DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
404 BNA Dr., Bldg. 200, Ste. 500 Nashville, TN 37217-2597 (615) 366-7801 Fax:(615) 366-7802 Industry Information: www.fda.gov/oc/industry	01/25/2010 - 02/05/2010* FEI NUMBER 1019003

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Michael D. Howell, Plant Manager

FIRM NAME	STREET ADDRESS
Baxter Healthcare Corporation	911 North Davis Avenue
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Cleveland, MS 38732-2106	Drug Manufacturer

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

The observations noted in this Form FDA-483 are not an exhaustive listing of objectionable conditions. Under the law, your firm is responsible for conducting internal self-audits to identify and correct any and all violations of the quality system requirements.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

Control procedures are not established which validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.

Specifically,

a) The firm failed to adequately validate the manufacturing process for Acetaminophen Injection, 10mg/mL solution. The firm processed a total of (b) (4) of which (b) (4) were found unacceptable per specifications such as fill volumes, head space vacuum, and dissolved oxygen. The firm did not successfully produce three sequential batches for NDA submission nor did they process three acceptable batches for stability purposes. Only batches (b) (4) appeared to have met acceptance stability criteria. The third batch, (b) (4) was found to be contaminated with foreign matter in addition to PM during stability sampling; regardless, this was counted as an acceptable stability batch in the NDA submission. The production of all of these batches was detailed to the sponsor but was not detailed in the NDA submission to the FDA.

b) The firm's 100% visual inspection prior to packaging and a higher level 100% visual inspection of an additional (b) (4) sample vial of the submitted stability batch (b) (4) for Acetaminophen Injection, 10mg/mL solution, failed to detect particulate and foreign matters that were subsequently detected in three 100mL vials upon stability sampling. This particulate and foreign matter was identified as a skin fragment, one piece of nylon, and three PETs.

c) Per record review, during processing (b) (4) stopper push throughs were observed for Batch # (b) (4) This observation was not observed during the processing of the other two stability batches (b) (4) The firm has documented a process change in its handling of rubber stoppers utilized on this product, in that they will begin to rinse these stoppers prior to use. This change was submitted to the sponsor but was not submitted as an NDA supplement to FDA. This closure rinsing procedure has yet to be validated. The firm has yet to identify, document, and eliminate potential sources for the PM and foreign matter.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Marvin D. Jones, Investigator Amanda K. Willey, Investigator	02/05/2010

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OBSERVATION 2

Records are not kept for the maintenance and inspection of equipment.

Specifically, the firm failed to document the placement of metal spacers in the (b) (4) CIP assembly unit and the replacement of the diaphragm in the (b) (4) line for the (b) (4) machine during the production run of the stability batch prior to the production of batch (b) (4) for the Acetaminophen Injection, 10mg/mL solution. Per equipment manufacturer's recommendations, metal spacers were inserted into the (b) (4) CIP assembly unit to increase the service life of the diaphragm. Subsequently, during the production of batch (b) (4) the operator noted water in the (b) (4) line post final filler prior to the (b) (4) machine. This batch was disposed of and the metal spacers were then removed from the (b) (4) CIP assembly unit. All batches prior to (b) (4) were processed without spacers, (b) (4) was processed with spacers, and (b) (4) was processed without spacers. The firm failed to requalify this equipment for these modifications.

During the production of batch # (b) (4) a CIP water leak was noted which had seeped into the electrical control panel via the electrical conduit from the (b) (4) CIP assembly unit. The firm has no documentation of the effect upon equipment operation of this water leak into the electrical control panel or how long this water seepage had occurred.

OBSERVATION 3

Acceptance criteria for the sampling and testing conducted by the quality control unit is not adequate to assure that batches of drug products meet each appropriate specification as a condition for their approval and release.

Specifically, a review of the NDA protocol for Acetaminophen Injection, 10mg/mL solution revealed that the specification for particulate matter does not have any set quantities/ limits of particulate matter to be observed during processing to ensure that the process is operating within a state of control. The protocol lists the visual acceptance criteria for PM as " (b) (4) (b) (4) ". During processing of the registration batches submitted to FDA, batch # (b) (4) was found to have 228 particulate matter (PM), batch # (b) (4) was found to have 47 PM, and batch # (b) (4) was found to have 63 PM. Per management, the firm utilizes a 100% visual inspection prior to packaging in order to remove any vials containing particulate matter. Our review of process and stability records determined this inspection does not appear to properly detect PM and/or foreign matter. The firm has not identified/determined any source of particulate matter found in the Acetaminophen Injection, 10mg/mL solution batches.

OBSERVATION 4

Products that do not conform to specifications are not adequately controlled.

Specifically, the firm failed to take proper corrective actions regarding the distribution of Evacuated Containers containing (b) (4) rinse. Initially, the firm noted an increase in pH of the 15% Potassium Chloride product during the one

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month accelerated stability study. An investigation by the firm determined that the Type II containers manufactured by a specific supplier were improperly treated on the internal surface, which allowed leaching of alkaline ions causing the pH to increase. The firm recalled its 15% Potassium Chloride products contained in this Type II containers based upon their investigation. The firm performed further testing of other products manufactured in the Type II supplier specific containers. A review, of the firm's stability testing data determined that the two liter Evacuated Containers (device) containing (b) (4) (b) (4) rinse were out-of- specification at 8 months (b) (4) and 9 (b) (4) months. The firm's final product specification for the (b) (4) rinse is pH (b) (4) These lots of the two liter Evacuated Containers containing (b) (4) were placed on hold but no recall was performed. Also, the firm's stability testing data demonstrates that the one liter Evacuated Containers containing (b) (4) rinse were out-of- specification at 12 months (b) (4). The firm has performed no corrective actions on the lots of one liter Evacuated Containers. The firm manufactures the following sizes of Evacuated Containers containing (b) (4) rinse, which were processed using the same supplier specific Type II containers: 250 mL, 500 mL, one liter, and two liter. The firm determined the root cause was the supplier specific Type II container that was being used caused the increase in pH and no proper corrective action has been performed regarding distribution of these evacuated containers by the firm.

*** DATES OF INSPECTION:**
01/25/2010(Mon), 01/26/2010(Tue), 01/27/2010(Wed), 01/28/2010(Thu), 01/29/2010(Fri), 02/05/2010(Fri)

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