DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
466 Fernandez Juncos Ave. San Juan, PR 00901-3223 (787)729-8500 Fax:(787)729-8765 Industry Information: www.fda.gov/oc/industry	04/06/2015 - 05/01/2015
	FEI NUMBER 2618677

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Mr. Enrique Perez Sanchez, Plant Manager

FIRM NAME	STREET ADDRESS
Baxter Healthcare Corporation	Road #144, #250
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Jayuya, PR 00664-1503	Manufacturer of Terminally-sterilized LVP & SVP

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.

DURING AN INSPECTION OF YOUR FIRM I OBSERVED:

QUALITY SYSTEM

OBSERVATION 1

The responsibilities and procedures applicable to the quality control unit are not fully followed.

There are no adequate procedures or review mechanism in place to ensure that routine laboratory activities are consistently evaluated by the Quality Unit.

Specifically, on 09/18/14, your Quality Control laboratory reported an Out-of-Limit (OOL) result for the initial Heparin testing of Heparin Sodium 2 Units/mL and 0.9 % Sodium Chloride Injection; Lot #N003129. The OOL assay result obtained for the initial sample was (b) (4) The established specification limits is 1.91 to 2.06 units/mL. Investigation PR (b) (4) was generated in order to evaluate potential sources that may be responsible for causing the OOL result obtained. As part of the initial investigation, a re-test was performed. The result obtained was (b) (4) which confirmed the original OOL result.

A re-test protocol was developed: (b) (4) (b) (4) The results of this re-test protocol showed (b) (4) respectively. In addition, the unreleased Lot (b) (4) also showed an OOL assay result of (b) (4) Based on the results obtained, your Quality Unit performed a root cause analysis and identified the potency of the raw material Lot (b) (4) as a potential root cause. Three (3) additional released Lots (#N003079, #N003087 & #N003061) were found that used the same raw material lot number.

On 09/26/2014, your Quality Unit issued an initial Field Alert Report (FAR) to inform about the confirmed OOL results for the two (2) unreleased Lots (b) (4) and also to mention that distributed product Lots #N003079, #N003087 & #N003061 were manufactured with the affected raw material Lot (b) (4)

On 10/02/2014, your Quality Control laboratory performed (b) (4) of each of the three (3) identified released lots. Lots (b) (4) showed results Out-of-Specifications (OOS). The results obtained are

AMENDMENT 1

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Jose E. Melendez, Investigator	05/26/2015

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
466 Fernandez Juncos Ave. San Juan, PR 00901-3223 (787)729-8500 Fax:(787)729-8765 Industry Information: www.fda.gov/oc/industry	04/06/2015 - 05/01/2015 FEI NUMBER 2618677

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Mr. Enrique Perez Sanchez, Plant Manager

FIRM NAME	STREET ADDRESS
Baxter Healthcare Corporation	Road #144, #250
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Jayuya, PR 00664-1503	Manufacturer of Terminally-sterilized LVP & SVP

(b) (4) respectively. The established specification is 1.80 to 2.20 U/mL. In addition, Lot # (b) (4) showed a result OOL (b) (4)

During the period of 10/03-08/2014, your laboratory conducted an assessment of the analytical data to identify the potential sources for the OOS and OOL results and found the following deviations to analytical procedure titled "(b) (4) (b) (4) IN HEPARIN SODIUM 2 U/mL in 0.9 % SODIUM CHLORIDE":

- (b) (4)
- (b) (4)
- (b) (4)

On 10/22/2014, your Quality Unit issued a second FAR to inform about the decision of rejecting Heparin Sodium 2 U/mL in 0.9 % Sodium Chloride Injection; Lots #N003129 & #N003103 and to voluntarily recall released Lots #N003079, #N003087 & #N003061. However, none of the investigation findings such as the aforementioned number of deviations to analytical procedure and inadequate laboratory practices were communicated to the agency at that time. Moreover, during the inspection, I observed that approximately (b) (4) of Heparin Sodium 2 U/mL in 0.9 % Sodium Chloride Injection were affected by similar laboratory deviations for the period from 2013 to 2014.

This tendency of deviations from the established control procedures and trainings denote the lack of supervisory responsibilities to prevent adverse events impacting the integrity of the laboratory operations and the lack of authority to exercise the control necessary for assuring the accuracy of the analytical results. Moreover, your Quality control unit did not capture either these events prior to releasing the drug products by ensuring data accuracy and integrity.

This a recurrent observation from previous FDA inspections conducted on 11-03-2011 & 09-09-2010.

OBSERVATION 2

Container closure systems do not provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product.

Specifically, your Quality Unit failed to implement adequate and reliable process controls for ensuring that distributed solution bags corresponding to (15 % CLINISOL, 10 % TRAVASOL, 10 % PREMASOL, 20 % PROSOL) drug products always comply with the attributes that they represent to possess for their intended use.
From January 2015 to March 2015, your firm has identified an increase in the number of customer complaints received due to missing or loose blue tip port protector for different solution bag products. This critical defect was acknowledged in each

of the approximately five (5) complaints reported corresponding to 15 % CLINISOL 500 mL Injection, Lot P326975; 10 % PREMASOL 500 mL Injection, Lot P327080; 20 % PROSOL 2000 mL Injection, Lot P327502; 10 % TRAVASOL 2000 mL Injection, Lots P320374 & P323394,. Field Alert Reports (FARs) were issued for each of the events.

Your firm established an action limit (Threshold) following the requirements of control procedure Doc # (b) (4) titled (b) (4) in that, if approximately five (5) complaints are received for a single lot regarding missing blue tip, actions need to be implemented. Therefore, up to now no action has been taken against aforementioned distributed drug products based on the referenced action limit. Nonetheless, your rationale fails to consider that this critical defect may increase the possibilities of exposing the patient to product contaminated at point of use. After this issue was brought to your attention during current inspection, your quality unit determined not to follow the approach of the action limit. Your firm still has not identified an exact source that may be responsible for causing the referenced defects. This a recurrent observation from WL 13-ATL-17 dated 05-31-2013 and WL 11-SJN-WL-04 dated 01-20-2011.

MATERIAL SYSTEM

OBSERVATION 3

Each lot of components and closures is not withheld from use until the lot has been sampled, tested, examined, and released by the quality control unit.

Your Quality Control Unit failed to implement adequate and reliable procedures to ensure that critical components received from your sister sites are appropriate for their intended use and meet with the requirements of safety and effectiveness of the final drug products.

Specifically, your firm's current practice for the receipt of in-coming materials from your sister sites (to include packaging components in direct contact with finished product and intended to assure finished product sterility) does not provide for a test and/or physical evaluation in order to approve them and determine that they are suitable for using into successive manufacturing activities. After this issue was brought to your attention during current inspection, your quality unit implemented control procedure (b) (4) titled (b) (4) (b) (4) that describes in details the procedures for sampling, testing, evaluating and releasing of the in-coming materials receipt from sister sites.

This is a recurrent observation from previous FDA inspections conducted in 02/11/2014.

LABORATORY CONTROL SYSTEM

AMENDMENT 1

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
466 Fernandez Juncos Ave. San Juan, PR 00901-3223 (787)729-8500 Fax:(787)729-8765 Industry Information: www.fda.gov/oc/industry	04/06/2015 - 05/01/2015
	FEI NUMBER 2618677

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Mr. Enrique Perez Sanchez, Plant Manager

FIRM NAME	STREET ADDRESS
Baxter Healthcare Corporation	Road #144, #250
CITY, STATE, ZIP CODE, COUNTRY Jayuya, PR 00664-1503	TYPE ESTABLISHMENT INSPECTED Manufacturer of Terminally-sterilized LVP & SVP

OBSERVATION 4

There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

- Your firm failed to conduct a thorough technical assessment of the data in order to confirm the origin and characterized the below Out-of-Alert (OOL) and Out-of-Specification (OOS) results that have been seen on Heparin Sodium 2U/mL and 0.9 % Sodium Chloride Injection assay testing.

Specifically, between the month of January and March 2015, your firm has been reported either OOS or OOL results for initial or final assay testing of Heparin Sodium 2U/mL and 0.9 % Sodium Chloride Injection. The established alert ***initial*** limits range is from (b) (4) The established alert ***final*** limits range is from (b) (4) The established product specifications range is from 1.80 to 2.20 U/mL. The Heparin Sodium Lots impacted by this atypical tendency in the final assay testing are: N003483; N003475; N003590 & N003632.

For example,

- Lot N003483 showed results in the range from 1.79 to 1.86 U/mL (Recommended for rejection)
- Lot N003475 showed results in the range from 1.75 to 1.94 U/mL (Recommended for rejection)
- Lot N003590 showed results in the range from 1.87 to 1.95 U/mL (Recommended for releasing)
- Lot N003632 showed results in the range from 1.88 to 1.96 UmL (Recommended for releasing)

On 01/16/2015, your QC Laboratory initiated Investigation PR (b) (4) due to the failure of the referenced Heparin Sodium lots. This investigation was also extended to the manufacturing process. (b) (4) (b) (4) corresponding to Heparin Sodium were evaluated. No assignable cause for the OOL and OOS obtained was identified.

Your firm concluded that the root cause for these results are related to the variability among analyts, method variability and not appropriate established limits, since those limits do not take in account the method variability within the initial and product alert limit. However, your analytical method validation report dated 11/2009, does not show such analyst and method variabilities. Moreover, the established limits during the validation activities are the current limits that have been using for releasing or rejecting commercial lots of Heparin Sodium. Up to now, your firm has failed to establish scientifically sound evidence in order to identify a definitive root cause and prevent reocurrence. Investigation PR (b) (4) is still in progress.

AMENDMENT 1

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Jose E. Melendez, Investigator	05/26/2015

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
466 Fernandez Juncos Ave. San Juan, PR 00901-3223 (787)729-8500 Fax:(787)729-8765 Industry Information: www.fda.gov/oc/industry	04/06/2015 - 05/01/2015 FEI NUMBER 2618677

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Mr. Enrique Perez Sanchez, Plant Manager

FIRM NAME	STREET ADDRESS
Baxter Healthcare Corporation	Road #144, #250
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Jayuya, PR 00664-1503	Manufacturer of Terminally-sterilized LVP & SVP

PRODUCTION SYSTEM

OBSERVATION 5

Control procedures are not established which monitor the output and 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.

There is no assurance that your firm has accurately identified the source that may be responsible for causing critical defects for different parenteral drug products.

From March 2014 to March 2015, your firm has received approximately eleven (11) customer complaints due to missing, fall off or loose blue tip port protector for 15 % CLINISOL, 10 % TRAVASOL, 10 % PREMASOL, 20 % PROSOL drug products. In all the events, there were no nonconformities, failures, rework or deviations documented in the batch records that could have contributed to the reported critical defects. The in-process testing were verified and also found within established specifications.

In 2013, your firm identified a number of corrective actions (b) (4) (b) (4) to improve the manufacturing process of the referenced parenteral solution bags. However, after the implementation of such actions, your firm continued receiving customer complaints for the same critical defects. For example,

- 03/18/2015, your firm received a consumer complaint (b) (4) which describes that the blue seal was not covering the bag spike port. The complainant also mentioned that the tip was stuck to the side of the bag. The solution bag corresponds to 15 % Clinisol Sulfite-Free Injection 500 mL; Lot P326975; Exp. Date 12/2015. According to the complaint investigation, this lot was manufactured on 12/02/2014. The product was manufactured at Filling Line (b) and packed at Packaging Line (b) No deviations were reported concerning to the manufacture and packaging of this lot. A retain sample evaluation was performed and was found to be acceptable. The complaint sample was visually inspected and the reported defect was confirmed. The investigation is still in progress.

- 03/11/2015, your firm received a consumer complaint (b) (4) which describes that the blue seal was not observed on the port of the solution container, but was observed attached to the back panel of the solution container. The solution bag corresponds to 10 % Premasol Injection 500 mL; Lot P327080; Exp. Date 12/2016. According to the complaint investigation, this lot was manufactured on 12/04/2014. The product was manufactured at Filling Line (b) and packed at Packaging Line # (b) No deviations were reported concerning to the manufacture and

AMENDMENT 1

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	José E. Melendez, Investigator	05/26/2015

packaging of this lot. A retain sample evaluation was performed and was found to be acceptable. The complaint sample was visually inspected and the reported defect was confirmed. A Corrective and Preventive Action (CAPA) investigations was not initiated as the result of this complaint. According to the complaint investigation, only one incidence was reported for subject lot; therefore, an accurate failure rate cannot be calculated to compare the threshold. As a result, no other investigation will be initiated.

- 03/06/2015, your firm received a consumer complaint (b) (4) The customer reported that the port covering on one Prosol solution bag was loose and drop off. The customer also reported that this event has been occurring more frequently with this product. In addition, mentioned that they have had about 12 bags with this issue (03/06/2015). According to the complaint investigation, the customer reported that they continued to use the bags. All affected bags are from the same lot number. The customer reported that there were other bags that had loose caps as well over the past few weeks. The solution bags correspond to 20 % Prosol Injection 2000 mL; Lot P327502; Exp. Date 12/2015. According to the complaint investigation, this lot was manufactured on 12/12/2014. The product was manufactured at Filling Line (b) and packed at Packaging Line (b) No deviations were reported concerning to the manufacture and packaging of this lot. A retain sample evaluation was performed and was found to be acceptable. The complaint sample was visually inspected and the reported defect was confirmed. The event will be discussed with the manufacturing operators. The investigation is still in progress.

The examples above discussed confirm that the approved in-process controls are not capable of detecting defects during the manufacturing process that could be changing the characteristics of the parenteral solutions; therefore, producing finished drug products that do not always meet with the established specifications.

This is a recurrent observation from previous FDA inspections conducted on 11/2011and 02/11/2014.

OBSERVATION 6

An NDA-Field Alert Report was not submitted within three working days of receipt of information concerning significant chemical, physical, or other change or deterioration in a distributed drug product.

According to control procedure (b) (4) titled "Global Field Alert Procedure" *a Field Alert Report must be filled with the Food and Drug Administration (FDA) within 3 working days from the receipt the information*. Nonetheless, a review of NDA-Field Alert Reports (FARs) initiated by your firm since March 2014 to April 17, 2015, disclosed a total of ten (10) FARs not being submitted by your Corporate Product Surveillance team within three (3) working days. All the FARs are related to Jayuya manufacturing process. These include issues related to several different sterile drug products such as labeling issues, leaks, damaged component and particle matter. Investigation (b) (4) was generated; however not all the

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
466 Fernandez Juncos Ave. San Juan, PR 00901-3223 (787)729-8500 Fax:(787)729-8765 Industry Information: www.fda.gov/oc/industry	04/06/2015 - 05/01/2015
	FEI NUMBER 2618677

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Mr. Enrique Perez Sanchez, Plant Manager

FIRM NAME	STREET ADDRESS
Baxter Healthcare Corporation	Road #144, #250
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Jayuya, PR 00664-1503	Manufacturer of Terminally-sterilized LVP & SVP

events were included in the referenced investigation even though these were deviations to the subject control procedure (b) (4)

This is a recurrent observation from WL 13-ATL-17 dated 05-31-2013, WL 11-SJN-WL-04 dated 01-20-2011 and previous FDA inspections conducted in 08/2010, 04/2013 & 02/2014.

AMENDMENT 1

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Jose E. Melendez, Investigator	05/26/2015