Inspections, Compliance, Enforcement, and Criminal Investigations

Hospira Inc. 5/9/13

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Chicago District
550 West Jackson Blvd., 15th Floor
Chicago, Illinois 60661
Telephone: 312-353-5863

May 9, 2013

WARNING LETTER

CHI-12-13

VIA UPS NEXT DAY

F. Michael Ball
Chief Executive Officer
Hospira, Inc.
275 N. Field Drive
Bldg. 2
Lake Forest, Illinois 60045

Dear Mr. Ball:

United States Food and Drug Administration (FDA) investigators conducted an inspection of your firm, Hospira, Inc., located at 275 N. Field Drive in Lake Forest, Illinois from January 29, 2013 through February 7, 2013. The investigators determined that Hospira, Inc. is a manufacturer of several Class II medical devices, including GemStar™ (ambulatory infusion system), Plum A+™ Infusion System, LifeCare PCA™ Infusion System, and the Symbiq™ Infusion Pump. Under Section 201(h) of the Federal Food, Drug and Cosmetic Act (the Act) [21 U.S.C. 321(h)], these products are defined as devices because they are intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or are intended to affect the structure or function of the body.

The inspection revealed that these devices are adulterated within the meaning of Section 501(h) of the Act [21 U.S.C. 351(h)], in that the methods used in, or the facilities or controls used for, their manufacturer, processing, packing, or holding are not in conformity with the current Good Manufacturing Practice (CGMP) requirements of the Quality System (QS) Regulation found at Title 21, Code of Federal Regulations (CFR), Part 820.

We received an interim response, dated February 14, 2013 from Zena G. Kaufman, Senior Vice President of Global Quality, regarding your firm's Device Compliance Master Plan, and a comprehensive written response, dated March 1, 2013, was received from Brian J. Smith, Senior

Vice President, General Counsel and Secretary, and Ms. Kaufman on behalf of Hospira. The response detailed your firm's corrective actions to the observations noted on the Form FDA-483, Inspectional Observations, issued to you on February 7, 2013 and included your firm's Compliance Master Plan. In addition, FDA acknowledges your firm's Global Device Strategy which was discussed with the Agency during meetings held on March 20, 2013 and May 2, 2013 and publicly unveiled on May 1, 2013. This long-term strategy includes plans to retire the GemStar and Symbiq Infusion Systems and replacement of these devices with remediated Plum A+ Infusion Systems and QCore Medical's Sapphire Infusion Pump, respectively. The plan also includes the retirement of Plum and PCA-branded legacy Infusion Systems and replacement with remediated Plum A+ Infusion Systems. FDA has significant concerns, however, with the timeliness of your firm's plan to replace Symbiq, GemStar and other legacy infusion pumps with remediated Plum A+ infusion pumps. We address these responses below, in relation to each of the noted violations. The violations include, but are not limited to, the following:
Design Controls:

1. Failure to establish and maintain adequate procedures to ensure that the design requirements relating to a device are appropriate and address the intended use of the device, including the needs of the user and patient. The procedures shall include a mechanism for addressing incomplete, ambiguous, or conflicting requirements. The design input requirements shall be documented, reviewed, and approved, as required by 21 CFR 820.30(c). Specifically, the design control of your Plum A+ infusion pump is inadequate in that:

a. Battery specifications are not clearly defined as design inputs. Examples of battery specifications that are not defined as design inputs are: **(b)(4)** and **(b)(4)**.
b. The type of battery, **(b)(4)**, was not specified as a design input.

2. Failure to establish and maintain adequate procedures for verifying device design to confirm that the design output meets the design input requirements. The results of the design verification, including identification of the design, methods, the date, and the individuals performing the verification, shall be documented in the design history file (DHF), as required by 21 CFR 820.30(f). Specifically, the design verification of your Plum A+ infusion pump is inadequate in that it did not verify that your battery could consistently meet specifications over time. Design verification studies did not prove that your battery would last for the life expectancy of the Plum A+ infusion pump, which is 10 years.

We have reviewed your response regarding points 1 and 2 and have determined that it is inadequate because although you commit to installing new batteries in all Plum A+ products, this process is not expected to start until August 2013 and is not expected to be completed until the end of the first quarter of 2015. Your response fails to address interim actions for the Plum A+ pumps that are on the market that contain batteries with the potential to fail. In addition, the response does not include documents to support the statements made in the response. For example, the response indicates that a corrective action, CAPA **(b)(4)**, had been implemented regarding the Plum A+ battery, and a new design specification, **(b)(4)**, was implemented; however, these documents were not included with the response for review.

3. Failure to establish and maintain adequate procedures for validating the device design, including risk analysis, as required by 21 CFR 820.30(g). For example, your risk assessment, #**(b)(4)**, dated February 4, 2013, for "GemStar Backward Motor Movement Issue for Overdose" is inadequate in that the risk level was calculated to be Acceptable with Justification (AWJ); however, the risk assessment does not document the reasons why the risk level is AWJ when the risk assessment indicates that there are no design risk control measures in place that mitigate the hazard of overdosing.

We have reviewed your response and have determined that it is inadequate because your response does not include rationale as to why the risk analysis was determined to be Acceptable with Justification when your firm had no measures in place to mitigate the risk which has the potential

for patient overdose.

4. Failure to establish and maintain plans that describe or reference the design and development activities and define responsibility for implementation, as required by 21 CFR 820.30(b). The plans shall be reviewed, updated, and approved as design and development evolves. Specifically, your firm failed to update the Design and Development Plan for "Project: GemStar Rollback (CAPA **(b)(4)**" which was opened on April 18, 2012 to address the backward motor movement issue with GemStar infusion pumps and was found to be in the design 'concept' phase as of February 5, 2013. Your firm's plan was not updated as it evolved and when the following plan milestones were not met:

Milestones	**Dates**
Design Input Review complete	Q2, 2012
Design Output Review complete	Q2, 2012
First Article of Inspection of Prototypes complete	Q2, 2012
Verification Report Complete	Q3, 2012
Design Transfer Review complete	Q3, 2012
CR Structure Package approved / released	Q3, 2012
First Lot to Stock	Q4, 2012

We have reviewed your response and have determined that the adequacy of your response cannot be determined at this time because the proposed corrective actions, including design change procedure revisions and a review of all serialized device Design and Development Plans to ensure compliance, are not yet complete.

Corrective and Preventive Action:

5. Failure to establish procedures for corrective and preventive action, as required by 21 CFR 820.100(a). For example:

a. Your CAPA system implementation is inadequate in that you do not trend component failures. For example,

   i. Your firm did not analyze or trend **(b)(4)** component failures identified in your Plum A+ infusion pump complaint investigations. Your firm received **(b)(4)** on APP board" **(b)(4)** complaints between January 1, 2011 and January 30, 2013. As of February 1, 2013, your firm has not addressed the issue which causes the Plum A+ infusion pump to stop functioning.

   ii. Your firm failed to follow CAPA procedures which state that each site will track and trend event and root cause for use in management review meetings. For example, Hospira's San Jose, California site repaired/refurbished 20,067 infusion pumps since July 17, 2012, and the site does not track and trend the failed component replacements to provide to Hospira's Lake Forest, Illinois corporate site where management review meetings are conducted. In addition, the failed components are not identified as a data source for analysis nor are they trended in your CAPA system to assess whether a preventive or corrective action is indicated and to ensure that components are performing according to infusion pump design specifications.

b. CAPA **(b)(4)** was opened on May 25, 2011 to address Plum A+ pump battery failures which can cause a delay or interruption of critical therapy. Your firm has failed to implement the identified corrective actions in this CAPA, such as a software upgrade to change the risk profile; battery replacement to reduce the probability of occurrence; battery supplier approval with increased controls; and notification to customers, despite

the fact that your firm has received 311 complaints for code E321 documenting battery failures and 11 MDRs documenting a stoppage of critical drug delivery as of January 31, 2013.

c. CAPA **(b)(4)** has failed to address Error X091, Backward Motor Movement, for the Gemstar pump which is a malfunction alarm code that indicates backward motor movement and causes the pump to stop infusion which can lead to a delay or interruption of therapy. CAPA **(b)(4)** was opened on July 1, 2010 to address 232 complaints that were received for Gemstar pumps from June 1, 2008 to June 1, 2010 for the X091 code. Between November 1, 2010 and October 31, 2012, an additional 448 related complaints and one MDR report were received, and for the time period from January 28, 2011 through January 28, 2013, 496 complaints for X091, Backward Motor Movement, have also been received while this CAPA has remained open.

6. Failure to establish and maintain procedures for implementing corrective and preventive actions (CAPA) to include requirements for analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems, as required by 21 CFR 820.100(a)(1). Specifically, your complaint trending is inadequate in that you had approximately 33,238 device complaints between July 17, 2012 and January 29, 2013, and you do not trend your complaint "analysis" codes which are determined as a result of your investigation of returned devices to evaluate whether a corrective or preventive action would be indicated. For example,

a. Omniflow infusion pump: Review of the "analysis" data field for Omniflow complaints revealed failures, including blown fuses, motor base assemblies, power supply printed wire assemblies, as well as battery and transducer failures.
b. Plum A+ infusion pump: Review of the "analysis" data field for Plum A+ complaints revealed failures of the bubble sensor printed wire assembly within the printed circuit board, battery, touch key pad assembly and front case assembly.

7. Failure to establish and maintain corrective and preventive action procedures that include requirements for ensuring the corrective and preventive action is effective, as required by 21 CFR. 820.100(a)(4). Specifically, your firm documented an "effectiveness check is not required" for 18 of the last 20 "closed" Lake Forest medical device CAPAs.

We have reviewed your response regarding points 5, 6 and 7 and have determined that the adequacy of your response cannot be determined at this time because many of the promised corrective actions with regard to CAPA are currently in progress. For example, your CAPA Remediation Plan, which is expected to address gaps in your CAPA process from a systems process, is not expected to be generated until April 15, 2013. In addition, numerous revisions to **(b)(4)**, "Exception Reporting (ER) and CAPA Management Procedure" with respect to the inclusion of component failures as inputs into the CAPA system, and clarification on definitions and the escalation process, appropriate CAPA inputs, and effectiveness checks, are not expected to be completed until May 31, 2013.

Records:

8. Failure to review, evaluate and investigate, where necessary, complaints involving the possible failure of a device to meet any of its specifications, as required by 21 CFR 820.198(c). For example, your firm's complaint handling system is inadequate in that:

a. Your repair facility replaced 58,438 failed components in 20,067 infusion pumps from July

2012 to January 2013, and these device component failures were not entered into your complaint system when a complaint is defined, by your firm's procedures, to be: any communication that alleges deficiencies related to the reliability, durability, or performance of a product after its release for distribution.

b. Your infusion pump complaint investigations are inadequate in that you replace components and close complaints without further investigation to determine if, for example, the failure is expected, the complaint represents a design, manufacturing, or supplier issue, or a problem that is occurring across product families. For example, between January 1, 2009 and January 30, 2013, you had **(b)(4)** on APP board" **(b)(4)** failures for the Plum A+ infusion pump, and no further investigation was conducted after the component was replaced.

We have reviewed your response and have determined that it is inadequate because it lacks detail on how your firm's complaint handling system will be revised to ensure complaints are investigated moving forward.

Purchasing Controls:

9. Failure to establish and maintain procedures that ensure records of acceptable suppliers, contractors, and consultants are maintained, as required by 21 CFR 820.50(a)(3). Specifically, your records for "G", a supplier of batteries for Plum A+, PCA Lifecare and Plum XLD devices, were not adequately maintained. For example, an audit of the supplier, conducted March 18, 2011, revealed three (3) major observations which are to be tracked for proper closure based on supplier CAPA plan according to your supplier evaluation procedure, **(b)(4)**; however, an updated action plan, dated January 10, 2012, showing that all major observations had been closed, was not included with the supplier's audit file.

We have reviewed your response and have determined that it is inadequate because it does not specifically address the issue of adequate record maintenance for suppliers.

Document Controls:

10. Failure to establish document control procedures, as required by 21 CFR 820.40. For example, there is conflicting information in your Plum A+ complaints. Specifically, the designated root cause field on the complaints indicates "not applicable"; however, the investigation summary contains a root cause. The information contained in the investigation summary section is not tracked and trended in your CAPA system.

We have reviewed your response and have determined that the adequacy of the response cannot be determined at this time because the corrective actions with respect to revisions to the Complaint Summary Form are not yet complete. In addition, the response does not clearly indicate how you intend to revise your Complaint Summary Form to address this concern.

Medical Device Reporting:

Our inspection also revealed that your GemStar™ (ambulatory infusion system), Plum A+™ Infusion System; LifeCare PCA Infusion System; and the Symbiq™ Infusion Pump are misbranded under Section 502(t)(2) of the Act 21 USC 352 (t)(2), in that your firm failed or refused to furnish material or information respecting the devices that is required by or under Section 519 of the Act, 21 USC 360i, and 21 CFR Part 803 – Medical Device Reporting (MDR) Regulation. Significant deviations include, but are not limited to:

11. Failure to include in your firm's 3500A reports, known or reasonably known information about the outcome attributed to the adverse event, as required by 21 CFR 803.52(b)(2).

For example: Complaints 851299, 20678, 11781 and 12384 refer to an attributed outcome of

death that was not checked in Box B2 of the 3500A. The information was initially known to your firm and should have been provided in the initial MDR submitted to FDA.

We reviewed your firm's response, dated February 14, 2013, and conclude that is not adequate. Although your firm submitted supplemental MDRs to FDA that provided the correct outcome attributed to the event in Block B2 of the 3500A form, the procedure provided in your firm's response to address this issue does not describe the corrective actions taken to ensure that complete MDRs will be submitted to FDA.

12. Failure to adequately develop, maintain and implement written MDR procedures, as required by 21 CFR 803.17. For example, after reviewing your firm's MDR procedure titled "Post Marketing Medical Device Reporting to the FDA," SOP **(b)(4)**, Approval date November 15, 2012, the following issues were noted:

a. SOP **(b)(4)**, Rev. R03 does not establish internal systems that provide for timely and effective identification, communication, and evaluation of events that may be subject to MDR requirements. For example:

i. There are no definitions of what your firm will consider to be a reportable event under 21 CFR Part 803. To facilitate the correct interpretation of reportable event and to assure the quality of MDR submissions, the procedure should include definitions based on 21 CFR 803.3 for the terms "become aware," "caused or contributed," "malfunction," "MDR reportable event," and definitions for the terms "reasonably known" and "reasonably suggests," found respectively in 21 CFR 80.50(b) and 803.20 (c)(1).

b. SOP **(b)(4)**, Rev. R03 does not describe how it will address documentation and record-keeping requirements, including:

i. Documentation of adverse event related information maintained as MDR files.

ii. Systems that ensure access to information that facilitates timely follow-up and inspection by FDA as required by 21 CFR 803.17(a)(3).

You should take prompt action to correct the violations addressed in this letter. Failure to promptly correct these violations may result in regulatory action being initiated by the Food and Drug Administration without further notice. These actions include, but are not limited to, seizure, injunction, and/or civil money penalties. Also, federal agencies may be advised of the issuance of Warning Letters about devices so that they may take this information into account when considering the award of contracts.

Please notify this office in writing within fifteen (15) working days from the date you receive this letter of the specific steps you have taken to correct the noted violations, including an explanation of how you plan to prevent these violations, or similar violations, from occurring again. Include documentation of the corrective action you have taken. If your planned corrections will occur over time, please include a timetable for implementation of those corrections. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your response should be sent to: Carrie Ann Plucinski, Compliance Officer, Food and Drug Administration, 550 W. Jackson Blvd., 15th floor, Chicago, IL 60661. Refer to the Unique Identification Number (CMS case # 394420) when replying. If you have any questions about the content of this letter, please contact Ms. Plucinski at 312-596-4224.

Finally, you should know that this letter is not intended to be an all-inclusive list of the violations at

your facility. It is your responsibility to ensure compliance with applicable laws and regulations administered by FDA. The specific violations noted in this letter and in the Inspectional Observations, Form FDA-483 (FDA-483), issued at the close-out of the inspection may be symptomatic of serious problems in your firm's manufacturing and quality assurance systems. FDA expects your corporate management to undertake a comprehensive and global assessment of your operations immediately to ensure that medical devices conform to FDA requirements.

Sincerely,
/S/
Scott J. MacIntire
District Director

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