U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Hospira Australia Pty Ltd. 9/26/14

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

Warning Letter

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WL: 320-14-15

September 26, 2014

Mr. Andrew Holder
Vice President Operations
Hospira Australia Pty, Limited
1 Lexia Place, Mulgrave
Victoria 3170, Australia

Dear Mr. Holder:

During our inspection of your pharmaceutical manufacturing facility, Hospira Australia Pty, Limited located at 1 Lexia Place Mulgrave, Victoria 3170, Australia, dated February 24 through March 1, 2014, investigators from the U.S. Food and Drug Administration (FDA) identified significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211. These violations cause your drug product(s) to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 351(a)(2)(B), in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP.

We have conducted a detailed review of your firm's response dated March 21, 2014 and note that it lacks sufficient corrective actions. We also acknowledge receipt of your firm's additional correspondence dated May 21, 2014.

Our investigators observed specific violations during the inspection, including, but not limited to, the following:

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

   a. Several out-of-specification (OOS) results for the impurity **(b)(4)** (**(b)(4)**) from the stability studies of multiples batches of **(b)(4)** Injection were inadequately investigated.

In April 2013, testing at the **(b)(4)** stability interval for batch **(b)(4)** resulted in OOS values for **(b)(4)**. The results obtained for one of the three vials tested in duplicate were OOS, with values of **(b)(4)**% and **(b)(4)**% (specification: avg. of 3 vials NMT **(b)(4)**%). Your firm's investigation PRID 128835, initiated on April 29, 2013, concluded that the **(b)(4)** in the **(b)(4)** of the vials was the cause for the OOS, but no action was taken with respect to the affected batch. This investigation also referenced an earlier OOS result of **(b)(4)**% for the same impurity for batch **(b)(4)** at the 12-month stability interval. You concluded that the OOS for batch **(b)(4)** was an isolated event and no action was taken with respect to the affected batch.

In December 2013, investigation PRID 159836 was opened to evaluate the **(b)(4)** content in the **(b)(4)**. **(b)(4)** vials from stability batch **(b)(4)** were tested for **(b)(4)** content resulting in values ranging from **(b)(4)**% to **(b)(4)**% in the **(b)(4)**. The investigation stated "if the **(b)(4)** levels are above **(b)(4)**%, then the **(b)(4)** results are either above the specification (of NMT **(b)(4)**%) or very close to the specification."

In January 2014, testing at the **(b)(4)** stability interval for batch **(b)(4)**, resulted in OOS values for **(b)(4)**. The results obtained for one of the three vials tested were **(b)(4)**% and **(b)(4)**%. As part of this investigation, **(b)(4)** additional vials were tested and three rendered OOS values of **(b)(4)**%, **(b)(4)**%, and **(b)(4)**%.

An "Interim Process Validation Study Report," approved on February 28, 2014, concluded that two of the **(b)(4)** filling needles (#**(b)(4)** and #**(b)(4)**) may be the cause of vials with greater than **(b)(4)**% **(b)(4)** in the **(b)(4)**. We are concerned with the potential vial-to-vial variability in **(b)(4)** levels in the **(b)(4)**, which was found by your firm to directly effect the level of the **(b)(4)** impurity present in your finished product.

We acknowledge your firm's commitment to resolve the issues related to increased levels of **(b)(4)** in your product; however, we remain concerned that you do not know the actual levels of this impurity in distributed lots of **(b)(4)** Injection.

In response to this letter, provide evidence for your investigation conclusions related to the increase in **(b)(4)**, including a review of all opened and closed OOS investigations associated with this problem, along with your detailed corrective action plan. Also, provide justification for your practice of averaging individual results of OOS **(b)(4)** impurity values.

Inform this office of any additional action you plan to take with respect to the batches distributed in U.S. market.

b. No effective corrective action and preventive action plan were implemented to address the recurrent findings of foreign matter (specifically, **(b)(4)** particles) in **(b)(4)** injection drug product.

Our inspection revealed that in May 2012, your firm received a notification that visible particles were detected in **(b)(4)** injection finished product. The information also included that the visible **(b)(4)** particles were potentially associated with the **(b)(4)** form of **(b)(4)** active pharmaceutical ingredient (API). However, your investigation into this issue did not observe visible particles in reserve samples examined.

In September 2012, your firm received a customer complaint and initiated investigation PRID 99517 that confirmed that **(b)(4)**-like particles were present in reserve samples of **(b)(4)** injection batch **(b)(4)**. The investigation PRID 99517 also reported **(b)(4)**-like particles found in **(b)(4)** injection batch **(b)(4)**. This investigation concluded that the root cause could not be determined and that the description of particles did not appear to correlate with particles reported in the May 2012 notification. Nevertheless, on December 12, 2013, (15 months after the investigation was initiated), your firm confirmed that the **(b)(4)** isolated from the **(b)(4)** injection drug product were identified as both **(b)(4)** and **(b)(4)** forms of the API.

It was not until March 2014, that your firm issued a "Dear Healthcare Provider" letter recommending a visual inspection of the vials prior to use and a filter before administration.

Despite the investigational efforts from 2012 to 2014, your firm has not implemented adequate corrective action related to the presence of **(b)(4)** particles in your **(b)(4)** injection drug. We remain concerned that **(b)(4)** particles are intermittently observed in reserve samples, and no validated analytical method to detect the presence of the **(b)(4)** and/or **(b)(4)** in the API or finished product has been established. You are responsible for ensuring the quality, safety, and integrity of your firm's products. A fundamental part of this responsibility is preventing the release of defective products and assuring timely resolution of problems that occur.

In response to this letter, provide your firm's plan to prevent or mitigate the formation of **(b)(4)** particles in batches of **(b)(4)** injection drug. Also, provide a copy of the proposed analytical method to detect the presence of these **(b)(4)** particles.

2. Your firm failed to establish written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess (21 CFR 211.100(a)). For example,

The information related to the increase in levels of **(b)(4)** (refer to #1a above) raises concern about the validation of your **(b)(4)** manufacturing process. Your firm identified a correlation between the increase in the **(b)(4)** impurity and **(b)(4)** exceeding **(b)(4)**%. However, this was not addressed in a subsequent study to demonstrate that the process remains in a state of control. Provide a comprehensive protocol for the revalidation of your process as it relates to **(b)(4)** process (Filling Stage) in removing **(b)(4)** in the **(b)(4)**.

3. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42(c)(10)(iv)).

Your firm does not have a scientific justification for alternating the use of **(b)(4)** and **(b)(4)** for sampling by settle plates and swabs on different **(b)(4)**. We are concerned that you may have underestimated the number and type of bacterial species that are present on the **(b)(4)** you use **(b)(4)** because you have no data to support the equivalent sensitivity and efficiency of bacterial recovery on the **(b)(4)** media as for **(b)(4)**. FDA expects that microbial culture media used for environmental monitoring be validated as capable of recovering fungi (i.e., yeast and molds), as well as bacteria. Appropriate trending of environmental monitoring data depends on consistent methods to provide an indication of the amount and type of microbiological organisms present.

In response to this letter, provide a copy of your report comparing the **(b)(4)** and **(b)(4)** media if you intend to use them interchangeably, or an alternative program that more reliably detects both kinds of microbes. We acknowledge your firm's commitment to perform a risk assessment to determine the appropriate frequency of **(b)(4)** settle plate monitoring. Provide a copy of this assessment.

Our inspectional documented that your firm lacks an effective corrective action and preventive action (CAPA) program, which is required in part by CGMP regulations 21 CFR 211.192, 211.198, and 211.180(e). A CAPA program is essential to support a consistent state of control. We urge you to improve your CAPA program to better enable your production and quality units to fulfill their critical responsibility of delivering consistent product quality. Please review FDA CGMP regulations and related FDA guidance on this topic: Guidance for Industry, ICH Q10 Pharmaceutical Quality System (see, e.g., section IV.B).

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence and the occurrence of other violations.

If, as a result of receiving this warning letter or for other reasons, you are considering a decision that could reduce the number of finished drug products produced by your manufacturing facility, FDA requests that you contact CDER's Drug Shortages Program immediately, as you begin your internal discussions, at drugshortages@fda.hhs.gov so that we can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Program also allows you to meet any obligations you may have to report discontinuances in the manufacture of your drug under 21 U.S.C. 356C(a)(1), 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. In appropriate cases, you may be able to take corrective action without interrupting supply, or to shorten any interruption, thereby avoiding or limiting drug shortages.

Until all corrections have been completed and FDA has confirmed corrections of the violations and your firm's compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug product manufacturer. In addition, your failure to correct these violations may result in FDA refusing admission of articles manufactured at Hospira Australia Pty Limited, Mulgrave, Victoria, Australia into the United States under Section 801(a)(3) of the Act, 21 U.S.C. 381(a)(3). The articles may be subject to refusal of admission pursuant to Section 801(a)(3) of the Act, 21 U.S.C. 381(a)(3), in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of Section 501(a)(2)(B) of the Act, 21 U.S.C. 351(a)(2)(B).

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct and prevent the recurrence of violations, and provide copies of supporting documentation. If you cannot complete corrective actions within fifteen working days, state the reason for the delay and the date by which you will have completed the corrections. Additionally, if you no longer manufacture or distribute the drug product(s) at issue, provide the date(s) and reason (s) you ceased production. Please identify your response with FEI # 3001174929.

Please send your reply to:

Rafael Arroyo
Compliance Officer
FDA/CDER/OC/OMPQ/DIDQ
10903 New Hampshire Ave.
White Oak Building 51, Room 4235
Silver Spring, MD 20993

Sincerely,

/S/
Thomas Cosgrove, J.D.
Acting Director
Office of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research