DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

DEC 23 1996

Certified-Return Receipt Requested

WARNING LETTER

Mr. Dennis R. Bruns
President and Chief Executive Officer
Hilton Head Medical Center and Clinics
25 Hospital Center Boulevard
Hilton Head Island, South Carolina 29926

Dear Mr. Bruns:

During October 16-18, 1996, Ms. Stephanie Hubbard, an investigator with the Food and Drug Administration (FDA), inspected the Hilton Head Medical Center and Clinics Institutional Review Board (IRB). The purpose of the inspection is to determine if the IRB's procedures for the protection of human subjects comply with FDA regulations, published in Title 21, Code of Federal Regulations, Parts 50 and 56 [21 CFR 50 and 56].

A copy of the list of Inspectional Observations (FDA-483) left with Dr. Lucas at the end of the inspection is enclosed. The deviations noted in our inspection include, but are not limited to the following:

1. **Failure to prepare detailed written procedures for conducting the review of research, including periodic review. [21 CFR 56.108(a), 56.115(a)(6)]**

   The Hilton Head Hospital Institutional Review Board Guidelines (The Guidelines) are incomplete or inaccurate as follows:

   a. The Guidelines do not include a complete list of materials required to be submitted to the IRB for the initial review and approval of research proposals (i.e., investigator's brochures, advertisements if applicable, etc.).

   b. The IRB is not following The Guidelines for receipt and distribution of materials submitted by the clinical investigators. The IRB should amend the procedures to reflect the current process or follow The Guidelines as written.

   c. The Guidelines do not describe how the IRB determines significant versus non-significant risk for investigational devices.

d. The Guidelines do not require a majority of the IRB membership to be present for full committee review. The IRB currently consists of nine members. A majority is five members. The Guidelines often state that four members are required to conduct reviews.

e. The procedures for the emergency use of a test article do not include the steps for the IRB's review of subsequent use of a test article.

f. The Guidelines do not indicate that the IRB has a systematic method in place for informing and reminding clinical investigators of their reporting responsibilities (i.e., anniversary review dates, progress reports due, final reports due, reporting of serious unanticipated adverse events within a defined time period, etc.). For example, a document that appears to be a final report to the IRB for the study indicates that subject experienced "worsening pleural effusion" requiring hospitalization. The subject was subsequently withdrawn from the study. This was a serious adverse event and should have been reported immediately to the IRB, not just in the final report.

We suggest that such events be reported to the sponsor and IRB concurrently in order to track trends that may occur locally or to allow the IRB to make inquiries of the sponsor regarding broader trends of the study.

g. The Guidelines, as written, may not require clinical investigators to maintain their research records for an adequate period of time. The Guidelines require clinical investigators to maintain their own research records for at least three years "after termination of the study." Clinical investigator regulations [see 21 CFR Part 312.62(c)] require that records of studies be maintained for two years following the date a marketing application is approved. If an application is not filed or not approved by FDA, clinical investigators are required to retain records until two years after the investigation is discontinued and FDA is notified.

h. The Guidelines do not include appendices identified in the Table of Contents and referred to in the text. Dr. Lucas, the Chair of the IRB, located a copy of "Research Activities Which May be Reviewed Through Expedited Review Procedures" during the inspection and indicated that he would label the document for attachment to The Guidelines as Appendix B. Appendices C and D, "Investigation Use of Marketed Products" and "Assurance of Compliance with the Cooperative Oncology Group," were not available for inspection. Appendix A, "A Current Membership List," was not attached to The Guidelines.

i. The Guidelines contain outdated references regarding the participation of individuals and/or organizations which are not currently involved in IRB activities. Examples include but are not limited to the following:

i. The Guidelines mention the participation of the "President of Medical Staff" in the receipt and distribution of research proposals. This individual is not involved in the submission process.

ii. The Guidelines mention the initial review and expedited review activities by the "Executive Committee." Dr. Lucas indicated that he is not aware of the existence of a body known as the Executive Committee of the IRB.

iii. Studies exempted from IRB review are subject to the review of the "Research Committee." Dr. Lucas indicated that he was not aware of the committee.

j. The expedited review procedures state that this review is used for those protocols which meet the criteria for expedited review "or" which involve no more than minimal risk to the subjects. The "or " should be replaced with "and" as described in the Federal Register Vol. 46, No. 17 Tuesday, January 27, 1981, 46 FR 8960.

2. **Failure to determine frequency of review for a study. [21 CFR 56.108(a)(2)]**

The IRB did not assign a periodic review frequency to the study

3. **Failure to ensure prompt reporting to the IRB of changes in research activity. [21 CFR 56.108(a)(3)]**

a. The study closure date could not be determined. A document that appears to be a final report submitted to the IRB for the study was not dated.

b. The study closure date could not be determined from IRB records at the time of inspection. We note that Dr. Lucas received a memorandum from the clinical investigator on 10/17/96 indicating that the study closed in 1994.

c. There is no documentation of the submission of progress reports to the IRB since approval of the study on 11/3/93.

4. **Failure to require that information given to subjects as part of informed consent is in accordance with 50.25. [21 CFR 56.109(b)]**

The Model Informed Consent form approved by the IRB for the study entitled " ," does not contain all required elements of informed consent. The consent form does not identify whom to contact for answers to questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

5. **Failure to conduct continuing review of research. [21 CFR 56.109(e)]**

a. There is no documentation of continuing review or approval activities in 1994, 1995, or 1996, for the study since the 11/14/94 review of adverse events.

b. The IRB determined that the status of a subject in the study should be reviewed at a convened meeting after completion of the second cycle of treatment. The IRB did not convene to review the study after the second cycle. Dr. Lucas reported the status of the subject to the IRB on 3/28/96, while the subject was in his fourth cycle of treatment. Dr. Lucas indicated that there was nothing to report after the second cycle, but there is no record in the IRB files to indicate why the pre-determined review did not occur as scheduled.

6. **Failure to retain copies of all research proposals and supporting documents. [21 CFR 56.115(a)(1)]**

a. The IRB files did not contain a copy of the protocol and informed consent for the study at the time of inspection. We note that Dr. Lucas obtained copies of these documents and filed them after the deficiency was observed by the FDA investigator.

b. The Clinical Investigator's Brochure for the study was not maintained on file or submitted to and reviewed by the IRB. The protocol references the brochure for identifying unexpected adverse events which require reporting.

c. The written notification of approval to the clinical investigator of the study directed the clinical investigator to submit a copy of the completed informed consent which had been signed by the subject before treatment started. The consent form was not in the IRB files at the time of the inspection. Dr. Lucas obtained a copy of the signed consent form from the clinical investigator after the deficiency was observed by the FDA investigator.

7. **Failure to maintain adequate documentation of IRB activities. [21 CFR 56.115(a)(3)]**

The IRB records fail to document the historical progression and outcome of decisions made by the IRB regarding the status of Dr. Rajko Medenica, his subjects, and his protocols since IRB minutes of September 26, 1994.

8. **Failure to prepare correspondence and maintain copies of all correspondence between the IRB and the investigators. [21 CFR 56.115(a)(4)]**

There does not appear to be adequate correspondence between the IRB and clinical investigators regarding initial and continuing review. For example:

a. There was no record of written approval to the clinical investigator for the study in the IRB files at the time of inspection. We note that Dr. Lucas wrote a memorandum to the clinical investigator acknowledging approval of the study five and one-half months after approval when the deficiency was noted by the FDA investigator .

b. The IRB required the clinical investigator of the study to submit his progress notes for each subject visit (approximately one treatment/visit per week according to the protocol). Only two visit reports dated 10/23/95 and 01/03/96 are documented in the IRB files.

c. The IRB files contained no notification of IRB receipt and actions for the submission of the progress notes for the study or for final reports received from studies.

9. **Failure to maintain a current listing of IRB members as described in 21 CFR 56.115(a)(5).**

Although a list of the IRB membership was available, the list did not include all of the elements described in the federal regulations for all members such as earned degrees, representative capacity, indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution (e.g., full-time employee, part-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant).

Information regarding the background of the members was collected from each member in the form of a resume, memo, written paragraphs, or hand-written notes on a copy of the memo requesting the information. The collected information should be compiled into a concise list.

The FDA investigator notes that the IRB may not be maintaining records for seven years as is prescribed in The Guidelines. During the 1995 inspection, records from 1991 were available for review. Records prior to 1992 were not available to the FDA investigator for this inspection. Please explain where records prior to 1992 are kept, why they were available for the 1995 inspection, and why they were not available for this inspection.

The Hilton Head Medical Center and Clinics Guidelines often refer to an assurance document with DHHS/OPRR. The Multiple Project Assurance (MPA) document approved by the DHHS is a commitment to follow the DHHS regulations, but does not necessarily meet the requirement for written procedures in 21 CFR 56.108 -- IRB functions and operations. There are significant differences between the DHHS regulations (45 CFR 46) and the FDA regulations (21 CFR 50 and 56) which apply to research involving products regulated by FDA. These differences are outlined on pages 123-124 of the FDA IRB Information Sheets (copy enclosed).

This letter is not intended to be an all-inclusive list of deficiencies with the IRB. The IRB is responsible to adhere to each requirement of the law and relevant regulations.

Based upon the similarities of deficiencies noted in the 1995 and 1996 inspections such as deficiencies in organizational guidelines, operational procedures, recordkeeping practices, and apparent lack of understanding of the applicability of the FDA regulations, we have no assurance that your procedures are adequately protecting the rights and welfare of human subjects of research. As described in section 56.120 of the regulations left with Dr. Lucas at the close of the inspection, failure to make adequate corrections may result in regulatory action being initiated by the Food and Drug Administration. These actions include, but are not limited to, withholding approval of new studies, direction that no new subjects be added to ongoing studies, termination of ongoing studies, and notification of State and Federal regulatory agencies.

Please notify this office in writing, within 15 working days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step taken to prevent a recurrence of similar violations. If you cannot respond within the 15 day time frame, please call our office and explain the circumstances for the delay.

If your institution does not have the resources to bring your IRB into compliance with federal regulations, it is acceptable for you to use another IRB. Please notify us if you intend to disband the Hilton Head Medical Center and Clinics Institutional Review Board.

Your response should be sent to the Food and Drug Administration, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Rockville, Maryland 20852-1448, Attention: James C. Simmons, HFM-600.

Sincerely,

for James C. Simmons
Director
Office of Compliance
Center for Biologics Evaluation
and Research

Enclosures

FDA Form 483, List of Inspectional Observations
FDA Information Sheets (includes 21 CFR Parts 50 and 56)
21 CFR Part 312

cc:

Charles T. Lucas, M.D.
Chairman, Hilton Head Medical Center and Clinics IRB
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Hilton Head Island, South Carolina 29926

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