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

Hospira Spa 3/31/15

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: 320-15-08

March 31, 2015

Mr. Michael Ball
Chief Executive Officer
Hospira S.p.A.
275 N. Field Drive
Lake Forest, IL 60045
USA

Dear Mr. Ball:

During our May 5-9 and 12-13, 2014 inspection of your pharmaceutical manufacturing facility, Hospira S.p.A., located at Via Fosse Ardeatine 2, Liscate, Italy, 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 products 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 June 4, 2014 and note that it lacks sufficient corrective actions. We acknowledge receipt of your firm's correspondence dated August 4, 2014, October 2, 2014, December 4, 2014, and February 9, 2015

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

1. Your firm failed to establish and 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)).

Your firm did not evaluate all critical operations during dynamic airflow studies to determine risk to product sterility.

a) Your firm did not evaluate significant aseptic interventions during dynamic airflow studies (smoke studies) to determine how the movement of air and personnel during aseptic operations could pose risks to product sterility. For example,

i. Your smoke studies did not evaluate the impact of operators pushing **(b)(4)** vials down a chute while simultaneously removing a **(b)(4)** located **(b)(4)** the chute to load vials in the designated **(b)(4)**. The inspection documented that **(b)(4)** from the vials during this **(b)(4)** vial transfer operation, potentially exposing the product in the vials to contaminants from personnel or the surrounding environment. In addition, during our inspection, the investigator observed operators reaching over the **(b)(4)** vials during this operation, an action which could compromise product sterility by introducing microbiological contaminants.

Your investigation on February 18, 2013, documented that you were aware of problems caused by the **(b)(4)** vial loading operation. *Exception report record, PR ID 119409*, noted that the **(b)(4)** vial loading operation frequently results in rough aseptic transitions. However, our investigator observed operators continuing this practice over a year after you closed PR ID119409. It did not appear that you had acted on your findings to correct this problem or prevent its recurrence, and the sterility of your products may have been compromised in the meantime.

ii. You did not perform smoke studies to demonstrate unidirectional airflow for set-up activities of the aseptic fill line or for the **(b)(4)** transfer of **(b)(4)** vials from the vial holding area to the **(b)(4)**. Your smoke studies also did not show unidirectional airflow above the un-stoppered vials that pass **(b)(4)** the stopper loading chute. Without smoke study data to demonstrate that air flows unidirectionally over these critical operations and processing steps, you cannot show that your processes are designed to prevent microbiological contamination of your products or provide adequate assurance of product sterility.

iii. We also note that your stopper **(b)(4)** creates air turbulence in the area around the stopper loading chute, which could lead to additional opportunities for microbiological contamination.

The examples listed above show how disruptions to the unidirectional flow of air could lead to the contamination of product in exposed vials. We acknowledge your response that you have performed smoke studies, and made limited modifications to the operation in an effort to reduce risks posed by the design deficiencies identified in our inspection. For example, we note that you made some minor changes to reduce rocking of the **(b)(4)** during the **(b)(4)** vial transfer operation described above in 1. a) 1. However, your response is inadequate because you have not

committed to provide a thorough design assessment. You also failed to provide a video of the new smoke studies you indicated that you performed.

In response to this letter, please describe further design modifications you will make to mitigate the contamination hazards in your operation, including, but not limited to, the examples discussed above in examples 1. a)1-3. Also, provide a copy of the video/DVD depicting smoke studies you performed to demonstrate unidirectional airflow during the manufacturing operations described above.

b) Your firm rejected possible integral units (i.e., units with intact container/closure systems) from media fills without a written justification or explanation. For example, during media fill batch **(b)(4)** (June 2012), you rejected 5 vials as "tilted" and you also rejected 250 vials during the **(b)(4)** process without explanation or justification. Similarly, during media fill batch **(b)(4)** (December 2013), you rejected 21 vials as "tilted" and you also rejected 30 vials during the **(b)(4)** process without explanation or justification. During the inspection, your management told the investigator that the vials you rejected as "tilted" would likely be fully stoppered and integral. Your media fill batch records did not include any further rationale for rejecting these vials, although many of them were likely integral.

When you perform a final product inspection of units immediately following a media fill run, all integral units should proceed to incubation. Units found to have defects not related to integrity (e.g., cosmetic defects) should be incubated; units that lack integrity should be rejected. Erroneously rejected units should be returned promptly for incubation with the media fill lot. After incubation is underway, any unit found to be damaged should be included in the data for the media fill run because the units might be representative of drug product released to the market. Any decision to exclude non-integral units from the final run tally should be fully justified and you should fully explain the deviation in your media fill report. If a correlation emerges between difficult to detect damage and microbial contamination, you should conduct a thorough investigation to determine its cause.

We acknowledge that you completed a media fill performance qualification. However, your protocol, *Shut Down Media Fill Qualification Protocol KC4103-PQ*, is inadequate because it does not provide criteria that adequately defines when vials are to be rejected. In your response to this letter, provide your categorization criteria and justification for rejection of vials from a media fill.

These violations are similar to those found during the October 2012 inspection of your Irugattukottai, Sriperumburdur, India manufacturing site. Dynamic airflow study and media fill deficiencies were noted in Warning Letter (WL: 320-13-18), issued May 28, 2013. Your response to that warning letter stated that you implemented your *Global Quality Strategy* and *Global Quality Plan* in February 2013for your manufacturing facilities. Provide evidence of the effectiveness of your implemented global corrective actions and preventive actions.

2. 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).

For example, your firm failed to conduct a thorough investigation for 103 complaints for **(b)(4)** injection related to discoloration of **(b)(4)** or **(b)(4)** solution between November 1, 2011 and October 31, 2013, and a more recent complaint on April 3, 2014. Many customer complaints have

stated that the product changed to a **(b)(4)** color, rather than the normal "**(b)(4)**" appearance. You concluded that the root cause for the discoloration was the **(b)(4)** of the product. Your investigation is inadequate because you failed to evaluate the impact that **(b)(4)** may have on the quality of the product and to correlate the level of **(b)(4)** degradant with the amount of discoloration observed. Your investigation also failed to consider that the discoloration might have been caused by the failure to perform a step in the manufacturing process in an **(b)(4)** environment. Specifically, you mention that some vials may have **(b)(4)** as a result of them **(b)(4)** shelf during the stoppering manufacturing phase. You state that the unloading of the vials from the **(b)(4)** to **(b)(4)** is not performed **(b)(4)** and that there is a potential for **(b)(4)** ingress.

We acknowledge your commitment to continue the investigation of **(b)(4)** levels in **(b)(4)** vials per protocol KC3601-ENG. However, your response does not adequately address the impact of the effect of **(b)(4)** in that your medical assessment lacks an evaluation of whether the degradant poses a risk to patients.

In addition, your firm has not adequately addressed vulnerabilities in your manufacturing process that can be addressed to prevent the potential ingress of **(b)(4)**.

Please provide a protocol and timeline for the assessment of your manufacturing process to control the level of **(b)(4)** in the vial **(b)(4)**. Also, include your scientific rationale that the level of the **(b)(4)** degradant has no meaningful impact on product quality.

Please also explain whether your firm will be identifying and quantifying the **(b)(4)** degradant, and any other major degradants, and if you have determined that appropriate specification limits should be established.

In your response, you indicate that your appearance specification (**(b)(4)**) is subjective. Please explain how you intend to qualify the appearance specification for the **(b)(4)** finished product.

3. Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b)).

Specifically, your high performance liquid chromatography (HPLC) and gas chromatography (GC) data acquisition software, TotalChrom®, did not have sufficient controls to prevent the deletion or alteration of raw data files. During the inspection, the investigator observed that the server that maintains electronic raw data for HPLC and GC analyses (the J drive) contains a folder named "Test," and that chromatographic methods, sequences, and injection data saved into this folder can be deleted by analysts. The investigator also found that data files initially created and stored in the "Test" folder had been deleted, and that back-up files are overwritten **(b)(4)**.

In addition, because no audit trail function was enabled for the "Test" folder, your firm was unable to verify what types of injections were made, who made them, or the date or time of deletion. The use of audit trails for computerized analytical instrumentation is essential to ensure the integrity and reliability of the electronic data generated.

Your response indicates that you have added computer controls to prevent the deletion of folders and files in the J drive for electronic raw data. However, you provide no evidence demonstrating how your firm will prevent deletion of newly created folders and files in each of your computer

systems. We acknowledge your commitment to hire a third party consultant to address the inadequacies of your data systems. However, your response is inadequate as it fails to address how you will enable and review audit trail functions for all of your analytical computer systems.

In response to this letter, provide specific details about the comprehensive controls in place to ensure the integrity of electronic raw data generated by all computer systems used to support the manufacture and testing of drug products. Your response should demonstrate an understanding of your processes and the appropriate controls needed for each stage of manufacture that generates electronic raw data, as well as for your laboratories.

We identified a similar inspectional finding during the December 2013 inspection of your Irugattukottai, Sriperumburdur, India, manufacturing facility and noted this finding in an Untitled Letter, issued April 16, 2014. Explain how your firm will implement global corrective actions and preventive actions concerning computer controls and provide a timeline for implementation.

4. Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards (21CFR 211.194 (a)).

a) Our investigators identified your practice of performing trial sample injections for HPLC analyses. For example, trial injections of **(b)(4)** stability samples (lot **(b)(4)** and **(b)(4)**) were acquired in the “Test” folder prior to official testing. Immediately after the trial injections were completed, the official samples were analyzed. The trial injection raw data, captured in the back-up files, were deleted from the test folder.

b) You retested analytical samples without reporting original results in laboratory records. Because of this practice, you are unable to assure that all raw data generated is included and evaluated when you review analytical test results to determine whether your products conform with their established specifications and standards.

For example, **(b)(4)** lot **#(b)(4)** failed the content uniformity test, where sample #8 of **(b)(4)** resulted with a value **(b)(4)**%. Your firm proceeded to retest the sample on a different instrument without initiating an out-of-specification (OOS) investigation, as required by your chemistry laboratory investigation standard operating procedure, SOP QAG-097. These injections were not reported as part of the original data or included in your laboratory investigation report. Subsequently, the electronic raw data files were deleted. Moreover, there is no procedure describing the use of re-injections for standards or samples on a different system to verify an original result.

Your response indicates that the “Test” folders were used to equilibrate the analytical columns and to determine when the system was ready for analysis. It is your responsibility to follow validated methods that include specific procedures to assess the suitability of your instruments. Neither the ICH document Q2R, "Validation of Analytical Procedure: Text and Methodology," nor the United States Pharmacopoeia (USP), General Chapter <1058>, "Analytical Instrument Qualification," provides for use of “trial” injections as part of a validated method. Your rationale that you retested failing samples on different analytical instrumentation to evaluate system suitability is inadequate. See USP General Chapter <621>, “Chromatography,” which discusses system suitability tests and the use of replicate injections of a standard preparation or other standards to determine if the requirements for precision are satisfied.

These are serious CGMP violations that demonstrate that your quality system does not adequately ensure the accuracy and integrity of the data you generate to support the safety, effectiveness, and quality of the drug products you manufacture. We acknowledge your commitment to work with a third party consultant to conduct a comprehensive assessment of your firm's manufacturing, laboratory, and quality operations. However, it is your responsibility to ensure that the third party audit includes a full evaluation of sophisticated electronic systems and the potential for manipulation of such systems. In response to this letter, provide the following to the Agency:

1. A comprehensive evaluation of the extent of the inaccuracy of the reported data. As part of your comprehensive evaluation, provide a detailed action plan to investigate the extent of the deficient documentation practices noted above;

2. A risk assessment regarding the potential effect on the quality of drug products. As part of your risk assessment, determine the effects of your deficient documentation practices on the quality of the drug product released for distribution; and

3. A management strategy for your firm that includes the details of your global corrective action and preventive action plan.

a) As part of your corrective action and preventive action plan, describe the actions you have taken or will take, such as contacting your customers, recalling product, conducting additional testing and/or adding lots to your stability programs to assure stability, monitoring of complaints, or other steps to assure the quality of the product manufactured under the violative conditions discussed above.

b) In addition, as part of your corrective action and preventive action plan, describe the actions you have taken or will take, such as revising procedures, implementing new controls, training or re-training personnel, or other steps to prevent the recurrence of CGMP violations, including breaches of data integrity.

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 S.p.A located at Via Fosse Ardeatine 2, Liscate, Italy 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 products at issue, provide the date(s) and reason(s) you ceased production. Please identify your response with FEI # 3004640070.

Please send your reply to:

Christina Alemu-Cruickshank
Compliance Officer
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Manufacturing Quality
Division of Drug Quality I
White Oak, Building 51 room 4233
10903 New Hampshire Ave.
Silver Spring, MD 20993

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

More in Compliance Actions and Activities (/ICECI/EnforcementActions/default.htm)

Warning Letters (/ICECI/EnforcementActions/WarningLetters/default.htm)

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