DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

By Certified Mail - Return Receipt Requested

Jack Hank, M.D., Executive Director
Great Lakes College of Clinical Medicine
1407-B North Wells Street
Chicago, Illinois 60610

JUL 21 2000

Dear Dr. Hank:

This letter is in reply to the Great Lakes College of Clinical Medicine (GLCCM) Institutional Review Board's (IRB's) letter dated May 26, 2000. The GLCCM IRB response letter includes revised written procedures and describes the proposed corrective actions for some of the violations described in our warning letter dated March 9, 2000, and in our follow-up letter dated April 13, 2000.

This letter is addressed to you because you represent the parent institution that is responsible for the operation of the GLCCM IRB. Although the IRB has made some progress in attempting to correct the deficiencies, many issues remain unresolved. We believe that it is important that you be directly involved in the resolution of these issues, and we request that future correspondence in this matter originate from the GLCCM parent institution.

We have the following comments about the IRB's letter dated May 26, 2000. Statements designated with "➡➡" indicate that we request a specific response or additional information.

1. **Written procedures.**

   A. We have the following comments about the May 5, 2000, version of the IRB written procedure document entitled "Basic Policy for Protection of Human Research Subjects":

      Section IV.H. The phrase "the chairperson shall review all ongoing research annually and provide his findings to the secretary" is vague. The Chairperson's specific role in conducting initial and continuing review should be specified here and elsewhere in the procedures.

      Section IV.I. (1) This section does not describe how alternate members are selected or trained. (2) The IRB appears to permit regular members who do not attend the meetings of the American College for Advancement in Medicine (ACAM) to be absent from at least two of the four

members who will be delegated to perform the in-depth review of a research proposal. We note that the "RULES" document for clinical investigators states that the initial review of the research project will be performed by at least two IRB members. (2) After receiving the IRB meeting packet two weeks prior to the next IRB meeting, will each member review all research proposals in full? Section V.B.3 states that the IRB will review the informed consent for each project, but Section V.B.1 suggests that the review of the full project may be delegated to only one or more member(s) who are assigned the in-depth review. (3) The procedure does not describe how controverted issues are resolved.

Section V.B.5. (1) The procedures should clarify whether protocol modifications that have been accepted by the primary reviewer are further reviewed, discussed, and voted on by the full IRB. If the modifications represent a significant revision to the protocol, will the study be deferred to the next meeting? If the modifications are minor administrative changes, how will the full IRB be notified? Please clarify whether members who are not the "primary reviewer(s)" will have the opportunity to discuss the comments returned to the clinical investigator in advance of the IRB meeting. It is possible that IRB members will disagree with the in-depth reviews, and that the research proposal will require additional review.

Section V.B.7. (1) The revised procedures have not clarified that the IRB must document the determination of significant/nonsignificant risk for research involving investigational medical devices. Our letter dated April 13, 2000, suggested that the significant risk/non-significant risk device determination should be described separately in the procedures. (2) As described in our letter dated April 13, 2000, the procedures should clarify how the IRB will determine the risks associated with a particular study. (3) The procedures should define the options for periodic review intervals, such as quarterly, semi-annually, or annually, and provide a brief explanation to guide the IRB members to make consistent decisions for the frequency of periodic review.

Section V.B.9.c. (1) The purpose of the reference to "community attitudes" in the regulations is to assure sensitivity to such issues in IRB review of proposed research, not to determine whether the "community attitudes, laws and morals are more restrictive than Federal requirements." Federal law does not mandate morals and community attitudes. Please revise. (2) Appendix F was not submitted as part of the May 26, 2000 response. The referenced form was not included with the other new forms developed by the IRB.

Section V.C. (1) Please explain how the IRB will process a continuing review report that arrives after the deadline and misses the next meeting of the IRB. Will the study be suspended until the next convened meeting? (2) As mentioned in our letter dated April 13, 2000, this section does not describe whether the continuing review report should be sent to the IRB Chair or to the Secretary. (3) The form entitled "Continuing Review Form" states that the completed form should be sent to the IRB Administrator. This section of the procedures does not mention the role of the IRB Chairperson, although the Chairperson's roles are briefly described in section IV.H. Are copies of the periodic reports sent to the Chairperson? (4) Who reviews the periodic reports for completeness?

Section V.D. This section does not adequately describe how protocol revisions will be processed. Will the protocol revision be reviewed by the primary reviewer(s)?

Section VI.A.6. The purpose of this section is unclear as to the clinical investigator's obligation to monitor the research projects according to Appendix E of the written procedures. Appendix E appears to represent an IRB policy that does not belong in this section of the procedures.

Section VI.A.10 refers to the emergency use of a test article. As stated in our letter dated April 13, 2000, this section should be expanded to describe in detail how the IRB will process the reports of an emergency use of a test article. We note that instructions for clinical investigators regarding the emergency use of test articles are described in section IX.A.2.

Section VI.A.12. The references to the regulations regarding charging for investigational medical devices should be cited as 21 CFR 812.7. This matter was addressed in our letter dated April 13, 2000, but the corrections are incomplete.

Section VII.C. The term "Chief Investigator" should be defined.

Section VII.D. (1) The second and third sentences imply that the adverse event is reviewed by the IRB Secretary, who then notifies the Chairperson. The procedure should clarify who is responsible for review of adverse event reports. As described in our letter dated April 13, 2000, the procedures should identify whether the initial expedited review of adverse events will be conducted by the Secretary or by the Chairperson. (2) As described in our letter dated April 13, 2000, the written procedures should define what process will be used when adverse events are submitted by the Chairman or Secretary for studies they are conducting. How will conflict of interest concerns be addressed for this situation?

(3) As described in our letter dated April 13, 2000, please clarify how the IRB will proceed if the expedited review of the adverse event indicates that the study should be stopped, or if the study will require more frequent continuing review.

Section IX.A.1. (1) Several of the requirements listed under the heading "Basic elements of informed consent" are formatting requirements that should be listed separately from a listing of the actual elements of informed consent. (2) In item [j.], the procedures should emphasize that the costs associated with this study are clearly described. (3) In item [k.], a reference to FDA should only be included in informed consent documents for studies under FDA jurisdiction. It is misleading to imply to potential study subjects that FDA has reviewed a study that is not actually under FDA jurisdiction.

Section IX.A.5. The referenced document (p. 89-90) is not attached to the written procedures.

B. We have the following comment on the IRB's document entitled "RULES":

Item 8. Please explain the statement "Any study exceeding one year without approval will be terminated."

C. We have the following comments on the IRB's document entitled "Investigational Project Guidelines":

Introduction. (1) Page 2 states that if federal funding is obtained, there will be specific guidelines to follow. This information is misleading because the clinical investigator would be obligated to submit the research proposal to another IRB that has a Multiple Projects Assurance, a Single Project Assurance, or a Cooperative Project Assurance granted by the Department of Health and Human Services Office for Human Research Protections. The GLCCM IRB does not have an Assurance in place. (2) The written procedure document should be revised to include the requirement that the IRB assess potential federal funding for a proposed research project.

Informed consent. Page 7. (1) The information regarding the period of time a clinical investigator must retain consent forms is incorrect. Clinical investigators shall retain consent forms and case histories for a period of two years following the date a marketing application is approved for the drug or biologic for the indication for which it is being investigated, or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and FDA is notified, according to 21 CFR 312.62(c) for investigational drugs, and to

21 CFR 812.140(d) for medical devices. This item was previously included in our letter dated April 13, 2000, and was not addressed in the IRB's response letter. (2) In item 11, reference to FDA should only be included in informed consent documents for studies under FDA jurisdiction. It is misleading to imply to potential study subjects that FDA has reviewed a study that is not actually under FDA jurisdiction.

Termination of a Project/Protocol. Page 9. The revisions to this section, as described in our letter dated April 13, 2000, are not adequate. This section addresses two different circumstances: if a clinical investigator discontinues a study, and if the IRB terminates a study. These are distinct situations that impose different responsibilities upon the clinical investigator, and, therefore, should be separated. The written procedures should describe how the IRB will operate in these situations.

Continuing Review. Page 9. (1) Clinical investigators do not submit "continuing review;" rather, they submit a progress report that is reviewed by the IRB to determine whether the ratio of risks and benefits has changed during the time period. (2) If a study was terminated, it is inappropriate to refer to it as a "terminated proposal." (3) The requirement to resubmit a study protocol and informed consent document for studies of longer than five years' duration is not described in the IRB's written procedures.

Adverse Reactions. Page 9. This revision does not accurately describe the IRB's policy as defined in the written procedures.

2. IRB Membership. [21 CFR § 56.107].

A. The IRB's letter dated May 26, 2000, states that a new non-affiliated member has been recruited for the IRB. We have reservations that a single non-affiliated member will provide sufficient diverse viewpoints to balance those of the GLCCM members. We are disappointed that the IRB did not go further in addressing this important issue.

B. We have concerns that at least some of the IRB members do not fully understand (1) FDA's jurisdiction over the clinical study of investigational drugs and medical devices, and (2) that the regulation of investigational biological products is not identical to the regulation of investigational drug products. At least one IRB member does not understand that investigational biological products are not subject to the policies of drug compounding by pharmacies. We do not have confidence that all IRB members are able to provide knowledgeable reviews of studies involving FDA regulated products, or to be an information resource for clinical investigators.

C. Several IRB members failed to respond to the IRB's letter describing suspension of the IRB's activities. For example, study S081 was terminated due to a lack of response from the clinical investigator, who is an IRB member. As of May 26, 2000, no responses had been provided by the IRB members who submitted studies M013, M029, and S082. We also note that the IRB does not have a policy regarding the removal of IRB members who do not comply with IRB policies.

3. **Informed consent documents. [21 CFR § 56.107].**

The IRB's response dated May 26, 2000, states that the IRB reviewed the approved consent forms for all approved studies, and that all except one were determined to be deficient. Our request for copies of the revised consent forms will be found below.

4. **We have the following comments regarding the study entitled "Induced Malaria as Therapy for HIV Infection."**

Dr. Heimlich reported to FDA in a recent undated letter (copy provided in the IRB's letter dated May 26, 2000) that the study is being conducted with approval by the appropriate Chinese authorities. In that case, it is more accurate to state that the IRB "terminated its oversight" of the study rather than "terminated" the study. The GLCCM IRB does not have the authority to terminate a study in another country.

5. **We have the following comments about the IRB's response to the list of information requested in FDA's letter dated April 13, 2000.**

A. We requested that the IRB submit a list of each study that was active, on hold, or pending before the restrictions were imposed on March 9, 2000. For each study, we requested that the IRB clearly identify whether the IRB believes the study is subject to Parts 50 and 56 of the FDA regulations.

The IRB provided a list of studies, but failed to identify the studies that are subject to parts 50 and 56 of the FDA regulations. →→ Please submit this information.

B. We requested that the IRB submit the following information for those studies which the IRB believes are subject to Parts 50 and 56 of the FDA regulations:

i. A copy of the letter from the IRB notifying the clinical investigators of FDA's restrictions for the IRB. It appears that the IRB misinterpreted our request. →→ Rather than submit a copy of the generic letter to all clinical investigators, we request that you submit a copy of the personalized letter sent to each clinical investigator.

ii. We requested a copy of the clinical investigator's letter acknowledging that enrollment was suspended, and the investigator's plan to either (1) terminate the study, or (2) submit the study to another IRB for review; in this case, we requested the identity of the new IRB that will review the research. We have the following comments from our review of the list of studies submitted with the letter dated May 26, 2000:

a. Of the 26 studies that are identified in the IRB's list, only five such letters were submitted with the IRB's letter dated May 26, 2000. →→ Please submit the remaining letters or explain why there is no response. Please explain why there are entries in some of the "comments" boxes for which no letters were submitted with the IRB's response.

b. The "comments" box states "need statement" for seven studies, is blank for three studies, and "...is checking" for one study. →→ Please explain.

c. During the inspection, IRB representatives asked the FDA investigator whether specific studies are subject to FDA jurisdiction. It is not appropriate to use an investigator's preliminary comments in response to a question during an inspection as the basis for the IRB's determination as to the need for an IND or IDE. Such a determination cannot be made without adequate review of the research proposal. The IRB should refer questions about the two specific studies to the FDA Center for Drug Evaluation and Research for complete evaluation.

d. The notations in the "comments" boxes demonstrate that the IRB does not appear to understand the separate concepts of minimal risk and nonsignificant risk (as used to describe studies with investigational devices).

e. It appears the IRB has accepted the clinical investigator's assessment that some studies do not require an IND or IDE but there is no documentation that the IRB performed an independent assessment, as requested in 5A. above.

C. We requested additional explanations of what actions the IRB has taken or will take regarding the following activities:

i. How and when the IRB plans to re-review the protocols to determine whether the research should be conducted under an IND or IDE. The IRB response letter states "the Secretary re-reviewed all protocols and provided a list to the Board as whether or not he felt the protocols needed an IND or IDE." The IRB did not submit the list to FDA. →→ Please submit this information.

ii. How and when the IRB will inform clinical investigators that the research may not be re-initiated unless and until an IND or IDE has been submitted and is permitted to proceed (i.e., not on clinical hold). The IRB's response states that the request for IND or IDE information was sent to investigators in a letter dated April 18, 2000. →→ Please submit a copy of each personalized letter to each clinical investigator.

iii. How and when the IRB plans to re-evaluate the informed consent document(s) for each study to assure that they include all required elements described in 21 CFR 50.25.

→→ Please submit the protocol and the revised/approved consent form for each study under FDA jurisdiction. Please include the IND or IDE number, or an explanation as to why each study is exempt from the requirement to obtain an IND or IDE.

Conclusion

The actions taken by the IRB as of May 26, 2000, are not adequate to permit FDA to remove the restrictions upon the IRB. The IRB remains under the following restrictions imposed on March 9, 2000, in accordance with 21 CFR 56.120(b)(1) and (2):

- ***no new studies that are subject to Parts 50 and 56 of the FDA regulations are to be approved by your IRB, and***
- ***no new subjects are to be admitted to ongoing studies that are subject to 21 CFR Parts 50 and 56 until you have received notification from this office that adequate corrections have been made.***

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

These restrictions will remain in effect until the IRB has demonstrated that it has corrected the extensive violations previously cited. The IRB must demonstrate that it is able to critically review research proposals for the risks to the safety and welfare of the human subjects, to critically evaluate proposed informed consent documents, to determine whether proposed research is under FDA jurisdiction, and to satisfy membership requirements. The restrictions will not be removed solely based on revision of the written procedures.

We will review your response and determine whether the actions are adequate to permit the IRB to resume unrestricted activities. The 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 include, but are not limited to, the termination of all ongoing studies approved by the IRB and the initiation of regulatory proceedings for disqualification of the GLCCM IRB.

Your written response should be addressed to:

Ms. Patricia Holobaugh (HFM-664)
Division of Inspections and Surveillance
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448
Telephone: (301) 827-6347

Sincerely,

Steven A. Masiello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation
and Research

cc: James Carter, M.D., IRB Chair
Great Lakes College of Clinical Medicine
430 Tulane Avenue
New Orleans, Louisiana 70112

L. Terry Chappell, M.D., Secretary
Great Lakes College of Clinical Medicine IRB
122 Thurman Street
Post Office Box 248
Bluffton, Ohio 45817