

GMP TRENDS®

DISTRICT ADDRESS GMP Trends Inc. P.O. Box 8001 Boulder, Colorado 80306		DATE OF ISSUE December 15, 2009
		C.I. ISSUE Issue #790
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED To: Responsible Person, Director of Quality Assurance		
FIRM NAME Pharmaceutical and Related Industries	STREET ADDRESS 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:		
<p><i>EDITED EXCERPTS FROM ACTUAL 483 OBSERVATION REPORTS BY FOOD AND DRUG ADMINISTRATION INVESTIGATORS</i></p> <p>MANUFACTURING CONTROLS</p> <p>1.Written procedures are not established 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.</p> <p>Specifically, the procedure is not adequate to conduct analysis of data to produce meaningful trending. Annual Product Review procedure states that the Annual Product Review (APR) is compromised of summary reports including API manufacturing, API analytical testing, drug product manufacturing, drug product analytical testing, and product complaints. Each summary report is to include an analysis of the data and summary of the trends. For example:</p> <p>a. The APR procedure states Quality Assurance is responsible for compiling the summary report for product complaints and product complaints with adverse events including trends. Neither the APR procedure nor the complaint procedure provide adequate instruction to conduct meaningful trend analyses. Product Complaint System states that trending will be performed quarterly by Quality Assurance. The procedure doesn't define the minimum data to be analyzed nor does it include trending of adverse events which were not directly reported as product quality complaints, but may possibly relate to product quality. Such adverse events are analyzed by pharmacovigilance for trends. Documentation of complaint trending for was reviewed. Complaint data trended included open vs. closed, turn around time (actual & average), classification, category, product, and U.S. vs. Foreign complaints. Information was not consistently analyzed each quarter or for the year.</p> <p>b. Complaint classification type (I-III) was not trended for Q4 or the Year. U.S. vs. Foreign complaints were not trended during Q1 or Q2. Complaint category was not trended in Q2 and incorrect values were noted in the YTD trending of categories. The firm has no other procedure for the trending of data.</p> <p>c. Additionally, the Annual Product Review procedure does not require evaluation of returned drug product.</p> <p>2.Deviations from written production and process control procedures are not recorded and justified.</p> <p>Specifically, there is no assurance that all manufacturing deviations are documented. For example:</p> <p>a. tablets were observed to contain black specks during tablet inspection. Investigation into the black specks states that during compression the operators observed the product sticking to the punch tips. The operator was instructed by the supervisor to remove and clean the upper and lower punches and then polish the punch tips. The dies and feed frame were also removed and cleaned. None of this was documented on the "Compression Data Sheet" which shows no problems were encountered in compression.</p> <p>b. During the compression of batch, tablets were compressed below the action limit of 7.0 kp. The "Compression Data Sheet" does not indicate that there were any problems with compression although the entire batch was compressed at a range of 4.4. kp to 6.1 kp which is below the target tablet hardness of, and below the action limit of 7.0. An investigation for this batch was not initiated until when the batch did not meet yield specifications. The low yield was attributed to broken tablets.</p>		
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DURING A REVIEW OF INSPECTION REPORTS OF U.S. FIRMS (I) (WE) OBSERVED:

MANUFACTURING-STERILE PRODUCT CONTROLS

1.Aseptic process areas are deficient regarding the system for monitoring environmental conditions.
Specifically, until, the written procedures for microbiological monitoring of the aseptic core did not require investigations of all microbial growth found in the Class 100 areas of the aseptic filling rooms. Previous editions of SOP's defined the action limit for air samples and critical surfaces in the Class 100 areas as microbial growth greater than cfu/cubic meter or rodac plate. Alert limits for these samples were not defined in either SOP. As a result, samples from these critical locations with cfu were not evaluated for impact on product, investigated as environmental excursions or trended as over alert or action limit samples. For example:
 - a. **An air sample collected in the Class 100 area of Aseptic Filling Room on found cfu/cubic meter. The isolate was identified as a Streptomyces species. The sample was not considered over alert or action limits and was not investigated as an environmental excursion.**

2.There is a failure to thoroughly review the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been thoroughly distributed.
Specifically, the written procedure for monitoring airborne particulate levels is not always followed. On, during the aseptic filling of Injectable, we observed the isokinetic probe, which was being used to monitor non-viable particles, on a stand about 2 feet away from and one foot above the filling line near the turntable. The probe was aligned at a 90 degree angle to the HEPA filtered air flow. The Microbiology Manager explained they have two tripods for the probes. He said only one of the two can be set at a 90 degree angle. SOP states, "An isokinetic probe should be affixed to a tripod or stand at an approximate angle of and adjusted to work height."

3.Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design to facilitate operations for its intended use.
Specifically, on two occasions, we observed vials without stoppers and vials with improperly-seated stoppers leaving the filling area to be capped. For example:
 - a. **On, we observed a vial of lot with an improperly-seated stopper successfully pass through the on-line vision system for stopper detection and proceed toward the capping machine. We mentioned this to the operator who stopped the line and rejected the vial before it could be capped.**
 - b. **On, we observed numerous vials of lot without stoppers entering the capping area on Line** The Vial and Stopper Reconciliation sheet from the completed batch record for lot documented 505 vials missing stoppers rejected from the filling area and 645 missing stopper/seal rejects from the capping area. We also observed a vial without a stopper that the on-line vision system for stopper detection did not detect that proceeded toward the capping machine. We mentioned this to the operator who stopped the line and rejected the vial before it could be capped.

4.Clothing of personnel engaged in the manufacturing and processing of drug products is not appropriate for the duties they perform.
Specifically, the protective eye goggles worn by operators who enter and work in the Aseptic Core, including those who enter the critical Class 100 areas of the aseptic filling lines, are not sterilized before use. According to written procedures, goggles are sanitized with before and after use and stored in a UV light cabinet between uses. Goggles are not sampled as part of the microbiological monitoring of personnel.

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FORM GMP VOLUME I SUPPLEMENTS PREVIOUS EDITIONS INSPECTIONAL OBSERVATIONS
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DURING A REVIEW OF INSPECTION REPORTS OF U.S. FIRMS (I) (WE) OBSERVED:

LABORATORY CONTROLS

1.Drug product component testing is deficient in that at least one specific test to verify the identity of each component is not performed.

Specifically, the component (API's and excipients) suppliers' COA's are accepted in lieu of full testing, but a specific identity test is not conducted; routine evaluation of the suppliers' COA is not conducted; and retest dates for components are not established or assigned. (Repeat deficiency.)

2.Record keeping practices did not assure that the quality unit could detect missing documentation and procedures were inadequate.

Specifically, the firm has no written procedures which address the reporting and handling of out of specification (OOS) results. In interviews with two analysts in regard to the handling of OOS results including failed controls, it was stated that while there are no separate incident reports or logs for tracking this information, the information is recorded on the individual test sheets. It is noted in this regard that:

- a. **One analyst stated that there were at least two OOS results in his memory. The firm was able to show me the initial reports. These reports stated that the tests were repeated, however, I noted that the initial report does not reference the retest. The retest report was not filed with the initial report and was not readily identified or available for review.**
- b. **The other analyst commented that he had experienced failed controls during testing. I asked on two occasions for those reports to be located, but no test sheets were presented by the end of this inspection.**

3.The calibration of instruments and apparatus is not done at suitable intervals with provisions for remedial action in the event accuracy and/or precision limits are not met.

Specifically, the High Performance Liquid Chromatograph (HPLC), Gas Chromatograph (GC) and the System used for the testing of the Active Pharmaceutical ingredients, such as derivatives, and finished products such as tablets, lack complete performance testing at suitable intervals. This is evidenced by the following:

- a. **The GC routine qualification performed by quality control (QC) personnel does not include the test for the flame ionization (FID) and thermal conductivity (TCD) detectors and the reproducibility test for the auto-injector as part of the routine calibration conducted every months. These tests are only conducted during instrument overall re-qualification performed every years by the QC personnel as per SOP "Operational Qualification and Re-qualification of Analytical Laboratory Instruments and Equipment."**
- b. **The HPLC routine qualification, performed internally and through an outside contractor, does not include the test for the HPLC detector and the gradient test for the HPLC pump as part of the routine calibration conducted every months. These tests are only conducted during the instrument overall re-qualification performed every years by the QC personnel as per SOP**
- c. **The instrument qualification for the, used for the sample extraction of dissolution baths, does not include a test that would evaluate the sample carry over, if any, when used for dissolution profiles. The operation qualification conducted every months does not include such a test. The procedure included on the calibration worksheets and the associated SOP does not mention such qualification.**

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MEDICAL DEVICE-MANUFACTURING CONTROLS

1.Procedures to control the design process of the device were not complete.

Specifically, procedure does not define or instruct on the complete handling of software issues and bugs. The firmware, including versions were components of the devices used in design validations and/or the devices transferred to production. The firmware versions lack complete version release descriptions such as release notes including the known unresolved and resolved software issues or bugs. In addition, these procedures do not reflect the firm’s actual handling practices for the control and closure of the issues or bugs. Some of the unresolved software bugs or issues were closed without completion and transferred to another project for the next generation of

2.Appropriate sources of quality data are not adequately analyzed to identify existing and potential causes of nonconforming product and other quality problems.

Specifically,
 - a. **Per Quality Trending Policy and Procedure, Corporate Quality does not analyze trends submitted by Quality to determine if further actions are necessary to identify potential or existing quality issues. For example, there were five trends/out-of-control data points reported to Corporate Quality in a memo dated None of these trends/points have been analyzed further.**
 - b. **Multiple failure codes may be entered for one complaint. The first failure code is entered by based upon information known at the time of the reported event. Subsequent codes entered by reflect the actual cause of the event. All codes trended are not distinguished between the initial reported failure code and any other subsequent codes. Trending is not accurately represented because the codes trended may not be related to the cause of the event.**
 - c. **Failure code “No Cause” utilized in trending has multiple meanings, such as: scheduled maintenance, installation, training, and no cause of the failure. Trending of the “No Cause” code does not distinguish between the multiple meanings. There are approximately “No Cause” codes.**
 - d. **The Return Product Evaluation Process Procedure specifies certain Mandatory Evaluation Complaint Codes that are required to be evaluated for obsolete products. There is no documented rationale to explain why other Evaluation Complaint Codes are excluded from the data analysis.**

3.Employee training is not fully documented.

Specifically, training records for two off-site Customer Service Agents who take customer calls for products, were not complete. For example, records did not show the agent’s familiarization with or competency with Technical Advisories, Recall Notices, and the Troubleshooting Guide. Records for both agents did not show completion of recent training modules “Complaint Handling,” “Good Promotional Practices,” and “What is a Medical Device and How is it Regulated?”

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