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

APR 1 3 2000

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

Dear Dr. Chappell:

This letter is in response to the Institutional Review Board's (IRB's) letter dated March 17, 2000, in which the IRB replied to the Food and Drug Administration (FDA) warning letter dated March 9, 2000. The response letter includes revised written procedures and describes the proposed corrective actions for some of the violations described in our letter. However, the IRB did not submit acceptable explanations for several significant deviations. Our review of your reply letter does not alter our view that the activities of the Institutional Review Board (IRB) represent significant violations of the regulations governing the proper oversight of clinical studies involving investigational products.

Our comments regarding your explanations will be addressed below. Questions designated with "➡➡" indicate that we request a response and additional information.

1. **Written procedures for conducting the review of research, including periodic review. [ 21 CFR 56.108(a), 56.115(a)(6) ]**

   A. We have the following comments about the March 17, 2000, version of the IRB written procedure document entitled "Basic Policy for Protection of Human Research Subjects":

   ***Section II.*** This section contains an incorrect reference to the "Federal Drug Administration."

   ***Section V.E.*** The procedures do not describe whether IRB members serve an unlimited period of time or are selected to serve for a defined term.

***Section V.F.*** Given the IRB's policy that it will review only the research of Great Lakes College of Clinical Medicine (GLCCM) members, this section should be expanded to provide examples of conflicts of interest that would require an IRB member to recuse himself/herself from deliberation for the initial or continuing review of a study. In addition, the written procedures should explicitly define how the IRB will consider research proposed by IRB members.

***Section V.H.*** In your response letter, please explain how the IRB Chair "supervises all activities of the IRB" when the current Chair lives hundreds of miles from the IRB office. Please explain how the Chair delegates expedited reviews to the Secretary when the documents are submitted only to the Secretary. It appears that the Chair does not see the documents and that the Secretary performs all expedited reviews. Please explain how the Chair designation is a functional position rather than an honorary title.

***Section V.I.*** (1) The position designations for IRB members require clarification. For example, the term "Affiliated by Laboratory" is without meaning. Each member should be designated as either affiliated or non-affiliated, and either scientific or layperson. (2) The roster should identify whether each IRB member is a member of the American College for Advancement in Medicine (ACAM) if the IRB reviews research submitted by ACAM; see item 1B, below. (3) We suggest that the Membership Roster be removed from the text of the written procedures and moved to an appendix. The membership roster is a separate document that may require frequent updates, whereas the written procedures should require less frequent revisions. (4) Additional comments about the IRB membership are found in item 2, below.

***Section VI.*** (1) This section does not describe how the administrative staff processes research proposals submitted for initial review. Some of this information is include in the IRB's "Investigational Project Guidelines" but is missing from the written procedures. (2) What are the deadlines for submission for consideration at the next scheduled meeting? A deadline is included in the IRB's "Investigational Project Guidelines" but is missing from the written procedures. (3) How will incomplete submissions be processed? (4) The response letter dated March 17, 2000, indicates that projects are now assigned a tracking number. The meeting minutes of February 25, 2000, show designations such as "M010" and "S084." The written procedures should explain the meaning of the letter and number designations so that the IRB may assign the designations in a consistent manner.

***Section VI.B.*** This section does not contain a reference to the requirement that the IRB consider the attitudes of the community in which the study is to be conducted. The procedures in *Section VII.A.12.d.* address the issue but are inadequate, as described below.

***Section VI.B.2.*** (1) There are several topics in this section. We suggest that this section be further divided so that critical elements are not overlooked. (2) It appears that you intend for this section to describe the membership requirements for a convened meeting. Please revise the sentence to clarify how the abstentions based on conflicts of interest will affect the quorum. (3) If a quorum of members is no longer met due to abstentions, the IRB may not vote to approval new research or continuing reviews. (4) The reference to minimal risk or significant risk projects and to the IRB's determination of whether proposed research involves a significant risk device should be moved to different sections. We suggest that the significant risk/non-significant risk device determination should be separate from a discussion of minimal risk/expedited review because these are distinct determinations that must be made by the IRB. From our review of the procedures and the meeting minutes of February 25, 2000, it appears that the IRB is confusing these designations.

***Section VI.B.5.*** This section should state that modifications will be required before the IRB will approve the research.

***Section VI.B.6.*** Please clarify the purpose of this section. Does this statement apply to the determination of community attitudes described in *Section VII.A.12.c?*

***Section VI.C.*** (1) The meaning of the first sentence is unclear. (2) The second sentence appears to belong in section *VI.B.* instead of this section. Who will inform the investigator when the periodic report will be due? (3) This section does not describe whether the continuing review report should be sent to the IRB Chair or to the Secretary. (4) The revised procedures describe that the IRB will suspend a project if the clinical investigator fails to provide a periodic report or submits an incomplete periodic report. The written procedures should describe how the IRB will process a periodic report that is subsequently submitted and is deemed complete. Will the study remain suspended until the next quarterly meeting of the IRB? (5) The content of progress reports should be described in detail so that clinical investigators will provide the IRB with interpretable periodic reports. The FDA warning letter dated March 9, 2000, noted examples of inadequate periodic reports that did not provide interpretable information to the IRB. The revised procedures do not

establish what information must be provided in the periodic reports, or the format in which the information should be presented. The IRB may choose to develop a report form so that all required information will be in a standard format.

***Section VI.E.*** (1) The procedures should identify whether the initial expedited review of adverse events will be conducted by the Secretary or by the Chair. The procedure states that "if the reviewer determines that the adverse event was serious or presented unanticipated risks to human subjects, the IRB will notify the FDA immediately." The process for the reviewer to report this to the Chair or Secretary is not defined. This process should be explained so that IRB members understand how they are to proceed in this instance. (2) The written procedures should define what process will be used when adverse events are submitted by the Chair or Secretary for studies they are conducting. How will conflict of interest concerns be addressed for this situation?

***Section VII.A.1.*** This section does not describe whether the IRB will require an Investigational New Drug Application (IND) or Investigational Device Exemption (IDE) before the IRB will review the study. Will the IRB review a study that FDA placed on clinical hold (for an IND) or has been disapproved (for an IDE)?

***Section VII.A.6*** should be expanded to explain what constitutes a "monitoring plan" and describe what type of studies would require such a plan.

***Section VII.A.10*** should be expanded to describe in detail how the IRB will process the reports of an emergency use of a test article.

***Section VII.A.12.*** (1) It appears that this section should be incorporated into *Section VI* because none of the research is local to the IRB.
(2) To avoid possible confusion, we suggest the use of a word other than "regulations" in the opening sentence to this section. These statements may reflect IRB policy but they do not state an FDA regulation.

***Section VII.A.12.c.*** (1) It is not acceptable for the GLCCM IRB to review research to be conducted in foreign countries. All foreign research studies should be reviewed by the appropriate Ministry of Health or equivalent office for that country. All references to research conducted outside of the Unites States should be removed from the IRB's written procedures.

(2) This section does not define how the IRB will assess community attitudes regarding specific proposed research. For example, will the IRB conduct on-site assessments? Who will the IRB contact in this matter? It will be important for the IRB to document the discussions and findings to confirm that the information was obtained from sources independent from the proposed research study, and unbiased (neither a proponent nor an opponent) toward the proposed research.

***Section VII.A.12.d.*** Please explain how the IRB will gather this information. Will the IRB make these assessments before a proposed study is placed on the agenda for the next meeting? Who will make the decisions that the qualifications of the sponsor, investigators, and institutions are adequate?

***Section VII.A.13.*** The references to the regulations regarding charging for investigational products may be cited as 21 CFR 312.7, or 21 CFR § 812.7. The current format is incorrect.

***Section VIII.A.*** This section should be expanded to explain in detail what happens if the reviewer disapproves the matter under expedited review. For example, is the research suspended, or is the matter deferred until the next regularly scheduled meeting? Are copies of the materials distributed to each IRB member for discussion at the next meeting?

***Section VIII.B.*** The procedures should explain how the Secretary will notify the IRB members of expedited review approvals, such as through correspondence, discussion at the next IRB meeting, or through some other type of communication.

***Section VIII.C.*** Will new investigators and institutions be assessed according to *Section VII.A.12.d*?

***Section VIII.D.*** Please explain the IRB procedures 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.*** The inspection revealed that the IRB uses a checklist to provide a status report or summary of each study. In your response to Item 12.J in FDA's warning letter, you stated that "the checklist was just a personal note, not part of the official IRB file." The written procedures should describe the systems and tools, such as paper files, checklists, and/or computer system, used to track the status of each project and maintain the records described in *Section IX.*

***Section IX.A.2.*** The meeting minutes should document that previously requested protocol changes and/or clarifications have been received by the IRB.

***Section IX.A.3.*** The written procedures should describe how the meeting minutes will document how the periodic review of research is conducted.

B. The written procedures should explain the relationship between the ACAM and the GLCCM IRB since the IRB conducts two of its quarterly meetings during the semi-annual ACAM conferences. The written procedures should define whether the IRB will review research proposals submitted by ACAM members. Can ACAM or GLCCM override the decisions made by the IRB? Are members of ACAM represented on the IRB in addition to Dr. Rozema? If the IRB does not review research proposed by ACAM members, please explain why the GLCCM IRB meets at the semi-annual ACAM meetings. If no formal agreement is in place for such review, you may respond to these issues in your response letter.

C. Will the IRB cooperatively review research that is to be conducted at hospitals or other institutions that have an institutional IRB? If so, the written procedures should explain how these arrangements will be processed. The third sentence in *Section VII.A.12.d* implies that hospitals may only be used for emergency services.

**2. IRB Membership. [ 21 CFR § 56.107 ]**

The purpose of non-affiliated members is to provide the IRB with viewpoints outside of the GLCCM. Non-affiliated members help ensure that the IRB membership is diverse and represents community attitudes. Because the IRB is not local for the majority of the studies reviewed, the IRB will need to develop new policies to ensure that the IRB membership will include diverse perspectives and community attitudes. The current membership structure does not invite open discussion of scientific matters because all IRB members have demonstrated affiliations with the GLCCM. Given the nature of the IRB's convened meetings in varying locations, we anticipate that corrections may require the consideration of significant changes to the IRB's operations.

Your response letter states your belief that Ms. Buckley qualifies as the IRB's sole member who is not otherwise affiliated with the institution. Your response explains that one year ago Ms. Buckley left the employment of Dr. Guilford, a scientific member of the IRB, and that she is not affiliated with GLCCM in any other way. We disagree with your response. Ms. Buckley's former employment

by a GLCCM IRB member creates a connection to the institution. Ms. Buckley's current self-employed status does not remove the connection or the perspective she acquired during her recent involvement as an IRB member.

Likewise, your suggestion that Dr. Jaffe might also be considered "unaffiliated" is also not reasonable. Your response letter states that Dr. Jaffe speaks "for GLCCM from time to time." This relationship suggests a connection that renders Dr. Jaffe an inappropriate choice to be a non-affiliated member because he may not represent a viewpoint independent from the GLCCM perspective.

FDA believes that the IRB should be able to recruit individuals who have no circumstantial connections with the IRB. The IRB should strive to add members who have no connections of any sort to the activities of the GLCCM. It is essential that the IRB consider the viewpoints of members who are independent from GLCCM so that the IRB will include diverse perspectives to help assure that the rights and welfare of study subjects are considered during the review of proposed research.

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

Your response states that the IRB will discuss the consent form examples cited in the warning letters at the next IRB meeting scheduled for May 5, 2000. The consent forms submitted by Dr. Page and Dr. Heimlich and approved by the IRB are representative examples of deficient consent forms. The consent forms for other studies are also deficient.

→→ Please describe what steps the IRB will take to re-review the consent form for each study that was active before the IRB suspension went into effect on March 9, 2000.

4. **We have the following comments on the IRB's form titled "Investigational Project Guidelines":**

***Introduction.*** The second paragraph of page 1 should be deleted for the following reasons: (1) The purpose of an IRB is to protect the rights and welfare of the human subjects of research. (2) The IRB does not supervise or oversee the activities of approved research studies. (3) The statement regarding the IRB's status according to FDA regulations is incorrect and is superfluous to this document. (4) For information about studies with biological products, you may contact the Center for Biologics Evaluation and Research at 800-835-4709 or 301-827-1800.

Page 2 states that the IRB is to be notified when funding is obtained. Depending on the source of any funding, the IRB may be required to obtain a Multiple Projects Assurance, a Single Project Assurance, or a Cooperative Project Assurance by the Department of Health and Human Services Office for Protection From Research Risks. The written procedures should be revised to incorporate the IRB's assessment in this regard.

Page 2 refers to a "Rules" sheet which was not enclosed with the IRB's response letter.

***Project/Protocol Information.*** Page 4 does not request an IND or IDE number.

***Project/Protocol Information. Item 8*** (page 6) should be revised to separate the possible costs involved in the study. As addressed in item 1K of the warning letter dated March 9, 2000, FDA prohibits charging for investigational drugs and biologics unless specifically approved with the limitations described in 21 CFR § 312.7. The limitations for charging for investigational devices are set forth in 21 CFR § 812.7. Clinical investigators should separate costs associated with the investigational product from other costs so that the IRB may determine whether the research conforms to FDA requirements in this regard.

***Informed consent.*** Page 8. 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 in 21 CFR 812.140(d) for medical devices.

***Termination of a Project/Protocol.*** Page 10. (1) This paragraph 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 10. The IRB has not developed a form for continuing review.

***Adverse Reactions.*** Page 10. Clinical investigators are required to report all unanticipated problems involving risk to human subjects or others. Please clarify the time frames in which these reports are to be submitted to the IRB.

5. **We have the following comments regarding the GLCCM web site's description of the IRB.** The web s te contains the following statement: "The IRB has met National Institutes of Health guidelines." This statement is misleading in that as of March 9, 2000, your IRB has not been granted a Multiple Projects Assurance, a Single Projec: Assurance, or a Cooperative Project Assurance by the Office for Protection From Research Risks. →→ Please remove this statement from your web site.

6. **We have the following comments and questions regarding the February 25, 2000, meeting minutes that were submitted with the IRB's response dated March 17, 2000:**

   A. Regarding study M022, the minutes state "this study was approved 9/20/97 and was placed on hold for over one year." Meeting minutes should provide sufficient background to explain the history in such situations. →→ Please explain why the approved study was placed on hold, and describe the circumstances that have since changed to allow the study to proceed.

   B. The IRB's uses of the term "significant risk" in reference to studies that do not involve a medical device. Please refer to the discussion in item 1 above regarding the written procedures *Section VI.B.2.*

7. **We have the following comments regarding the IRB's review and approval of the study entitled "Induced Malaria as Therapy for HIV Infection."**

   We strongly disagree that the IRB properly considered the scientific merit of the study and that the protocol minimized risks to subjects concerning this study, as expressed in you response letter dated March 17, 2000, for the following reasons:

   A. The protocol is inadequate in that it does not describe what testing is done to screen the malarial parasite donors. The direct injection of blood from a malaria parasite donor into a study subject would not be permitted in the U.S. because cultured malaria parasites are available. The IRB did not review information about how subjects and malaria parasite donors are recruited and screened.

   B The statement in the response letter that "the IRB's approach [to this study] was no different than if the research was conducted in the U.S." demonstrates that the IRB appears to lack the expertise or experience to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice.

C. We reject your position that the IRB was able to consider the community attitudes of the Chinese population in which the research was to be conducted. Given the great differences between Chinese and American cultures, we do not accept that the GLCCM was capable of understanding Chinese attitudes about the research. This is one reason, among many, that the academic institution in China that was associated with the research, as referenced in your response letter, should have obtained governmental and approval from a local IRB (or equivalent body).

D. Although Dr. Heimlich's Foundation is apparently underwriting this research study, he has no responsibilities for subject screening, study procedures, or evaluation of the subjects, and appears to have no direct supervisory role over the study. Dr. Heimlich is not obligated to obtain IRB approval for his limited involvement in this study, and, indeed, in this case, it was inappropriate for him to do so.

E. The IRB file for this study did not contain the Chinese translation of the protocol or consent form. In general, when study subjects are non-English speakers, the IRB must assure that the consent form translation is accurate.

F. Please describe the IRB's efforts to determine that this study had been approved by the appropriate office in the Ministry of Health and by the local institution(s) where the research was conducted.

The IRB should rescind approval of this study and defer the human subject protection responsibilities to the responsible Chinese authorities. →→ Please provide documentation that the IRB has informed the Chinese clinical investigator of his responsibility to obtain the appropriate Chinese government and local institutional approval for the research.

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, and to satisfy membership requirements. The restrictions will not be removed solely based on revision of the written procedures.

In addition, please submit the following information in your response:

1. Please provide a list of each study that was active, on hold, or pending before the restrictions were imposed on March 9, 2000. For each study, clearly identify whether you believe the study is subject to Parts 50 and 56 of the FDA regulations.

2. For those studies which you believe are subject to Parts 50 and 56 of the FDA regulations, please provide the following:

   A. A copy of the letter from the IRB notifying them of FDA's restrictions for the IRB.

   B. 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; identify the new IRB that will review the research.

   C. Please explain 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.

      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).

      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.

      iv. How and when the IRB will review the Internet advertising of studies previously approved by the IRB. References to GLCCM IRB approval should be removed from the web pages.

3. Please explain whether the GLCCM Executive Director or other person or group will review and/or approve the IRB's written procedures.

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 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.

Your written response should be addressed to:

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Sincerely,

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