DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

M2731N

JUN 23 1999

WARNING LETTER

Pam Corliss
Chief Executive Officer
Atlantic Medical Center
400 N. Clyde Morris Boulevard
Daytona Beach, Florida 32114

Dear Ms. Corliss:

Between March 30 and April 5, 1999, Mr. Jose R. Rodriguez, an investigator with the Food and Drug Administration (FDA), Florida District Office, conducted an inspection of the Institutional Review Board (IRB) at Atlantic Medical Center. The purpose of that inspection was to determine whether the IRB's activities and procedures relating to 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 serious violations 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 Mr. Keith Ferguson, Pharmacy Manager. The description of violations that follows is not intended to be an all-inclusive list of IRB deficiencies.

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

Meeting minutes are inadequate and were available for only two IRB meetings. At the April 4, 1998, meeting, the studies approved included the [redacted] and [redacted] at the July 8, 1998, meeting, protocols [redacted] were approved. There were no records showing that any other IRB meetings had been held. The minutes were not in sufficient detail to show, for example, the voting for the studies reviewed/approved. The principal investigators for the studies approved at these meetings were not identified, and protocol names/numbers were not specified. In addition, risk determinations (significant/nonsignificant) for device studies were not documented in the meeting minutes.

Correspondence from the IRB to the investigators for additional information, for conveying IRB decisions, etc., and from the IRB to the institution's administration conveying IRB decisions, was often lacking. There were no records of continuing review activities, including progress reports. The protocol and consent for study [redacted] were not found in the IRB files.

The clinical investigator for study [redacted] reported to the IRB information on numerous serious adverse events that had occurred in study subjects. There was no documentation that the IRB reviewed or considered these events.

The status of all studies submitted to the IRB is unclear (e.g., pending, approved, disapproved, ongoing, or closed). Also, it is unknown if the IRB assumed responsibilities for oversight of any ongoing studies at this institution at the time the IRB was organized, reportedly on April 28, 1998.

Although your IRB composition appears to be adequate, the IRB roster does not include all information contained in section 56.115(a)(5). Also, you should specify which member(s) meet the "nonscientist" requirement. Such information is needed to assure that the quorum requirements of 21 CFR 56.108(c) are met.

2. Failure to provide written notification of IRB decisions and perform continuing review at the required frequency [56.109(e) and (f)]

Four studies [redacted] were approved at the two IRB meetings held. However, for [redacted] and the [redacted] no records were found regarding the notifications to the clinical investigators and the institution of the approval of these studies. An approval letter to the clinical investigator was found for the [redacted] (or [redacted] as it is referred to in other correspondence). Although the approval letter states the study was approved at the July 10, 1998, meeting, the meeting minutes were dated July 8. Based on correspondence dated December 8, 1998, from [redacted] had apparently been approved, but an approval letter to the CI and the institution was not found.

[redacted] submitted requests for approval of protocols and informed consents for protocols [redacted] and [redacted] on October 9 and 30, 1998, respectively. There was no documentation that these protocols were reviewed by the IRB and either approved or disapproved. [redacted] submitted correspondence dated November 3 and 20, 1998, for [redacted] These documents indicated that the study was pending full board review at the next IRB meeting. It is unclear if the IRB reviewed this study and either approved or disapproved it.

Note that an IRB is required to notify investigators and the institution in writing of its decision to approve or disapprove any proposed research activity. If a research activity is disapproved, the investigator must have an opportunity to respond, either in person or in writing, to this determination.

Continuing review for approved studies had not been conducted, and no progress reports were located. If the two studies approved at the April 28, 1998, meeting had been scheduled for annual review at the time of initial approval, progress reports should have been submitted in sufficient time for the IRB to review those reports prior to expiration of the approval.

3. Failure to have and follow adequate written procedures as required by 21 CFR 56.108(a) and (b)

Each IRB that reviews clinical studies subject to Parts 50 and 56 of the FDA regulations must have and follow written procedures that describe the IRB's functions and operations. Your current document "Investigational Drug Policy (No. 1160)" does not meet the FDA requirement. The procedures required by sections 56.108(a) and (b) need to be developed, documented, and implemented at your institution. Other areas that need to be addressed include, but are not limited to, the following: 1) a description of the IRB's authority and operations, 2) expedited review procedures (see section 56.110), 3) evaluation of adverse event reports, 4) significant/nonsignificant risk determinations for device studies (see also 21 CFR 812.66), and 5) procedures for suspending or terminating IRB approval and notifying the investigator, the institution, and FDA of the termination, as required by section 56.113. Also, a system should be implemented and followed for determining the status of approved studies and for assuring that on-going studies are reviewed within the time intervals set by the IRB at the time of initial review and approval.

4. Failure to implement expedited review procedures in accordance with 21 CFR 56.110(b) and (c)

The IRB's use of expedited review procedures fails to meet FDA requirements. From the limited IRB documentation available, we cannot tell if, for example, Amendments [redacted] would have been eligible for expedited review by the IRB Chairman. The Chairman, via expedited review, also approved an informed consent for this protocol. Furthermore, the actions are not documented in subsequent meeting minutes. Also, there is no procedure for keeping all members advised of research proposals that have been approved under the expedited review procedure.

You should be aware that expedited review procedures may be followed only for initial and continuing review of research involving no more than minimal risk, and for minor changes in on-going approved research. Also, the IRB must adopt a timely method for keeping all members advised of proposals that have been approved under expedited review.

5. Failure to ensure that informed consent documents comply with the requirements of 21 CFR 50.25

Consents for some of the studies approved by the IRB did not contain all required information. For example, the consent for the [redacted] did not specify contact persons for further questions about the research and subjects' rights, or whom to contact in the event of a research-related injury. Also lacking was a statement that significant new findings developed during the study that may relate to the subject's willingness to continue would be provided. It is the IRB's responsibility to review consent documents and assure that the required elements are adequately covered.

Based upon the deficiencies found during this inspection, we have no assurance that your IRB procedures are adequately protecting the rights and welfare of human subjects of research. For this reason, and pursuant to 21 CFR 56.120, no new studies subject to Parts 50 and 56 of the FDA regulations should be approved by your IRB until this office has been provided assurance that adequate corrections have been made. This restriction does not apply to the emergency use of an investigational product when the conditions described in 21 CFR 56.102(d) exist and the procedures followed by your institution meet or exceed the requirements described in 21 CFR 56.104(c). Neither does this restriction relieve the IRB from receiving and reacting to proposed amendments, reports of unexpected and serious reactions, and routine progress reports from ongoing studies.

Within fifteen (15) working days of receipt of this letter, please provide this office with written documentation of any specific steps you have taken or will be taking to bring your Institutional Review Board into compliance with FDA regulations. The corrective actions should include the following: development of adequate written procedures (simply restating or rewording the federal regulations does not meet the requirement for written procedures); a report of the status of all studies submitted to and/or reviewed by the IRB (pending, approved, disapproved, ongoing, closed); a status of continuing review activities; and an accounting of any studies that were ongoing when the present IRB was established. If corrective action cannot be completed within 15 working days, state the reason for

the delay and the time within which the corrections will be completed. Failure to respond can result in further regulatory action without additional notice.

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 I, 2098 Gaither Road, Rockville, Maryland 20850, Attention: Barbara A. Crowl. A copy of this letter has been sent to FDA's Florida District Office, 555 Winderley Place, Suite 200, Maitland, Florida 32751. We request that a copy of your response also be sent to that office.

Please direct all questions concerning this matter to Ms. Crowl at (301) 594-4720.

Sincerely yours,

Lillian J. Gill
Director
Office of Compliance
Center for Devices and
Radiological Health

cc: Wahba Wahba, M.D.
Chairman, Institutional Review Board
Atlantic Medical Center
1360 Mason Avenue
Daytona Beach, Florida 32117

Michael Carome, M.D.
Compliance Oversight Branch, MSC 7507
Office for Protection from Research Risks
National Institutes of Health
6100 Executive Boulevard, Suite 3B01
Rockville, Maryland 29892-7507