

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

DISTRICT ADDRESS AND PHONE NUMBER		DATE(S) OF INSPECTION
8050 Marshall Drive, Suite 205 Lenexa, KS 66214 (913)495-5100 Fax: (913)495-5115		10/16/2017 - 10/27/2017
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED		FBI NUMBER
Carole A. Johnson, Site Leader		1925262
FIRM NAME	STREET ADDRESS	
Hospira Inc. A Pfizer Company	1776 Centennial Dr.	
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED	
McPherson, KS 67460	Human Sterile 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.

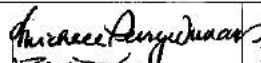
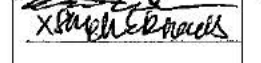

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

Specifically,

- A. You have received approximately 50, 43 and 46 lack of effect complaints for Bupivacaine HCl with Dextrose (Marcaine) lots 550503A, 641003A and 641403A, respectively. These complaints were received from approximately 02/09/2016 to 10/26/2017. A trend notification and a Supplemental Medical Review were conducted, but no action or additional testing was performed. To date, there has not been any additional testing or adequate trend analysis performed for these lots.
- B. During retain examination of Hydromorphone HCl lot 510053 (ANDA 078591), 15 of ^{(b)(4)} vials exhibited particulate matter, which was identified on 07/15/2016 as silicone based. This investigation began on 07/12/2016 and was not completed until 07/27/2017, with a recall initiated on 07/31/2017.
- C. The complaint investigation for a vial of Vancomycin HCl for Injection lot 632153A (ANDA 062912), is inadequate in that it did not address potential inadequacies of the visual inspection process. A complaint vial was returned with a hair partially embedded in the stopper section that is inside of the vial. During the complaint investigation, the visual

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inspection process was not identified as a contributing factor for the distribution of the returned product.

- D. During the (b) (4) requalification run the (b) (4) asset no. (b) (4) depyrogenation tunnel located on Line (b) (4), two of the (b) (4) endotoxin challenge samples failed to meet the acceptance criteria of a 3-log reduction of endotoxin indicators. During this Validation No. 0062.00-17-0028 "Depyrogenation Endotoxin Indicator Study" performed 1/10/17, two of the (b) (4) samples had results that achieved a log reduction of (b) (4) and the second sample yielded a result of (b) (4). As a part of this investigation, you reported complaints were evaluated. You did not look at adverse events reported during the time you had acceptable qualification results reported until the time when the failing endotoxin indicator results were reported during the (b) (4) Tunnel Validation.

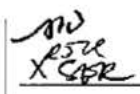
REPEAT OBSERVATION from 6/8/2016

OBSERVATION 2

Employees engaged in the manufacture and processing of a drug product lack the training required to perform their assigned functions.

Specifically,

Employees performing your incoming quality visual inspection process associated with your glass components are not adequately trained. Your employees do not utilize physical glass components nor do you objectively measure this training process. This incoming quality inspection is critical to the prevention of container/closure integrity defects which affect critical attributes such as sterility and potency. The glass components are used as the primary container in all your sterile products including but not limited to Vancomycin HCl Injectable (numerous ANDA/NDAs), Marcaine HCl/Bupivacaine

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HCl Injectable (numerous ANDA/NDAs), Levophed/Norepinephrine Bitartrate Injectable (ANDA/NDA 007513), Diltiazem HCl Injection (ANDA 074941, 075853), etc.

OBSERVATION 3

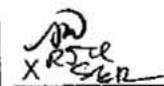
Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design to facilitate operations for its intended use.

Specifically,

You have not appropriately qualified your automated visual inspection labeling process used as your in-process control for lot and expiry label defects.

- A. Your qualification required the successful rejection of approximately (b)(4) defective units and it did not provide any detail surrounding the magnitude of the lot or expiry defects presented to your visual inspection equipment. Additionally, your equipment is designed to reject defective units when (b)(4) of the surface area of the lot or expiry is missing.
- B. You manually inspect approximately (b)(4) finished units for defects including but not limited to lot and expiry critical text. Batch sizes for these products and packaging configurations routinely approach (b)(4) units. Therefore, your sampling size is inadequate to provide statistical assurance for lot and expiry defects. Additionally, these types of defects are classified as general appearance and assigned an AQL of (b)(4).

This process affects products to include but not limited to your ADD-Vantage configurations such as Diltiazem 500mg, Vancomycin 500mg/750mg/1g, Erythromycin 100mg, and Azithromycin 500mg.

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TYPE ESTABLISHMENT INSPECTED

Human Sterile Drug Manufacturer

OBSERVATION 4

Reserve samples from representative sample lots or batches of drug products selected by acceptable statistical procedures are not examined visually at least once a year for evidence of deterioration.

Specifically,

Your SOP does not appropriately classify deterioration to your critical text, namely lot number and expiry. You classify faded print to the critical text fields of lot number and expiry as minor with AQLs for this defect type of (b) (4). A randomly selected retain review of Vancomycin HCl Injectable Lot 67230DD identified approximately (b) (4) units with faded lot numbers.

REPEAT OBSERVATION from 6/8/2016

OBSERVATION 5

Cleaning procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not followed.

Specifically,

- A. The mop used to clean the walls of the filling room with (b) (4) was stored upright on a cart that also contained a box of sterile (b) (4) wipes used for cleaning. The mop was observed to be dripping onto the floor, and had the potential to drip into the container of sterile (b) (4) wipes when the lid was removed to obtain a clean wipe. This storage configuration has the potential to spread contamination cleaned from a wall to areas that are cleaned with the sterile (b) (4) wipes, such as windows and plexiglass in the filling room.
- B. (b) (4) cleaning of windows and plexiglass with (b) (4) in the (b) (4) filling room is not documented in the Sanitation Log Book, only the walls and ceilings being cleaned with (b) (4) is

**SEE REVERSE
OF THIS PAGE**

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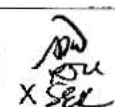
documented. While two different sporicidal agents are used in this room, they are not rotated so that each surface type is cleaned with two different sporicidal agents.

- C. On 10/21/17, during the aseptic cleaning of (b) (4) filling room, we observed employee, User ID no. (b) (6), perform cleaning and sanitization operations which included the following inadequate cleaning practices.
1. Overlapping strokes were not always used when cleaning the walls.
 2. Missed cleaning different areas in the room, including but not limited to the reject bin and sample port.
 3. The employee was observed stepping back onto the cleaned floor area where he had mopped and did not re-mop that area.
- D. During the aseptic simulation (media fill) of Line (b) (4) you do not record or simulate all activities/interventions which occur during routine sterile processing operations. For example, the frequency for the activities you classify as "Inherent Interventions" such as loading stoppers, fill volume checks, traying vials, etc. are not accounted for during your aseptic fill operations.

OBSERVATION 6

An NDA-Field Alert Report was not submitted within three working days of receipt of information concerning a failure of one or more distributed batches of a drug to meet the specifications established for it in the application.

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- A. On 01/10/2017, an Out of Specification (OOS) result was obtained for Vancomycin HCl for Injection lot 620203A (ANDA 065455), during potency assay testing at the (b)(4)-month stability timepoint. The initial result was not invalidated, and you had inadequate documentation to attribute the assignable cause to analyst error. (b)(4); additional samples completed testing on 01/27/2017, and were within specification. The time elapsed between these two events was 13 working days, and a Field Alert Report (FAR) was not filed for the original OOS result.
- B. On 2/1/2017, you received a complaint for defect type missing label associated with Vancomycin HCl lot 610403A. A Field Alert Report was not filed until 3/1/2017.
- C. Demerol Injectable Lot no. 490903A reported in PR ID 1539131 which was created July 11, 2016. This report documents the reserve sample for this product had been reviewed on 7/1/6 by employee UID (b)(6) and found a Critical A crack/damaged unit on (b)(4)/49003A, which was confirmed by MQ Supervisor UID (b)(6). The Initial FAR was not filed until July 18, 2016 for this event.
- D. Labetalol Hydrochloride Inj. USP 5 mg/mL, 4 mL in 5 mL Carpuject Luer Lock, lot no. 55595LL reported in PR ID: 1539291 created on July 11, 2016, reported reserve samples were evaluated on 7/5/15 by employee UID (b)(6) who found a Critical A crack/damaged unit on (b)(4)/55595LL which was confirmed by MQ Supervisor UID (b)(6). The Initial FAR was not reported until July 18, 2016.

REPEAT OBSERVATION from 8/16/2013 and 6/8/2016

OBSERVATION 7

Written records of investigations into the failure of a batch or any of its components to meet specifications do not always included the conclusions and follow-up.

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In your Annual Product Reviews for the following products you identify trends but fail to initiate appropriate corrective and preventive actions to address and correct these failures.

- A. Marcaine HCl 0.75% w/Dextrose 8.25% Injection, for the review period of 4/2/2016 to 4/1/2017 you identified a trend with 367 complaints classified as Lack of Effect, which caused this complaint type to exceed your trend limit.
- B. Hydromorphone HCl Injection USP, 10mg/mL/Vial, for the review period 6/11/2016 to 6/10/2017 you identified your visual inspection process as a root cause and you failed to incorporate corrective and preventive action.


REPEAT OBSERVATION from 4/23/2014 and 6/8/2016

OBSERVATION 8

Procedures describing the handling of written and oral complaints related to drug products are deficiently written.

Specifically,

Your complaint handling procedure does not require you to procure the lot number from your customer in the event it is not provided at initial intake. You have received approximately 285 complaints without a lot number of approximately 1510 total complaints received. This represents approximately 20% of all complaints. Products which represent this process include but are not limited to Glatopa/Glatiramer Acetate Injection, (b) (4) Injection, Makena/HydroxyProgesterone Injection, Epinephrine Injection, etc.

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OBSERVATION 9

Deviations from written test procedures are not recorded and/or justified.

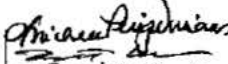
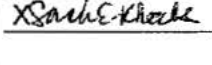
Specifically, during sterility testing on 10/19/2017, dynamic monitoring of the isolator conditions during testing was not observed. SOP QC0695.40, *Environmental Monitoring Inside the* (b) (4) Isolator, requires that contact plates are taken (b) (4) and a viable air sample is taken (b) (4).

OBSERVATION 10

Drug products are not stored under appropriate conditions of temperature so that their identity, strength, quality, and purity are not affected.

Specifically,

- A. You currently store raw materials and equipment which list temperature storage requirements on their labels in your In-coming Warehouse which is not temperature and humidity controlled. For example, Mannitol lot no. (b) (4) was observed in the warehouse which is used to manufacture over 9 sterile injectable products. The label on this product had temperature storage requirement of (b) (4) degree Celsius.
- B. There is a temperature recorder located in the In-coming warehouse which is not always monitored and reviewed in accordance to your SOP no. QC0877.00 "Monitoring of Recorders". In addition, you have not performed a temperature mapping study of this area.

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