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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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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

Richard J. Kagan, M.D.
3229 Burnet Avenue
Cincinnati, OH 45229

Dear Dr. Kagan:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection conducted at your clinical site from March 16 to June 21, 2006, by an investigator from the FDA Cincinnati District Office. The purpose of this inspection was to determine whether activities and procedures related to your participation in the clinical study "Burn Wound Repair with Cultured Skin Substitutes," Investigational Device Exemption (IDE) G980023, complied with applicable federal regulations. Cultured Skin Substitute (CSS) 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 Dr. Boyce's written response, dated October 6, 2006, to the noted violations.

The inspection was conducted under a program designed to ensure that data and information contained in requests for IDEs, 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 C.F.R.) Part 812 -Investigational Device Exemptions and Part 50- Protection of Human Subjects. 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, and our subsequent review of the inspection report are discussed below:

1. Failure to ensure an investigation is conducted in accordance with the signed agreement with the sponsor, the investigational plan, and applicable FDA regulations and any conditions of approval imposed by the FDA or the Institutional Review Board including failure to ensure that informed consent was obtained. [21 CFR 812.100, 812.110(a) and (b), and 21 CFR 50.27(a)]

You failed to adhere to the above stated regulations. Examples of this failure include but are not limited to the following:

- A. The Institutional Review Board (IRB) approved the informed consent form (ICF) on September 6, 2000. The first [] subjects enrolled between April 15, 1998 and July 17, 2000, and signed informed consents that were not approved by the IIRB

Dr. Boyce's response indicates that only approved ICFs will be available to the clinical investigators. Unsigned, expired consent forms are to be destroyed with the exception of the file copy. Also, he indicates that prior, blank versions will be removed when a new ICF has been approved. However, FDA requests information regarding who will be responsible for this procedure and who they will report to.

- B. In the investigational plans dated [] [] the protocol-required assessments were either not completed or not performed at the specified time frames. Examples of this failure include but are not limited to the following:

1. The protocol required that the qualitative outcome assessments be performed on Post-Operative Dates (POD) [] and []; the investigator global assessment be required on POD [] and []; and the qualitative assessment of engraftment be performed on POD [] and []. Assessments audited for [] subjects were found to be incomplete, performed on incorrect days, or not completed at all. For example, the qualitative assessment of engraftment for subject [] was left blank. Subject [] had the required investigator global assessment on POD [] but it was required by protocol to be completed on POD []. Subject [] had his qualitative outcome and global assessments completed on POD [] instead of POD [].

2. The protocol requires wound cultures to be obtained on the following POD: [] [] A total of [] subjects' records were audited. There were no wound cultures obtained at the required times indicated in the protocol. Subject [] had cultures collected on POD []. Subject [] had wound cultures collected on POD []. Subject [] wounds were cultured on POD [].

3. The protocol requires that the [] of each [] application be taken on the following POD: [], and [] of the grafts

on POD [redacted] were not taken or not completed within the specified protocol time frames for [redacted] subjects' records audited. For example, the following subjects did not have [redacted] as required: [redacted] on POD [redacted] on POD [redacted] and [redacted] on POD [redacted] days.

4. The protocol required all subjects to receive both CSS and autografts, in order to compare the two treatments. Subjects [redacted] only received the CSS dressing. Since one of the objectives of the study is to perform direct comparisons of CSS and conventional skin autograft, it was important for the subjects to receive both dressings at the same time.

Dr. Boyce has revised the protocol to [redacted] during the [redacted] after grafting and to establish [redacted]. He states that the current study contains [redacted] that are not relevant to the demonstration of safety and effectiveness of the CSS. Specifically, Dr. Boyce suggests a [redacted] to take and assess [redacted].

Although FDA may consider a [redacted] as appropriate for assessing qualitative outcomes, [redacted] when doing the assessments for obtaining data concerning a wound. Such [redacted] could affect accurate observations and outcomes. Please indicate your rationale for these [redacted].

2. **Failure to report and accurately document unanticipated and anticipated adverse device events to the sponsor and the reviewing IRB. [21 CFR 812.140(a)(3)(ii) and 812.150(a)(1)]**

You failed to adhere to the above stated regulations. Examples of this failure include but are not limited to the following:

- A. Ten subjects needed to be regrafted with the CSS or with an autograft after the CSS failed on certain burned areas. None of the ten subjects' unanticipated adverse events were listed in the subjects' case report forms (CRFs) nor were they reported to the IRB or sponsor as per regulation. For example, subject [redacted] had less than 35 percent engraftment on September [redacted] 2002 with CSS and was regrafted with split-thickness autograft on September [redacted] 2002. Subject [redacted] received CSS to the [redacted] on August [redacted] 2003 but on September [redacted] 2003 the site was reported to be macerated. [redacted] needed regrafting of the [redacted] due to the failure of the CSS. Poor mechanical quality of the skin grafts was cited as the reason. These failures were not documented in the subject's CRFs nor were they reported as adverse events.

B. At least [redacted] subjects' records audited indicated that anticipated adverse events were experienced including development of necrotic tissue, pneumonia, and elevated temperatures, which were not reported to the Sponsor or the IRB as per regulation. Specifically, subject [redacted] developed an elevated temperature and itching on February [redacted], 2002; subject [redacted] experienced bouts of sepsis and infection and cellulitis of the right upper extremity stump between [redacted] and [redacted] and subject [redacted] became febrile and developed sepsis on [redacted].

Since one of the goals of the study is to determine the effectiveness of the CSS, and the study is not limiting an evaluation of effectiveness to select situations in which regrafting is needed, FDA does not understand the basis for why Dr. Boyce is limiting an unanticipated event to only certain situations in which regrafting is needed. Please provide a scientific rationale for why Dr. Boyce states that "regrafting is an anticipated event" in a study designed to determine the effectiveness of CSS and submit it to the Office of Device Evaluation (ODE) for review.

**3. Failure to maintain accurate and complete case histories for each subject.
[21 CFR 812.140(a)(3)]**

You failed to adhere to the above stated regulation. [redacted] subjects' records audited did not have complete and accurate CRFs. For example, subjects [redacted] do not have any documentation on the Site Biopsy Log and subject [redacted] has a blank photography log in the CRFs. Dr. Boyce's response states that Standard Operating Procedures (SOP) for clinical research have recently been implemented at your hospital and these procedures should aid in having data collection transferred to CRFs in a timely and efficient manner. Dr. Boyce states that education, training, and routine reference to these procedures are expected to reduce omissions. FDA requests the training schedules and methods that will be utilized to educate the staff regarding these procedures.

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 clinical investigator to ensure compliance with the Act and applicable regulations.

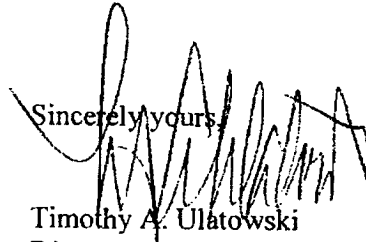
Within fifteen (15) working days of receiving this letter, please provide written documentation of the actions you have taken or will take to correct these violations and prevent the recurrence of similar violations in current or future studies for which you are the clinical investigator. Please provide 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 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 C.F.R. 812.119.

You will find information to assist you in understanding your responsibilities and planning your corrective actions in the FDA Information Sheets Guidance for Institutional Review Boards and Clinical Investigators, which can be found at <http://www.fda.gov/oc/ohrt/irbs/>. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. Send your response to: Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, 9200 Corporate Boulevard, HFZ-310, Rockville, Maryland 20850, Attention: Linda D. Godfrey, Chief, Program Enforcement Branch.

A copy of this letter has been sent to the Cincinnati District Office at 6751 Steger Drive, Cincinnati, Ohio 45237. Please send a copy of your response to that office.

If you have any questions, please contact Linda D. Godfrey at (240) 276-0125 or at Linda.Godfrey@fda.hhs.gov.

Sincerely yours,



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

Cc: (purged)

