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DEPARTMENT OF HEALTH & HUMAN SERVICES



Public Health Service

Food and Drug Administration
9200 Corporate Blvd
Rockville MD 20850

APR 26 2007

WARNING LETTER

Via Federal Express

Robert A. Bishop II, President
Silimed, Inc.
11220 Grader Street, Suite 100
Dallas, Texas 75238-2454

Dear Mr. Bishop:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection conducted at your firm during the period of January 4 through January 11, 2007, by an investigator from the FDA Dallas District Office. The purpose of the inspection was to determine whether your activities as a Sponsor of the studies for [REDACTED] under [REDACTED], complied with applicable federal regulations. The [REDACTED] 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). This letter also requests prompt corrective action to address the violations cited and discusses your written response, dated January 24, 2007, to the list of inspectional observations issued at the conclusion of the inspection.

The inspection was conducted under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE), Premarket Approval (PMA) applications, and Premarket Notification submissions (510(k)) 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 revealed serious violations of Title 21, Code of Federal Regulations (21 CFR) Part 812 -- Investigational Device Exemptions and Section 520(g) (21 U.S.C. 360j(g)) of the Act. At the close of the inspection, the FDA investigator presented an inspectional observations form FDA 483 for your review and discussed the observations listed on the form with you. The deviations noted on the FDA 483, your written response, and our subsequent review of the inspection report are discussed below:

- 1. Failure to ensure proper monitoring of a clinical investigation, and failure to select monitors qualified by training and experience to monitor the investigational studies [21 CFR 812.40, and 812.43(d)].**

This includes a repeat of a violation cited in the last Sponsor inspection in January 2003.

As a sponsor, you are responsible for submitting written procedures for monitoring the investigation and for ensuring proper monitoring of the investigation by adequately qualified

and trained monitors. Our review of your firm's records related to the clinical investigations being conducted under [REDACTED] revealed a number of violations associated with your monitoring commitments as outlined in the [REDACTED]. Specifically:

- a.) The monitoring plan you submitted to FDA with your [REDACTED] states, "Audit by central monitor should take place about 3 months after initiation." The central monitor is identified in the monitoring plan as Ms. [REDACTED], RN. There were no records to indicate that Ms. [REDACTED] has conducted any on-site monitoring visits since the studies were first initiated in 2003.

In your written response to this observation, you stated that Ms. [REDACTED] has delegated this responsibility to the Regional Clinical Research Associates (RCRAs) and you further stated that these audits occur on a quarterly basis. This response is inadequate in that you have not provided any supporting documentation.

- b.) According to Silimed's standard operating procedure (SOP) "[REDACTED] one of the clinical monitor's responsibilities is to "schedule a pre-study trial Initiation visit once Institutional Review Board (IRB) approval is received." There were numerous instances in which the pre-study trial initiation visit took place before receiving IRB approval. For example:

i. For the Continued Access Study:

- The pre-study trial initiation visit for site [REDACTED] (Dr. [REDACTED]) occurred on 9/9/04, but IRB approval was not obtained until 9/21/04.
- The pre-study trial initiation visit for site [REDACTED] (Dr. [REDACTED]) occurred on 9/7/04, but IRB approval was not obtained until 10/19/04.
- The pre-study trial initiation visit for site [REDACTED] (Dr. [REDACTED]) occurred on 9/2/04, but IRB approval was not obtained until 10/15/04.
- The pre-study trial initiation visit for site [REDACTED] (Dr. [REDACTED]) occurred on 9/8/04, but IRB approval was not obtained until 9/20/04.
- The pre-study trial initiation visit for site [REDACTED] (Dr. [REDACTED]) occurred on 9/8/04, but IRB approval was not obtained until 9/20/04.

ii. For the Second Core Study:

- The pre-study trial initiation visit for [REDACTED] (Dr. [REDACTED]) occurred on 12/5/05, but IRB approval was not obtained until 12/8/05.
- The pre-study trial initiation visit for [REDACTED] (Dr. [REDACTED]) occurred on 3/21/06, but IRB approval was not obtained until 3/30/06.

In your written response to this observation, you stated that the clinical investigators knew that they were not to begin implanting the study devices until IRB approvals were obtained. You also stated that Silimed will retrain all "Site Monitors and CRAs on the SOPs ... by February 9, 2006." This response is not acceptable in that you have not provided any explanation and supporting documentation regarding how this training will be accomplished. Also, please provide documentation that this retraining has occurred for applicable staff.

c.) The monitoring plan you submitted to FDA with your [REDACTED] requires on-site monitoring "once a month." There were numerous instances in which the study sites did not receive monthly monitoring visits. For example, for the [REDACTED] Study:

- Dr. [REDACTED] had only [REDACTED] monitor visits in 23 months from January 2004 through November 2006.
- Dr. [REDACTED] had only [REDACTED] monitor visits in 37 months from November 2003 through November 2006.
- Dr. [REDACTED] had only [REDACTED] monitor visits in 28 months from September 2003 through December 2005. Dr. [REDACTED] site was discontinued for non-compliance.
- Dr. [REDACTED] had only [REDACTED] monitor visits in 40 months from August 2003 through November 2006. Dr. [REDACTED] site was discontinued for non-compliance.

In your written response to this observation, you stated that Silimed will retrain all site monitors on their responsibilities and SOPs, and that the trained CRAs or the Regulatory Affairs Manager will perform the monthly visits if a site monitor is unavailable. This response is not acceptable in that you have not provided any explanation and supporting documentation regarding how this training will be accomplished. Also, please provide documentation that this retraining has occurred for applicable staff.

d.) According to Silimed's SOP "Conducting an audit of an investigator," clinical study sites are to have quarterly audits by the RCRA, and these audits must be attended by the site monitor. There were numerous instances in which no quarterly audits were conducted, and there were also instances where the audits took place but there was no site monitor in attendance. For example, for the [REDACTED] Study:

- Dr. [REDACTED] had no Site Monitor at [REDACTED] of 11 quarterly audits.
- Dr. [REDACTED] missed [REDACTED] of 12 quarterly audits and had no Site Monitor at [REDACTED] of the 10 audits that were conducted.
- Dr. [REDACTED] missed [REDACTED] of 9 quarterly audits and had no Site Monitor at 4 of the 7 audits that were conducted.
- Dr. [REDACTED] missed [REDACTED] of 12 quarterly audits and had no Site Monitor at [REDACTED] of the 6 audits that were conducted.

In your written response to this observation, you stated that Silimed has hired 2 new Contract Research Associates (CRA) to conduct the audits. Please provide documentation to verify that the new CRAs are adequately qualified and trained to perform this task. Your response also noted that the SOP has been revised to remove the requirement for a site monitor at all audits. This is an acceptable corrective action.

e.) The monitoring plan you submitted to FDA with your [REDACTED] states that "The [REDACTED] will also conduct audits of the [REDACTED]. There was no documentation in the study records to show that the [REDACTED], designated as [REDACTED], has conducted any audits of the central monitor or Silimed since the studies were initiated in 2003.

In your written response, you provided a letter from the CRO which stated that [REDACTED] has audited Silimed, Inc. Dallas, Texas [REDACTED]. This response is not acceptable in that you have not provided sufficient documentation that these audits have been performed, including documentation showing which systems or processes were audited, when the audits were performed, and the name of the person or persons who conducted the audits.

- f.) As a sponsor, you are required to select monitors qualified by training and experience to monitor an investigational study. According to records found in your firm's files, none of the 15 site monitors currently monitoring the clinical trials under [REDACTED] had prior monitoring experience. Your SOP for [REDACTED] (versions dated 12/5/03 and 12/25/05) states that the central monitor is responsible for ensuring complete training of monitors within 90 days of their appointment, and that monitors with little or no monitoring experience would receive training offered by either [REDACTED] or [REDACTED]. Files for site monitors revealed that this training was not completed within 90 days for most of the site monitors, and that these persons performed site monitoring visits and/or audits before being completely trained. For example:
- i. [REDACTED] - previous employment was a golfing instructor. Training records consisted of documentation of "Site Monitor Training" by Ms. [REDACTED] in March 2004 and a Silimed "Training and Educational Meeting" in September 2005. There was no record of [REDACTED] or [REDACTED] training.
 - ii. [REDACTED] - previous employment was in sales. Training records consisted of documentation of a Silimed "Training and Educational Meeting" in September 2005 and Silimed SOP training in December 2003. There was no record of [REDACTED] or [REDACTED] training.
 - iii. [REDACTED] - previous employment was in sales. Training records consisted of documentation of "Product Training/Site Monitor Training" by Mr. [REDACTED] and Silimed SOP training in June 2006. There was no record of [REDACTED] or [REDACTED] training.

In addition, many of the Employee Training Records reviewed were incomplete and missing signatures and/or dates.

In your written response to this observation, you stated that you have put into place a checklist for each site monitor to verify training that is completed within 90 days of hire. This response is not acceptable in that you have not provided sufficient documentation to show that all site monitors have been or will be adequately trained in accordance with your SOP. In addition, the checklist you provided with your response does not indicate the name of the person being trained, their date of hire (for gauging when 90 days is met), or completion of the [REDACTED] or [REDACTED] training course as required by your SOP.

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

This is a repeat of a violation cited in the last Sponsor inspection in January 2003.

The inspection revealed that many of the study records were incomplete, inaccurate, or inconsistent. For example:

a.) Silimed's SOP "Sponsor Record Keeping" requires that regulatory files for each clinical investigator must include copies of all IRB approvals. Several IRB approvals were missing from the files. Specifically, for the [REDACTED] Study:

- Dr. [REDACTED] ([REDACTED]) had no record of initial IRB approval in 2002 or renewal of approval in 2004.
- Dr. [REDACTED] ([REDACTED]) had no record of renewal of IRB approval in 2006.
- Dr. [REDACTED] ([REDACTED]) had no record of renewal of IRB approval in 2004, 2005, or 2006.

b.) Monitoring Visit Reports are inaccurate or inconsistent. For example:

i. In your response letter, you stated that, even though some study sites were initiated before receiving IRB approval (as noted above in paragraph 1b), no implants were shipped to the investigators. However, many of these clinical investigators had documentation in their Initiation Visit Reports indicating they had received the study devices before receiving IRB approval. Specifically:

- For the [REDACTED] Study, each of the initiation visit reports for Dr. [REDACTED] ([REDACTED]), Dr. [REDACTED] ([REDACTED]), Dr. [REDACTED] ([REDACTED]), and Dr. [REDACTED] ([REDACTED]) notes that the monitor "confirmed receipt of implants."
- For the [REDACTED] Study, the initiation report for Dr. [REDACTED] ([REDACTED]) notes that the monitor "confirmed receipt of implants."

ii. The Initiation Visit Reports from one [REDACTED] ([REDACTED]) indicate that she conducted [REDACTED] initiation visits in [REDACTED] days, only [REDACTED] of which notes that it was by telephone. Specifically:

- On 8/25/04, she initiated the Continued Access Study at sites in [REDACTED], [REDACTED], and [REDACTED] locations in [REDACTED].
- On 8/26/04, she initiated the Continued Access Study at sites in [REDACTED] and [REDACTED] locations in [REDACTED].

3. Failure to notify FDA within 5 working days of receipt of notification of use of an investigational device without obtaining informed consent [21 CFR 812.150(b)(8)].

This is a repeat of a violation cited in the last Sponsor inspection in January 2003.

According to information in your study records, an investigator for the [REDACTED] Study, Dr. [REDACTED] ([REDACTED]), was found to have implanted the study device in several subjects prior to obtaining informed consent. Specifically, a monitoring visit report for Dr. [REDACTED] ([REDACTED]) site, dated 4/13/04, indicated that [REDACTED] subjects received the study device before the consent form was signed. Your Regulatory Affairs Manager told the FDA investigator that Silimed's review of the violations showed that only [REDACTED] subjects actually consented after implantation of the study

device. Sponsors are required to notify FDA within 5 working days of any report of use of an investigational device by a clinical investigator without first obtaining informed consent. In addition, Silimed's SOP "Sponsor Reporting" states that the Administrator and Regulatory Affairs Supervisor are responsible for these reports. There is no record that the use of the study device on several subjects at Dr. [REDACTED] site without first obtaining their informed consent was ever reported to FDA by the Administrator, Regulatory Affairs Supervisor, or any other employee of your firm.

The violations described in this letter are not intended to be an all-inclusive list of objectionable practices that may exist at Silimed, Inc. It is your responsibility to ensure adherence to each applicable requirement of the Act and all pertinent Federal regulations.

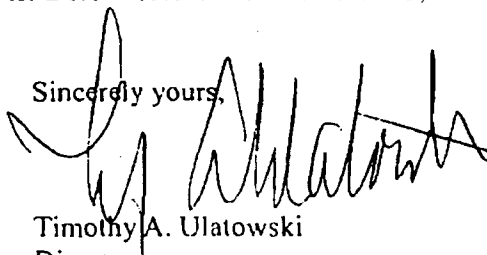
Within fifteen (15) working days of receiving this letter, please provide written documentation of the additional actions you have taken or will take to correct these violations and prevent the recurrence of similar violations in current or future studies for which you are the study sponsor. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you. Please send your response to:

Food and Drug Administration
Center for Devices and Radiological Health, Office of Compliance
Division of Bioresarch Monitoring, Special Investigations Branch (HFZ-311)
2094 Gaither Road, Rockville, Maryland 20850
Attn: Ms. Doreen Kezer, MSN/Chief, Special Investigations Branch

A copy of this letter has been sent to FDA's Dallas District Office, 4040 North Central Expressway, Suite 300, Dallas, TX 75204. We request that you copy the Dallas District Office on your response.

If you have any questions, please contact Ms. Doreen Kezer at 240-276-0125, or Doreen.kezer@fda.hhs.gov.

Sincerely yours,



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