DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
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FEDERAL EXPRESS

WARNING LETTER

Eugene P. Trani, Ph.D.
President
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910 West Franklin Street
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Dear Dr. Trani:

During the periods of August 25 through 28, and September 23, 1998, and May 24 through 26, 1999, Mr. Gerald Mierle, an investigator with the Food and Drug Administration (FDA), Baltimore District Office, conducted inspections at Virginia Commonwealth University/Medical College of Virginia (VCU/MCV) Committee on the Conduct of Human Research (CCHR), an institutional review board (IRB). The purpose of those inspections was to determine whether the activities and procedures of the IRB concerning the review of clinical research involving FDA regulated products complied with applicable FDA regulations. FDA officials from the Center for Devices and Radiological Health who participated in the August 1998 inspection with Mr. Mierle were Charma A. Konnor, R.Ph., and Marian S. Linde, R.N.

Our review of the inspection reports and copies of VCU/MCV CCHR records submitted by the FDA district office revealed violations from Title 21, Code of Federal Regulations (21 CFR) Part 56 - Institutional Review Boards, Part 50 - Protection of Human Subjects and Part 812 - Investigational Device Exemption. These objectionable conditions were listed on the Form FDA-483, "Inspectional Observations,"

which was presented to and discussed with Mr. William L. Dewey, Vice President, Research and Graduate Studies, at the conclusion of the inspections. The description of violations that follows is not intended to be an all-inclusive list of practices that are in violation of federal regulations.

1) Failure to have and follow written procedures for IRB functions and operations in accordance with 21 CFR 56.108, 56.115(a)(6), and 812.66.

The IRB lacks written procedures that adequately describe the functions and operations of the IRB. The IRB maintains a large three-ring binder in the IRB administrative secretary's office that contains IRB information, including IRB policy and regulatory information. However, it contains errors and fails to describe standard operating procedures for all pertinent regulations. For example, the IRB lacks:

- written procedures that describe initial and continuing review of research and how its findings and actions are reported to the investigator and the institution;
- written procedures about determining which projects require review more often than annually;
- written procedures for determining which studies are significant risk (SR) versus non-significant risk (NSR) for medical device investigations (21 CFR 812.66); and
- written procedures for maintaining proper IRB membership that describe the selection of members and length of term, the removal of members, the use of alternate members, the use of consultants, and the training program for IRB members.

In addition, the August 13, 1998, IRB meeting convened without proper IRB membership. The prisoner consultant was not present during discussion of a prisoner protocol entitled, [redacted]

2) Failure to comply with expedited review rules in accordance with 21 CFR 56.110.

The IRB failed to review adverse events at a convened meeting. Instead, adverse events are reviewed by an expedited process. Also, our records indicate that in many cases the review and approval of changes to the protocol and informed consent were conducted in violation of the expedited review rule.

For example, on Monday, February 23, 1998, the CCHR Chairman approved an amendment to the protocol and informed consent in the [redacted] to include pediatric patients. This study does not qualify for expedited review because it is a significant risk device study, and adding a pediatric population to the eligibility criteria is a major change. Enclosed is a reference paper about expedited review, Categories of Research that may be Reviewed by the IRB through an Expedited Review Procedure (November 1998), that may be useful to the IRB.

3) Failure to adequately review the informed consent document, advertisements for research subjects, and continuing research activities in accordance with 21 CFR 56.109.

The IRB failed to include several items required under 21 CFR 50.25 in their "Standard Consent Format Instructions" for investigators. For example, the following required items are missing from the consent instructions:

- a statement that the study involves research;
- a description of the procedures to be followed;
- a statement that not joining the study will in no way affect or jeopardize the patient's current or future quality of care; and

- a list of contacts (including phone numbers) the subject should call for answers to questions about the research, and in case of research related injury.

The IRB failed to review all advertisements for the recruitment of research subjects at convened meetings. Reportedly, the secretary reviews all advertisements and forwards advertisements to the IRB Chairman when she needs help.

The IRB failed to perform continuing review of approved studies in accordance with regulations. For example, the records show the CCHR secretary was appointed a voting member of the IRB for the purpose of compiling a report of continuing-review studies. An IRB member can give special attention to a particular continuing-review study when the member has questions or objections. Otherwise, this compilation of continuing-review studies is presented to the committee for a block vote. The agency does not accept block votes for approval of studies of FDA-regulated products. Each continuing-review study must be voted upon individually.

4) Failure to take appropriate regulatory action to suspend or terminate IRB approval of research when IRB requirements are not followed. (21 CFR 56.113)

The IRB failed to secure compliance with its written policy that states studies will be administratively terminated when annual review notices or requested consent form changes are not received by the IRB. Records from the August 1999 inspection show that there were several instances where the clinical investigator failed to submit continuing review information and the IRB did not administratively

terminate the studies. Examples of protocols that were out of compliance with IRB policy were:

- CCHR #[redacted] (comparison of two marketed drugs);
- CCHR #[redacted] (randomized trial of [redacted]; and
- CCHR #[redacted] (follow-up study of [redacted]).

5) Failure to maintain IRB records as described in 21 CFR 56.115.

IRB meeting minutes were not in sufficient detail to document actions taken by the IRB. For example, the IRB meeting minutes did not document the results of voting by recording the number of members voting for, against, and abstaining for both the original and continuing review of studies.

We are concerned that your lack of written procedures 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. Because of the seriousness of the violations found during the inspections, in accordance with 21 CFR 56.110(d) the FDA suspends the VCU/MCV CCHR's use of expedited review for all FDA regulated products. This suspension is effective upon receipt of this letter and will continue until such time as the IRB is in full compliance with 21 CFR parts 50 and 56 as determined by your response to this letter and a future FDA re-inspection.

We acknowledge receipt of Drs. William L. Dewey and Robert L. Campbell's June 4, 1999, letter, which was in response

to the inspectional observations presented by Mr. Mierle. Their letter acknowledged that written procedures need to be in place. Also, they explained the IRB's ongoing efforts to assemble the elements for a formal Standard Operation Procedure (SOP) manual. This letter will become part of our official file.

If procedures have been implemented, we request that you submit a copy of these written procedures to us as part of your response to this letter. If appropriate written procedures have not yet been put into place, or are not put into place immediately, we may take further action as authorized by 21 CFR 56.120.

If you have not already done so, we strongly suggest that you convene a working group staffed with qualified people who are knowledgeable in and experienced with IRB policy and regulations to undertake the task of writing standard operating procedures that are in compliance with 21 CFR 50, 56, and all conforming regulations. Enclosed is a copy of the FDA Information Sheets, Guidance for Institutional Review Boards and Clinical Investigators, a valuable resource for writing standard operating procedures. For assistance writing IRB procedures covered under 45 CFR 46, you should contact a representative in the Office for Protection from Research Risks (OPRR), National Institutes of Health [(301) 496-7041].

Within fifteen (15) working days of receipt of this letter, please provide in writing the specific steps the IRB, the institution, or both have taken or will take to correct these violations and to prevent the recurrence of similar violations in current or future studies. Any submitted corrective action plan must include projected completion dates for each action to be accomplished.

You should direct additional responses to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch I (HFZ 311), 2098 Gaither Road, Rockville, Maryland 20850, Attn: Marian Linde, Nurse Consultant. If you have any questions or require additional time to respond, you may contact Ms. Linde at 301) 594-4723, extension 139. A copy of this letter has been sent to our Baltimore District Office, North Virginia Resident Post, 101 W. Broad St. #400, Falls Church, Virginia 22046. We request that a copy of your response be sent to that office and to the Office for Protection from Research Risks.

Sincerely,

Marma A Kouroy, R.Ph.

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

Enclosures (2)
1. FDA Information Sheets, Guidance for Institutional Review Boards and Clinical Investigators
2. Copy of November 1998, Categories of Research that May be Reviewed by the IRB through an Expedited Review Procedure

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