Kansas City District Office
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February 14, 2017

WARNING LETTER

Ref: CMS Case: 506761
DELIVERY VIA UPS

Mr. Ian C. Reed Chairman and CEO Pfizer Inc.
235 East 42nd St. New York, NY 10017

Dear Mr. Reed:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Hospira Inc., a Pfizer Company at 1776 Centennial Drive, McPherson, Kansas, from May 16 to June 8, 2016.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

The inspection also revealed that Hospira Inc. failed to submit field alert reports to FDA as required by section 505(k) of the FD&C Act, 21 U.S.C. 355(k), 21 CFR 314.81(b)(1) (new drug applications), and 21 CFR 314.98 (abbreviated new drug applications).

We reviewed your June 29, 2016, response in detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigators observed specific violations including, but not limited to, the following.

1. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

During our inspection, we reviewed reports from multiple investigations that you conducted into complaints regarding the presence of visible particulates in several of your sterile injectable products. The presence of visible particulates in sterile injectable products is an indication of a significant loss of control in your manufacturing process and represents a severe risk of harm to patients. We documented that your investigations into these product quality defects were inadequate and failed to spur appropriate corrective actions and preventive actions.

Vancomycin Hydrochloride for Injection
For example, on December 31, 2015, you received a complaint of particulate matter in a vial of vancomycin hydrochloride for injection, lot 565003A. After examining the vial and your retain samples, on January 11, 2016, you determined that the contaminant was cardboard. You concluded that the most probable source of contamination was related to the handling of your vial stoppers. However, on February 8, 2016, you closed the investigation without a comprehensive evaluation of the extent of the contamination and without taking further corrective actions.

On February 24 and April 15, 2016, you received additional complaints of particulate matter, also confirmed to be cardboard, in other vials of the same lot without taking any further action.

The presence of multiple foreign particulates in your products is unacceptable. Extrinsic contaminants, such as cardboard, pose a significant risk to patients and indicate that your process for manufacturing sterile injectable products is out of control.

Although you recalled lot 565003A on May 6, 2016, you did not do so until more than four months after receiving the initial product complaint and determining that products in the lot had been contaminated with cardboard. Moreover, you received additional complaints about the same problem in the intervening time period but failed to take further action.

Ketorolac Tromethamine Injection
On September 16, 2015, you received a complaint about particulate matter in an unspecified number of vials of ketorolac tromethamine injection, 30 mg/mL, lot 46205DD. You confirmed the presence of particulate matter in the returned product complaint samples and then found that 190 out of **(b)(4)** your retention samples from this lot also contained visible particulates.

Your investigation into this matter was inadequate. For example, your investigation report indicates that "[t]en representative [retention] samples were sent to the Particle Lab for further evaluation." Your report does not provide a scientific rationale for selecting only **(b)(4)** vials for testing, nor does it explain the nature and purpose of the testing and examination you conducted as part of the investigation. Furthermore, although your investigation indicates that you found brown agglomerates during production of lot 46205DD, you concluded that this was "most likely . . . caused by the **(b)(4)** during the mixing process based on a previous assessment." Although your investigation indicates that the particles are similar to particles found in other lots of the

same product, you failed to determine the specific identity and source of the particles in lot 46205DD. You released lot 46205DD because "the presence of **(b)(4)** was found to be intrinsic to the manufacturing process." However, you did not determine whether the same problem may have affected other lots, nor did you document any corrective actions taken in response to the deviation.

You did not conduct a comprehensive assessment of the particulate matter observed in the distributed vials and retention samples, including its specific identity and whether other lots were affected. You failed to provide either a scientific rationale for the conclusions you reached in your investigations or information on the methodologies used during your testing.

In response to this letter, provide:

- your rationale for not conducting chemical analysis of the particulates observed in ketorolac tromethamine injection, 30 mg/mL, lot 46205DD, and implementing appropriate actions to prevent recurrence of this event;
- updates on your root cause analysis of the particle contamination events and your corrective action and preventive action (CAPA) plan;
- an evaluation of the nature and extent of particulates present in retain samples for all distributed lots of your sterile drug products that remain within expiry and for which you have received one or more complaints of particulate matter;
- an evaluation of any lots that were found to contain intrinsic or extrinsic particulate matter during manufacturing but were subsequently released; and
- the corrective actions you propose to initiate against compromised products that remain on the market.

2. Your firm failed to establish valid in-process specifications (21 CFR 211.110(b)).

You routinely manufacture sterile injectable products without defect (alert or action) limits for both semi-automated and fully-automated in-process visual inspections. For example, your visual inspection procedures instruct operators to ignore or discount established in-process defect limits whenever you make a change to your manufacturing process, including changes to your visual inspection program. Our investigator noted many complaints related to particulate matter in sterile injectable products manufactured at your facility, indicating that the lack of defect limits for visual inspections may have resulted in the release of products that otherwise would not have been distributed.

In response to this observation, you committed to:

- performing a retrospective review of released batches by comparing the observed in-process visual inspection reject data against previously established historical limits;
- applying historical in-process visual inspection rejection limits to currently manufactured batches until you can establish and implement revised limits; and
- revising in-process visual inspection procedures to clarify the requirements for when new in-process visual inspection reject limits will be established in response to changes to the manufacturing process including changes to materials used in the manufacturing process.

Your response is inadequate because you did not indicate whether these changes apply to both products manufactured under your label and products you manufacture under contract for your customers.

3. Your firm failed to follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

During the inspection, our investigators observed multiple examples of practices that represent significant risks to the sterility of your finished products.

Poor Aseptic Technique
During the inspection, our investigator observed operators manufacturing hydromorphone lot 651903A. The investigator observed the introduction of a bottle of sterile water with a shrink-wrapped plastic tamper-resistant seal into the **(b)(4)** isolator material transfer chamber. Inserting bottles with intact tamper seals into the chamber is specifically prohibited by your firm's **(b)(4)** isolator SOP MF0732.00. The isolator uses **(b)(4)** to sterilize objects placed inside the chamber, but the **(b)(4)** cannot penetrate plastic seals. If a water bottle is inserted into the chamber with an intact seal, only the exposed surfaces of the bottle would be rendered sterile. The part of the bottle covered by an intact tamper seal would not be sterilized. Removal of the seal could compromise the sterility of the surrounding aseptic manufacturing environment.

Our inspection documented that at least two, and possibly four, of your operators observed the presence of this sealed bottle in the chamber, despite the explicit prohibition in the SOP. Our investigator identified this issue during production, and you were unable to explain why your operators did not recognize this problem.

In response to this letter, provide an assessment of how this poor aseptic practice may have affected the quality of your products.

Poor Personnel Monitoring Technique
Our investigators observed personnel in aseptic manufacturing areas using **(b)(4)** to sanitize their hands immediately before they touched personnel contact plates. Sanitizing hands immediately before conducting personnel monitoring significantly reduces the likelihood of detecting microbiological contamination in the aseptic manufacturing environment. Indeed, your own training procedures note that employees should not use **(b)(4)** immediately before performing personnel monitoring.

In your response, you committed to observing operators during personnel monitoring, revising your aseptic processing training, and conducting additional aseptic processing training for personnel who work in aseptic processing areas. Your response is inadequate because you only reviewed the microbiological environmental monitoring data for two lots of product: Nimbex NX20 lot 65105DD filled on line **(b)(4)** and vancomycin M-6535 lot 65090DD, filled on line **(b)(4)** You did not evaluate environmental data from other lots that may have been affected by similar poor sampling techniques.

In response to this letter, provide a summary and assessment of personnel monitoring and environmental data for other lots aseptically filled on lines **(b)(4)** and **(b)(4)**. Also indicate the changes you will make to your environmental monitoring program procedures to ensure that samples taken accurately reflect the level of environmental control present during manufacturing.

4. Your firm failed to control rejected in-process materials under a quarantine system, to prevent their use in manufacturing or processing operations for which they are unsuitable (21 CFR 211.110(d)).

Your procedure MF0502.00 **(b)(4)** *Inspection Machines* for the online semi-automated visual inspection of vials allows **(b)(4)** to reinspect rejected units and place them with acceptable units. This procedure does not require operators to quarantine initially rejected units for later reinspection, account for the number of units that are subjected to reinspection, or document the difference between the initial inspection results and reinspection results. Accordingly, the procedure is inadequate to ensure that potentially defective or otherwise unsuitable **(b)(4)** units are not reintroduced into the manufacturing process.

In your response, you propose to rewrite procedure MF0502.00 to create an indeterminate status after detecting "anomalous" units **(b)(4)** semi-automated visual inspection process. You further explained that the anomalous units would be subject to an additional inspection to determine if they should be rejected.

Your response is inadequate because you have not provided a justification for retaining units that fail your firm's visual inspection requirements.

5. Your firm failed to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity (21 CFR 211.160(b)).

You lack scientifically sound and appropriate sampling plans for inspection and analytical activities conducted at your facility. For example, you do not inspect all reserve samples from each lot selected for the yearly visual examination to identify any evidence of drug product deterioration. There is no scientific justification for the number of reserve samples you select for examination. You also lack appropriate statistical sampling plans for the inspection of **(b)(4)** paper label rolls as described in your Monograph Y-011-AM. Statistically appropriate sampling plans provide assurance that the samples you select for inspection or analysis are representative of the lot or batch from which they are drawn.

In response to this letter, provide your detailed assessment and justification for each statistical sampling plan used for materials, processes, and products at your facility.

Post-Market Reporting Violations

The inspection also revealed that Hospira Inc. failed to submit field alert reports to FDA as required by section 505(k) of the FD&C Act, 21 U.S.C. 355(k), 21 CFR 314.81(b)(1) (new drug applications), and 21 CFR 314.98 (abbreviated new drug applications). For example, you failed to submit a field alert report after discovering extensive label deterioration. You received numerous complaints indicating label adhesion and deterioration defects, and performed retention sample evaluations between April 20, 2015, and June 25, 2015 in connection with such complaints. For example, your investigation of azithromycin ADD-Vantage, lot 49335DD, determined that 148 out of **(b)(4)** retain samples had varying degrees of adhesion defects. Further, your investigation showed at least 8 different lots of different products had significant label deterioration. Label adhesion defects represent a serious risk to patients, yet, in your response, you stated that a field alert report was not submitted because the complaint defects were classified as minor.

Repeat Violations at Multiple Sites

FDA cited similar CGMP violations at other facilities in your company's network.

1. Hospira Healthcare India Pvt., Ltd. FEI 3008386908: Warning Letter 320-13-18 was issued May 28, 2013. Charges included failure to follow appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile.
2. Hospira, Inc., FEI 1021343 and FEI 1048698: Warning Letter 10-ATL-12 wasissued for two U.S. facilities on April 12, 2010. Charges included failure to have adequate written procedures for production and process controls designed to assure that drug products have the identity, strength, quality, and purity they purport or are represented to possess.
3. Hospira Australia Pty, Limited, FEI 3001174929: Warning Letter 320-14-15 was issued on September 26, 2014. Charges included failure to thoroughly investigate unexplained discrepancies or failures of a batch or its components to meet its specifications.
4. Hospira S.p.A., FEI 3004640070: Warning Letter 320-15-08 wasissued for your Italy facility on March 31, 2015. Charges included failure to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile.

These repeated failures at multiple sites demonstrate that your company's oversight and control over the manufacture of drugs is inadequate.

Your executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance. You should immediately and comprehensively assess your company's global manufacturing operations to ensure that systems and processes, and ultimately, the products manufactured, conform to FDA requirements.

Conclusion

Violations cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these violations, for determining the causes, for preventing their recurrence, and for preventing other violations in all your facilities.

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b) and allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

Correct the violations cited in this letter promptly. Failure to promptly correct these violations may result in legal action without further notice including, without limitation, seizure and injunction. Unresolved violations in this warning letter may also prevent other Federal agencies from awarding contracts.

Until these violations are corrected, we may withhold approval of pending drug applications listing your facility. We may re-inspect to verify that you have completed your corrective actions. We may also refuse your requests for export certificates.

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

Send your electronic reply to Miguel.Hernandez@fda.hhs.gov or mail your reply to:

Miguel Hernandez
Compliance Branch Director
U.S. Food and Drug Administration
Kansas City District Office
8050 Marshall Drive, Suite 205
Lenexa, Kansas 66214

Please identify your response with FEI 1925262.

Sincerely,
/S/
Cheryl A. Bigham
District Director
Kansas City District
Office of Regulatory Affairs