DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation
and Research
1401 Rockville Pike
Rockville MD 20852-1448

February 12, 2008

By Certified Mail – Return Receipt Requested
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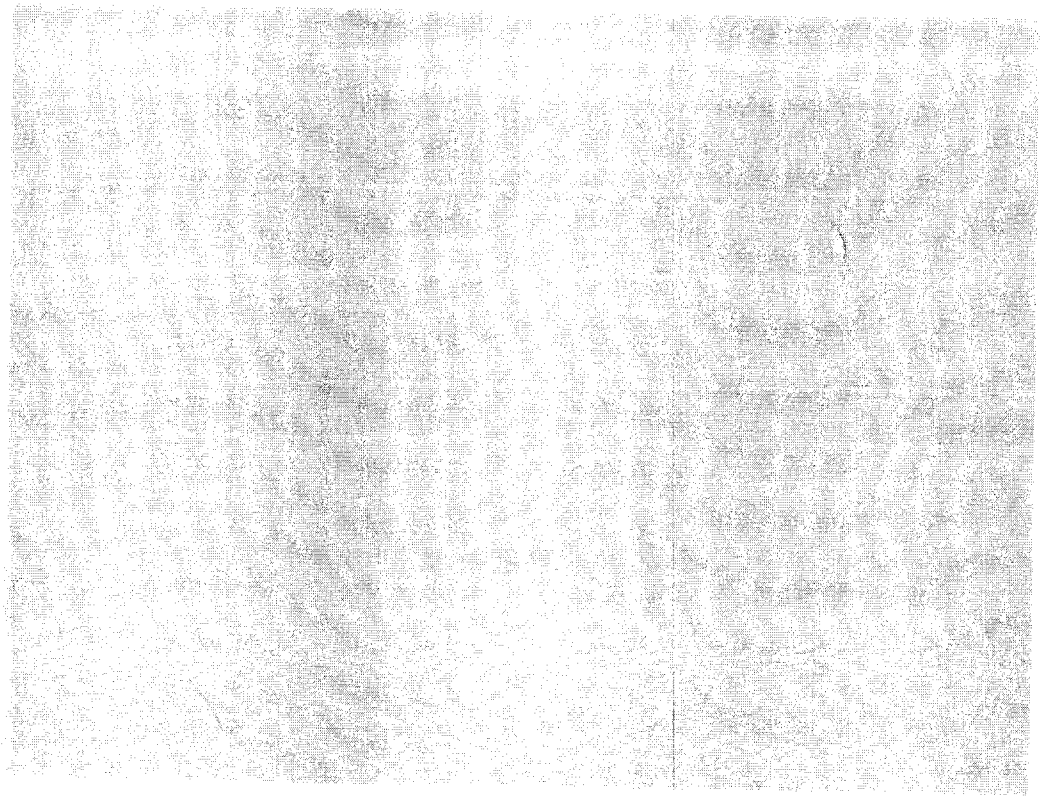
CBER –08-02

Warning Letter

Michael S. Miller, D.O.
The Wound Healing Center
1030 South Fourth Street
Terre Haute, Indiana 47807

Dear Dr. Miller:

This letter describes the results of a Food and Drug Administration (FDA) inspection that was conducted from October 15 through November 5, 2007. An FDA investigator met with you to review your conduct of clinical studies. FDA conducted this inspection under the agency's Bioresearch Monitoring Program, which includes inspections designed to review the conduct of research involving investigational products. The studies reviewed at the time of inspection include:



At the end of the inspection, a Form FDA 483, Inspectional Observations, was issued and discussed with you.

We have determined that you violated regulations governing the proper conduct of clinical studies involving investigational drugs and devices, as published in Title 21, Code of Federal Regulations (CFR), Parts 50, 312, and 812 (available at http://www.gpoaccess.gov/cfr/index.html). The applicable provisions of the CFR are cited for each violation listed below. Studies 1 and 2 involve the clinical evaluation of investigational drugs regulated under 21 CFR Part 312. Studies 3 and 4 involve the clinical evaluation of investigational devices regulated under 21 CFR Part 812.

1. **You failed to ensure that informed consent was obtained in accordance with 21 CFR Part 50. [21 CFR §§ 312.60 and 812.100].**

   A. Study 2:

      i. The informed consent forms for the following subjects were not signed and dated by the subjects at the time of the screening visit when study-related procedures were initiated.

Subject	Screening visit date	Comment
	6/5/06	On 7/6/06 the study coordinator wrote that the subject "inadvertently left out this signature page."
	6/19/06	Subject signed the consent form on 8/30/06, but records indicate the subject participated in the study only from 6/16/06 until 6/26/06.
	7/6/06	A notation on the informed consent form entered by the "Person Explaining Consent" on 09/07/06 states "When originally signing this document, the subject overlooked this signature page. He returned at my asking on 8-30-06 and signed the page but signed it for the original date. I also forgot to sign. I signed when the subject returned for signature."
	2/8/07	The informed consent form was signed by the subject on 05/14/07 and by the "Person Explaining Consent" on 04/30/07.

      ii. The informed consent forms for Subjects [redacted] were signed by the "Person Explaining Consent" on a date different from when the forms were signed by the subjects. Accordingly, it is not clear if the subject signed the consent form at the time of consent.

   B. Study 3 -- The informed consent form for subject [redacted] was not dated by the subject.

2. **You failed to ensure that investigations were conducted according to the investigational plan, the signed agreement, and applicable FDA regulations in order to protect the rights, safety, and welfare of the subjects under your care. [21 CFR §§ 312.60 and 812.100].**

A. Study 1

i. Subject -- You randomized Subject into the study on 3/26/07 although this subject met a criterion for screen failure. The initial measurement of this subject's wound on 2/19/07 was 15.1 square centimeters (cm^2). On 3/26/07 the subject's wound had decreased to 7.8 cm^2, a greater than 30% reduction in ulcer size. Protocol section states "if the wound has changed in size, relative to the first measurement taken in screening, either by a) decreasing by ...the subject is considered a screen failure and must be discontinued from the run-in period and revert to their standard prescribed therapy." In addition, protocol section requires a wound infection assessment to be performed during the screening phase. Instead, according to the laboratory report, you collected the subject's target wound swab during Week 1.

ii. Subject -- Protocol section requires the collection of blood samples and a wound infection assessment "performed during the screening phase." Page 23 of the Day 0 Case Report Form (CRF) states "did not take blood samples or wound swab."

iii. Subject -- You randomized Subject into the study on 4/2/07 although this subject met a criterion for screen failure. The initial measurement of this subject's wound was 7.8 cm^2 on 3/12/07 and increased to 8.7 cm^2 on 4/2/07, representing a greater than 10% increase in size. Protocol section states "if the wound has changed in size, relative to the first measurement taken in screening, either by ...c) has increased by ..the subject is considered a screen failure and must be discontinued form the run-in period and revert to their standard prescribed therapy."

B. Study 2

i. Subject -- You continued this subject in the study although this subject met a criterion for screen failure. Protocol section requires subjects have a Body Mass Index (BMI) less than This subject's BMI was 52.7 at the screening visit on 6/5/06.

ii. Subject – You removed this subject from the study because the subject received the test article wound intended for subject According to a Memo to the File you signed on 2/10/07, "this was due to an error on the part of the

research coordinator based in a misinterpretation of the study protocol on dispensation. Education and review of the protocol and proper identification of the correct to be dispensed were reviewed with the research coordinator and the Principal Investigator by the protocol monitor."

Protocol section requires that an X-ray of the target be obtained during the Screening/Standard Care Run-in Period. This subject did not have an X-ray taken within two weeks of randomization into the study. The subject entered the study on 6/19/06 and the X-ray was obtained on 5/31/06.

iii. Subject -- You continued this subject in the study although this subject met a criterion for screen failure. Protocol section 4.1 requires eligible subjects to be between 18 and 85 years of age. The subject's date of birth is The subject was 87 years old at the time of screening on 6/19/06.

C. Study 3

i. Subject -- You violated the following protocol requirements: you did not obtain screening photographs or a screening tracing; you performed the run-in phase and screening X-ray on the same day as the Baseline Visit (Treatment Visit T1, Day 0), and you performed the T1-A visit (Evaluation 48-72 hours after Day 0 [Baseline] Treatment Visit T1) more than 72 hours after visit T1.

ii. Subject -- You enrolled this ineligible subject who had no palpable pulses in either the right or left foot, as documented on the "Screening Period – Visit S1" CRF. Protocol section requires each subject "to have adequate circulation to the foot as evidenced by a palpable peripheral pulse on the study target foot."

iii. You collected information for study visits T1A and T2A (Evaluations 48-72 hours after Day 0 [Baseline] Treatment Visit T1) by telephone. Protocol section 9 requires that visits T1A and T2A include changing of the outer at your clinical site.

D. Study 4

i. Subject – You enrolled this subject into the study although this subject met several criteria for screen failure. Protocol section requires a subject's ankle-brachial index (ABI) by Doppler be greater than or equal to but less than or equal to and a subject's toe-brachial index (TBI) by Doppler be greater than or equal to Protocol section excludes subjects with screening hemoglobin less than This subject's ABI was equal to 1.375, TBI equal to 0.5, and screening hemoglobin was 10.1 g/dl.

ii. Subject - You enrolled this subject into the study although the subject's screening hemoglobin of 10.8 g/dl met the exclusion criterion for the study. Protocol section excludes subjects with screening hemoglobin values less than

3. You failed to prepare and maintain adequate, accurate, complete, and current records pertinent to the investigations. [21 CFR §§ 312.62(b) and 812.140(a)(3)].

A. Study 1

i. Subject - An "Out of Range Analytes Summary" of laboratory results for a sample collected on 3/26/07 showed no evidence that you reviewed or determined the clinical significance of these results. Section "Blood Sampling /Wound Swab" of the "Week-2 Page 15 of CRF provides the instruction "Returned Lab reports must be reviewed, signed and dated by the investigator and any out of range lab results assigned clinical significance."

A laboratory report shows the subject's target wound swab was collected on 3/26/07, however, CRFs for that date indicate that a wound swab was not collected.

The "Initial Assessments" CRFs are incomplete in that item 4 of the exclusion criteria is not marked regarding the exposure of visible bone, tendon, or fascia around the target wound.

A hand-written list of medications included in the subject's file showed no subject identification or the date the information was obtained.

Week 1 Page 31 of the CRFs does not show the initials of the individual applying the Placebo treatment to the study subject and does not record a response to the question "Is the Placebo transport product must not be applied)." The CRF further states "All boxes must be ticked Yes to proceed."

You failed to sign the Wound Evaluation Progress Notes dated 3/5/07, 3/12/07, and 3/19/07.

The CRFs for this subject are incomplete in that the following CRF pages are not signed and dated: 8, 9, 12, 15, 18, 22, 24, 27, 32, and 37.

ii. Subject - The CRFs do not include information regarding the medications used by the subject. The CRFs are incomplete in that pages 7, 12, and 18 do not have a "Yes" or "No" response required for all of the items. CRF pages 12 and 47 are not signed or dated to confirm the data recorded at the visits are accurate and complete.

iii. Subject -- CRFs are incomplete in that the following CRF pages are not signed and dated: 8, 9, 15, 18, 22, and 24. You did not sign the Wound Evaluation Progress Notes dated 3/12/07 and 3/19/07.

iv. Subject --The Initial Assessments CRF shows the target wound is on the left leg. The Lower Extremity Venous Evaluation was performed on the right leg and photographs were taken of the right leg.

An "Out of Range Analytes Summary" of laboratory results for a sample collected on 3/26/07 showed no evidence of your review or any explanation of the clinical significance of the results. The CRF section regarding "Blood Sampling" states "Returned Lab reports must be reviewed, signed and dated by the investigator and any out of range lab results assigned clinical significance."

You did not sign or date the laboratory report for a wound swab collected on 3/26/07 that showed heavy growth of *Staphylococcus aureus* and Beta Hemolytic Streptococcus Group B. The CRF section regarding the collection of a wound swab states "Returned swab report must be reviewed, signed, and dated by the Investigator" but there is no indication that you assessed the significance of the microbial growth.

You did not sign or date CFR pages 8, 9, 12, 15, 18, 22, 24, 27, 32, 37 and 42 to verify that the CRF was accurate and complete.

tracings of ulcers on 4/23/07 and 4/30/07 did not identify the individual performing the ulcer tracings.

B. Study 2

i. Subject -- The "Screening/Standard Care Run-In (Day -14 to -11)" CRF shows a response of "No" to exclusion criteria item 7 indicating the subject has a BMI of less than This information conflicts with the demographics CRF in that this subject is 5 feet tall and weighs 270 pounds, a calculated BMI of 52.7. This form is incomplete in that the "Informed Consent" and the "Vital Signs" sections are blank; the BMI, Ethnicity, and Date of Diagnosis fields of the "Demographics" section have no data entered; and there is no response to the question "Laboratory samples collected?"

ii. Subject -- Study records conflict regarding death of this subject. An undated unsigned notation in the study file states this subject was withdrawn because the subject "passed away." According to a Memo of Record that you signed on 6/18/07, this subject was alive as of 8/31/06, signed the consent form on 8/30/06 (see item 1A, above) and died sometime after 8/31/06. At the time of the FDA inspection it was determined the subject was still alive and was scheduled for a leg amputation in October 2007.

iii. Subject -- This subject's BMI is incorrectly calculated on the "Screening/Standard Care Run-in (Day -14 to -11)" CRF as 39. The subject's weight is listed as 215 pounds and height is 6 feet one inch. The subject's correct BMI is 28.4.

iv. Subject -- A hand-written list of medications in the subject's file showed no subject identification or the date the information was obtained.

C. Study 3

i. Subject -- There are no laboratory test results in the subject's records. Protocol section specifies the laboratory tests required during the screening period. The Source Document Worksheet for Subject shows the subject's laboratory tests were within normal parameters.

ii. Subject -- The "TREATMENT PHASE – Visit T2 / Week 1" CRF for subject enrollment number dated 9/8/06 indicates post-debridement photographs of the target ulcer were obtained. No photographs were present in the subject's files.

The subject randomization records and the Subject Master Log are discrepant. Subject randomization records show this subject was enrolled as enrollment number and in the treatment group on 8/25/06. The Subject Master Log shows that the initials of enrollment number are and the initials of enrollment number are The randomization records show subject initials as for both enrollments and

D. Study 4 -- No photographs are in the files for subjects

Section of the protocol requires digital photographs to be taken at the time of baseline screening. The CRFs indicate that photos were taken.

4. **You failed to maintain accurate, complete and current records relating to the receipt, use, and disposition of drugs and devices. [21 CFR §§ 312.62(a) and 812.140(a)(2)].**

A. Study 2 -- The "Study Drug Accountability Log" shows "unk" for the initial date of receipt of the study drug. The log also shows one tube dispensed on 7/13/06. The subtraction of this makes the number of on hand 24. The next entry in the log shows 25 were returned to the sponsor due to water damage.

B. Study 4 -- The Accountability Log is incomplete in that "unk" was recorded for the Lot Number and Expiration Date for 49 of 60 subject entries during the period 1/10/05 through 3/14/05.

The violations described above are not intended to be an all inclusive list of problems that may exist with your clinical studies. It is your responsibility as a clinical investigator to ensure compliance with the Act and all applicable 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 clinical investigator. In addition, please provide a complete list of all clinical trials in which you have participated for the last five years, including the name of the study and test article, the name of the sponsor, the number of subjects enrolled, and the current status of the study. Failure to respond to this letter and to take appropriate corrective action could result in the FDA taking regulatory action without further notice to you. In addition, FDA could initiate disqualification proceedings against you in accordance with 21 CFR 312.70 and 812.119.

Please send your written response to:

Christine Drabick, Division of Inspections and Surveillance (HFM-664)
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Suite 200N
Rockville, Maryland, 20852-1448
Telephone: (301) 827-6221 or (301) 827-6323

We also request that you send a copy of your response to the FDA office listed below.

Sincerely,

Mary A. Malarkey

Mary A. Malarkey, Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

cc: Joann Givens, Director
Detroit District Office
Food and Drug Administration
300 River Place, Suite 5900
Detroit, Michigan 48207