DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
FDA Denver District Office 6th Ave. & Kipling St.-Bldg. 20 DFC Denver, CO 80225 Industry Information: www.fda.gov/oc/industry	05/07-05/11/2012
	FEI NUMBER 3005231248

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Brian J. McCudden, Vice President, API Strategy & Boulder Operations

FIRM NAME	STREET ADDRESS
Hospira Boulder, Inc.	4876 Sterling Dr.
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Boulder, Colorado 80301	Active Pharmaceutical Ingredient 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.

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

1) Your firm has released product without the documentation of a robust process that yields a high degree of assurance in the performance of the manufacturing process.
*This is a repeat observation from the June 21, 2011 FDA audit.

a) Specifically, the Carboplatin manufacturing process has not been validated and 18 lots of Carboplatin has been commercially distributed.

b) Furthermore, the pH method for Carboplatin cannot be assured of accurate results for the finished product and stability testing of pH between the establishment of the procedure U-QCM-0603, rev. 1, dated 12/15/2006 entitled "pH Analysis of Carboplatin" and U-QCM-0603, rev. 3, dated 12/16/2011 entitled "pH Analysis of Carboplatin". This time period incorporates all 18 commercially distributed lots of Carboplatin USP for injection.

c) Per QCO.01.002, entitled "Issue Elevation Assessment Form", effective date 06/30/2011, Carboplatin lot# (b) (4) failed 6 month stability pH testing. This lot was commercially distributed.

18 commercially distributed lots include:

(b) (4)

Finished Product Lot#
Y011654A
Y021711A
Y021711A
Y021711A
Y031711A
Y031711A
Y031711A
Y031711A
Y021654A

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	L Buytaert - Hoefen Erika V. Butler	Kimberley A. Hoefen Erika V. Butler	05/11/2012

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(b) (4)

Y021654A
Y041711A
Y061711A
Y041711A
Y061711A
Y061711A
Y041711A
Y031709A
Y061711A
Y041711A
Y061711A
Y061711A
Y031654A

2) A 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.

Specifically, out of specifications (OOS) were observed on stability API samples which are used to support an application drug product currently on the market. For example, laboratory investigations:
PR# 66560, confirmed OOS 6 month room temperature (RT) stability sample for Carboplatin, API lot (b) (4) was OOS for pH. Distributed finished product lot #Y061711A Carboplatin USP for injection.

PR# 72518, Carboplatin, API 12 month RT stability sample lot (b) (4) was OOS for assay. Issue awareness date March 05, 2012. Investigation completed May 01, 2012. Distributed finished product lot #Y021711A Carboplatin USP for injection.

PR# 73478, Pentostatin, API 3 month RT stability sample lot (b) (4) and 24 month RT stability sample lot; (b) (4) was OOS for assay. Issue awareness date March 12, 2012. Investigation completed April 12, 2012. Distributed finished product lots #Z014870A and X014870A/Z014870A Pentostatin for Injection 10 mg (Nipent) respectively.

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PR# 56424, Pentostatin API 18 month RT stability sample lot (b) (4) was OOS for assay. Issue awareness date October 28, 2011. Investigation completed November 29, 2011. Distributed finished product lots#X014870A/Z014870A Pentostatin for Injection 10 mg (Nipent).

PR# 73822, Sodium Nitroprusside, API 3 month RT stability sample lot (b) (4) was OOS for impurities. Issue awareness date March 14, 2012. Investigation in-progress.

PR# 74054, Pamidronic Acid, API 12 RT stability sample lot (b) (4) was OOS for assay. Issue awareness date March 15, 2012. Investigation completed April 13, 2012. Distributed finished product lots #Y024947A, Y034947A, Y044947A, Y054947A, Y064947A, Y074947A Pamidronate Disodium Injection (ROW).

In addition, your written procedure U-QAA-))18 Rev. 1 titled: Hospira Boulder Site Elevation Process does not take into account triggering the issue elevation process for unconfirmed stability failures which can not be invalidated within th (b) (4) time frame.

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

Specifically, Pentostatin (b) (4) stability sample # (b) (4) analyzed on 03/8/2012 was OOS for assay with the second preparation result of 98.4% (limit (b) (4)). No conclusive cause of the OOS was found. A Pre-Approval Test Protocol was generated and executed to retest the stability sample (b) (4) samples were prepared and (b) (4) generate the (b) (4) retest results. The retest results also produced an out of specification. The re-test assay results for the samples are as follows:

Preparation/Injection: Assay Result

(b) (4)

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(b) (4)

*Out of specification

(b) (4) were used to determine the retest OOS result was an outlier. The retest OOS result was discarded and not used in the evaluation of the stability sample in question. There is no documentation to support that if one variable is deemed an outlier that the other variables are acceptable and unrelated to the outlier variable. In addition, there are no standard operating procedures of the (b) (4) which was used in the data analysis to distinguish how outliers were identified.

4) Written procedures are not established for the cleaning of equipment, including utensils used in the manufacture, processing, packing or holding of a drug product.

Specifically,
Validation of procedures for cleaning equipment that are used interchangeably between active pharmaceutical ingredients such as; vessel reactors, isolators, pumps and hoses has not been completed. Active pharmaceutical ingredients manufactured at your facility include: Carboplatin, Paclitaxel, Pamidronic Acid, Pentostatin, Sodium Nitroprusside, Tromethamine, Irinotecan, and Oxaliplatin. In addition, your firm attempted to perform cleaning validation for Paclitaxel API without an approved protocol from Quality Assurance detailing how the cleaning validation was to be executed. The validation was not successful due to a manufacturing deviation during the process.
*This is a repeat observation from the June 21, 2011 FDA audit.

5) Your quality control unit lacks the responsibility for approving or rejecting all laboratory procedures impacting the identity, strength, quality, and purity of the drug product.

Specifically, directions for the (b) (4) laboratory instrument standard operating procedure were changed via an e-mail dated 05/25/2010, without approval of the quality control unit. The e-mail stated: ***"Last night we had another

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sample that caused the shutdown of the (b) (4) ***However, it should be noted that the (b) (4) shutting down on a sample could also be due to the presence of volatiles". ***"So here's what to do"*** (b) (4)

(b) (4)

GMP assays run on the (b) (4) include:
a) U-QCM-0819, rev. 1, dated 05/20/2009, entitled (b) (4) for the determination of (b) (4) (b) (4) in the Carboplatin raw material (b) (4)

b) U-QCM-0821, rev. 2, dated 09/17/2009, entitled '(b) (4) of In-Process Samples by (b) (4)' for the determination of (b) (4) content for in-process Carboplatin samples.

c) U-QCM-0814, rev. 4, dated 07/15/2011, entitled '(b) (4) of In-Process Samples by (b) (4)' for the determination of (b) (4) in Oxaliplatin and Carboplatin samples.

d) U-QCM-1040, rev. 2, dated 01/15/2010, entitled "Cleaning Validation for (b) (4) " for the determination of (b) (4) in cleaning validation samples.

6) There is no documentation of the thorough review of failures to meet specifications impacting the identity, strength, quality, and purity of the drug products.

Specifically, four out of specification (OOS) results were reported for the Carboplatin (b) (4) finished product release specification by a contract laboratory, (b) (4)

a) OOS-09-046, dated 10/15/2009, documented an OOS for (b) (4) for Carboplatin lot# (b) (4) and stated: ***"The probable cause of the OOS is unknown"***. A retest was performed on additional samples of the same lot. ***"The original result will be overturned and the average of the reportable retesting results for the hypothesis retesting plan will be reported"***. A process development representative stated: ***"the method was not suitable for this material"***. The finished product that the API was used in was commercially distributed lot# Y061711A.

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b) OOS-10-056, dated 05/13/2010, documented an OOS for (b) (4) for Carboplatin lot# (b) (4) and stated: ***"(b) (4) did not have enough data to statistically eliminate the original result as an outlier, but do state in their report that the original result may be due to normal analytical variance inherent in any test or it may be due to an analytical laboratory error"***. A retest was performed on additional samples of the same lot. ***"Boulder Hospira believes that there is sufficient data, supported by the three retests, to overcome the original result. The average of the reported (b) (4) retest results will be reportable results"***. The finished product that the API was used in was commercially distributed lot# Y031711A.

c) PR# 38733, dated 05/25/2011, documented an OOS for (b) (4) for Carboplatin lot# (b) (4) and stated: ***"The root cause of the OOS was determine by (b) (4) was that there was an unidentified laboratory error". ***"The original OOS result was overturned and determined to be statistical outlier"***. A retest was performed on additional samples of the same lot. ***"The reportable result on the CofA for (b) (4) will be the average of the (b) (4) retest results"***. The finished product that the API was used in was commercially distributed lot# Y061711A.

d) PR# 69037, dated 02/09/2012, documented an OOS for (b) (4) for Carboplatin lot# (b) (4) and stated: ***"this method is inadequate This method has a hostry of requiring repeat analysis due to aberrant results that do not meet specification". ***"A cross-funational ER investigation***did not indicate any process issues that could have contributed to the (b) (4) being out of specification"***. A retest was performed on additional samples of the same lot. ***"The retests could not reproduce the original results"***. This lot was was rejected because of a (b) (4) finished process specification failure.

7) Materials are not stored in a manner to prevent degradation, contamination and cross-contamination.

Specifically, during the inspection walk-through on 5/7/12, it was noted that fiber drums of starting materials were stored on the floor of the raw material warehouse cage. (b) (4)
(b) (4)
observed on the floor with approximately 5 other raw materials. Your firm was not following SOP U-MMB-0006, which states, "For all warehousing areas fiber drums and all containers under (b) (4) gallon size must be stored off of the ground regardless of hazard classification."
This is a repeat observation from the June 21, 2011 FDA audit.

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