DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WARNING LETTER

AUG 15 2008

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Luis A. Medina, M.D.
IRB Chairman
Hospital Municipal de San Juan
PMB 498
P.O. Box 70344
San Juan, PR 00936

Ref: 08-HFD-45-0801

Dear Dr. Medina:

Between November 15 and 21, 2007, Lt. Luis O. Rodriguez, representing the Food and Drug Administration (FDA), inspected the Institutional Review Board (IRB) at Hospital Municipal de San Juan. The purpose of this inspection was to determine whether the IRB procedures for the protection of human subjects complied with Title 21 of the Code of Federal Regulations (CFR), Parts 50 and 56. These regulations apply to clinical studies of products regulated by FDA. We are aware that at the conclusion of the inspection, our investigator presented and discussed with you, a Form FDA 483, Inspectional Observations.

From our review of the establishment inspection report, the documents submitted with that report, and your written response dated December 3, 2007, we conclude that the IRB did not adhere to the applicable statutory requirements and FDA regulations governing the protection of human subjects. We with to emphasize the following:

1. The IRB has not prepared and maintained adequate documentation of IRB activities. Minutes of IRB meetings have not been prepared in sufficient detail to show actions taken by the IRB [21 CFR 56.115(a)(2)].

   a. For protocol [ ] "Phase I/II, Open-Label, Pharmacokinetic and Safety Study of a Novel [ ] the IRB sent a letter to the clinical investigator dated August 19, 2006 stating that the IRB re-approved the protocol. There is no mention of protocol [ ] in the

minutes of the August 10, 2006 IRB meeting or in any other documentation. Therefore, due to the lack of adequate detail in the IRB meeting minutes and other documents, we are unable to confirm that the study was re-approved at a convened meeting as required by FDA regulations. [See 21 CFR 56.108(c)].

b. All approval decisions must be made during a convened IRB meeting or through the expedited review process. [See 21 CFR 56.108(c)]. Approval decisions from convened IRB meetings must be in the IRB meeting minutes [21 CFR 56.115(a)(2)].

Our inspection revealed nine instances in which approval dates correspond with IRB meeting dates, but IRB actions are not documented in the minutes as noted in the table below:

Protocol	Document	Date of Approval	IRB Meeting Date	Approval Documented in Minutes?
	Spanish/English Consent Form Amendment	2/9/06	2/9/06	no
	Spanish/English Consent Forms for Specimen Storage	2/8/07	2/8/07	no
	Assent waiver	2/9/06	2/9/06	no
	English/Spanish Consent Forms for Specimen Storage	2/9/06	2/9/06	no
	English/Spanish Information Sheet	2/9/06	2/9/06	no
	Amendment #4	8/10/06	8/10/06	no
	Continuing Review	2/8/07	2/8/07	no
	Progress Report	2/8/07	2/8/07	no
	Change of Principal Investigator in Consent Forms	9/13/07	9/13/07	no

In addition, our inspection revealed three instances in which approval dates do not correspond to IRB meeting dates, and there is no documentation explaining the type of review procedure used. San Juan IRB's expedited review procedure states that all members will be informed about expedited review approvals by discussing those approvals at the following meeting; therefore, any expedited review approvals should have been noted in the meeting minutes of the subsequent IRB meeting. [See 21 CFR 56.110(c) and San Juan IRB's Written Procedures].

Protocol	Document	Date of Approval	IRB Meeting Date	Approval Documented in Minutes?
[redacted]	Patient Instructions	10/3/05	10/13/05	no
	Continuing Review	8/19/06	8/10/06	no
	Continuing Review	2/16/07	2/8/07	no

2. For other than expedited reviews, the IRB does not always review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas [21 CFR 56.108(c)].

   Our inspection revealed that the IRB reviewed and approved research at the April 20, 2006, meeting without the presence of at least one member whose primary concerns are in nonscientific areas. According to the Attendance Sheet for the April 20, 2006 meeting, the following members were present: Dr. Luis A. Medina (pediatrician), [redacted] (epidemiologist), [redacted] (pharmacist) and [redacted] (registered nurse). [redacted] (community representative) and [redacted] (legal advisor) were both excused from this meeting.

3. The IRB failed to follow FDA regulations pertaining to review of research, which require that an IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity [21 CFR 56.109(e)].

   a. For protocol [redacted] there is no documentation in the IRB's files that the investigator was notified of the October 3, 2005 approval of a Patient Information Sheet. In addition, on January 30, 2006, the clinical site submitted three documents to the IRB pertaining to Specimen Storage at Repositories funded by NICHD: 1) Information Sheet (Spanish and English); 2) Repository Consent Form for Parent (Spanish and English); and 3) Repository Consent Form For Youth (Spanish and English). There is no documentation that the investigator was notified of the approval of the consent forms.

   b. For protocol [redacted] "Intensive Pharmacokinectic Studies of [redacted] there is no documentation in the IRB's files that the investigator was informed of the April 20, 2006 approvals of Consent Forms for Specimen Storage Funded by the National Institute of Child Health and Human Development (NICHD), and Parent Fact Sheets (English and Spanish).

4. In approving research in which some or all of the subjects are children, the IRB failed to determine that all research is in compliance with 21 CFR Part 50, Subpart D, Additional Safeguards for Children in Clinical Investigations [21 CFR 56.111(c)].

   The IRB failed to make determinations that research was in compliance with 21 CFR Part 50, Subpart D, in protocol [ ] among others. Subpart D requires the IRB to make a determination that the clinical investigation meets the requirements of one of these categories of research [50.51 (minimal risk), 50.52 (greater than minimal risk, but presenting the prospect of direct benefit), or 50.53 (greater that minimal risk and no prospect of direct benefit)]. San Juan IRB made determinations under Department of Health and Human Services regulations under Title 45, Part 46, Subpart D – Additional Protections for Children Involved as Subjects in Research in correspondence with investigators without referencing 21 CFR Subpart D. In addition, the determinations of protocol [ ] compliance with Title 45, Part 46, Subpart D are internally inconsistent.

   In the IRB's May 17, 2007 correspondence to the investigator for protocol [ ] "A Phase I Study of the Safety, Tolerance and Pharmacokinetics of [ ] notifying of IRB approval of Version 2.0 of the protocol and the Spanish and English Informed Consents, the IRB states "the protocol complies with the regulation 45 CFR §46.406 that implies "research involving minimal risk and no prospect of direct benefit to individual subjects but likely to yield generalizable knowledge about the subject's disorder or condition to subjects or others." The IRB has misstated this regulation, as 45 CFR 46.406 pertains to research involving **greater** (emphasis added) than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

   Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests [21 CFR 56.102(i)]. In September 13, 2007 correspondence to the investigator for protocol [ ] in which the IRB approved a change in principal investigators, the IRB states that "the protocol complies with the regulation 45 CFR §46.404 that implies research not involving greater than minimal risk to subjects or others." However, as a phase I study of investigational drugs, protocol [ ] does not appear to meet the definition of minimal risk.

We acknowledge your statements that you reviewed your written procedures, revised certain IRB voting requirements, and implemented an internal review of the meeting minutes; however, your response does not adequately address all of the observations noted during our inspection. We request that you implement a procedure that will ensure timely review of the meeting minutes for accuracy. In addition, you must implement a procedure to ensure that all IRB members are informed when an expedited review procedure is used and documentation of expedited review. The IRB must also implement a procedure to ensure that correspondence regarding all IRB actions is issued to investigators. Finally, the IRB must develop procedures for review of clinical investigations that involve children as research subjects. We note that the IRB has been attempting to do this using Department of Health and Human Services regulations, 45 CFR Part 46. For clinical investigations of FDA-regulated products, the IRB must find and document that the clinical investigation(s) meet the requirements of FDA regulations, 21 CFR Part 50, Subpart D – Additional Safeguards for Children in Clinical Investigations. The IRB may approve only those clinical investigations that satisfy the criteria described in 50.51 (clinical investigations not involving greater than minimal risk), 50.52 (clinical investigations involving greater than minimal risk, but presenting the prospect of direct benefit to individual subjects), or 50.53 (clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition).

This letter is not intended to be an all-inclusive list of deficiencies for the protocols reviewed and approved by the IRB. It is your responsibility to assure that San Juan IRB's practices and procedures fully comply with all applicable statutes and regulations. Because of the departures from FDA regulations discussed above, please inform this office, in writing, within fifteen (15) working days of your receipt of this letter, of the actions you have taken or plan to take to prevent similar violations in the future. Failure to adequately and promptly explain the violations noted above may result in regulatory action without further notice.

If you have any questions, please contact Constance Lewin, M.D., M.P.H., at 301-796-3397; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

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Sincerely yours,

Leslie K. Ball, M.D.
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