DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
US FDA Kansas City District Office 8050 Marshall Dr. Suite 205 Lenexa, KS 66214 913-495-5100 Industry Information: www.fda.gov/oc/industry	4/14-23/2014
	FEI NUMBER 1925262

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Andrew F. Knudten, Vice President of Operations, Plant Manager

FIRM NAME	STREET ADDRESS
Hospira, Inc	1776 Centennial Drive
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
McPherson, KS 67450	Human and Veterinary Drug Manufacturer

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DURING AN INSPECTION OF YOUR FIRM I (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,

Your process validation studies failed to establish documented evidence which provides a high degree of assurance the drugs (b) (4) mg/vial and (b) (4) manufacturing processes will consistently produce a product meeting its predetermined specifications and quality attributes. Your validation activities as defined in QC1201.00 Generation, Approval and Processing Validation Related Documents, QC1216.10 Process Validation are deficient.

Two procedures outline your process validation requirements; QC1201.00 Generation, Approval and Processing Validation Related Documents and QC1216.10 Process Validation. These documents state (QC1216.10 Process Validation) "***A minimum of three consecutive acceptable studies will be performed, unless otherwise determined through the science and risk based approach consistent with QVO.19.001 and requirements in QVO.19.005, Process Validation, Drugs." and (QC1201.00 Generation, Approval and Processing Validation Related Documents) "Invalid test or run is not considered a failure or nonconformance. It requires only documentation of the circumstances causing the test to be considered invalid. Invalid tests do not break a string of consecutive tests unless otherwise specified by a protocol."

On 4/22/2014, your validation manager said only an out of specification (OOS) for an attribute or specification failure of the drug product is considered in breaking a string of consecutive tests.

During the inspection the following was discovered:

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	Tara L. Greene Eric M. Mueller Cody D. Rickman Ashley A. Mutawakkil	Tara L Greene Eric M Mueller Cody D Rickman Ashley A Mutawakkil	4/23/2014

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You identified the three (3) process validation (PV) lots as, (b) (4) (6/19/13), (b) (4) (12/13/13), and (b) (4) (2/20/14) for (b) (4) which are intended for commercialization and distribution. However six (6) other lots are used in a majority of the qualification studies to include lots (b) (4) (b) (4) for studies defined to include, but not limited to solution mixing, fill uniformity, solution manufacturing hold time, lyophilizer (b) (4) – Product Qualification, and line cleaning validations, PV studies. Two of these lots, (b) (4) and (b) (4) were OOS for failure of assay demonstrating sub-potent product, yet they were used to support validation efforts.

Specific to lot (b) (4) this lot was deemed not usable (ER 79193) for fill uniformity validation determination, but was used to support validation in solution mixing.

- PQR0183.TNK-12-20 Compounding Equipment Cleaning Validation Report (b) (4) mg, (b) (4). Lots (b) (4) (OOS), and (b) (4) (OOS), were used as process validation supporting lots.
- PQR0056.00-13-07 Solution Manufacturing Hold Time – Final Report for (b) (4) mg/Vial (b) (4), Formulation (b) (4) Lots (b) (4) (OOS), (b) (4) non-consecutive lots were used as process validation supporting lots.
- PQR0510.20-13-16 Final Report for Solution Mixing and Fill Uniformity, (b) (4) mg, (b) (4) mL Vial.
  - o Solution Mixing lots (b) (4) (OOS), (b) (4) non-consecutive were used as process validation supporting lots.
  - o Fill Uniformity lots (b) (4) were used as process validation supporting lots.
- PQR0821.10-13-02 Lyophilizer (b) (4) – Product Qualification for (b) (4) ng/Vial, Formulation (b) (4) Lots (b) (4) (OOS), (b) (4) and lot (b) (4), consecutive lots were used as manufactured supporting lots.

For the three (3) PV lots identified there are eight (8) total deviations identified during the manufacturing, (b) (4) (b) (4)

For (b) (4) Product Cleaning Validation Interim Report PQR0183.VL7661-13-01 Sixteen (16) deviations are noted in the cleaning validation report; investigation numbers, LI 62276, ER 64368, 0183.VL7661-11-1185_DEV 1, 167 data invalidation, 0183.VL7661-12-0424_DEV 1, 0183.

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VL7661-12-0424_DEV 2, 0183.VL7661-13-0151_DEV 2, 0183.VL7661-13-0576_DEV 2, 0183. VL7661-13-0580_DEV 2, V0183.VL7661-13-0581_DEV 2, ER 79049, ER 78660, 0183.VL7661-13-0151_DEV 1, ER 136639, ER 136914, ER 137742. Deviations occurred for items including, but not limit to, OOS conductivity, elevated bioburden levels and inappropriate specifications, aborted automated cleaning process, failed cleaning specifications, laboratory errors in analysis and sample preparation, corroding stainless and rouging on filling manifold, and OOS for particulate matter. Your conclusion was that the cleaning validation is not complete due to the inaccuracies, OOSs, and the number of exception reports. You failed one run (b) (4) due to the OOS Validation Deviation 0183.VL7661-12-0424_DEV 1(online conductivity OOS reading of (b) (4) µS/cm which paused the cleaning cycle, specification for conductivity is (b) (4) µS/cm) and executed one more validation run, (b) (4) These lots were non-consecutive runs.

Your Procedure QVO 19.005 Performance Qualification Procedure; Solution Drug Product Commercial Manufacturing, Approach 1a. states: "***All data from relevant studies during design, and other production shall be used to determine the manufacturing conditions in the PQ. Normal manufacturing conditions and scale must be sufficiently modeled in the approach to the PQ.***"

OBSERVATION 2

Written records of investigation of a drug complaint do not include the findings of the investigation and the follow-up.

For Example,

You have failed to justify in consumer complaint investigation (1877778, opened 8/28/13 and closed 11/11/13) why it is not possible to directly attribute the complaint defect of black particulate matter in the product to your manufacturing operations for hydromorphone, lot: 27600LL. Your investigation defined the particulate (from the returned sample) as consisting of glass, stainless steel and oil.

Specifically,
Consumer complaint investigation 1877778 documents "Due to the complaint sample having been accessed it is not possible to directly attribute the defect to the manufacturing process of the lot."

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This statement is not justified and appears to be in contradiction to the findings in your related Exception Report (ER 117398, opened 2/5/13 and closed 9/5/13) of similar black particles consisting of glass, oil and stainless steel identified in fentanyl citrate, lot 25680LL. This lot was rejected due to similar-type particulates identified during manufacture.

In the instance of the complaint investigation 1877778, the possible correlation of particles (found in a consumer complaint sample) to your manufacturing operations was negated because the product hydromorphone HCl, lot: 27600LL had been accessed (punctured to access the medication within the unit, meaning no longer a sealed integral unit) by an outside consumer in a manner in which was intended.

This is significant because it is difficult to quantify how many times consumer complaint returned samples have not been confirmed due to consumer/customer (typically a health professional) accessing your drug products despite known similar problems with the product or other products produced in a similar fashion.

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