DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

WARNING LETTER

OVERNIGHT DELIVERY

Ref. No. : 98-HFD-340-1001

OCT 23 1997

Dennis Hall
President
Baptist Health System
Emmett R. Johnson Building
3500 Blue Lake Drive
Birmingham, Alabama 35283-0605

Dear Mr. Hall:

From February 27 to March 6, 1997, Patricia S. Smith, an investigator with the Nashville District Office of the Food and Drug Administration (FDA), conducted an inspection of the Baptist Medical Center-Montclair (BMCM) Institutional Review Board (IRB). The purpose of this inspection was to determine whether your procedures for the protection of human subjects complied with Title 21, Code of Federal Regulations (CFR), Parts 50 and 56 [see appendices B and C in enclosure #1]. These regulations apply to clinical studies of products regulated by FDA. This inspection was also to confirm that adequate correction of the violations noted during the inspection of March 29-31, 1991, had been made.

At the conclusion of the inspection, Ms. Smith issued a Form FDA 483 [enclosure #2] to Richard O. Russell, Jr., M.D., IRB Chairman, which described the deviations from requirements specified under 21 CFR Part 50 and 56 that she had identified during the inspection. Ms. Smith also discussed these observed deficiencies with Karl M. Nelson, Ph.D., IRB Administrator, and Bettye G. Means, IRB Secretary.

Our review of the inspection report and accompanying documentation shows that your IRB is operating significantly out of compliance with FDA regulations as contained in 21 CFR Parts 50 and 56. Further, the inspection report shows that the IRB has failed to correct the violations noted during the previous inspection of March 29-31, 1991, as described in our July 17, 1991, letter to you [enclosure # 3]. The cited violations discussed below may not be all inclusive of the deficiencies in your IRB operation. You are responsible for assuring compliance with all FDA regulations specified under 21 CFR Parts 50 and 56.

IRB Procedural Violations

1. Each IRB that reviews clinical studies subject to 21 CFR Parts 50 and 56 of the FDA regulations must have and follow written procedures that specifically describe the IRB's functions and operations, as required by 21 CFR 56.108 [see Appendix H entitled "**A Self-evaluation Checklist for IRBs**" in enclosure #1]. The inspection report shows that your IRB has failed to take corrective actions to assure that the IRB's written procedures are in compliance with applicable FDA regulations under 21 CFR Parts 50 and 56 in response to the procedural deficiencies described in our July 17, 1991 letter to you [see item I.1. in enclosure #2].

2. The FDA regulations require that a majority of IRB members, including at least one member whose primary concerns are in nonscientific areas, be present to constitute a quorum and that approval of research requires a majority vote of those present [21 CFR 56.108(c)]. The inspection report shows that the IRB has failed on numerous occasions to have a majority of the IRB members present when reviewing and approving proposed research at convened meetings [see item II.2. in enclosure #2]. For example, the 1994-95 IRB roster records 13 voting IRB members [enclosure #4], however, the minutes for the September 14, 1995, IRB meeting documents that only five voting IRB members were present (at least seven voting members were required for a quorum) [enclosure #5].

3. The written operating procedures for your IRB must describe the process to be followed for conducting continuing review of ongoing research [21 CFR 56.108(a)(1)] and for determining which projects require continuing review more often than once a year [21 CFR 56.108(a)(2)]. The IRB procedures should insure that a progress report is received from the clinical investigator and continuing review is performed prior to the expiration date of the specified approval period which is not to exceed one year [21 CFR 56.109(e)]. The inspection report shows that, in many cases, the IRB has conducted continuing reviews of ongoing studies significantly past the expiration of the annual approval period [see item III.1. in enclosure #2]. Further, the inspection report shows that the IRB has conducted continuing review of ongoing previously approved studies absent written progress reports from clinical investigators [see item III.1. in enclosure #2].

4. The inspection report shows that the IRB Chairperson reviews and approves the continuing review of research studies by the use of an "expedited" approval procedure [see item III.2. in enclosure #2]. This "expedited" approval procedure does not meet the requirements of 21 CFR 56.110. Continuing review of active studies that do not meet the criteria for expedited initial review, as outlined in 21 CFR 56.110(b), must be conducted at a convened meeting of a quorum of the IRB membership.

5. The inspection report shows that the IRB Secretary approved an "emergency use" of an investigational drug by the use of an "expedited" approval procedure [see enclosure #6 and item III.2. in enclosure #2]. This "expedited" approval procedure for emergency use of an investigational drug does not meet the requirements of 21 CFR 56.110. A clinical investigation that is subject to regulation by FDA must not be started without review and approval at a convened meeting by the IRB unless one of the following conditions apply: (a) the study involves no more than minimal risk, as defined in 21 CFR 56.110(b) and is eligible for expedited IRB review, (b) the condition is life-threatening, as described in 21 CFR 56.102(d) of the regulations and the procedures outlined in 21 CFR 56.104(c) are followed, or (c) the requirements for IRB review and approval have been waived by the FDA.

IRB Membership Violations

6. The inspection report shows that the IRB has failed to formally appoint and identify alternate members [see items II.1., 2. and 3. in enclosure #2]. Although the use of alternate

members is not specifically addressed in the IRB regulations, FDA accepts this procedure provided that the alternate IRB members are formally appointed and identified on the IRB roster [21 CFR 56.115(a)(5)].

IRB Record Violations

7. The inspection report shows that, on several occasions, the minutes of IRB meetings have failed to document the vote on IRB actions, as required by 21 CFR 56.115(a)(2) [see item IV. in enclosure #2]. Further, the IRB minutes, at least on one occasion, have failed to document the non-participation of an IRB member due to a conflicting interest in the proposed research to be voted on, as required by 21 CFR 56.107(e) [see item IV. in enclosure #2].

8. The inspection report shows that the minutes of IRB meetings show all persons in attendance without differentiating representative status, i.e., staff, non-voting IRB members, alternate IRB members, investigators, visitors, etc. [see items II.1. and 3. in enclosure #2]. The inspection report also shows that the IRB has failed to document and maintain an IRB roster that contains an accurate listing of IRB members, as required by 21 CFR 56.115(a)(5) [see item II.1. in enclosure #2]. Accordingly, the IRB has failed to prepare minutes that are in sufficient detail to show IRB member attendance and the numerical results of voting IRB members at convened meetings, as required by 21 CFR 56.115(a)(2).

Administrative Restrictions

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

- *no new studies that are subject to 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 apply to the emergency use of an investigational material when the conditions described in 21 CFR 56.102(d) exist and the procedures followed by your institution meet or exceed the requirements described in 21 CFR 56.104(c). Neither do these restrictions relieve the IRB from receiving and reacting to proposed amendments, reports of unexpected and serious reactions and routine progress reports from ongoing studies.

Please inform this office, in writing, within fifteen (15) working days from the date of receipt of this letter, of the corrective actions you have taken or plan to take to bring the procedures of your IRB into compliance with FDA's regulations. If your response is not adequate, we may take further administrative sanctions as authorized by 21 CFR 56.120 and 56.121. These sanctions may include, but are not limited to, the termination of all previous studies approved by your IRB and the initiation of regulatory proceedings for disqualification of your IRB.

We are enclosing a copy of the FDA Information Sheets for your information [enclosure #1]. If you have any questions, please contact Mr. Anthony E. Rodgers at (301) 594-1026, Fax: (301) 594-1204. Your written response should be addressed to:

Anthony E. Rodgers, Acting Team Leader
Human Subject Protection Team, (HFD-343)
Division of Scientific Investigations
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

Sincerely yours,

David A. Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations
Office of Compliance
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