**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
FOOD AND DRUG ADMINISTRATION

| DISTRICT ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
|---|---|
| 11630 W. 80th Street<br>Lenexa, KS 66214<br>(913) 752-2100 Fax:(913) 752-2111<br>Industry Information: www.fda.gov/oc/industry | 11/28/2011 - 01/04/2012*<br>FEI NUMBER<br>1925262 |

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

**TO:** R. Bryan Grice, Director of Operations

| FIRM NAME | STREET ADDRESS |
|---|---|
| Hospira Inc | 1776 Centennial Dr |
| CITY, STATE, ZIP CODE, COUNTRY | TYPE ESTABLISHMENT INSPECTED |
| Mcpherson, KS 67460-9301 | 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.

**DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:**

## OBSERVATION 1

There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

Specifically,

Your firm has not validated the (b) (4)% vision light inspection testing with regard to personnel qualification, inspection speeds and technique to include using a seeded qualification panel against production line speed for Carpuject, ampuls, liquid filled and lyophilized vials on manufacturing lines (b) (4) and (b) (4) These lines are used to manufacture drug products including but not limited to Marcaine HCl (Bupivicaine), Demerol HCl Inj (Meperidine), Morphine Sulfate Inj, Heparin Lock Flush Solution USP, Humalog 100 (human recombinant insulin), Fabrazyme (agalsidase beta) and Vancomycin HCl.

Procedure QPO.15.004 Visible Particulate Procedure (effective 05/15/09) on page 2 of 7 states "Requirements" and describes the manufacturing inspection process "***Parenteral products must be (b) (4) inspected in-process for visible particulate.***" page 3 of 7 under Examination states "*** (b) (4) (b) (4) ***" ; and "*** (b) (4) (b) (4) ***". Page 4 of 7 of this same procedure under Quality Inspection states "*** (b) (4) '.

On 11/30/11 we witnessed (b) (4)% vision inspection on line (b) (4) and (b) (4) for Epinephrine Inj. USP, 1:1000, 1 mL Ampuls lot 112653A; (b) (4) line Morphine Sulfate Inj. USP 2 mg/mL 1 mL in 2.5 mL Carpuject, lot 11845LL; and inspection of lyophilized Vancomycin HCl for Injection, USP, 1 g, 20 mL in 25 mL vial, lot 11206DD. We observed:

- There is no inversion of any vial, ampul or cartridge to facilitate particulate inspection.
- For Carpuject configurations employees were viewed inspecting units for about (b) (4) seconds by taking approximately (b) (4) inches of vertically positioned cartridges (target outer diameter (b) (4) ") at one time, rolling them back and forth to assess the units before continuing to a new set. This is estimated to account for (b) (4) units inspected at once which over the span of (b) minute approximates (b) (4) units inspected in (b) (4) seconds.
- Training Course Plan PKT0215.02 details objectives and requirements of training. The course plan and those

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| | Tara L Breckenridge, Investigator<br>Richard L. Rutherford, Investigator<br>Michele L. Obert, Investigator | 01/04/2012 |

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for ampuls and lyophilized product do not include the use of a seeded qualification panel (known defects inserted into a sample lot of "good" product to assess the trainee's aptitude in finding defects). A seeded qualification panel assures the inspection process is adequate to detect particulate matter, glass particulate, seals, proper stopper and plunger placement etc.

- Vision inspection employees performing inspection of lyophilized product verbally stated they do not inspect the top of the lyophilized cake. Semi-automated vision system equipment is not set up to facilitate inspection of the top of the cake, only the top of the flip top cap.

## OBSERVATION 2

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established and written.

Specifically,

The design of the personnel entryway, personnel and material traffic flow, and gowning practices promotes the propagation of microbial contamination. The following was observed during the entirety of the inspection 11/28/11-1/4/12. This is applicable to all drug products, ~(b) (4) different pharmaceutical configurations.

Procedure MF0101.01 General Rules and Regulations: Aseptic Areas (effective Dec 16 2011) states "***The McPherson Aseptic Manufacturing areas are the most critical manufacturing locations in our site operations.***" Training Course Plan PRT0106 attachment 2 under Importance of Correct Gowning (bullet 2) states "***Protecting the product from particulate and microbial contamination.***" Dedicated plant clothing is intended to mitigate the ingress of dirt, debris and microorganisms into the cleaner areas of the plant. However, it was observed aseptic filling room personnel are allowed to frequent common public area's such as administrative offices, restrooms, and the cafeteria without being required to change out of dedicated plant scrubs and shoes which are then worn back into aseptic fill rooms under aseptic gowning. There is common interaction and comingling of personnel in street clothing and those performing manufacturing in the aseptic core.

Failure to mitigate the ingress of dirt, debris and microorganisms is exampled by:

- men and women's locker rooms and personal area required to don factory attire and factory dedicated shoes prior to entering into the manufacturing areas is not delineated to avoid cross contamination of street clothing to factory clothing. Lockers where street clothing/shoes and plant shoes are kept are shared.
- There is no record or document which dictates factory shoes are cleaned/sanitized on a routine basis.
- Aseptic personnel are required to don factory attire and dedicated shoes used to reduce the ingress and presence of objectionable microorganisms yet employees can and do access the production staging warehouse, cafeteria, restrooms and office corridors which are uncontrolled environments.
- Aseptic personnel are required to don a disposable lab coat prior to entering the cafeteria in order to protect their plant uniform. However, they disposable coats can be reused up to (b) (4) days.

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Media Fills and environmental monitoring show:

- Gram positive spore forming bacillus species (soil born microorganisms) have been recovered 158 times from Grade A and Grade B areas in 2011. In addition, there have been 170 above action level findings on three (3) filling line rooms, (b) (4) and (b) (4) since November 2010. None of the 10 exception reports reviewed identified a root cause for the presence of microorganisms.
- The men and women locker rooms are not included in the Environmental Monitoring (EM) Program; the pre-gowning rooms have not been sampled on the entry side of the demarcation line to determine the presence or absence of objectionable microorganisms (e.g., spore forming bacillus species) and the microbiology department has not taken into consideration whether these gown rooms could be a source and/or root cause for the bacillus microbial contamination.
- The environmental monitoring carts are not included during routine monitoring of ancillary equipment in the sterile corridors.
- There were 2 unacceptable media fills for 2010 and 2011 which includes a microbial failure and a growth promotion failure. For the same time frame there were 5 hits in which positive vial(s) were identified.
- For the (b) (4) Lot (b) (4) run (b) (4) media fill failure, conducted 7/13/2011 *Alternaria alternate*, *Curtobacterium* species, *Staphylococcus epidermidis, Micrococcus terreus* and *Arthrobacter* species were recovered. Supplemental EM data from the same time frame as the media fill similarly identified *Alternaria alternate* in the (b) (4) room, (b) (4) component preparation room, the SPA corridor, and gowning rooms. *Arthrobacter* species was identified in gowning rooms on 7/12/2011 and 7/14/2011. No definitive root cause was determined per the exception report.

## OBSERVATION 3

Establishment of the reliability of the container supplier's report of analyses is deficient in that the test results are not appropriately validated at appropriate intervals.

Specifically,

Your firm has not qualified the process of tailgating (pre-delivered/pre-pulled samples by the glass vendor) glass container samples. Verification of accuracy from the vendor against glass container samples collected in house has not been performed. This applies to (and includes but is not limited to) glass components used in the manufacture of Fabrazyme (agalsidase beta), Epinephrine, Hydromorphone HCl, Heparin, Vancomycin HCl, Marcaine HCl (Bupivicaine), and Morphine Sulfate.

These vendor pulled samples are used for qualifying a lot of glass for use in lieu of internally pulled samples. These samples are used to assure an accurate, representative, statistically valid lot of glass, to be released and used in production, meets specifications.

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SOP QC0900.04 Pre-Delivered Samples and Tailgate Samples effective 9/09/2005 and SOP QC0900.04 Pre-Delivered Samples and Tailgate Samples effective 11/18/2011 state I. C. "*** (b) (4) (b) (4) *** This qualification has never been performed. The term "comparable" has not been statistically defined for what "comparable" would actually comprise when assessing the relevance of a sample pulled to represent ~ (b) (4) to (b) (4) glass units.

Further, you have not established the reliability of the supplier's analyses through appropriate validation of the suppliers test results at appropriate intervals.

Verification of the component specifications to the vendor's release specifications (vendor glass certification and testing) is not performed to assess annealing, lehring, shoulder angle and glass thickness at critical areas with specific respect the Carpuject configuration. Glass components have not been microscopically examined.

A recall was initiated on 7/8/2011 for Carpuject iSecure configurations due to cracks/breaks found in the glass cartridges including Midazolam Inj. USP, Heparin Sodium Inj. USP, Ketorolac Tromethamine Inj. USP, Ondansetron Inj. USP, Diazepam Inj. USP.

## OBSERVATION 4

Test devices are deficient in that instruments, apparatus, gauges, and recording devices not meeting established specifications are used.

Specifically,

The alarms for the (b) (4) humidity probes in the walk-in (b)(4)°C/(b)(4)% RH stability room, containing all uncontrolled drug products held for stability testing, were turned off after 10/22/2008. The humidity was out of specification on 6 different occasions after 10/22/2008 through 7/8/2011. There were 4 above humidity events and 2 below humidity events. The longest events lasted from 5/19/2011 to 7/8/2011. This recorder is checked daily by Manufacturing Quality personnel but they only looked for an alarm they did not look at the actual readings.

| Date / Date Range | Length of Excursion | Reason for Excursion |
|---|---|---|
| 18 - 20 JUL 2009 | 37.5 hours | (b) (4) |
| 25-26 SEPT 2010 | 31 hours | |
| 28 SEPT 2010 | 11.5 hours | |
| 29-30 SEPT 2010 | 37 hours | |
| 30 DEC 2010 | 8 hours | |
| 19 MAY - 8 JUL 2011 | 400 hours (50 days) | |

Further, humidity is only checked in the middle of the room during requalifications of the (b)(4)°C/(b)(4)% RH stability room M732. You have not verified the humidity is uniform throughout the entire room by mapping humidity in the corners of the room during requalification.

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## OBSERVATION 5

Adequate exhaust systems or other systems to control contaminants are lacking in areas where air contamination occurs during production.

Specifically,

Smoke studies are not representative of actual production practices which assess whether or not appropriate air changes and laminar air flow exists and can be maintained in a Grade A filling area.

On 12/2/2011 I observed an intervention on the (b) (4) line at the needle assembly hopper during the filling of Labetalol HCl Inj. USP 5 mg/mL lot (b) (4). The hopper was vibrating to move the assemblies into position. The operator opened the door and removed multiple assemblies using forceps. The intervention lasted for more than 20 seconds. The smoke study for this type of intervention did not have the hopper vibrating and the operator opened the door removed one assembly and closed the door in approximately 10 seconds. During the smoke study, I observed smoke beginning to enter into the hopper area before the operator closed the door. The firm did not have data to support longer interventions similar those observed and there were no interventions demonstrating the vibrating hopper.

The smoke studies do not include the effect upon room pressure and laminar air flow when doors are opened to the sterile corridor simulating personnel and materials movement into and out of the aseptic filling room. Additionally, environmental monitoring activities are not routinely included in the smoke studies.

## OBSERVATION 6

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

Specifically,

During the annual review of the reserve samples as well as for any reviews conducted as part of a complaint investigation, quality employees are required to assess the reserve samples to determine if the product in question meets visual specification. It was determined product specifications are not used in this examination. When asked how the employee knows what product is supposed to look like, the response was the employees are very familiar with the product. It was not verbally stated a finished product monograph is ever consulted during this review.

These procedures are similar for approximately (b) (4) different product configurations manufactured in 2011 for this site.

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