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Inspections, Compliance, Enforcement, and Criminal Investigations

CardioMEMS, Inc. 6/5/12



Department of Health and Human Services

Public Health Service
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993-000

June 5, 2012

WARNING LETTER

VIA UNITED PARCEL SERVICE

Timothy Y. Cowart, J.D. LL.M.
Vice President, Regulatory Affairs
CardioMEMS, Inc.
387 Technology Circle, NW
Suite 500
Atlanta, GA 30313

Dear Mr. Cowart:

The purpose of this Warning Letter is to inform you about serious violations of Title 21, Code of Federal Regulations (CFR) Part 812 - Investigational Device Exemptions, and 21 CFR Part 50 - Protection of Human Subjects. The U.S. Food and Drug Administration (FDA) conducted an inspection at CardioMEMS, Inc. (CardioMEMS), from November 15, 2011, to November 30, 2011, with investigators from the FDA Atlanta District Office and the FDA Center for Devices and Radiological Health. This inspection was conducted to determine whether CardioMEMS' activities as sponsor of the clinical study "CHAMPION: CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III heart failure patients," CardioMEMS HF Pressure Measurement System, Investigational Device Exemption (G060187), and Premarket Approval application (P100045), complied with applicable federal regulations. CardioMEMS HF Pressure Measurement System is a device as that term is defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. § 321(h), because it is 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 letter also requests prompt corrective action to address the violations cited and discusses your firm's written response, dated December 14, 2011, to the noted violations.

The inspection was conducted under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE), Premarket Approval applications, and Premarket Notification submissions (510(k)s) are scientifically valid and accurate. Another objective of the program is to ensure that human subjects are protected from undue hazard or risk during the course of scientific investigations.

Our review of the inspection report prepared by the district office, other study related files, and material presented at the December 8, 2011, Circulatory System Devices Panel meeting (Panel meeting) revealed serious violations of 21 CFR Parts 812 and 50, concerning requirements prescribed under section 520(g) of the Act, 21 U.S.C. § 360j(g). These violations and your firm's

written response are discussed below.

1. Failure to submit an accurate investigational plan in an IDE application including a written protocol describing the methodology to be used [21 CFR 812.20(b)(2) and 21 CFR 812.25(b)]

Your firm, as a sponsor of a significant risk device, as defined in 21 CFR 812.3(m), is responsible for submitting an IDE application to FDA. The IDE application shall include an accurate investigational plan, including a written protocol describing the methodology to be used and an analysis of the protocol demonstrating that the investigation is scientifically sound. Your firm failed to submit an accurate investigational plan that included a protocol that accurately reflected how the study would be conducted. Specifically, the study protocol your firm submitted for IDE approval (G060187) did not indicate that your firm would make (b)(4) recommendations to study investigators for medical management of (b)(4). However, the Sponsor Executive Summary provided to FDA by CardioMEMS for the Panel meeting and CardioMEMS' presentation at the Panel meeting described making these (b)(4) recommendations to the clinical investigators. Additionally, the record of an e-mail that your firm purportedly sent to FDA on July 25, 2007, that was provided to FDA investigators, also described making these (b)(4) recommendations to the clinical investigators.

Your firm's practice of making (b)(4) recommendations to the clinical investigators compromised the validity of the study and the study results. Because additional individualized medical management (potentially beyond what the clinical investigators normally would have done) was provided only to (b)(4), it is difficult to compare the (b)(4) and arrive at an accurate determination of the safety and effectiveness of this investigational device. Due to the manner in which the study was conducted, the safety and effectiveness of your firm's investigational device without this (b)(4) intervention by your firm remains untested, and therefore unknown.

2. Failure to maintain accurate, complete, and current records of correspondence relating to an investigation [21 CFR 812.140(b)(1)]

A sponsor shall maintain accurate, complete, and current records of all correspondence with another sponsor, a monitor, an investigator, an IRB, or FDA, including required reports. Some of your firm's records of correspondence with FDA are inaccurate. Additionally, some of the records of your firm's correspondence with a clinical investigator are inaccurate. For example:

- a. Your firm provided FDA investigators a record of an e-mail sent to FDA on (b)(4), that differed from the actual e-mail that FDA received on the same day. The records of the e-mail provided during the inspection contained material information about the procedures for your firm's study, which was omitted from the e-mail that FDA received. Specifically, the following statement from your firm's record of the e-mail was not in the e-mail sent to FDA: "[w]e will (b)(4)."
- b. Your firm provided (b)(4) an apparently altered Device Return Form in which the original comment containing a (b)(4). This discrepancy in the records of the study subject's complain raises questions regarding your firm's assurance of the safety of study subjects. As (b)(4) was an unanticipated adverse event, altering the complaint does not change the fact that the original complaint of possible (b)(4) should have been evaluated clinically, as required by 21 CFR 812.46(b)(1).

As previously noted, your firm's conduct may have biased the study results, which raises significant questions about the reliability of the effectiveness data in the study P100045. Additionally, the omissions, inaccurate submissions, and discrepant records, discussed above, also raise questions about the integrity and reliability of data and information provided by your firm to FDA.

3. Failure to provide investigators with the information they need to conduct the investigation properly [21 CFR 812.40]

A sponsor is responsible for providing investigators with the information that they need to conduct the investigation properly. However, your firm made arrangements for (b)(4) to visit the sponsor site for an evaluation of his device, because he reported having difficulty (b)(4), without informing the clinical investigator (b)(4). Your firm's actions deviated from the investigational plan and failed to provide the clinical investigator with the information he needed to conduct the study properly. It

is necessary to inform the investigator of study related procedures so that the investigator can have complete and current study subject case history records, and submit current reports of deviations from the investigational plan to FDA, as required by 21 CFR 812.150(a)(4).

Furthermore, because your firm's actions with respect to **(b)(4)** were not in the investigational plan they were not reviewed by an IRB, as required by 21 CFR 812.42.

Your firm's response states that, because a malfunction of the **(b)(4)** implanted in and belonging to **(b)(4)** has neither occurred nor been confirmed, and a **(b)(4)** was performed only to confirm the **(b)(4)**, a notification to the IRB or FDA was not warranted. Your firm's response further states that the informed consent and the Return Merchandise Process Standard Operating Procedure (SOP) were revised to reflect the possibility of a subject being evaluated at your firm's facility.

Your firm's response is inadequate because, even though the informed consent and Return Merchandise Process SOP were revised to reflect the possibility of a subject evaluation occurring at your firm's facility, it does not address the need for your firm to provide its clinical investigators with all the information that they need to conduct the investigation properly under the Act and its implementing regulations. Furthermore, your firm's response does not provide assurance that, going forward, your firm will inform investigators when it evaluates a subject at your firm's facility, thereby providing investigators with the information that they need to conduct the investigation properly. Your firm's response also does not discuss revising the investigational plan to ensure that all investigators are aware that your firm may request a subject to come to your firm's facility for an evaluation. These assurances and revisions will help ensure that your clinical investigators' records are accurate, complete, and current.

We acknowledge your firm's plan to provide clinical management personnel with additional training on internal SOPs and Good Clinical Practices to ensure that proper study conduct is maintained at all times. Please submit documentation of training, including names and titles of the instructors and personnel trained, and all completion dates, to avoid the recurrence of this problem in the future.

4. Failure to include a complete description of the procedures to be followed in the informed consent given to subjects in the study [21 CFR 50.25(a)(1)]

A sponsor is responsible for ensuring that informed consent is obtained in accordance with 21 CFR Part 50 (21 CFR 812.43(c)(4)(iii)). Among other requirements, 21 CFR Part 50 requires that the following information be provided to each subject: a statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental. Your firm's informed consent document's description of the study procedures is incomplete in that it fails to indicate that representatives of your firm would make specific clinical recommendations to the clinical investigators.

The violations described above are not intended to be an all inclusive list of problems that may exist with your firm's clinical study. It is your firm's responsibility as the sponsor to ensure compliance with the Act and applicable regulations.

Within 15 working days of receiving this letter, please provide documentation of the additional actions that your firm has taken or will take to correct these violations and to prevent the recurrence of similar violations in current or future studies for which your firm is the study sponsor. Any submitted corrective action plan must include projected completion dates for each action to be accomplished as well as a plan for monitoring the effectiveness of your firm's corrective actions. Failure to respond to this letter and take appropriate corrective action could result in FDA taking regulatory action without further notice to your firm.

Your firm's response should reference "CTS # G060187/E002" and be sent to:

Attention: Anne T. Hawthorn
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance
Division of Bioresearch Monitoring

10903 New Hampshire Avenue
Building 66, Room 3504
Silver Spring, Maryland 20993-0002.

A copy of this letter has been sent to FDA's Atlanta District Office, 60 Eighth Street NE, Atlanta, GA 30309. Please send a copy of your firm's response to that office.

The Division of Bioresearch Monitoring has developed introductory training modules in FDA-regulated device clinical research practices, which are available on the FDA website. The modules are for persons involved in FDA-regulated device clinical research activities. These modules are located at the following website address: <http://www.fda.gov/Training/CDRHLearn/ucm162015.htm>¹.

If you have any questions, please contact Anne Hawthorn, (301) 796-6561, Anne.Hawthorn@fda.hhs.gov.

Sincerely yours,

/S/

Steven D. Silverman
Director
Office of Compliance
Center for Devices and
Radiological Health

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1. <http://www.fda.gov/Training/CDRHLearn/ucm162015.htm>