



AUG 29 2008

Food and Drug Administration
Center for Devices and
Radiological Health
9200 Corporate Blvd
Rockville, MD 20850

WARNING LETTER

VIA FEDERAL EXPRESS

Gretchen S. Johnson
President/CEO
KeraCure, Inc.
101 N. Wacker Drive, Suite 606
Chicago, IL 60606

Dear Ms. Johnson:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection conducted at KeraCure, Inc., from April 8 to May 7, 2008, by an investigator from the FDA Chicago District Office. The purpose of this inspection was to determine whether activities and procedures related to your participation in the clinical study (b)(4)

(b)(4)

complied with applicable federal regulations. The (b)(4) 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.

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 (PMA), 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 several violations of Title 21, Code of Federal Regulations (21 CFR), Part 812 – Investigational Device Exemptions. 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 Form FDA 483 and our subsequent review of the inspection report are discussed below:

- 1. Failure to prepare and submit complete, accurate, and timely reports of unanticipated adverse device effects evaluated under 21 CFR 812.46(b) to FDA and**

all reviewing IRBs and participating investigators within 10 working days after you first receive notice of the effect [812.150(b)(1)].

Sponsors are responsible for preparing and submitting complete, accurate, and timely reports of unanticipated adverse device effects (UADE) to FDA, all reviewing Institutional Review Boards (IRB), and all participating investigators within 10 working days after they first receive notice of the effect. Examples of your failure to adhere to the above regulation include, but are not limited to, the following:

a. Subject (b)(6) ((b)(4)) was treated with the investigational device beginning (b)(6), was admitted to the hospital on (b)(6) with an (b)(6), (b)(4) and the (b)(4), (b)(6). An initial Serious Adverse Event (SAE) report was sent to the sponsor on June 12, 2007, with a follow-up report on August 13, 2007; however, there is no documentation that you reported this UADE to FDA, all reviewing IRBs, or participating investigators as required by the above stated regulation.

b. Subject (b)(6) ((b)(4)) was (b)(4) with the investigational device beginning on (b)(6). Subject presented with (b)(6) (b)(4), (b)(6) (b)(4), (b)(6). Your monitor sent this information to you via facsimile on October 18, 2006, but it was not sent to the Institutional Review Board (IRB) until November 28, 2006, and it was not sent to FDA until December 13, 2006, two months after you received notice of the event. The IRB closed the study at this site effective December 14, 2006. There is no documentation that you notified all reviewing IRBs and participating investigators of this UADE.

c. Subject (b)(6) ((b)(4)) was treated with the investigational device beginning (b)(6), was hospitalized on (b)(6) (b)(4), (b)(6) (b)(4), (b)(6). Your monitor notified you of this UADE on March 6, 2008. The FDA and the IRB were not notified of this UADE until April 9, 2008, approximately 30 days later. There is no documentation that you notified all reviewing IRBs or any participating investigators.

2. Failure to either promptly secure non-compliant investigators' compliance with the investigational plan and applicable FDA regulations or discontinue shipments of the device to these investigators and terminate their participation in the investigation [21 CFR 812.46(a)].

Sponsors who discover that any investigator is not complying with the signed agreement, the investigational plan, applicable FDA regulations, or any conditions of approval imposed by the reviewing IRB or FDA shall promptly either secure compliance or discontinue shipments of the device to the investigator and terminate the investigator's participation in the investigation. Subsequent to learning of protocol violations at four

sites, you failed to secure investigator compliance, you continued to ship investigational devices to investigators, and you failed to terminate their participation in the investigation. Examples of your failure to adhere to the above regulation include, but are not limited to, the following:

a. Monitoring reports documented enrollment violations at least three study sites. For example:

- A monitoring visit report for site (b)(4) dated (b)(4) documented that subject (b)(6), (b)(4) (b)(4), (b)(6) between screening and baseline visits, which is an exclusion criterion. Subsequent to this date, you sent at least six additional shipments of the investigational device to the site and the subject received (b)(4), (b)(6)

- A monitoring visit report for site (b)(4) dated June 29, 2006, noted an inclusion criteria violation for one subject, and (b)(4) (b)(4) levels were not measured for another subject, in violation of the protocol. Additional protocol deviations were noted during monitoring visits conducted on November 7, 2006 (b)(4) (b)(4), July 31, 2007 (b)(4), (b)(6) (b)(4), (b)(6)), October 4, 2007 (b)(4) and (b)(4), (b)(6) (case report form omissions, (b)(4) missing, informed consent form (ICF) not witnessed by clinical investigator (CI) or designee). Despite repeated deviations, you failed to secure investigator compliance or discontinue shipment of the device. You did not close the site for non-compliance issues until February 13, 2008, a year and a half after the initial report of protocol deviations.

b. The study coordinator at site (b)(4) sent seven memos to you, dated December 8, 2006, regarding protocol deviations. In addition, monitoring reports dated June 14, 2006, September 7, 2006, and December 6, 2006, documented three, one, and five protocol deviations, respectively, such as: (b)(4) visits occurred on the same day, ICF version was not signed, (b)(4) were not performed, a non-IRB approved ICF was used, failure to have source documentation verifying subject eligibility, one subject was enrolled with no (b)(4) and the (b)(4) was not complete. The Western Institutional Review Board Protocol Deviations/Violations Log lists ten deviations for this site from April 12, 2006 through December 7, 2006. However, you failed to secure compliance or stop shipment of the device, and did not close the study at this site until December 14, 2006.

3. Failure to ensure proper monitoring of the investigation [21 CFR 812.40].

Sponsors are responsible for ensuring proper monitoring of the investigation. You failed to adhere to this regulation in that you failed to follow the monitoring plan in the IDE submission dated July 17, 2003, which requires that reports of on-site visits be made, appropriate follow-up activities be conducted, and necessary corrective actions be carried out. Examples of your failure include, but are not limited to, the following:

- a. Site (b)(4)
 - i. The (b)(4), (b)(6) monitoring visit report noted that for subject (b)(6) the run-in phase visit (b)(4) was performed on the same day as the Baseline Treatment Visit (b)(4) and that the (b)(4) visit was performed more than 72 hours after Visit (b)(4) contrary to the protocol. In addition, the report documents that the Amendment (b)(4) informed consent was not signed by the subject. However, the June 26, 2006 follow-up letter to the site does not include these deviations.
 - ii. The study monitor witnessed a protocol violation on September 8, 2006. However, the September 27, 2006 follow-up letter to the site does not include this deviation.
- b. Site (b)(4) The August 22, 2006, monitoring visit report noted that subject (b)(6) had a protocol deviation of an increase of (b)(4), (b)(6) between the screening and baseline visits, which is an exclusion criterion. However, the September 5, 2006, follow-up letter to the site does not include this deviation.
- c. Site (b)(4) A May 2006 letter from FDA required a revision to the ICF to include information explaining the possibility of exposure to (b)(4) (b)(4). The monitor at site (b)(4) signed off that they checked the ICFs for this site. However, the informed consent document used at site (b)(4) did not include the information required by FDA's May 2006 letter. Five subjects at this site have been screened and consented since November 9, 2006. The June 5, 2007, and November 5, 2007, monitoring visit reports and the follow-up letter to the site all failed to note this deviation.

4. Failure to maintain accurate, complete, and current records of shipment and disposition of investigational devices [21 CFR 812.140(b)(2)].

Sponsors are responsible for maintaining accurate, complete, and current records of shipment and disposition of investigational devices. Examples of your failure to comply with this requirement include the following incomplete entries in your Device Accountability and Disposition Logs:

- a. Site (b)(4) Shipping records document that Lot # (b)(4) was delivered to the site on April 18, 2007; however, there is no documentation of the disposition of this lot on your Device Accountability Log.
- b. Site (b)(4)

- i. There is no documentation in your records of the disposition of Lot (b)(4) (b)(4) which was delivered on September 1, 2006.
- ii. One device from Lot (b)(4) was used on subject (b)(6) on September 1, 2006, yet you have no shipping records for this lot.

5. Failure to obtain signed investigator agreements that indicate whether the investigator was involved in an investigation or other research that was terminated [21 CFR 812.43(c)(3)] and include sufficient accurate financial disclosure information to allow the sponsor to submit a complete and accurate certification or disclosure statement as required under 21 CFR part 54 [21 CFR 812.43(c)(5)], and failure to maintain accurate, complete, and current records of signed investigator agreements [812.140(b)(3)].

Sponsors must obtain from each participating investigator a signed agreement that indicates whether the investigator was involved in an investigation or other research that was terminated and 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 investigation and for 1 year following the completion of the study. Sponsors must maintain accurate, complete, and current records of these agreements. You failed to obtain the aforementioned information from at least 20 participating investigators. Examples of your failure include, but are not limited to, the following:

- a. At least (b)(4) (82%) investigators did not complete the section of the investigator's agreement which required documentation of whether or not the investigator was involved in an investigation or other research that was terminated.
- b. Site (b)(4) You have no financial disclosure information for (b)(6) (b)(6) enrolled three subjects in 2007, two of whom received (b)(4) the investigational device.
- c. Site (b)(4) (b)(6), did not sign an investigator agreement until April 14, 2008, during the FDA inspection. However, (b)(6) has been screening and enrolling subjects since December 11, 2007.

6. Failure to prepare and submit complete, accurate, and timely reports to FDA and all reviewing IRBs and participating investigators of an IRB's withdrawal of approval of an investigation within 5 working days after receipt of the withdrawal of approval [21 CFR 812.150(b)(2)].

Sponsors are responsible for notifying FDA and all reviewing IRBs and participating investigators of any withdrawal of approval by a reviewing IRB within 5 working days after receipt of the withdrawal of approval. The IRB closed site (b)(4) to recruitment on September 19, 2007, due to serious adverse events at the site. You failed to notify the

Page 6 – Gretchen S. Johnson

principal investigator of this closure until January 14, 2008, almost four months later. You also failed to report this closure to FDA, all reviewing IRBs and all participating investigators.

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

On August 8, 2008, we received your response dated August 6, 2008, to the Form FDA 483. We will conduct a complete review of your corrective and preventive actions. Therefore, in the interim, no response to this Warning Letter is necessary. We will send you separate correspondence addressing the adequacy of your response.

A copy of this letter has been sent to the Chicago District Office, 550 W. Jackson, Suite 1500, Chicago, IL, 60661. Please send a copy of your response to that office.

If you have any questions, please contact Doreen Kezer by telephone at (240) 276-0125 or by electronic mail at doreen.kezer@fda.hhs.gov.

Sincerely yours,



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