

# GMP TRENDS®

DISTRICT ADDRESS  GMP Trends Inc. P.O. Box 8001 Boulder, Colorado 80306	DATE OF ISSUE April 1, 2011  C.I. ISSUE Issue #821
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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
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CITY, STATE AND COUNTRY United States of America and Worldwide	TYPE OF ESTABLISHMENT INSPECTED Pharmaceutical and Medical Device
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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 describing the warehousing of drug products are not followed.  
**Specifically, the Warehouse Vault Room ....., used for the storage of ..... was never qualified, including initiation of a mapping study, by the firm. This room is only monitored for temperature using a single probe located on the right-hand side of the vault's door, on the near wall, approximately 5 ft above the floor.**
2. ....The responsibilities and procedures applicable to the quality control unit are not in writing.  
**Specifically,**
  - a. Firm failed to establish standard operating procedures to designate responsibilities, fulfill regulatory requirements and develop internal procedures for filing NDA-Field Alert Reports with the FDA District Office.
  - b. Firm failed to establish standard operating procedures for the distribution and control of master formulation cards in electronic format.
  - c. An obsolete version of Standard Operating Procedure ....., was presented for review during the walk-thru of the facility. A more stringent procedure needs to be in place to ensure the proper distribution of current standard operating procedures and removal of the obsolete version by QA.
3. ....The firm lacks an effective means of tracking and trending quality events, including deviation reports, laboratory investigations, and corrective and preventative action reports.  
**Specifically, the firm's current procedures for conducting annual reviews for these quality events does not include any attempts to trend similar types of events (i.e., stability sample container closure system failures), but instead classifies large groupings of events under general concepts like "Equipment," "Human Error," and "Process Operation."**
4. ....Written procedures have not been developed for the surveillance and evaluation of post marketing adverse drug experiences.  
**Specifically,**
  - a. The established procedure for adverse drug experiences (SOP .....) lacks specific requirements and steps to be followed regarding literature surveillance for new reports of adverse drug experiences.
  - b. Specific steps to be followed in the evaluation of post marketing adverse drug experiences are listed in an uncontrolled, unapproved (decision-tree) document, rather than being part of an established, written procedure having documented approval by the Quality Assurance unit.
5. ....Drug product production and control records, are not reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed.  
**Specifically, Quality Assurance does not review the OTC drug product production and control records which are produced by contract manufacturing and are received into the ..... warehouse and distribution center.**

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INSPECTIONAL OBSERVATIONS

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

## MANUFACTURING-STERILE PRODUCT CONTROLS

1. ....The master production and control records are deficient in that they do not include complete instructions.  
**Specifically, the master record for ..... instructs posting of photos of acceptable and unacceptable seals on vials. The photos are not controlled as part of the master record.**
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.  
**Specifically,**
  - a. In review of deviation ....., bulk media fill lot ....., the bacteria plate was incubated ..... longer. The deviation was incomplete and did not indicate the incubation of a negative control. No corrective and preventive action generated to assess the significance of the problem.
  - b. In review of deviation ....., Environmental Surface Monitoring Excursion, bacteria was isolated from sample site ....., The bacteria isolated was Staphylococcus epidermis, a human flora. Investigation did not include the environmental monitoring of the operators or the airlock. A corrective and preventive action was not generated and implemented, and the investigation was incomplete due to missing environmental data.
3. ....The observations which follow primarily related to the GMP inspectional coverage conducted under in accordance with the Pre-Approval Inspection compliance program .....  
**This observation lists specific concerns found regarding the aseptic filling line in room ..... which was in operation on a number of days during the current inspection as well as concerns that impact other aseptic filling rooms. With respect to room ....., the firm has not provided adequate scientific rationale for design of the line or environmental monitoring protocol. Observation of the aseptic filling of ..... during the current inspection, related discussions with management/personnel and review of documentation related to aseptic filling operations found:**
  - a. Viable monitoring of the class 100 filling room is limited to a ..... minute active sampling each day in the center of the room. There is no other viable monitoring of the environment.
  - b. Observation of production in room ..... found that one panel of the curtains around the class 100 area was unhinged and the top and side edges were hanging about .....
  - c. No "smoke studies" have been conducted for this or any other aseptic filling room. The firm conducts annual room certification, however, this does not encompass any evaluation of air flow direction/air flow patterns but rather only verification of pressure differential. Further, they have not conducted any air flow studies under "active" conditions.  
**Note: Observations are applicable to all aseptic filling rooms.**
  - d. The firm has not employed environmental isolates either in growth promotion testing of microbiological media (post media fill growth promotion) or in the evaluation of effectiveness of disinfectants. In fact, they have never performed identification of organisms found in personnel and environmental monitoring in class 100 areas.
  - e. The firm does not employ a positive control in the validation of depyrogenation by the ..... oven used to prepare containers for aseptic filling.

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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:			
<b>LABORATORY CONTROLS</b>			
1. ....For the pre-approval inspection (PAI) covering ANDA ..... and cGMP inspection, the following observation is made.  <b>The firm manufactured test batch ..... based on commitments in submitted amendment to ANDA ..... As per the minor amendment, the firm revised the formulation to eliminate the need to a pH adjustment and committed to develop and validate test methods for Chromatographic Purity for the API and Finished Product (including stability study samples) and Residual Solvent test methods for the two APIs. Observations below concern issues found with respect to the current status of the implementation of those commitments.</b>			
2. ....The observations which follow primarily related to the GMP inspectional coverage conducted in accordance with the Pre-Approval Inspection compliance program.			
a. <b>The firm completed method validation for product ..... almost one year prior to the current inspection, however, the reports have not yet been written. It is noted that there are validation reports from other products which have also not been written despite the fact that the validation exercises were completed many months ago. For example, process validation batches were made ....., and testing was completed the next month. The process validation reports have still not been written.</b>			
b. <b>There is no procedure for method transfer from the R&amp;D laboratory to the QC Chemistry laboratory.</b>			
c. <b>Review of the firm's investigation reports for years ..... found a number of investigations of out of specification (OOS) results for which the initial test results were invalidated despite the fact that review of the laboratory operations and interviews of analysts found non laboratory error or other specific contributing causes. The focus of this observation is that the final evaluation of all data including retest data may be used to make a decision on batch disposition, however, the initial data should be invalidated only based on identification of a root cause. Examples examined during the current inspection included investigations .....</b>			
3. ....The validation of the chromatographic purity test for ..... is deficient, in that:			
a. <b>Test results from forced degradation studies used to demonstrate that the method is free from interferences and is capable of determining the stability of the finished product ("stability-indicating method") failed to meet acceptance criteria for peak purity. For a number of stress conditions, the evaluation using ..... detector, yielded results showing the peak angle to be greater than the peak threshold. When presented with this observation the R&amp;D management acknowledged that results fail to meet acceptance criteria.</b>			
b. <b>System suitability testing is limited to an ..... There are no system suitability requirements to ensure adequate resolution of impurities. It is noted that a previous method that was validated for assay was subsequently found to be inadequate for stability-indicating purposes due to interference from a degradant and placebo which interferes with the active peak.</b>			
4. ....Corrective and preventative actions related to investigations into unexplained discrepancies or the failure of a batch are not consistently implemented in a timely fashion.  <b>Specifically, the corrective action, CAPA ....., was initiated in response to Laboratory Investigation ..... The corrective action was to retrain analyst ..... The corrective action's expected completion date was ....., actual date of completion was ..... (9 weeks).</b>			
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DURING A REVIEW OF INSPECTION REPORTS OF U.S. FIRMS (I) (WE) OBSERVED:

## **MEDICAL DEVICE-MANUFACTURING CONTROLS**

1. ....Procedures to ensure that all purchased or otherwise received product and services conform to specified requirements have not been adequately established.

**Specifically, there are no established procedures to ensure that suppliers conform to specified requirements. The firm did not establish the following:**

- a. **There is no documentation demonstrating how the firm evaluated .... suppliers.**
- b. **There is no documentation showing the type and extent of control to be exercised over the product, the services and the suppliers.**
- c. **There is no documentation describing or referencing the specified requirements, including quality requirements for purchase or otherwise received product and services.**

2. ....A process whose results cannot be fully verified by subsequent inspection and test has not been adequately validated according to established procedures.

**Specifically, the firm could not provide documentation for the validation of the sterilization process for .... products labeled as sterile. Additionally, evidence indicates the currently used gamma radiation sterilization cycle may not be adequate to sterilize the .... device. The current sterilization cycle specifies acceptance of material that receives between a minimum of ....kGy and a maximum of ....kGy of gamma radiation. Validation protocol .... calls for the use of the average bioburden from .... lots to be used to set the gamma radiation dosage level. This dosage form only provides dosage levels for a maximum average bioburden of 1,000,000 cfu. The dosage level for 1,000,000 cfu is a minimum of 36.3 kGy to sterilize at a Sterility Assurance Level (SAL) of .... Your current sterilization cycle specification allows for an acceptance of material that receives a minimum of .... kGy. The lots sampled for this protocol and other lots that were being manufactured during this same time period were released for distribution based on the current sterilization cycle specifications.**

3. ....Procedures for finished device acceptance have not been adequately established.

**Specifically,**

- a. **Finished device acceptance procedures do not ensure that finished devices are quarantined or otherwise adequately controlled until acceptance criteria are met. Sterile lot .... was packaged for .... customers. The finished product testing for customers .... passed and product was distributed. The finished product testing for customer .... failed post sterile ....., but product was still distributed. A statement to the batch record by the Regulatory Affairs Manager states “released by ....., on .....” (..... is the EVP of the firm.) On ....., an OOS was initiated to address the failed results. On ....., the decision to release this product per .... EVP was revised per reconsideration. The remaining cases were scrapped. However, .... cases had already been distributed and no action was taken on the distributed cases.**
- b. **There is no procedure addressing the “confirmatory testing” currently being implemented during microbiological testing. Currently, Sterile .... is being tested for .... post-sterilization. The specification is listed as no growth for both tests. Since ....., ten lots have shown growth on the initial test. In each case, a second sample was checked and found negative for growth. The passing results were reported and the failed results were not addressed. No OOS Investigation was initiated to investigate the failing results.**

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