

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER 60 Eighth Street NE Atlanta, GA 30309 (404) 253-1161 Fax: (404) 253-1202 Industry Information: www.fda.gov/oc/industry		DATE(S) OF INSPECTION 07/25/2011 - 08/04/2011*
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Jonathan Waldron, Vice President Rocky Mount Operations		FEI NUMBER 1021343
FIRM NAME Hospira, Inc.	STREET ADDRESS Hwy. 301 N. + 4285 North Wesleyan Blvd.	
CITY, STATE, ZIP CODE, COUNTRY Rocky Mount, NC 27804	TYPE ESTABLISHMENT INSPECTED Sterile Pharmaceutical 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 WE OBSERVED:

OBSERVATION 1

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 already distributed.

Specifically,

A. The firm did not have data to support the release of the following lots due to inadequate laboratory investigations and/or manufacturing investigations. They failed to investigate out of specification (OOS)/out of target (OOT) laboratory results as per SOP QCP 05.002, "Laboratory Investigations Procedure". Additionally, laboratory investigations have lacked scientific justification to support the dismissal of OOS/OOT results and conclusions of the investigations.

1. PR 26496- Atropine Sulfate Injection, Lots 96-335-DK, 01-593-DK, 02-101-DK, 02-379-DK: Each of these lots had in-process low OOS Atropine Sulfate assay results and the associated laboratory investigations (which confirmed the OOS results) are as follows: PR26348, PR28389, PR29089, and PR28493, respectively. The OOS results were invalidated with no justification. PR26496 is the exception report opened to further investigate the OOS results and states that these 4 lots will be released to market as all complied with the Finished Product specification of (b) (4). The root cause was determined to be an incorrect drug factor used for the API lot. The investigation states, "The difference between the original and the new factor accounts for a reduction of 1.0% in product assay. This amount (1%) would be enough to bring the low Atropine Assay observed in all impacted lots within their respective specifications." Two other lots (95-263-EV and 01-630-EV) which also had in process low OOS Atropine Sulfate assay results and included in this investigation were rejected due to low OOS finished product assay results of 97.6% and 97.7% (Spec (b) (4)). PR26496 was approved by the Site Quality Director.

Additionally, there were no manufacturing assessments conducted concurrently during Phase II of the laboratory investigations (only (b) (4) retests performed) listed above.

PR 29089 had a Phase II- Production Investigation Form (PIR) approved on 2/25/11 but the lab investigation had already been approved by the laboratory manager on 2/16/11. This is an unapproved form from a previous version of SOP QCP.05.002 that continued to be utilized by laboratory personnel even though the SOP had been revised.

PR 28943 had a PIR approved on 2/21/11 but the lab investigation had already been approved by the laboratory manager on

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PR 26348 only had a PIR form.

2. PR 30701- Quelicin Injection, USP, Lot 02-071-EV: This lot had low OOS in-process pH results of 4.1 (Specification: (b) (4)) for the mixing top sample (VCR 10091) which were confirmed (b) (4) retest (4.16, 4.17, 4.11 and 4.20) in laboratory investigation PR 30550. The lab investigation states that there was no lab error found. PR 30701 is the exception report opened to further investigate the OOS result and concluded that the lot could be released based on the within specification finished product pH of 4.4 (Specification: (b) (4)). PR 30701 was approved by the Site Quality Director.

3. PR25272- Dobutamine HCl Injection, Lot 95-916-KL: The low OOS Dobutamine assay result of 93% (Specification: (b) (4)) for the in-process sample was invalidated even though a clearly assignable laboratory error was not determined. Remeasurement of the original sample (92%) confirmed the OOS result. An additional 6 retests were performed on the original sample (99%, 97%, 98%, 96%, 76%, and 96%). The original OOS result and the OOS retest result were invalidated with no justification. Only the within specification retest results were reported. Additionally, there was no exception report initiated even though no clearly assignable laboratory error was found.

4. PR29150- Precedex Injection, Lot 01-104-DK: The high OOS Dexmedetomidine assay result of 104% (Specification: (b) (4)) for the finished product (sample prep #2) was invalidated even though a clearly assignable laboratory error was not determined. Only the within specification results obtained during the (b) (4) retest were considered valid. Additionally, there was no manufacturing assessment performed; the investigation only included a PIR form.

5. PR30568/PR42409- Heparin Sodium in 0.45% Sodium Chloride Injection, Lot 02-933-FW: This lot had low OOS finished product results for (b) (4) heparin potency of 94% (Assay Target: (b) (4)) and Final Product Limits: (b) (4). (b) (4) A retest of the original sample as well as (b) (4) of lot samples were retested (90% 91%, 94%, 92%, respectively). The final reportable result was 92%. Specification 60.07651ALLCODE for Heparin Sodium in 0.45% Sodium Chloride Injection, requires the following- "Due to the nature of the biological assay and to assure that the product is within the final product limits, when the assay is outside of the assay target, retests will be made from the (b) (4) (b) (4) of the lot over (b) (4) days. If the average of the replicate is within (b) (4) the lot is acceptable." The firm performed an analysis of covariance (ANCOVA); this stability analysis determined the product lot is expected to remain within the required potency value specifications until the assigned expiration date. The lot was released for distribution based on the stability analysis. However, the firm has no justification for this analysis or release of this lot which did not meet the acceptance criteria as specified in 60.07651ALLCODE.

6. PR 32308/PR42417- Heparin Sodium in 0.45% Sodium Chloride Injection, Lot 03-548-FW: This lot had low OOS finished product results for (b) (4) heparin potency of 92% (Assay Target: (b) (4)) and Final Product Limits: (b) (4). (b) (4) A retest of the original sample as well as (b) (4) of lot samples were retested (91% 94%, 91%,

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93%, respectively). The final reportable result was 92%. Specification 60.07651ALLCODE for Heparin Sodium in 0.45% Sodium Chloride Injection, requires the following- "Due to the nature of the biological assay and to assure that the product is within the final product limits, when the assay is outside of the assay target, retests will be made from the (b) (4) of the lot over (b) (4) days. If the average of the replicate is within (b) (4) the lot is acceptable." The firm performed an analysis of covariance (ANCOVA); this stability analysis determined the product lot is expected to remain within the required potency value specifications until the assigned expiration date. The lot was released for distribution based on the stability analysis. However, the firm has no justification for this analysis or release of this lot which did not meet the acceptance criteria as specified in 60.07651ALLCODE.

7. LIR-SOL/RM-000855- Quelicin Injection, USP, Lot 94-180-EV: The high OOS in process assay for succinylcholine chloride of 108% (Specification (b) (4)) was invalidated even though no clearly assignable lab error was found. Exception Report ER 6398 was opened but there was no manufacturing investigation performed. Only (b) (4) retest on the original sample and a resample were tested and found to be within specification. ER 6398 concluded, "As probable root cause has been identified as lab error, likely in the form of incorrect dilution of sample, the original OOS result is not representative of the lot (b) (4) retesting of the lot meets specification, as well as all other release testing." ER 6398 was approved by the Site Quality Director.

8. LIR-SOL/RM-000895- Desmopressin Acetate Injection, Lot 95-383-EV: The low OOS in process assay result for Desmopressin acetate of 95.0% (Spec (b) (4)) was invalidated even though no clearly assignable lab error was found. ER6596 was opened but there was no manufacturing investigation performed. Only a (b) (4) retest on the original sample was performed and the results found to be within specification. This ER states, "The (b) (4) replacement test as well as the (b) (4) retest results obtained for the lot did not confirm the original OOS result, confirming that the originally observed OOS result was not sample related but a laboratory error. A combination of equipment and standard preparation error is the most likely root cause." ER596 was approved by the Site Quality Director.

9. LIR-SOL/RM-000886- Ropivacaine HCl Injection, Lot 95-618-DK: The high OOS in process assay result for Ropivacaine HCl of 104.7% (Spec (b) (4)) was invalidated even though no clearly assignable lab error was found. ER6566 was opened but there was no manufacturing investigation performed. Only a (b) (4) retest on the original sample was performed and all results found to be within specification. The ER states, "The (b) (4) retest from the original sample lot 95-618-DK did not reproduce original OOS result. The (b) (4) retest performed confirmed that the OOS result during the original run is not inherent to the lot 95-618-DK sample but related to the original sample preparation. Incomplete homogenization of the sample, pipetting or dilution error during the original sample preparation could have been the source of the OOS originally reported." ER6566 was approved by the Site Quality Director.

B. The firm failed to investigate out of specification (OOS) laboratory results as per SOP QCP 05.002, "Laboratory Investigations Procedure". Additionally, laboratory investigations have lacked scientific justification to support the dismissal of OOS/OOT results and conclusions of the investigations.

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1. The firm failed to adequately investigate in process OOS pH results for Quelicin Injection, USP, Lot 02-284-EV during the mixing revalidation (VCR 10091). An unapproved laboratory investigation form (WCQLIR) was used to investigate the results. This form was an attachment to SOP B6120_0200, "Procedures for In-Process Product Testing" effective 12/8/08. The procedure was revised on 10/12/09 to remove the WCQLIR form and stated that all in process OOS results are to be investigated per SOP QCP 05.002, "Laboratory Investigations Procedure".

However, form WCQLIR continued to be utilized for not only in-process testing but also finished product testing in the Quality Control laboratory to invalidate data without a formal laboratory investigation. Also, on 3/31/11, a new corporate SOP was implemented (SOP QCO.01.006, "Laboratory Data Handling Practices Procedure") which allows invalidation of data if objective evidence shows that the test method was not followed, system suitability requirements were not met, instrument failure occurred after starting the analysis, a dilution/mixing/pipetting error occurred, or other errors as described in the "Example Data Invalidation Form" attached to this procedure. The SOP also states "Scientific due diligence to support that data are invalid must be documented on a data invalidation form (an example is provided in Attachment A). There must be a clear scientific justification of why a Laboratory Investigation Report (LIR) is not required and the rationale must be approved by the lab management, prior to invalidating the data set."

This procedure is in direct conflict with the requirements of Corporate SOP QCP.05.002, "Laboratory Investigations Procedure" which states that only pre-run/post-run system suitability failures or miscalculations do not initially require a laboratory investigation.

There were approximately 250 invalidation events (not related to system suitability failures) in the Analytical Services Laboratory from January 2009 to present. There have been over a thousand invalidation events (not related to system suitability failures) in the QC Laboratory from January 2009 to present. These have been categorized as analyst error, instrument failure, poor chromatography, method related, and other. Examples include the following: standard preparation error, sample preparation error, instrument stopped during analysis, inadequate cleaning of equipment, extraneous peaks in chromatograms, retention time shifts during HPLC analysis, interfering peaks, possible mobile phase contamination, poor peak separation, poor integration, titration stopped before end point reached, and unknown peaks in IR spectra.

2. PR 31194/PR32399- Dopamine HCl in 5% Dextrose Injection, Lot 02-315-KL: This lot had an in-process OOS Dopamine assay result of 102.7% (Specification: (b) (4)). Remeasurement of the original sample (102.1%) confirmed the OOS result. An additional (b) (4) testing was performed on a resample (102.9%, 104.0%, 103.9%, 103.5%, and 104.0%). This batch was discarded by manufacturing and a second batch was made with the same lot number. This lot then had an in-process OOS Dopamine assay result of 102.7% (Specification: (b) (4)). Remeasurement of the original sample (102.2%) confirmed the OOS result. An additional (b) (4) testing was performed on a resample (102.9%, 104.0%, 103.9%, 103.5%, and 104.0%). There was no Quality Management approval for the resampling and no manufacturing assessment conducted concurrently during Phase II of the laboratory investigation. PR32399 states that the root cause was found to be an incorrect drug factor for API lot 01-007-DP which resulted in less API being used than required. However, the firm failed to evaluate other lots of product made with this API lot.

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C. Corporate SOP QCP 05.002, "Laboratory Investigations Procedure" does not require that a full scale manufacturing investigation is to be performed when the Phase I lab investigation does not determine a clearly assignable laboratory error. It allows (b) (4) retests to be performed when a clearly assignable cause has not been determined with only a manufacturing assessment; a full scale manufacturing investigation is only required if the retest results are still OOS.

OBSERVATION 2

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,

A. The firm has failed to conduct method transfers for the following:

Fentanyl Citrate Injection, USP- Assay and Impurities by HPLC (Method 90.C-2209 in use since 8/20/08).
Quelicin (Succinylcholine Chloride) Injection, USP- Assay and Identification by HPLC (Method 90.C-0915 in use since 8/20/81)
Ketorolac Tromethamine Injection, USP- Assay and Identification by HPLC (Method 90.C-1603 in use since 2/22/95)
Dopamine HCl Injection, USP- In process Assay by UV (Method 90.C-0739 in use since 01/11/78)

B. Corporate SOP QVO.19.012, "Chemical Test Methods Validation Procedure" does not require that method verifications are done at the laboratory site where the method will be utilized. The firm has failed to conduct method verifications at this site for the following:

Atropine Sulfate Injection, USP - Assay by HPLC (Method 90.C-0850 in use since 3/30/80)
Dopamine HCl Injection, USP- Assay and Identification by HPLC (Method 90.C-0895 in use since 12/2/80)

C. The current corporate SOP QVO.19.014, "Test Method Transfer Procedure" effective on 06/05/09 states that formal method transfer studies are not required in the following instances:

When test procedures employing the techniques are already in use by the receiving laboratory and therefore, the method is not new.

When the receiving lab analysts are trained by the R&D or originating lab scientist.

D. Corporate SOP QVO.19.014, "Test Method Transfer Procedure" (versions effective 04/17/07 through 10/31/08) stated that formal method transfer studies were not required in the following instances:

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When test procedures employing the techniques are already in use by the receiving laboratory and therefore, the method is not new.

When the test procedure has built-in controls to verify the performance with each use.

When based on professional judgement a formal transfer study is not required but the rationale must be documented.

When the receiving lab analysts are trained by the R&D or originating lab scientist.

OBSERVATION 3

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

Specifically,

The firm's quality control unit failed to conduct adequate manufacturing and laboratory investigations as per SOP QCP05.002 and as a result there were numerous product lots released for distribution that had failing in-process and/or finished product results. Additionally, they failed to conduct adequate method transfers for numerous analytical methods including Fentanyl Citrate Injection, Atropine Sulfate Injection, and Dopamine HCl Injection.

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