DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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WARNING LETTER

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

NOV 10 1999

Federal Express

Richard E. Peck, M.D.
Interim President
University of South Florida
4202 East Fowler Avenue, ADM 241
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Dear Dr. Peck:

During the period of July 16 through August 20, 1999, Ms. Shari Hamilton, an investigator from the Food and Drug Administration's (FDA) Florida District Office inspected the University of South Florida Health Science Center Institutional Review Boards 01 and 01B (referred to as the IRB). The purpose of that inspection was to determine whether the IRB's activities and procedures for the protection of human subjects involved in clinical studies of FDA-regulated products complied with applicable FDA regulations.

Our review of the inspection report and exhibits submitted by the district office revealed that there were deviations from the requirements of Title 21, Code of Federal Regulations (21 CFR), Part 56 - Institutional Review Boards, and Part 50 – Protection of Human Subjects. The violations were listed on the Form FDA 483, "Inspectional Observations," which was presented to and discussed with you, Ms. C. Priscilla Pope, Director, Sponsored Research and Acting Director, Division of Compliance Services; Ms. Glenda S. Taaffe, Assistant Director, Division of Compliance Services; Dr. Barry B. Bercu, IRB Chairman; and Ms. Rhonda Hendrix, Executive Assistant to the Vice President of Research. The description of violations that follows is not intended to be an all-inclusive list of IRB deficiencies.

IRB Operations

Failure to have and follow written procedures for IRB functions and operations in accordance with 21 CFR 56.108 and 812.66.

There are no written procedures that adequately describe the functions and operations of the University of South Florida (USF) IRB. For example, the IRB lacks:

- written procedures that describe how it addresses investigator noncompliance with IRB requirements;
- written procedures to ensure prompt submission of progress reports or that describe the IRB's policy when progress reports are not received prior to IRB approval expiration;

- written procedures that describe what actions the IRB takes against investigators who fail to report adverse events, changes in research, and emergency use in a timely manner;
- written procedures for distinguishing between significant risk (SR) and non-significant risk NSR) device studies; and
- written procedures for IRB support staff to follow for processing adverse event notifications, proposed new studies, continuing review, and changes in procedure applications.

In addition to the above, the IRB failed to:

- review processing changes in research by full board review; and
- notify FDA that the continued review of study [redacted] was disapproved on August 18, 1998.

Expedited Review

Failure to follow written procedures for expedited review in accordance with 21 CFR 56.110(b)(2).

- The IRB used expedited review procedures to conduct continuing review for at least eight studies that failed to meet expedited review criteria as described in the IRB's Policy and Procedures Manual.

- In March 1999, the IRB implemented use of new expedited review criteria for research previously approved by a convened IRB. However, no training was conducted and documented to ensure proper use of the new procedure by the IRB staff.

Research Tracking

Failure to prepare and follow detailed written procedures for conducting the review of research, including periodic review in accordance with 21 CFR 56.108(a) and (b) and 56.115(a)(6).

The IRB failed to prepare adequate written audit procedures for their new primary tracking system "INFO-ED." Further, the IRB failed to implement verification checks and to establish, maintain, and audit the INFO-ED computer system to ensure that

"critical" information such as status, approval period or review category was entered or updated correctly. For example:

- During the inspection, database records and office files were compared for accuracy; many examples were noted which indicated that the database contained errors that affected adequate continuing review. For example, the wrong approval period (8/11/98 to 7/31/99) was entered for study [redacted] into the INFO-ED system. The IRB approval ended on 11/18/98, according to an IRB approval letter dated 11/19/97. Thus the study remained out of compliance for eight months beyond the IRB approval period and without IRB notification or action until July 1999.

- The review category for at least five studies was incorrectly added/updated as expedited when full IRB review was required. Data entry personnel incorrectly updated the wrong field in recording current expedited review activity. These incorrect entries changed the review category of the entire study.

- A review of 23 studies in the INFO-ED system with the status of New, Pending, or Conditional Approval, revealed that the status was not correctly updated for nine of the studies (eight were approved and one was disapproved). Three of the approved studies were beyond their approval period and were not tracked as due for continuing review.

Failure to prepare and maintain adequate documentation of IRB activities in accordance with 21 CFR 56.115(a)(2) and (a)(5).

The IRB failed to maintain adequate documentation of historical IRB membership. Only the current IRB roster was available for review. IRBs are required to maintain such records for at least three years.

Currently, the USF IRB is responsible for monitoring over 850 active studies. It is our understanding that USF intends to initiate a third IRB, 01C, which will be chaired by the same individual who is responsible for chairing the other two IRBs (01 and 01B). With the initiation of a third IRB, it appears that this person will have even less time to spend individually on these IRBs. According to the USF IRB's records, the IRB chairperson currently dedicates approximately 50 percent of his

time on IRB activities. Given the increasing number of studies that are being reviewed by USF, we are concerned that USF plans to have one individual chairing all three IRBs. It appears that the failure of the IRB to meet its obligations and responsibilities is related to the lack of sufficient staff and proper training.

Many of the deviations cited during the inspection were also noted during FDA's March 1998 inspection of the USF IRB. Based upon the recurring deficiencies in organizational guidelines, standard operating procedures, recordkeeping practices, and lack of improvement in the areas of continuing review and misuse of expedited review procedures, we are concerned that your procedures and practices may not adequately protect the rights and welfare of human research subjects. Also, we are concerned that your IRB activities and responsibilities are not in compliance with FDA regulations.

We acknowledge receipt of Dr. George Newkome's letter of August 27, 1999, which was in response to the inspectional observations presented by Ms. Hamilton. We also acknowledge the letters and status reports of October 1 and 18, submitted by Dr. Newkome. Those letters and status reports describe the IRB's ongoing efforts to correct deficiencies observed during the recent inspection. We note that USF has retained an outside audit firm, [redacted] to assist in the process of validating studies that had been inappropriately reviewed as "expedited continuing review" and also for auditing internal validation processes associated with the INFO-ED computer system. Those letters and status reports will become part of FDA's official files.

We note that the IRB has drafted a policy for significant/nonsignificant risk determination of investigational devices but the IRB has not completed its review and implementation of that policy. We understand that the IRB has revised several of its standard operating procedures (SOPs), including those for noncompliance of clinical investigators, emergency use approval follow-up, and study tracking. We also note that the IRB has revised its Data Entry Guide for INFO-ED to assist IRB staff in using the INFO-ED computer system.

We are enclosing a copy of the FDA Information Sheets, Guidance for Institutional Review Boards and Clinical Investigators for your information and to assist you in revising your IRB's written operating procedures. Appendix H, entitled "A Self-evaluation Checklist for IRBs," of the enclosure, provides additional information to assist you.

Within fifteen (15) working days of receipt of this letter, please provide this office with written documentation of any specific additional steps you have taken or will be taking to bring your IRB into compliance with FDA regulations. The corrective actions should include revisions to the IRB's written procedures and the timeframes within which these procedures will be developed and implemented. Please be aware that your corrective actions may be verified during a future FDA inspection. Your failure to adequately respond to this letter may result in further administrative actions against your IRB, as authorized by 21 CFR 56.120 and 56.121. These actions may include, but are not limited to, the termination of all ongoing studies approved by your IRB and the initiation of regulatory proceedings for disqualification of your IRB.

You should direct your response to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch II (HFZ-312), 2098 Gaither Road, Rockville, Maryland 20850, Attn: Robert K. Fish, Consumer Safety Officer. A copy of this letter has been sent to our Florida District Office, 555 Winderley Place, Suite 200, Maitland, Florida 32751. We request that a copy of your response be sent to that office.

Please direct all questions concerning this matter to Mr. Robert Fish at (301) 594-4723, ext. 138.

Sincerely yours,

for Lillian J. Gill
Director
Office of Compliance
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Enclosure

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