DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

| DISTRICT ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
|---|---|
| 8050 Marshall Drive, Suite 205<br>Lenexa, KS 66214<br>(913)495-5100 Fax:(913)495-5115 | 7/23/2018 - 8/8/2018*<br>FEI NUMBER<br>1925262 |

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Carole A. Johnson, Site Leader

| 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 initiated an investigation on 11/27/2017 emanating from mold contamination results read on 11/18/2017 in your Grade A filling area. This event resulted in the rejection of approximately (b)(4) batches of finished product manufactured on (b)(4) filling line. This investigation is inadequate because you did not appropriately identify the scope of the investigation, establish the root cause and implement preventive actions or initiate the investigation in a timely period. You suspended production activities on 12/8/2017 after three mold isolates were recovered in these areas and to establish the root cause. You visually identified apparent dried product residue on the underside of the lyophilization trayer bed / product path on 12/9/2017. You made no attempt to identify this residue. You sampled the area of the residue which resulted in the recovery of 11 CFUs of mold on 12/15/2017. You identified additional mold isolates near this affected area procured from apparent product residue. You identified a potential source of contamination and sampled this area without conducting a scientifically established sampling plan or worst-case sample locations. You returned to manufacturing during late December 2017. You identified inadequate cleaning as a cause for the

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apparent product residue on or about 12/9/2017. You identified additional apparent product residue on approximately 7/31/2018 at the same location it was identified on 12/9/2017.

B. You failed to adequately investigate approximately 9 previous events when an unknown foreign material / gel was observed adhering to the High Efficiency Particulate Air (HEPA) filter screens. The metal screens are a part of the ceiling in all cleanrooms and are located approximately 4" – 8" from the face of the HEPA filters. On 7/24/2018, we observed an apparent "gel" or other foreign material in the (b) (4) line adhering to the HEPA filter screen, later identified as an approximately 3 mm x 3 mm "gel". You failed to document the investigation contemporaneously as well as who inspected the room. You did not immediately extend this investigation to other areas even though this "gel" is used as a part of your HEPA filters. This gel is used throughout your facility in cleanrooms as an integral part of your HEPA filters.

C. You initiated an investigation on 9/26/2017 because of a potential data integrity event associated with an in-process auditor per PR ID 2011571. The auditor performed visual inspection operations affecting approximately (b) (4) lots manufactured from 7/6/2015 through 9/22/2017. The investigation is inadequate because you did not scientifically justify why you chose to analyze the retain data of approximately (b) (4) lots. Additionally, you requested lot #81660LL be returned to your control for further evaluation as it was distributed outside of your control.

D. You modified your validated parameters on approximately 5/19/2018 associated with your (b) (4) stopper washing process. You have no documentation supporting that you assessed the risk of this process change before it was implemented. Specifically, you did not verify that modifying the pressure (b)(4) to (b)(4) pounds per square inch or the use of a (b)(4) load versus a

(b) (4) load, does not adversely affect this process. Your Quality Site Director stated you would open an investigation on 7/31/2018 to assess the risk of this event.

E. You identified an activated Diphenhydramine Carpuject unit (critical defect) during your retain examination on 12/20/2017 of lot #73525LL. You identified an operator inappropriately re-incorporating ejected product back into your product stream as a root cause. You modified your written procedures on approximately 3/30/2018 and implemented this preventive action on approximately 4/30/2018. You did not perform any immediate action to prevent this re-occurrence in the interim.

**Repeat Observation from the 10/2017 and 6/2016**

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**OBSERVATION 2**

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.

Specifically,

A. On 11/27/2017, you opened an investigation initiated from mold recovered from a settle plate on line (b) (4) in your grade A area. You visually observed apparent product residue on the underside of the trayer bed. This product residue was sampled and yielded 11 CFUs of mold. You made no documented attempt to identify this residue nor how or when this residue was deposited. You identified apparent product residue in this same area again, on 7/31/2018.

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B. On 9/22/2017, you discovered information resulting in a potential data integrity event associated with an in-process auditor per PR ID 2011571. The auditor performed visual inspection operations affecting approximately (b) (4) lots manufactured from 7/6/2015 through 9/22/2017.

C. On 10/9/2017, you discovered a cracked needle hub (critical A defect) while performing a manufacturing quality audit of Morphine Sulfate Inj. USP, lot #80740LL. You did not submit a Field Alert Report for this event until 2/5/2018.

**Repeat Observation from 10/2017, 6/2016 and 8/2013**

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**OBSERVATION 3**

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile did not include adequate validation of the aseptic process.

Specifically,

A. While reviewing smoke studies conducted in room 323 for Lyophilizer (b)(4), the following deficiencies were noted:

1. Prior to unloading of the HEPA cart containing partially stoppered vials, an operator was observed checking the tray number using forceps. Tray check performance gives the operator an opportunity to be close to the partially stoppered vials. The action provides possible contamination of the partially stoppered vials.
2. While loading the Lyophilizer, the operator breached first air and smoke was observed to travel from the operator onto the tray containing partially stoppered vials.

3. Smoke studies conducted do not demonstrate worst case scenario as the lyophilizer was not fully loaded.

B. You have no documented scientific justification for personnel monitoring during aseptic filling. Per your Class 100 filling room process, personnel are monitored (b) (4) . During a shift, aseptic operators can gown and de-gown multiple times within a day and on the same shift without additional personnel monitoring.

C. While observing setup operations on line (b) (4) I observed tools used for interventions located in your grade A area in room 338. In order to use the tools, operators must first compromise first air principles.

**Repeat Observation from 6/2016 and 10/2012**

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**OBSERVATION 4**

Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the room and equipment to produce aseptic conditions.

Specifically,

A. On 7/23/2018, during the (b) (4) ) setup on (b) (4) fill line, (b) (4) were observed un-extended with occluded surfaces. (b) (4) fill line was being setup to produce Glatiramer Acetate Injection 20mg lot 911253F.

B. The following hazardous products are manufactured at the facility: Hydroxyprogesterone Caproate; (b) (4) ; Fentanyl Citrate; Dexmedetomidine HCL; Liraglutide. All the hormones and steroids manufactured at the facility utilize the same general cleaning room, Room

657. Room 657 is adjacent to (b) (4) Room 655 which opens to general corridor 436. While conducting your risk assessment, you failed to consider the following:

1. Room 657 and 655 are both under positive pressure. While cleaning of equipment used to manufacture Hazardous material in Room 657 there is a likelihood the (b) (4) could become contaminated with hazardous material. The contaminated (b) (4) room could allow contamination to escape into the general corridor.

2. Inadvertent release of the hazardous material can't be promptly detected as on 26th July 2018 since your current action alarms were set with a delay of (b) (4) ( (b) (4) ). Changes in the airflow would not be promptly detected.

**Repeat Observation from 6/2016**

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**OBSERVATION 5**

Your examination and testing of samples did not assure that the drug product and in-process material conformed to specifications.

Specifically,

Your manual / semi-automated / automated visual inspection processes are inadequate for the following:

A. Your operators are trained via the (b) (4) visual inspection training program which requires qualification specifically using a (b) (4) . You have not performed or have performed an inadequate scientific justification regarding your selection of (b) (4) as representative or worst case of all primary container closure systems such as ampules (~1 mL – 5 mL), amber vials, 100-mL vials, etc.

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B. On 7/24/2018, I observed 100-mL vials of lyophilized Vancomycin semi-automated inspection processes in room #623 for lot #911903A. Approximately 5 vials failed to make a complete turn during the inspection process during an approximate duration of (b) (4). A full revolution is a requirement to adequately inspect vials for critical A (seal integrity defects) as well critical B (particulate matter) defects. The vial rollers of the (b) (4) semi-manual visual inspection equipment appeared to be malfunctioning.

C. You have not performed a risk assessment used as an input in the development of your acceptable quality limits (AQLs). Specifically, you have not included the risk to consumers resulting from the use of defective product such as seal integrity attributes and particulate matter contamination.

D. You have not adequately assessed spinning parameters, such as rotation per minute (RPMs) of your (b) (4) semi-automated inspection equipment which affect the capability of your visual inspection process. Specifically, you have not established an RPM range or other parameter to control / facilitate the propulsion of particulate matter into solution / suspension immediately preceding the presentation of vials to your inspecting operators.

E. You have not adequately evaluated the risk that line speed presents to semi-automated visual inspection operations. You (b) (4) qualify your visual inspection operators using approximately (b) (4) of inspection time per unit. On 7/24/2018, we observed a line speed of (b) (4) during observation of Lyophilized Vancomycin HCl lot #911903A, room #623.

F. You have not established in-process defect limits regarding your visual inspection processes in the event a second visual inspection is required.

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G. You do not have a requirement preventing you from modifying your in-process limits established to monitor process control nor do you limit the amount you change your in-process limits.

H. During your statistical evaluation of in-process data used to establish / re-establish in-process limits, you exclude statistical outliers. However, you have not performed a substantive review of the investigation to determine if the statistical outlier is in fact a result of a special cause event.

I. You do not monitor long term drift during your establishment / re-establishment of in-process limits.

**Repeat Observation from 6/2016**

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**OBSERVATION 6**

Certificates of testing of containers are accepted in lieu of testing without establishing the reliability of the supplier's test results through appropriate validation of the test results at appropriate intervals.

Specifically,

You have not performed a risk assessment or have performed one which is inadequate. You have not fully qualified your vendor's Certificate of Conformance. Specifically, you have not inspected incoming molded glass vials for (b) (4). This defect type is included on your suppliers' Certificates of Conformance. You have no documented scientific justification precluding you from testing for this defect.

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**OBSERVATION 7**

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

Specifically,

Your training is inadequate for the following:

A. Retain inspectors / operators are trained via the (b) (4) visual inspection training program which requires qualification based using a (b) (4). You have no documented scientific justification establishing why the (b) (4) is representative or worst case of all primary container closure systems such as ampules (~1 mL – 5 mL), amber vials, 100-mL vials, etc.

B. You do not trend time elapsed since last personnel training regarding visual inspection processes. You have re-inspected approximately 300 of (b) (4) batches manufactured since approximately 10/10/2017.

C. You have no valid rationale for dismissing personnel training as a root cause for your positive sterility test noted in Laboratory Investigation PR ID 1993529. You did not trend to determine whether your analyst has previously performed positive sterility test.

**Repeat Observation from 10/2017**

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**OBSERVATION 8**

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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,

Your (b) (4) equipment which processes plungers and stoppers for your sterile drug products has not been performed adequately. You have not scientifically supported this process reduces particulate matter to an acceptable level. Your Process Qualification Report states this washing equipment should effectively remove particulates to an acceptable level. However, data used in this evaluation exhibit no reduction in particulates greater than (b)(4) microns in size and a reduction of one particulate from the approximate (b)(4) micron sized particles.

**Repeat Observation from 10/2017**

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