DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

WARNING LETTER

JUL 16 2001

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Anthony Rose
President/CEO
Catawba Memorial Hospital
810 Fairgrove Church Road
Hickory, North Carolina 286022

Dear Mr. Rose:

Between January 3 and 11, 2001, Mr. R. Edward DeBerry, representing the Food and Drug Administration (FDA), conducted an inspection of the Catawba Valley Institutional Review Committee (IRB). The purpose of this inspection was to determine whether your procedures for the protection of human subjects complied with Title 21, Code of Federal Regulations (CFR), Parts 50 and 56 [enclosure #1]. These regulations apply to clinical studies of products regulated by FDA.

Based on our evaluation of the inspection report and the documents submitted with that report, we conclude that the IRB has failed to adhere to pertinent federal regulations as required by 21 CFR Parts 50 and 56. At the conclusion of the inspection, Mr. DeBerry presented and discussed with you the items listed on Form FDA 483, Inspectional Observations [enclosure #2]. We note that a prior inspection of your IRB was conducted on December 7 - 9, 1994. At the conclusion of that inspection, a Form FDA 483 was presented to you and a post inspection letter, dated May 10, 1995, was issued [enclosure #3], notifying you of our findings. The letter requested that you respond within 90 days with remedial actions planned by your IRB. You failed to respond to our letter and we find that many of the problems noted in the 1994 inspection still exist. We wish to emphasize the following:

SUMMARY OF VIOLATIONS RELATED TO IRB FUNCTIONS AND OPERATIONS (21 CFR 56.108)

1. The IRB failed to develop and follow written procedures that specifically describe their function and operation to ensure the protection of human research subjects in clinical studies subject to 21 CFR Parts 50 and 56. The inspection report and exhibits included with the report show that your guidelines for carrying out the duties of the IRB do not include written procedures to ensure the following:

- reporting its findings of initial actions and continuing review of research to the clinical investigator and institution;
- determination of which projects require review more often than annually;
- prompt reporting to the IRB of changes in research activity;
- that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects;
- prompt reporting to the IRB, appropriate institutional officials and the FDA of anticipated problems involving risks to human subjects or others; any instance of serious or continuing non-compliance with the regulations and requirements of the IRB; and any suspension or termination of IRB approval.

2. The Catawba Valley Institutional Review Committee Guidelines fail to require that the IRB, except when an expedited review procedure is used, shall review proposed research at convened meetings at which a majority of the members of the IRB are present, and in order for research to be approved, it shall receive the approval of a majority of those members present at the meeting. The statement in your institution's guidelines, Section V. D., that "50% of voting membership constitutes a quorum for business transactions" does not meet the requirement of a majority, either for the purpose of convening a meeting or for the purpose of approving research. Proposed research was approved without a majority of members present during the meetings of 7/11/00 and 12/7/00, and you failed to have any documentation to verify that any meetings in 1998 or 1999 were held with a majority of members present.

3. Section V. F) of your institution's guidelines states that telephone ballots are acceptable in emergency circumstances. FDA does not consider this to be an acceptable practice since it does not allow for interactive discussion of issues among members.

SUMMARY OF VIOLATIONS RELATED TO IRB REVIEW OF RESEARCH (21 CFR 56.109).

The IRB failed to notify investigators and the institution, in writing, of its decision to approve or disapprove proposed research activity. There were no approval letters sent to the clinical investigators for the [ ] Breast Cancer Study [ ] or the [ ] Study.

SUMMARY OF VIOLATIONS RELATED TO COOPERATIVE RESEARCH (21 CFR 56.114)

There is no written agreement between the Catawba Memorial Hospital and the [ ] Medical Center which establishes the authority of Catawba Valley IRB to review studies at both institutions.

SUMMARY OF VIOLATIONS RELATED TO IRB RECORD KEEPING (21 CFR 56.115)

1. Meeting minutes of 10/30/97, 7/10/98, 5/12/99, 7/14/99, 1/17/00, 7/11/00, 10/2/00, and 10/16/00, are not in sufficient detail to document the number of members voting for, against or abstaining on actions taken by the IRB.

2. Meeting minutes for 1997 and 2000 document that individuals were listed as attending members, however, these individuals were not listed on the IRB roster as members. There was no roster available for 1998 and there were 4 undated versions of membership rosters for 1999, therefore, it was impossible to determine who were voting members at meetings during 1998 and 1999.

3. The IRB rosters fail to document representative capacity, indications of experience or other information sufficient to describe each member's chief anticipated contributions to IRB deliberations.

4. The IRB failed to review advertisements for subject recruitment. The IRB did not review advertising for the [ ]study, and for a generic ad for Diabetes and General Screening by [ ]The IRB responded to the [ ]request for review of the advertisement with a letter that stated that the IRB was not responsible for approving or authorizing advertising for studies.

In addition to the violations of 21 CFR Part 56, your guidelines fail to have written procedures to describe how your IRB will determine whether a medical device is classified as a significant or non-significant risk device. This is required by 21 CFR 812.66 .

Administrative Restrictions

We have no assurance that your procedures are adequately protecting the rights and welfare of human subjects of research. For this reason, in accordance with 21 CFR 56.120(b)(1) and (2),

- **no new studies** that are subject to the requirements of this part are to be approved by your IRB, and

- **no new subjects** are to be admitted to ongoing studies that are subject to this part.

These restrictions do not relieve the IRB of its responsibility for receiving and responding to reports of unexpected and serious reactions and routine progress reports of ongoing studies.

Because of the departures from FDA regulations discussed above, please inform this office, in writing, within 15 working days of your receipt of this letter, of the actions you have taken or plan to take to bring the procedures of your IRB into compliance with FDA regulations. Please include a copy of any revised documents, such as written procedures, with your response. Any plans of action must include projected completed dates for each action to be accomplished.

We will review your response and determine whether the actions are adequate to permit the IRB to resume unrestricted activities. 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 will 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.

Should you have any questions, please contact Dr. Antoine El-Hage at (301) 594-1032, FAX (301) 827-5290. Your written response and any pertinent documentation should be addressed to:

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, Maryland 20855

Sincerely yours,

Martin H. Cohen, M.D.
Acting Director
Division of Scientific Investigations, HFD-45
Office of Medical Policy
Center for Drug Evaluation and Research

Enclosures:
#1 21 CFR Parts 50 and 56
#2 Form FDA 483, Inspectional Observations
#3 Letter dated May 10, 1995, to Mr. Anthony Rose, President and CEO of Catawba Memorial Hospital, from Paul Goebel, Division of Scientific Investigations