that was generated on the computer prior to …..

5. .....Results generated from a laboratory instrument which failed to meet established system suitability specifications were not invalidated.

   Specifically, not all system suitability acceptance criteria were met during HPLC determination of related impurities testing of ….., USP lot ….., however, deviation investigation report ….. stated the analytical data were valid. The retest date of ….. was extended one year based, in part, on data obtained from this analysis.

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

MANUFACTURING-STERILE PRODUCT CONTROLS

1. .....Aseptic processing areas are deficient regarding systems for maintaining any equipment used to control the aseptic conditions.

   Specifically,

   a. The firm has not certified the clean rooms (ISO 5, ISO 7, and ISO 8) under dynamic conditions in the last 2 years.

   b. Two HEPA filters within the ISO 5 area appeared to have black splotchy patches with irregular boundaries. Additionally, all HEPA filters screening were observed to have a "rust" color on the outside within the ISO 5 and ISO 7 areas.

   c. The facility is not adequately designed and controlled to prevent influx of contamination from lesser controlled areas. The ceiling light fixtures within "Compounding Room ..... ISO 7" directly outside the barriers were observed to be lifted up (approximately 1/2 inch space between the light and the ceiling) and not flush with the ceiling.

2. .....Aseptic processing areas are deficient regarding systems for monitoring environmental conditions.

   Specifically, the firm's environmental monitoring plan is inadequate due to the fact that no surface samples are taken in the Prep Room (ISO 8) and the Gowning Room (ISO 8). Additionally, surface sampling in Compounding Room ..... (ISO 7) does not include cart handles, walls, floors, computer printer or cart wheels.

3. .....Laboratory controls do not include the establishment of scientifically sound and appropriate sampling plans and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality and purity..

   Specifically, despite previous citations regarding failure to conduct ..... testing of microbial isolates obtained from critical test samples or from environmental monitoring, the firm has failed to meet prior commitments to initiate such testing and to initiate an isolate library of specifically identified organisms for use in challenge testing. At an earlier inspection, it was found that ..... test kits purchased by the previous Microbiology Manager had never been used and were expired. The current inspection found that the replacements purchased subsequently have also not been used and a microbiologist with responsibility for isolates stated that some additional components have now expired. In the absence of an isolate library and use of those isolates in challenge testing of media and disinfectants, the firm has neither data regarding the species found within the facility nor the effectiveness of disinfectants to control those species. Identification of isolates is primarily limited to performance of a gram stain. In the interview of the same microbiologist referenced immediately above, she pointed out that they also streak isolates on ..... and record whether ..... observed upon incubation. The microbiologist could not explain what information is obtained from the use of ..... in terms providing ..... information about the unknown organism.

4. .....The written stability program for drug products does not include specific test methods.

   Specifically, the firm's method validation for the testing of the sterile ophthalmic products failed to demonstrate that the test method for related compounds is stability indicating. Specificity evaluation failed to demonstrate peak purity for the active ingredients.

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

MEDICAL DEVICE-MANUFACTURING CONTROLS

1. …..Risk analysis is incomplete.

   Specifically, SOP ….., "Risk Management Overview procedure," states the risk management documents should be continually reviewed and updated as new information becomes available such as "complaints" and "revised risk estimates" or failure modes. This procedure has not been adequately implemented.

2. …..There is no agreement with suppliers to notify you of changes in the product or service.

   Specifically, SCAR ….. was issued to your ….. diaphragm supplier with the following description of problem, "Diaphragm material not per specifications." This supplier corrective action was not verified by your firm until seven months later. Four months before the SCAR was verified, your firm received ….. diaphragms from your supplier. These diaphragms were manufactured into finished devices and distributed. There is no documentation to identify the material of the diaphragms was acceptable for use in the finished devices.

3. …..Procedures for design review have not been adequately established.

   Specifically,

   a. Your firm has not established procedures to ensure an individual(s) who does not have direct responsibility for the design stage being reviewed is present at design reviews.

   b. Your firm's design review of the design change, to upgrade your firm's ….. firmware to revision 2.0, did not document the presence of an individual who did not have direct responsibility for the design change.

4. …..Products that do not conform to specification are not adequately controlled.

   Specifically, you received ….. regulator assembly modules from your supplier. Product non-conformance report was generated for missing certificate of conformation and failing the ….. These non-conforming parts were used "as-is" under Deviation Authorization Justification ….. for the use of ….. These non-conforming components did not evaluate if the finished device would be adversely affected.

5. …..Procedures for corrective and preventative actions have not been adequately established.

   Specifically,

   a. SOP ….., "Corrective and Preventive Actions" does not include requirements for 1) verifying or validating the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device; and 2) ensuring that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such products(s) or the prevention of such problems.

   b. SOP ….., "Issues Procedure" does not require a defined time frame for implementation and action plans or review by the Head of the Department/CAPA Working Team; therefore issues are opened and a problem may be identified and another issue is subsequently opened identifying a previously identified unresolved issue.

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