
SUMMARY OF FINDINGS:

This inspection of a medical association Institutional Review Board (IRB) was conducted as follow-up to an inspection assignment dated 9/27/99 from Patricia A. Holobaugh, Center for Biologics Evaluation and Research, Bioresearch Monitoring, HFM-650. The assignment requests an unannounced, directed inspection of the referenced IRB and its operations. Additionally, the assignment requests specific information/documentation associated with the IRB's operations. Included in this request was the review of the files for at least six (6) studies that have been reviewed by the IRB. Three of the study files audited were specified in the inspection assignment while an additional three were selected from the IRB's list of studies approved since 1996 (see Exhibit 1). The IRB files that were audited as part of this inspection were associated with the following studies:

1. [REDACTED] (note the inspection assignment refers to this study and the Gene Activated Therapy or GAT study as two separate studies. However, this inspection revealed that the referenced studies were actually the same study);
2. [REDACTED]. Investigational Proposal for the Study of [REDACTED]
3. [REDACTED] - [REDACTED] (note-this study was never approved by the IRB as the Clinical Investigator (CI) never submitted all information needed to review the research proposal.);
4. [REDACTED]
5. [REDACTED];
6. [REDACTED]

The three studies selected for audit in addition to those referenced in the inspection assignment were chosen because they appear to be studies that involved FDA regulated articles.

A complete copy of the IRB's file for each of the above studies was obtained as part of this inspection. These files are attached as Exhibits 2-7, respectively

The previous inspection of this IRB was conducted on 10/16/97 and received a final classification of [REDACTED]

The current inspection was conducted in accordance with the inspection assignment and CP7348.809- Institutional Review Board. The deficiencies in the IRB's operations observed during this inspection are summarized as follows:

1. The IRB's written policies and procedures do not completely and accurately describe the actual policies and procedures employed by the IRB in it's review and approval/disapproval of proposed and ongoing clinical research.
2. IRB members having a conflict of interest in proposed research submitted to the IRB for review and approval are not always excluded from participating in the deliberation and voting on the research proposal.
3. Continuing review of approved research is not always conducted at convened meetings of the IRB.
4. The provision for expedited review of proposed research is not always appropriately applied by the IRB.
5. Review and approval of proposed research at convened meetings of the IRB is not always performed with a majority of the members present.
6. Research projects not qualifying for expedited review are not always reviewed and approved at convened meetings of the IRB.

In addition to the above observations, it also appears that this IRB does not consistently determine during it's review of proposed research whether or not the investigational article requires and/or has in place an Investigational New Drug Application (IND). The IRB has also approved Informed Consent (I/C) documents that appear to be significantly deficient in that they do not embody all of the basic elements required in such documents.

At the conclusion of this inspection, a FD-483, Inspectional Observations citing the above deficiencies, was issued to Dr. L. Terry Chappell, IRB Secretary. Betsey T. Angus, IRB Administrative Support Secretary, accompanied Dr. Chappell. Each of the observations cited in the FD-483 was acknowledged by Dr. Chappell and was discussed in detail. Dr. Chappell indicated that immediate action would be taken to implement corrective measures. In keeping with the Medical Device Industry Initiative

Pilot Expansion Program, each observation cited in the FD-483 was annotated as either "correction promised by 6/1/00" or "observation corrected but not verified".

HISTORY OF BUSINESS

The Great Lakes College of Clinical Medicine (GLCCM) was established in 1983 for the purpose of promoting alternative therapies in the treatment of chronic disease and educating healthcare professionals in the use of alternative therapies. The GLCCM membership is comprised of physicians throughout the United States and the World.

The GLCCM IRB was established in 1990 to serve as the central review authority for research proposals submitted by GLCCM members. Membership in the GLCCM is a prerequisite to having research proposals reviewed by the GLCCM IRB. Members are also required to attend at least one GLCCM meeting per year. The GLCCM IRB convenes formal meetings to review research four (4) times per year at the semiannual GLCCM meetings and at the semiannual meetings of the American College of Advancement of Medicine (ACAM). The current IRB Chairman is Dr. James P. Carter formerly of the Tulane University School of Medicine and Nutrition. Since the previous inspection, Dr. Carter has retired from Tulane University but remains active in the GLCCM IRB. Dr. Carter maintains an office at 430 Tulane Avenue, New Orleans, LA 70112.

The IRB Administrative Office is located at Dr. Chappell's Clinical Practice, The Celebration of Health Center, 122 Thurman St., PO Box 248, Bluffton, Ohio 45817. All study files and records pertaining to the IRB's activities are maintained at this location. Although Dr. Carter remains the IRB Chairman, all correspondence associated with this inspection should be forwarded to Dr. Chappell at the Celebration of Health Center.

I have reviewed all of the OEI data contained in FACTS for the GLCCM IRB and found no discrepancies. No changes were necessary.

PERSONS INTERVIEWED

As directed by the inspection assignment no prior notice was given to the IRB before beginning this inspection. Upon my arrival at the Celebration of Health Center, credentials were presented and an FD-482, Notice of Inspection with addendum was issued to L. Terry Chappell, IRB Secretary. Betsy T. Angus, IRB Administrative Secretary, accompanied Dr. Chappell. All information requested during this inspection was provided by Dr. Chappell and Ms. Angus.

Prior to the close of this inspection, a mutually agreeable date and time for the exit interview was set with Dr. Chappell. I was accompanied, Guy W. Cartwright, SCSO,

CIN-DO/COL-RP. At the beginning of the exit interview, a FD-483 - Inspectional Observations was issued to Dr. Chappell who was accompanied by Ms. Angus.

THE IRB MEMBERSHIP

The current IRB membership is comprised of 16-full time members and has both scientific and nonscientific representation as well as members not affiliated with GLCCM (E. Buckley, R.N., and B. Smith). The IRB currently does not use alternate members. A copy of the GLCCM membership for 1999 is attached as Exhibit 8. Additionally, a copy of the curriculum vitae for each IRB member is attached as Exhibit 9.

Based upon my review of the IRB meeting minutes and individual study files, I determined that IRB members with a conflict of interest in proposed research projects submitted to the IRB have participated in the deliberation and voting on the subject research. This deficiency was cited in the FD-483 and is discussed in greater detail in the "Objectionable Conditions/Discussion with Management" heading of this report.

WRITTEN PROCEDURES

A copy of the IRB's document entitled "Basic Policy for Protection of Human Research Subjects for the Great Lakes College of Clinical Medicine" is attached as Exhibit 10. This document represents the IRB's most current version of its written policies and procedures. A detailed review of this document was performed as part of this inspection. The document was found to be significantly deficient in that it fails to describe the actual procedures used by the IRB for conducting initial and continuing review of research and for reporting its findings to Clinical Investigator (CI); for determining which projects require review more often than annually and which projects require verification from sources other than the CI to ensure that no changes have occurred since the previous IRB review; for ensuring proper reporting to the IRB of changes in research activity and for ensuring that changes in approved research during the period of IRB approval are not initiated without IRB review and approval except when necessary to eliminate immediate hazards to the study subjects; for ensuring proper reporting of any unanticipated problems involving risks to human subjects or others and any instances of serious or continuing noncompliance with the IRB's requirements; and for ensuring prompt reporting of the IRB's suspension or termination of approval of research projects.

The IRB's written policies and procedures are for the most part taken directly from the applicable regulations including 21 CFR parts 50 and 56. In many instances, the policies and procedures are no more than a direct quote of the applicable regulations. It appears that this document was written not for the purpose of having a relevant, functional, and useful document for the IRB's operations but more for the purpose of

fulfilling a regulatory requirement for written procedures. This deficiency was cited in the FD-483 Inspectional Observation as observation number 1 and is discussed in greater detail under the "Objectionable Conditions/Discussion with Management" heading of this report.

INITIAL AND CONTINUING IRB REVIEW AND APPROVAL OF INVESTIGATIONAL USE OF FDA REGULATED PRODUCTS

The IRB has the authority to approve, modify or disapprove proposed research studies submitted by the GLCCM membership. The IRB also has the authority to modify or terminate approval of ongoing studies. Ms. Angus and Dr. Chappell informed me that no other institution may override negative or restrictive decisions imposed by the IRB.

The IRB does have a system in place for distributing materials associated with proposed research studies to IRB members. All prospective CIs are provided with an initial information packet that includes a cover letter, the IRB rules, application for membership in the GLCCM if not already a member, and the investigational project guidelines that include a project/protocol information sheet and questionnaire. A copy of the IRB information packet that is provided to each prospective CI is attached as Exhibit 11.

The minimum documentation requirements for initial review of research proposals by the IRB includes the completed project/protocol information sheets, the CI's curriculum vitae, the formal study protocol, and the I/C document. A preliminary review of the research proposal is typically conducted by three (3) IRB members who are usually selected by Dr. Chappell based upon the member's knowledge and expertise in the proposed area of research. If the project is accepted following preliminary review, it is slated for review at the next meeting of the IRB. Prior to the IRB meeting, a complete copy of the research proposal including the project/protocol information sheets, the CI's curriculum vitae, the formal study protocol, and the informed consent document is forwarded to each IRB member.

Ms. Angus asked me if it was necessary for each member to receive a complete copy of the research proposal material submitted by the CI. I informed her that this was not required and that it would be acceptable to provide the IRB members with a summary or abstract of the protocol and the informed consent document as long as at least one of the IRB's members is assigned to perform an in-depth evaluation of the research proposal, the informed consent document, and if available, the investigators brochure. I also informed Ms. Angus that each IRB member must have access to the complete research proposal if only the minimum required documents are provided to the members.

My review of the IRB's records including the meeting minutes and individual study files revealed that not all proposed research is reviewed at convened meetings of the IRB. Likewise, the IRB does not routinely perform continuing review of approved research projects at the IRB meetings. For example, a research project involving the use of ██████████ ██████████ in ██████████ and ██████████ individuals was not reviewed and approved at a convened meeting of the IRB. Instead, the research proposal materials were submitted to each IRB member for review. Voting on the study was accomplished by each member faxing his or her vote to the IRB Administrative Office.

In the case of continuing review, the required progress reports submitted by CIs are not reviewed and voted upon at convened IRB meetings. Instead, the progress reports are submitted to each IRB member for review but no discussion and voting to reapprove, put on hold, or terminate the study is performed. The IRB does not notify the CIs in writing of any actions taken as a result of the progress reports.

The above deficiencies were cited in the FD-483 and are discussed in greater detail under the "Objectionable Conditions/Discussion" with management heading of this report.

My review of the IRB's meeting minutes from 1996 to the present (Exhibit 12) revealed that although a majority of the IRB members is not always present at the convened meetings, research approvals are always granted by a majority of the IRB members present at the meeting. The IRB's failure to have a majority of the members present at convened meetings during which proposed research was reviewed and approved on was cited in the FD-483 and is discussed in greater detail under the "Objectionable Conditions/Discussion with Management" heading of this report.

The IRB's written policies and procedures do not describe how the IRB ensures that CIs have fully implemented required modifications to the research prior to enrolling study subjects. Also the IRB's policies and procedures do not include a procedure for making nonsignificant risk determinations for investigational devices. The IRB's written policies and procedures do indicate that the IRB will decide the frequency of review for given projects, however, the procedures do not describe the criteria (i.e. degree of risk) used to establish the continuing review frequency.

CONTINUING REVIEW OF RESEARCH

The IRB's policy for continuing review of approved research is that all approved studies require updates/progress reports at six-month intervals following the initial approval regardless of the risk associated with the study. I informed Ms. Angus and Dr. Chappell that the continuing review interval should be set on a study by study basis and that the criteria used to establish the continuing review interval should include the degree of risk

associated with the study. I indicated that, in some cases, the IRB may decide that the appropriate continuing review interval for a study should be the maximum of one year and for other studies involving higher degrees of risks to the study subjects, continuing review may need to be more frequent.

I was informed by Ms. Angus that progress report forms are forwarded to the CI prior to the six month due date. A copy of the update/progress report form used by the IRB is attached as Exhibit 13. My review of individual study files revealed that, in most cases, the CIs promptly submit the update/progress report forms as required by the IRB. Ms. Angus informed me that copies of all progress reports submitted by CIs are forwarded to each IRB member. Dr. Chappell reviews most of the progress reports submitted by CIs, however, progress reports are not evaluated by the full IRB at convened meetings, and no determination is made by the IRB as to whether the study should be amended, terminated, or allowed to continue as originally approved. As previously indicated, the CIs are not notified in writing regarding any action taken by the IRB on progress reports.

Except in those cases where protocols and I/C documents are amended after initial study approval, the protocol and informed consent document originally approved by the IRB continue to be used by the CIs. All protocol amendments and modifications to the informed consent document were found to be submitted to and approved by the IRB. Also serious/unexpected reaction reports appear to be promptly submitted to the IRB.

IRB REPORTING TO THE CLINICAL INVESTIGATORS AND THE INSTITUTION

Upon approval of a given study, the IRB notifies the CI in writing of its decision. An example of the letter forwarded to the CI is attached as Exhibit 14. The letter indicates the CI's responsibilities for reporting to the IRB any changes to the approved research prior to implementing the changes, and for promptly reporting any unanticipated problems involving risks to study subjects.

The letter also indicates that updates on the research must be submitted to the IRB twice a year and that noncompliance with this requirement and the IRB's rules will result in the termination of the research. The CI is provided with the IRB's rules and investigational project guidelines (see Exhibit 11) as part of the initial information packet forwarded to each prospective CI.

As previously reported, the IRB's policy for continuing review of approved research currently requires that progress reports be submitted twice a year for all studies. Establishing the continuing review interval is not a part of the IRB's initial review process and is not set on a study by study basis taking into consideration the degree of risk associated with the study.

I was informed by Ms. Angus that in the event a study is disapproved, the CI is also notified of the IRB's action in writing and the letter would include the IRB's reasons for disapproval. In the event that a study is disapproved by the IRB, the CI is given the opportunity to respond at a convened meeting of the IRB or in writing.

My review of the IRB's individual study files revealed that copies of all correspondence between the IRB and the CI including initial approval letters, and study updates/progress reports are maintained by the IRB.

EXPEDITED REVIEW

The IRB has employed expedited review procedures in the approval of proposed research. However, the IRB's use of expedited review procedures has not always been appropriate and may have been used, in at least one instance, as a means of granting interim approval of proposed research pending review at a later convened meeting of the IRB. One instance of such misuse of expedited review procedures involved a study entitled [REDACTED]

[REDACTED]. IRB members Chappell and Nielson on 12/22/97 initially approved this study using expedited procedures. The study was presented at a convened meeting of the IRB on 3/14/98 and was approved. The study did not meet the criteria for expedited review in that it does not appear in the Federal Register list of research categories exempted from full IRB review and did not involve only minimal risk to the study subjects nor did it involve only minor changes to previously approved research.

This example was cited in the FD-483 and is discussed in greater detail under the "Objectionable Conditions/Discussion with Management" heading of this report.

EMERGENCY REVIEW

The IRB does have a policy regarding the emergency use of a test article. The policy appears to be consistent with the current regulatory requirements in that emergency use of a test article is permitted as long as such use is reported to the IRB within five (5) working days and that any subsequent use is subject to IRB review (see page ____ of Exhibit 10). My review of the IRB records since 1996 revealed no instances of emergency use of a test article by a CI.

INFORMED CONSENT

Of the six- (6) study files selected for review during this inspection, five (5) had been approved by the IRB. Each of these studies has associated I/C documents. These documents were included in the IRB's initial review of the research proposals. As part

of the current inspection the I/C documents were evaluated for the required basic elements of informed consent and for any other apparent deficiencies. Four (4) of the I/C documents were found to contain significant deficiencies. These deficiencies are described as follows:

1. [REDACTED]
 - a. There is no statement indicating that the study involves research.
 - b. The expected duration of the subject's participation in the study is not stated.
 - c. There is no description of the procedures to be followed.
 - d. Procedures that are experimental are not identified.
 - e. There is no description of any reasonably foreseeable risks or discomforts to the subject.
 - f. Section 8. -Exculpatory language is used through which the subject is apparently made to waive their legal rights.
 - g. There is no statement indicating that participation in the study is voluntary and that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled.
 - h. There is no description of additional costs that may result from the subject's participation in the research.
 - i. There is no indication of the approximate number of subjects involved in the study;
 - j. Technical terminology such as cytokines, antibodies, tumor stem cells, macrophages, plasmapheresis, centrifugation, subcutaneously, and neoplasm are not defined or expressed in terms that are understandable to the layperson.

2. [REDACTED]
 - a. Section 1. -This statement appears to suggest that this investigational therapy is superior to conventional therapies ("a form of immunotherapy combined with appropriate nutritional support to effect a superior outcome as compared to conventional therapy").
 - b. There is no disclosure of appropriate alternative procedures or courses of treatment that might be advantageous to the subject.
 - c. Section 13. -The statement in this section appears to suggest that this investigational therapy is safe. ("Previous treatment of nine thousand patients in other countries provide adequate support and information that is reasonable, safe to begin this study.")
 - d. There is no statement indicating that participation in the study is voluntary and that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled to and that the subject may discontinue participation

in the study at any time without loss of benefits to which the subject is otherwise entitled.

3. [REDACTED]
 - a. The expected duration of the subject's participation is not clear.
 - b. treatment that might be advantageous to the subject if injury occurs and what they consist of.
 - c. There is no statement indicating that participation in the study is voluntary and that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled.

4. [REDACTED]
 - a. Under the section "Waiver of Liability", exculpatory language is used through which the subject or representative is made to waive the subject's legal rights.
 - b. On the signature page, the subject or representative appears to be only giving consent to allow publication of the research results and not to participate in the study.

The I/C documents for the studies referenced above are attached with the complete study files that were collected as part of this inspection (see Exhibits 2,3,5, & 7). Based upon the I/C document deficiencies noted above, it appears that the IRB's review of I/C documents is not always adequate.

OBJECTIONABLE CONDITIONS/DISCUSSION WITH MANAGEMENT

At the conclusion of this inspection, an exit interview was held with Dr. Chappell who was accompanied by Ms. Angus. I was accompanied by SCSO, Guy W. Cartwright. At this time, a FD-483, Inspectional Observations was issued to Dr. Chappell. Each of the observations cited in the FD-483 was discussed in detail with Dr. Chappell and Ms. Angus. In accordance with the Medical Device Industry Initiative Pilot Expansion Program, each observation was also annotated to reflect corrective action promised or corrective action implemented but not verified.

The observations cited in the FD-483 are listed and discussed as follows:

1. The document entitled "Basic Policy for Protection of Human Research Subjects for The Great Lakes College of Clinical Medicine is not a relevant and functional document in that it does not accurately and completely describe the actual policies and procedures employed by the IRB in its review and approval/disapproval of proposed and ongoing clinical research involving human subjects. The document is, in large part, no more than a compilation of direct quotes taken from Title 21,

Part 50 & 56 of the Code of Federal Regulations that contains the general requirements for the composition, operation and responsibility of Institutional Review Boards and the general requirements for Informed Consent of Human Subjects. **Observation annotated as correction promised by 6/1/00.**

As previously mentioned, a comprehensive review of the IRB's policies and procedures was performed as part of this inspection. I found that, for the most part, the subject document does not describe the actual policies and procedures used by the IRB in its operations. Instead, the document is filled with page after page of statements taken directly from the IRB and Informed Consent Regulations. I informed both Dr. Chappell and Ms. Angus that the intent of the regulations is to provide an IRB with the minimum requirements necessary to be in compliance and that they are written in a manner that affords an IRB the latitude and flexibility to fashion its policies and procedures in a manner that results in a document that is relevant, functional, and unique to the IRB's.

Dr. Chappell acknowledged this observation and indicated that the IRB would rewrite its policies and procedures to reflect the IRB's actual activities.

2. IRB members who have a conflicting interest in proposed research submitted to the IRB for review and approval are not always excluded from participation in the deliberation and voting on the subject research. In at least two instances, an IRB member having a conflicting interest in proposed research was allowed to take part in the deliberation and voting on the research.

For example, [REDACTED] an IRB member, was actively involved in deliberation and voting on the research projects entitled "[REDACTED] [REDACTED] and [REDACTED]". In the case of [REDACTED] study, [REDACTED] laboratory [REDACTED] manufactured the [REDACTED] vaccines used in the study and in the case of the [REDACTED] study, [REDACTED] laboratory served as the testing laboratory for the study until 6/98. [REDACTED] should have been excluded from deliberation and voting on these studies, however, he made the motion to approve both studies and was including in the voting. **Observation annotated as corrected but not verified.**

The minutes for the IRB meeting at which the [REDACTED] study was reviewed and approved (9/20/97) indicate that [REDACTED] made the motion to approve the study. Due to the fact that his laboratory would be involved in the preparation of the study vaccines as indicated in the study protocol, [REDACTED] had a conflict of interest in the study and should not have been involved in deliberation and voting process. The meeting

Part 50 & 56 of the Code of Federal Regulations that contains the general requirements for the composition, operation and responsibility of Institutional Review Boards and the general requirements for Informed Consent of Human Subjects. **Observation annotated as correction promised by 6/1/00.**

As previously mentioned, a comprehensive review of the IRB's policies and procedures was performed as part of this inspection. I found that, for the most part, the subject document does not describe the actual policies and procedures used by the IRB in its operations. Instead, the document is filled with page after page of statements taken directly from the IRB and Informed Consent Regulations. I informed both Dr. Chappell and Ms. Angus that the intent of the regulations is to provide an IRB with the minimum requirements necessary to be in compliance and that they are written in a manner that affords an IRB the latitude and flexibility to fashion its policies and procedures in a manner that results in a document that is relevant, functional, and unique to the IRB's.

Dr. Chappell acknowledged this observation and indicated that the IRB would rewrite its policies and procedures to reflect the IRB's actual activities.

2. IRB members who have a conflicting interest in proposed research submitted to the IRB for review and approval are not always excluded from participation in the deliberation and voting on the subject research. In at least two instances, an IRB member having a conflicting interest in proposed research was allowed to take part in the deliberation and voting on the research.

For example, Dr. George Kindness, an IRB member, was actively involved in deliberation and voting on the research projects entitled "[REDACTED] (REDACTED) and [REDACTED] (REDACTED)". In the case of [REDACTED] study, Dr. Kindness' laboratory ([REDACTED] (REDACTED)) manufactured the [REDACTED] vaccines used in the study and in the case of the [REDACTED] study, Dr. Kindness' laboratory served as the testing laboratory for the study until 6/98. Dr. Kindness should have been excluded from deliberation and voting on these studies, however, he made the motion to approve both studies and was including in the voting. **Observation annotated as corrected but not verified.**

The minutes for the IRB meeting at which the [REDACTED] study was reviewed and approved (9/20/97) indicate that Dr. Kindness made the motion to approve the study. Due to the fact that his laboratory would be involved in the preparation of the study vaccines as indicated in the study protocol, Dr. Kindness had a conflict of interest in the study and should not have been involved in deliberation and voting process. The meeting

minutes for 9/20/97 documenting Dr. Kindness' participation in the deliberation and voting activities are attached as Exhibit 12. The protocol for this study, which specifies the use of Dr. Kindness' laboratory for study vaccine preparation, is contained in the study file, which is attached as Exhibit 2.

The [REDACTED] study was reviewed and approved at the IRB meeting conducted on 4/25/97. As with the [REDACTED] study, Dr. Kindness participated in the deliberation and voting on this study as evidenced by the meeting minutes. The minutes indicate that Dr. Kindness made the motion to approve the study. Dr. Kindness' laboratory was used to perform the laboratory testing associated with this study until 6/98. Due to this conflict of interest, Dr. Kindness should have been excluded from the deliberation and voting process. The meeting minutes for 4/25/97 documenting Dr. Kindness' participation the deliberation and voting activities for this study are attached as 12. The [REDACTED] study file is attached as Exhibit 3.

I was informed by Dr. Chappell that the IRB's policy is not to allow IRB members with a conflict of interest in a given research proposal to participate in the deliberation and voting process. He indicated that in the case of the [REDACTED] study, the IRB was not aware at the time of approval that Dr. Kindness' lab would be used in the study. He also indicated that the IRB is very sensitive to this issue and currently makes every effort to ensure that IRB members do not participate in the deliberation and voting process for studies in which they have a conflict of interest. My review of the meeting minutes revealed no examples of this practice in 1998 or 1999.

3. Continuing review of approved research is not always conducted at convened meetings of the IRB. In most cases, updates/progress reports submitted by clinical investigators are not discussed at the IRB meetings. Copies of the updates/progress reports are distributed to the IRB members prior to the meetings, however, in most cases no discussion and voting takes place and no action (i.e. reapproval/termination) is taken. Likewise, the clinical investigators are not notified of actions taken by the IRB, if any, as a result of the submitted progress reports.
Observation annotated as correction promised by 6/1/00.

Ms. Angus informed me that the IRB currently requires updates on approved research every six- (6) months. She indicated that copies of the updates are forwarded to each IRB member for review. However, the progress reports are not currently discussed at the IRB meetings and no action such as reapproval, hold, or termination is taken. An example of the IRB's current handling of progress reports is seen in the meeting minutes. For example, the minutes from the meeting held on 5/7/99 (see Exhibit 12) indicate under Updates that "all updates received were reviewed by the board prior to the meeting, there was no discussion".

I informed Dr. Chappell that the study progress reports were considered an integral part of the continuing review process and that they should be included in the IRB's meeting agenda, discussed to the extent necessary, and a vote should be taken to reapprove, put on hold or terminate the research. I also indicated that the CI should be notified in writing of the IRB's action taken as a result of the progress report. Dr. Chappell acknowledged this deficiency and indicated that the IRB's revised written procedures would require that progress reports be reviewed at convened meetings of the IRB and that discussion and voting would be performed as part of the continuing review process.

4. The provision for expedited review of proposed research is not always appropriately applied by the IRB. For example, on 12/22/97 a research project designed to evaluate the clinical relevance of [REDACTED] with [REDACTED] was approved using expedited review procedures. **Observation annotated as corrected but not verified.**

This study involves the removal of lead from [REDACTED] patients using [REDACTED] delivered to the subjects in a rectal suppository. Based upon the regulatory criteria necessary for the use of expedited review procedures, it appears that this study did not qualify for such review and therefore should have been presented at a convened meeting of the IRB.

The study does not fall into one of the categories listed in the Federal Register and does not appear to involve only minimal risk. The minutes from the IRB meeting held on 3/14/98 indicate that the study was approved by expedited review on 12/22/97. The study was presented at the 3/14/98 meeting and was approved. Both safety and efficacy were a concern of the IRB as evidenced by statements in the meeting minutes including "Dr. Trowbridge-questioned the safety and efficacy with respect to absorption of [REDACTED] from suppositories in a [REDACTED] population".

A copy of the protocol for this study as well as the IRB approval letter are attached As Exhibit 15.

5. Review and approval of proposed research at convened meetings of the IRB is not always performed with a majority of the members present. For example, at the IRB meeting held on 5/1/98 only six (6) of the 16 members were eligible to vote due to three (3) members being excluded for conflict of interest. Although the quorum requirements were met at the beginning of the meeting with nine (9) of the 16 members present and eligible to vote, the quorum failed with the exclusion of the three- (3) previously eligible members. Deliberation and voting

was performed for the [REDACTED]
[REDACTED]. The research received unanimous approval by the (6) members present.

Likewise, at the IRB meeting held on 5/7/99, a majority of the members (10 of 16) were present at the beginning of the meeting. Two members were excluded due to conflict of interest and left the room for discussion and voting on revisions to the [REDACTED] Registry. As a result, the number of eligible members was reduced to eight (8) causing the quorum to fail. Nevertheless, deliberation and voting on the revisions proceeded. The revisions received unanimous approval from the eight remaining members.

At the IRB meeting held on 11/20/98 only eight (8) of the 16 members were present. Although a majority of the members were not present at this meeting, research projects were reviewed and approved. **Observation annotated as corrected but not verified.**

As previously indicated, the IRB meets four (4) times a year with two (2) meetings held at the semiannual GLCCM meetings and two (2) held at the ACAM meetings. Ms. Angus informed me that not all of the IRB members are members of the ACAM and, as a result, the number of IRB members present at the ACAM IRB meetings is typically lower than the number present at the GLCCM meetings. She indicated that as a result of the lower attendance at the ACAM meetings it has been difficult at times for the IRB to have a majority of the members present for the ACAM IRB meetings.

I informed Ms. Angus and Dr. Chappell that although the practice of submitting proposed research materials to IRB members for review and voting by phone polling or by FAX was not allowed, but that it was acceptable to have members who are not able to attend a meeting participate by teleconferencing. Ms. Angus indicated that the IRB would pursue this option for future meetings where a majority of the members may not be physically present.

The meeting minutes that document the above observations are attached as Exhibit 12.

6. Research projects not qualifying for expedited review are not always reviewed and approved at convened meetings of the IRB. In the case of the projects entitled [REDACTED] and [REDACTED] [REDACTED] study materials were forwarded to

the members and voting was accomplished by each member faxing their vote to the IRB office. Both projects were approved. **Observation annotated as corrected but not verified.**

Dr. Chappell brought it to my attention during the discussion of this observation that the latter example cited was not accurate. The meeting minutes for 9/21/96 appear to indicate that Dr. Schrader's [REDACTED] project was previously approved by FAX. Dr. Chappell pointed out that the FAX approval was not referring to the [REDACTED] project itself but to the addition of new investigators Platt, Resseger and Block. He indicated that the [REDACTED] project had been approved at an earlier meeting of the IRB. Post-Inspectional review of the previous EIR and Exhibits revealed this to be accurate. The [REDACTED] project was approved at the 9/18/93 meeting of the IRB. As a result, the latter example cited on the FD-483 referencing the [REDACTED] project was removed.

In the case of the [REDACTED] study, IRB members were forwarded the research proposal materials for review. The letter that accompanied the material indicated that the CI had submitted the research too late for the next meeting and that he would like to have the study reviewed A.S.A.P. Instead of scheduling the study for review at the next possible meeting, the IRB members were asked to FAX their vote on the study to the IRB office. The Faxed ballots used to approve this study are contained in the [REDACTED] study file, which is attached as Exhibit 7. I informed Dr. Chappell that voting by phone or by FAX was not acceptable due to the fact that there is no member interaction and discussion possible by using this method of approval. Dr. Chappell acknowledged this observation and indicated that in the future this method would not be used.

It should also be noted that [REDACTED] is an approved drug for use in the evaluation of exocrine pancreas function, the diagnosis of pancreatic carcinoma, and the diagnosis of gastrinoma. [REDACTED] is being investigated in this study for the treatment of [REDACTED], an extra label indication. There does not appear to be an approved IND in effect for this additional indication.

As previously mentioned, it appears that this IRB does not consistently determine whether or not test articles associated with proposed research require an Investigational New Drug Application (IND). In the past, the IRB has approved studies where the investigational article required an IND but did not have one in effect. Examples of this practice include the [REDACTED] Study, the [REDACTED] Study, the [REDACTED] Study, the [REDACTED] Study, the [REDACTED] Study, the study involving the use of [REDACTED] delivered in rectal suppositories for the removal of [REDACTED] patients. With the exception of the [REDACTED] Lead detoxification study, these studies were all approved at convened meetings of the IRB on 9/20/97, 4/25/97, & 9/18/93, 3/13/99, respectively. The [REDACTED] study, as indicated, was approved at two IRB meetings. The [REDACTED] Lead detoxification in [REDACTED] patients was approved by expedited review on 12/22/97.

The IRB does have a policy requiring potential CIs to submit documentation with research proposals that an approved IND is in effect if required. This policy is covered in the IRB Information Packet submitted to prospective CIs (see Exhibit 11).

ATTACHMENTS

1. Inspection Assignment Dated 9/27/99.
2. FD-482, Notice of Inspection.
3. FD-483, Inspectional Observations

EXHIBITS

1. List of Studies Reviewed by the IRB from 1996 to the Present.
2. [REDACTED] Study File.
3. [REDACTED] Study File.
4. [REDACTED] Study File.
5. [REDACTED] Study File.
6. [REDACTED] Registry Study File.
7. [REDACTED] Study File.
8. GLCCM IRB Membership Roster.
9. Curriculum Vitae for IRB Members.
10. GLCCM IRB Policies and Procedures.
11. IRB/Clinical Investigator Packet.
12. IRB Meeting Minutes from 1996 to Present.
13. Sample, IRB Update/Progress Report Form.
14. Sample, IRB Study Approval Letter.
15. Protocol and IRB Approval Letter for the Study [REDACTED]
[REDACTED]
[REDACTED]

Hugh M. McClure III

Hugh M. McClure III
Investigator 218



5221438 B

Quality Control Page

This document was provided by: FOI Services, Inc

11 Firstfield Road
Gaithersburg MD 20878-1704 USA
Phone: 301-975-9400
Fax: 301-975-0702
Email: infofoi@foiservices.com

Do you need additional U.S. Government information?

Since 1975, FOI Services, Inc has specialized in acquiring government files using the Freedom of Information Act. We have millions of pages of unpublished documentation already on file and available for immediate delivery.

Many of the documents you need are available for immediate downloading at:

www.foiservices.com

Unless specified otherwise, all of FOI Services' documents have been released by the U.S. Government under the provisions of the Freedom of Information Act and are therefore available to the general public. FOI Services, Inc. does not guarantee the accuracy of any of the information in these documents; the documents will be faithful copies of the information supplied to FOI Services, Inc.