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Food and Drug Administration
Center for Devices and
Radiological Health
9200 Corporate Blvd
Rockville, MD 20850**WARNING LETTER****Via Federal Express**

Roger Salvati
Vice President of Sales
Corin USA
10500 University Center Drive
Suite 190
Tampa, Florida 33612

Dear Mr. Salvati

The purpose of this Warning Letter is to inform you of objectionable conditions revealed during a Food and Drug Administration (FDA) inspection of Corin USA, to acknowledge receipt of your August 5, 2005 response to the Form FDA 483 "Inspectional Observations," and request that you implement prompt corrective actions. An investigator from FDA's Florida District Office conducted the inspection from June 13 through June 16, 2005, of the [REDACTED] study sponsored by Corin USA. The purpose of the inspection was to determine whether Corin USA activities and procedures relating to investigational studies of FDA-regulated products complied with applicable FDA regulations. [REDACTED] is a device as 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 because it is intended to affect the structure or any function of the body.

The inspection was conducted as part of the Bioresearch Monitoring Program which includes inspections designed to monitor the conduct of research involving investigational products and is designed to ensure that data and information contained in applications for Investigational Device Exemptions (IDE), Premarket Approval Applications (PMA), and Premarket Notification [510(k)] submissions are scientifically valid and accurate. Another objective of this program is to ensure that human subjects are protected from undue hazard or risk during the course of the scientific investigation.

Our review of the inspection report prepared by the district office revealed deviations from the requirements of Title 21, Code of Federal Regulations (21 CFR), Part 812 - Investigational Device Exemptions, Part 50 - Protection of Human Subjects, and Sections 301(a), 301(c), 501(f), 501(i), 502(o), and 520(g) of the Act [21 U.S.C. 331(a), 331(c), 351(f), 351(i), 352(o), 360j(g)]. At the close of the inspection, the FDA investigator presented the Form FDA 483 to [REDACTED] Regulatory Affairs Director (Corin Group Ltd.); [REDACTED] Clinical Studies Manager; [REDACTED]

[REDACTED] and [REDACTED], Regulatory Consultant for review and discussed the listed deviations. The deviations noted on the Form FDA 483 and our subsequent inspection report review as well as review of your response to the Form FDA 483 items are discussed below:

Shipment, delivery, and receipt of adulterated and misbranded devices in interstate commerce [21 U.S.C. 331(a), 331(c), 351(f), 352(o)].

Because you do not have marketing clearance or an investigational device exemption from the FDA for the Corin USA [REDACTED] with the intended use as a component in [REDACTED] for the reduction or relief of pain and/or improved function, the receipt and introduction into interstate commerce of the Corin USA [REDACTED] for this uncleared indication renders it adulterated under section 501(f)(1)(B) of the Act [21 U.S.C. 351(f)(1)(B)] for failure to obtain FDA premarket approval, and misbranded under section 502(o) of the Act [21 U.S.C. 352(o)] for failure to notify the agency of your intent to introduce the device into commercial distribution as required by section 510(k) of the Act [21 U.S.C. 360(k)]. For a product requiring premarket approval before marketing, the notification required by section 510(k) of the Act is deemed to be satisfied when a premarket approval application (PMA) for the indication is pending before the agency [21 CFR 807.81(b)]. By receiving, distributing, and shipping these adulterated devices, you committed prohibited acts under Sections 301(a) and 301(c) of the Act [21 U.S.C. 331(a) and (c)].

Our inspection showed that [REDACTED] Corin USA [REDACTED] that did not have 510(k) clearance or PMA approval and were not part of the [REDACTED] (IDE [REDACTED], PMA [REDACTED]) or any other IDE were received, shipped, and distributed through interstate commerce. Your August 5, 2005, response appears adequate. You acknowledged that Corin USA should have received FDA approval prior to shipping the [REDACTED] and have outlined what appear to be adequate steps to prevent such shipments in the future.

For future studies, please note that FDA recognizes that there are circumstances in which an investigational device is the only option available for a patient faced with a serious, albeit not life-threatening condition (hereinafter referred to as "compassionate use"). In these circumstances, FDA uses its regulatory discretion in determining whether such use of an investigational device should occur. For more information about compassionate use, you may refer to FDA's "Guidance on IDE Policies and Procedures," which includes a section on emergency use of unapproved devices, and can be found on the Internet at <http://www.fda.gov/cdrh/ode/idepolicy.html>. The guidance document speaks to those situations in which an investigational or unapproved device, respectively, is needed to save the life of a patient or to prevent irreversible morbidity. Unlike emergency use of an unapproved device, prior FDA approval is needed before compassionate use may occur. In order to obtain Agency approval, the sponsor should submit an IDE supplement requesting approval for a protocol deviation under 21 CFR 812.35(a).

Failure to control investigational devices [21 CFR 812.43(b)].

Under 21 CFR 812.43(b), sponsors must ship investigational devices only to qualified investigators who are participating in the investigation. However, Corin USA shipped investigational devices to persons (sales representatives) who are not physicians who were participating in the study and had signed an investigator agreement.

Your August 5, 2005, response is inadequate, in that you have not provided the specific steps you plan to take or have taken to prevent the shipment of investigational devices to persons who are not qualified investigators.

Failure to ensure adequate monitoring of an investigational study [21 CFR 812.40].

Pursuant to 21 CFR 812.40, sponsors are responsible for ensuring proper monitoring of the investigation. However, you failed to ensure proper monitoring of your investigators. Examples of your failure to ensure proper monitoring include, but are not limited to, the following:

- Dr. [REDACTED] did not submit case report forms (CRFs) for any subjects as required by 21 CFR 812.140.
- Dr. [REDACTED] failed to obtain a signed informed consent form for Subject [REDACTED] as required by 21 CFR 50.20, 50.25, and 50.27.

Your August 5, 2005, response is incomplete in that the details and specific steps related to monitoring were not included with your response. Please provide a copy of your formal standard operating procedure related to monitoring according to the IDE regulations, a log of the monitor's site visits, and the revised Complication Form. In addition, provide a timeline for future site monitoring visits.

Failure to submit complete, accurate, and timely reports of unanticipated adverse effects to the reviewing IRB and FDA [812.150(b)(1)].

Pursuant to 21 CFR 812.150(b)(1), sponsors must prepare and submit complete, accurate, and timely reports of unanticipated adverse device effects to the reviewing IRB, FDA, and participating investigators within 10 working days after first receiving notice of the effect. An example of your failure to submit complete, accurate, and timely reports of unanticipated adverse effects to the IRB and FDA includes the failure to properly report unanticipated adverse effects to the IRB and FDA for some of the study subjects including, but not limited to the following: [REDACTED] and Subject [REDACTED]

Your response appears adequate. Please provide a timeline related to completion of clinical sites' training on processing, evaluating, and reporting complications.

Failure to have an adequate investigator agreement [21 CFR 812.43(c)].

Pursuant to 21 CFR 812.43(c), a sponsor shall obtain from each participating investigator a signed agreement that includes sufficient accurate financial disclosure information to allow the sponsor to submit a complete and accurate certification or disclosure statement to FDA. The agreement also must contain a commitment from the investigator to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study. However, financial disclosure information and signed agreements were not obtained from the [REDACTED] participating investigators.

Your response appears adequate. We recommend that you obtain a completed Form FDA 3454 – Financial Disclosure form from each participating investigator prior to initiation of any studies.

Failure to maintain records of device shipment and disposition [21 CFR 812.140(b)(2)].

Under 21 CFR 812.140(b)(2), sponsors are required to maintain records of shipment and distribution of investigational devices. However, prior to May 2004, records of investigational device shipments to [REDACTED] investigator sites were not maintained.

Your response is incomplete, in that, you have not addressed the maintenance of records prior to May 2004. We recommend that Corin include a note to the study records related to returns of investigational devices.

Failure to submit reports to FDA [21 CFR 812.150(b)(4), 812.150(b)(5), 812.150(b)(6), and 812.150(b)(8)].

Under 21 CFR 812.150(b)(4), every 6 months, a sponsor must submit a list of the current investigators to FDA. However, Corin USA has not submitted the current list of all investigators' names and addresses every 6 months since approval of the study was granted.

Your response is inadequate, in that, you have not provided the specific steps you plan to take to ensure that current lists of all investigators are submitted to FDA. In addition, include a current list of all investigators with your response to this letter.

Under 21 CFR 812.150(b)(5), a sponsor of a study of a significant risk device must submit a complete and accurate annual progress report to the IRB and FDA. Corin USA 2002 and 2003 annual reports did not include the use of the [REDACTED] components, and were submitted late to FDA. The 2002 report indicates [REDACTED] protocol deviations; however, only one deviation is included in the report. Furthermore, during the inspection it could not be determined if the 2004 annual report was submitted to either FDA or the IRB. [REDACTED] Regulatory Consultant for Corin USA,

indicated that perhaps Corin USA believed that the PMA submission would substitute for the 2004 Annual Report.

Your response is inadequate, in that, you have not provided the steps that you plan to take to ensure that annual reports are submitted on time. With your response to this item, please provide the specific steps that you plan to take or have taken to ensure that your annual reports are submitted on time.

Under 21 CFR 812.150(b)(8), a sponsor must submit a copy of a report by an investigator of the use of a device without informed consent within 5 days of notice of such use. However, Corin USA failed to report to FDA within the required timeframes that investigational devices were implanted by Drs. [REDACTED] and [REDACTED] without obtaining informed consent.

Your response is incomplete. We highly recommend that any subjects who were implanted with investigational devices but did not sign an informed consent, be notified of the devices investigational status; asked to sign a patient permission document, and continue with follow-up visits per the study protocol. The patient permission document allows Corin USA and federal agencies to inspect, copy, and review their medical records and other source documents. In addition, send the letter and permission document to the reviewing IRBs for approval prior to having the clinical investigators contact the subjects.

In addition to the above violations of the Act and FDA regulations, we have identified inappropriate promotional claims. [REDACTED] promotional literature compares [REDACTED] and claims that the [REDACTED] device “demonstrates as good or better survivorship,” and contains case studies that make various claims about the safety and efficacy of the investigational device. Section 21 CFR 812.7 prohibits promotion of an investigational device; therefore, your device is adulterated under 501(i) of the Act. CDRH requests that Corin USA immediately cease dissemination of these violative promotional materials to study subjects, distribute information that provides information about what to expect during the clinical trial, and refrain from including case studies, testimonials, or any statements that imply that the device has been determined to be safe and effective.

The deviations cited above are not intended to be an all-inclusive list of deficiencies at your site. As a sponsor, it is your responsibility to ensure that investigations that you participate in are conducted in accordance with applicable FDA regulations.

Within 15 working days, you must respond to this letter in writing. You should be aware that FDA considers your actions to be serious violations of the law and may result in FDA taking regulatory action without further notice to you.

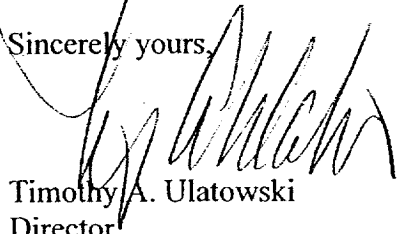
You should direct your response to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch

Monitoring, HFZ-312, 9200 Corporate Boulevard, Rockville, Maryland 20850.
Attention: Viola Sellman, Branch Chief.

A copy of this letter has been sent to the Food and Drug Administration, Florida District Office, 555 Winderley Place, Suite 200, Maitland, Florida 32751. We request that a copy of your response also be sent to the Florida District Office.

Please direct all questions concerning this matter to Viola Sellman at (240)276-0125.

Sincerely yours,



Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
Radiological Health