Cane S.p.A. 7/29/15

Department of Health and Human Services

Public Health Service
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

WARNING LETTER
JUL 29, 2015

VIA UNITED PARCEL SERVICE

Carlo Musso
Quality Director
Board Member
Cane S.p.A.
Via Cuorgne 42/a
Rivoli-Turino, 10098
Italy

Dear Mr. Musso:

During an inspection of your firm located in Rivoli-Turino, Italy, on February 16, 2015, through February 19, 2015, an investigator from the United States Food and Drug Administration (FDA) determined that your firm manufactures infusion pumps and infusion pump accessories, including the Crono S-PID-50 pump. Under section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. § 321(h), these products are 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 to affect the structure or function of the body.

This 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 manufacture, packing, storage, or installation are not in conformity with the current good manufacturing practice requirements of the Quality System regulation found at Title 21, Code of Federal Regulations (CFR), Part 820.

We received a response from a Quality Manager at your firm, dated March 10, 2015, concerning our investigator's observations noted on the Form FDA 483 (FDA 483), List of Inspectional Observations, which was issued to your firm. We address this response below, in relation to each of the noted violations. These violations include, but are not limited to, the following:

1. Failure to establish and maintain procedures for validating the device design, as required by 21 CFR 820.30(g). For example, your firm did not have a procedure or protocol for performing code testing on software used to control infusion pumps, written using **(b)(4)** software. Your firm failed to document test results, including the list of software defects found during code testing, because they were not recorded as they were discovered, nor were they accounted for in future code revisions, which can lead to unexplainable device malfunctions. Additionally, multiple pump repairs appeared to be related to failed firmware updates.

We reviewed your firm's response and conclude that it is not adequate. Your firm is writing and implementing a new software validation procedure based on FDA guidance documents. However, a software validation procedure was not provided with the response, and there was no discussion of a retrospective review of your software for your infusion pumps.

2. Failure to establish and maintain adequate procedures for receiving, reviewing, and evaluating complaints by a formally designated unit, as required by 21 CFR 820.198(a). For example:

   a. Your firm identified 501 repairs for Primary Immunodeficiency (PID) pumps in 2013 and 2014. 26 out of 30 repair and maintenance report records reviewed during the inspection were confirmed to include repairs that constituted complaints. These repairs, which included errors of piston operation and failures to sound alarms, had no evidence of complaint investigation or evaluation for MDR reporting.

   b. There was no documentation that an evaluation for MDR reporting was performed for the 32 infusion pump complaints received in 2013 and 2014.

We reviewed your firm's response and conclude that it is not adequate. Your firm described an additional complaint procedure, **"(b)(4)"** which covers field complaints. Your firm states it will revise procedures to ensure that repairs are handled as complaints, and require evaluation for MDR reporting and the need for investigation. However, updated procedures were not provided in the response, nor was there discussion of a retrospective review of previous repairs to determine whether they represented complaints or of previous complaints for MDR reportability.

3. Failure to establish and maintain adequate procedures for corrective and preventative action, as required by 21 CFR 820.100(a). For example, your firm's CAPA procedure does not describe how it will evaluate all sources of quality data to identify existing and potential nonconforming product, or other quality problems using appropriate statistical methodology. Analysis of repair and maintenance data was not conducted in 2013 and 2014.

We reviewed your firm's response and conclude that it is not adequate. Your firm is updating its CAPA procedure. However, no CAPA procedure was provided in the response, and there was no discussion of a retroactive analysis of repair data to ensure that there are no trends that may require opening a CAPA.

4. Failure to establish and maintain adequate procedures for quality audits, as required by 21 CFR 820.22. For example, your firm's quality audit procedure requires auditors to be independent. Section 3.4 of your quality audit procedure, "Internal Audits, Procedure **(b)(4)** Rev. 5, states **"[b)(4)."** However:

a. In 2014, the Quality Manager, responsible for the oversight of equipment, audited the area "Equipment of measuring, checking, and testing."

b. In 2013 and 2014, the Quality Manager Assistant audited the "Control of the electronic design." The Quality Manager Assistant conducted an audit in an area where they had responsibility.

c. In 2013 and 2014, the Quality Manager Assistant audited the area –"Control of the electronic design." This individual does not have the adequate training or background to review firmware verification or validations.

We reviewed your firm's response and conclude that it is not adequate. Your firm stated that it will appoint a trained auditor to conduct future audits that do not have direct responsibility over the audited areas. However, no discussion of a retrospective review of other internal audit records for independent auditors was included in the response. Finally, no updated quality audit procedure was provided or discussed in your response.

Given the serious nature of the violations of the Act, infusion pump devices manufactured by your firm are subject to refusal of admission under section 801(a) of the Act, 21 U.S.C. § 381(a), in that they appear to be adulterated. As a result, FDA is taking steps to refuse entry of these devices into the United States, known as "detention without physical examination," until these violations are corrected. In order to remove the devices from detention, your firm should provide a written response to this Warning Letter as described below and correct the violation(s) described in this letter. We will notify you regarding the adequacy of your firm's response(s) and the need to re-inspect your firm's facility to verify that the appropriate corrections and/or corrective actions have been made.

Also, U.S. 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. Additionally, premarket approval applications for Class III devices to which the Quality System regulation deviations are reasonably related will not be approved until the violations have been corrected.

Please notify this office in writing, within fifteen business days from the date you receive this letter, of the specific steps your firm has taken to correct the noted violations, including an explanation of how your firm plans to prevent these violations, or similar violations, from occurring again. Include documentation of the corrections and/or corrective actions (which must address systemic problems) that your firm has taken. If your firm's planned corrections and/or corrective actions will occur over time, please include a timetable for implementation of those activities. If corrections and/or corrective actions cannot be completed within fifteen business days, state the reason for the delay and the time within which these activities will be completed. Please provide a translation of documentation not in English to facilitate our review.

Your firm's response should be sent to: Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Field Inspections Support Branch, White Oak Building 66, Rm 2622, 10903 New Hampshire Ave., Silver Spring, MD 20993. Refer to CMS case #453171 when replying. If you have any questions about the contents of this letter, please contact: Daniel Walter at (301) 796-5587 or by fax at (301) 847-8139.

Finally, you should know that this letter is not intended to be an all-inclusive list of the violations at your firm's facility. It is your firm's responsibility to ensure compliance with applicable laws and regulations administered by FDA. The specific violations noted in this letter and in the Inspectional Observations, FDA 483, issued at the close of the inspection may be symptomatic of serious problems in your firm's manufacturing and quality management systems. Your firm should investigate and determine the causes of the violations, and take prompt actions to correct the violations and bring the products into compliance.

Sincerely yours,
/S/
Jan B. Welch, MHS, MT (ASCP) SB Acting Director
Office of Compliance
Center for Devices and
Radiological Health

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