

# Inspections, Compliance, Enforcement, and Criminal Investigations

**Linzer, Dov M.D. 6/12/09**

## **WARNING LETTER**

**CERTIFIED MAIL  
RETURN RECEIPT REQUESTED**

09-HFD-45-06-01

Dov Linzer, M.D.  
302 NW 179th Avenue, Suite 102  
HealthwoRx  
Pembroke Pines, FL 33029

Dear Dr. Linzer

Between December 3 and 15, 2008, CDR Ileana Barreto-Pettit, representing the Food and Drug Administration (FDA), conducted an investigation and met with you, to review your conduct of a clinical investigation (Protocol **(b) (4)** entitled **(b) (4)** of the investigational drug **(b) (4)** performed for **(b) (4)**).

This inspection is a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report, the documents submitted with that report, and your written response dated December 29, 2008, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We are aware that at the conclusion of the inspection, CDR Barreto-Pettit presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

**1. You failed to personally conduct or supervise the clinical investigation [21 CFR 312.60].**

When you signed the investigator statement (Form FDA 1572) for the above referenced clinical investigation, you agreed to take on the responsibilities of a clinical investigator at your site. Your general responsibilities (21 CFR 312.60) include ensuring that the investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; protecting the rights, safety and welfare of subjects under your care; and ensuring control of drugs under investigation. You specifically agreed to personally conduct the clinical studies or to supervise those aspects of the studies that you did not personally conduct. While you may delegate certain study tasks to individuals qualified to perform them, as clinical investigator, you may not delegate your general responsibilities. Our investigation indicates that your supervision of personnel to whom you delegated study tasks was not adequate to ensure that the clinical trial was conducted according to the signed investigator statement, the investigational plan, and applicable regulations, and in a manner that protected the rights, safety, and welfare of human subjects. Furthermore, FDA's investigation found that you had little involvement in this study.

According to the trial staff list for Protocol **(b) (4)**, your clinical research coordinators, **(b) (4)** and **(b) (4)**, were delegated responsibilities, including but not limited to, affirmation of inclusion and exclusion criteria and assessment of adverse events (AEs), serious adverse events (SAEs), and study endpoints. You had informed the FDA investigator that as you were inexperienced in conducting clinical trials, you mainly relied on your clinical research coordinators to conduct the study and complete the study's paperwork. In FDA's review of the resumes of Mr. **(b) (4)** and Ms. **(b) (4)**, who were the primary study coordinators during the time of enrollment and participation of the subjects in the study, these individuals did not appear to be qualified, certified, or significantly medically trained and licensed to be independently making judgments related to determination of eligibility of subjects for enrollment into the study and/or making the determination as to whether or not adverse events were related to the use of the investigational drug.

In addition, monitoring reports identified that, subsequent to the closure of this study at your site and the termination of both Mr. **(b) (4)** and Ms. **(b) (4)**, your site attempted to rectify the numerous deficiencies that were identified by the monitors during the monitoring visits. We note that new study coordinators were assigned the tasks of rectifying the case report forms (CRFs) with the source documentation and filling out AE and SAE Case Report Forms. In rectifying this information, source documents show that your new study coordinators were also making determinations as to whether AEs and SAEs experienced by subjects during the course of the study were related to the use of the investigational drug. FDA notes that it is unclear how your new study coordinators could adequately rectify the case histories at your site and also make the determinations that AEs and SAEs experienced by the subjects during the course of the study were related or not related to the use of the investigational drug, as they were not part of the original study.

Your lack of supervision over the study resulted in the significant findings as detailed below, and raises significant concerns with respect to data integrity and how you protected the rights, safety, and welfare of subjects who were enrolled into this study.

**2. You failed to obtain the informed consent of each human subject in accordance with 21 CFR part 50 [21 CFR 312.60].**

FDA's regulations at 21 CFR 50.20 state that, except as provided in 21 CFR 50.23 and 21 CFR 50.24, no investigator may involve a human being as a subject in research covered by the regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. The regulation specifies that an investigator shall seek such consent only under circumstances that provide the prospective subject or the subject's representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. Section 50.27 of FDA's regulations further provides that informed consent shall be documented by the use of a written consent document, which is to be signed by the subject or subject's representative only after the subject or the subject's representative is given adequate opportunity to read the document.

In a letter dated December 14, 2005, the IRB informed your site that they had approved the protocol and the informed consent document version 10/19/05. In a letter dated May 26, 2006, the IRB informed your site that they had approved the revised informed consent document (version 5/23/06), which included new information related to the background and purpose of the study, study treatment visits, and pregnancy risks, and requested that your site "have all currently enrolled subjects sign the revised consent at their next scheduled visit and use it for all new enrollees."

A. You failed to re-consent 7 subjects (#020, 022, 025, 033, 042, 044, and 045) with revised informed consent document version 5/23/06.

B. You failed to re-consent 11 subjects (#001, 007, 013, 024, 036, 041, 043, 048, 049, 053, and 056) in a timely manner at their next scheduled visit per the IRB's requirement. Specifically, the protocol specified that subsequent to the randomization of subjects into the study, subjects were to have monthly hepatic function tests performed; thus, your site was required to see the subjects at least monthly. In FDA's review of the documents, we note that several months had elapsed prior to your site re-consenting these subjects with the revised consent form. The revised informed consent document, version 5/23/06, provided information that may have affected the subjects' willingness to stay in the study, because it warned them of additional risks of participating in the study and also provided new information about the study. Thus, your delay in re-consenting these subjects with the revised consent document leads to significant concerns about the adequacy of your oversight over the study to ensure the protection of the rights, safety and welfare of the subjects enrolled in

this study.

C. Subject #060 signed the informed consent document to be enrolled into the study on August 17, 2006. Your site consented this subject into the study utilizing the outdated informed consent version 10/19/05. You should have utilized informed consent document version 5/23/06, which was in effect at the time the subject enrolled into the study.

Per your December 29, 2008 written response, you promised that in the future all subjects will be consented with all of the revised versions of the informed consent forms. In addition, you provided a standard operating procedure (SOP) detailing how your site will handle the informed consent documentation and process. FDA acknowledges your assurances that corrective actions have been taken to prevent similar findings from occurring in any future studies. While these corrective actions appear appropriate, it was the absence of such measures during the conduct of these trials that led to the violations listed above, and which raises our concern for your approach to assuring appropriate human subject protection.

**3. You failed to conduct the studies or ensure they were conducted according to the investigational plan [21 CFR 312.60].**

A. The protocol specified that to be included in the study, the subject was to have documentation of **(b) (4)** as follows:

1. There is electrocardiogram (ECG) documented **(b) (4)** on the day of screening or randomization;
2. The patient has had a symptomatic episode of paroxysmal or persistent **(b) (4)** documented by 12 lead ECG within six months prior to randomization; or
3. There is documentation of symptomatic or asymptomatic paroxysmal or persistent **(b) (4)** on two separate occasions, at least one day apart, one of which is within six months prior to randomization.

Source documents showed that Subjects #003 and #015 did not meet this inclusion criterion, but were randomized into the study and dispensed study drug.

B. The protocol specified that subjects with severe renal impairment (estimated creatinine clearance < 30 mL/min) were to be excluded from the study. Lab results identified that Subject #003's screening creatinine clearance was 21 mL/min and thus met this exclusionary criterion. We note, however, that your site randomized this subject into the study.

C. The protocol stated that subjects with active liver disease, including but not limited to (a) Persistent ALT, AST, Alkaline Phosphatase > 2 X Upper Limit of Normal (ULN); (b) known active Hepatitis C; (c) active Hepatitis B; and (d) active Hepatitis A were to be excluded from the study. The protocol further noted that patients with a known history of Hepatitis B or C must undergo hepatitis serology for Hepatitis B and C prior to inclusion in the study.

1. Records indicate that Subject #047 had screening visit lab samples taken for hepatitis testing on May 4, 2006 and the results of the screening labs faxed to your site on June 13, 2006 showed that the subject was positive for Hepatitis C. We note, however, that prior to receiving the results of the hepatitis screening, your site had already randomized the subject into the study and initiated treatment with the investigational drug on May 17, 2006.

2. Your site failed to perform hepatitis screening tests on Subjects #033, #042, and #056 to ensure that these subjects did not meet this exclusion criterion prior to randomization of the subjects into the study.

D. The protocol stated that subjects with contraindications to **(b) (4)** treatment were to be excluded from the study. Records indicate that Subject #062 had been hospitalized for **(b) (4)** toxicity with **(b) (6)** on **(b) (6)**, prior to enrollment into the study, and thus met this exclusion criterion. Your site, however, randomized this subject into the study on September 7, 2006.

E. The protocol stated that in addition to documented **(b) (4)**, the subject must have at least one protocol specified additional risk factor for **(b) (4)** in order to be included into the study. Source records indicate that Subject #009 did not meet any of the protocol specified additional risk factors for **(b) (4)** required for inclusion into the study. However, your site randomized this subject into the study.

F. The protocol specified that one of the safety tests to be conducted on subjects enrolled into the study was hepatic function testing. Specifically, the protocol required that hepatic function (ALT, AST, Alkaline Phosphatase, Bilirubin) testing was to be evaluated every month during the first 12 months of treatment and every four months thereafter. Based on the review of the results from these tests, additional procedures may be performed to ensure the safety of the subjects. In the review of the source documents at your site, FDA could not verify that your site performed hepatic function tests at monthly intervals. Examples include, but were not limited to the following:

Subject #	Month(s) of missing hepatic function tests
003	April 2006
011	April 2006
018	October, November & December 2006
024	August, September, November and December 2006
033	May and June 2006
049	September and October 2006
056	August and October 2006
062	October 2006

G. The protocol specified that whenever a patient terminated from the study, either prematurely or according to the protocol, a final follow-up visit (visit 98) was to be performed. At this visit, (1) information such as adverse events, bleeding events, efficacy events, and changes in concomitant medication since last visit were to be recorded, (2) study procedures such as a physical exam, vital signs, standard safety lab, and 12-lead ECG were to be performed, (3) study medication was to be collected and compliance calculated; and (4) laboratory sampling was to be done for safety and, if indicated, INR measurements were to be done. Records indicate that when Subjects #009 and #042 had their final follow up visit with your site, not all final follow up study procedures were performed on these subjects.

H. The protocol specified that all subjects were to have a 12-lead ECG done at baseline, annually, and at the final follow-up visit or upon permanent discontinuation of study medication. In FDA's review of the source documents for Subject #024, no baseline ECG could be found and no information could be found that a baseline ECG was performed.

I. The protocol specified that all AEs occurring during the course of the clinical study (i.e. from signing the informed consent onwards through the observational phase [post-treatment]) were to be collected, documented and reported to the Sponsor by the investigator according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the Investigator Site File. In addition, the protocol stated that all AEs, serious and non-serious, were to be fully documented on the appropriate CRFs. The protocol further stated that any serious or significant AE, whether or not considered related to the investigational product, and whether or not the investigational product had been administered, must be reported immediately by telephone/fax to the Sponsor. FDA's investigation found that your site failed to follow the protocol requirements for reporting of AEs. Examples include, but are not limited to, the following:

1. Medical records indicate that your site saw Subject #033 on June 29, 2006 and identified that the subject was experiencing occasional flashing lights in front

of her, that her heart rate was a little bit slow, and that she felt a little bit disoriented. Medical records further indicate that on August 17, 2006, your site also saw this subject and identified that the subject had fatigue, occasional problems with phlegm and mucous, and also had gas from the **(b)(4)** medication the subject was taking. FDA's investigation found no documentation that these AEs were reported to the sponsor.

2. Source records showed that after randomization of Subject #059 to **(b)(4)** on **(b)(6)**, the subject was hospitalized due to **(b)(6)** with **(b)(6)** toxicity. We note that your site filled out the SAE report concerning this subject's hospitalization on **(b)(6)**. FDA's investigation found no documentation that this SAE report had been submitted to the sponsor.

Per your December 29, 2008 written response, you noted that you and your clinical research coordinators have enrolled in the **(b)(4)** program for 2009, and that your site also created standard operating procedures (SOP) since January 2008. With respect to the findings, you noted that the final inclusion and exclusion criteria and the careful review and assessment of all the qualifying source documents and safety tests needed to qualify a subject for a clinical trial would be the sole responsibility of the investigator. In addition, you noted other corrective actions to include: (1) Implementation of training and execution of future protocols to the clinical research coordinators (CRCs); (2) A written promise that all safety tests are to be reviewed and assessed by the investigator during the required time frame as per the study protocol; (3) A written promise that all screening exclusionary results are to be repeated, compared and verified, and if values are not within the normal ranges, the subject is to be withdrawn from the study immediately and treated clinically; and (4) A written promise that all early termination visit procedures will be conducted for all early termination subjects.

The FDA notes that obtaining education serves as a positive step in helping you and your site understand the regulatory requirements related to conducting clinical research covered by the regulations. FDA notes, however, that there were discrepancies identified in our review of your SOPs with your noted promised corrective actions. Specifically, in review of the SOP entitled "Standard Operating Procedure for Responsibilities of the Research Team," the investigator's individual responsibility does not include ensuring and verifying eligibility of the subject into the study. From this SOP, it appears that the responsibility for determination of eligibility is left to the research nurse/coordinator and/or the data manager. This would be in direct contrast to your written promised corrective action that eligibility determination is to be the sole responsibility of the clinical investigator.

In addition, in review of Sections A and B of the SOP entitled "Standard Operating Procedure for Subject Management While on Study," FDA could not determine to whom you delegated the responsibilities for eliciting and documenting the subject's medical history, performing a complete or directed physical examination, establishing a subject's baseline signs and symptoms, ordering the tests/procedures that were directed by the protocol, assessing the subject for signs

and symptoms of any intercurrent illness, documenting adverse events appropriately, and instituting appropriate therapy if required by the subject's condition. Specifically, FDA was unsure if the responsibility was jointly delegated to the investigator and research nurse/coordinator, or if the investigator or the research nurse/coordinator could independently handle these responsibilities without the knowledge or oversight by the other. FDA notes that the latter, which would allow the research nurse/coordinator to perform these activities alone, is inadequate and is in direct contrast to your written promised corrective actions. Please clarify this in your response.

**4. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].**

A. Your site chose to use the sponsor's standardized forms as source documents to record and document information related to the subjects' study visits. Per the standardized form, your site was to "Complete the Inclusion/Exclusion Criteria Worksheet to evaluate for study eligibility." In the FDA investigator's review of 16 of 65 subject records at your site, there was no Inclusion/Exclusion Criteria Worksheet found for any of these subjects.

B. There were significant problems with the case histories at your site for all 16 subject records reviewed by the FDA investigator. Examples include, but were not limited to, the following:

1. For Subject #003:

i. The source document worksheets for Visit 4 were not completed.

ii. There were no case report forms (CRFs) in the subject's records for any of the subject's visits.

2. For Subject #015, the screening visit (March 15, 2006) hemoglobin count was 10.7 g/dL and the labs taken on April 3, 2006 showed the hemoglobin count as 7.8 g/dL. Thus, the subject's hemoglobin count decreased 2.9 g/dL, which, per the protocol, was considered a major bleeding event. Your site, however, inaccurately reported in the CRF that this event was a minor bleeding event.

3. For Subject #024:

i. Pages 20, 22, and 62 of the CRF for Visit 6 were missing from the subject's records.

ii. Your site made changes to several CRFs for Subject #024 in May 2008, which was over one year after the Subject's last study visit (January 9, 2007.) FDA's investigation was unable to confirm from the source records that after your site made the changes to the CRFs, that your site submitted those changed CRFs to the sponsor.

4. For Subject #033:

i. Your site checkmarked "No" to the question in the source documents for the Screening Visit that asked "Has the patient's ventricular function been assessed in the past 6 months?" However, your site then provided information related to an assessment that was made on December 12, 2005 that identified an "LV Ejection Fraction" of 40%. FDA's audit of this subject's record found no supporting documentation in this subject's records to verify any ventricular function assessment that was made on December 12, 2005.

ii. There were numerous date discrepancies in the source records for Visit 2. Specifically, the visit date and the date the subject was dispensed study medication per the dispensing/returning log was April 27, 2006.

However, April 26, 2006 was listed as the date the interactive voice response system (IVRS) was called to randomize the subject, the date the subject took the first dose of study medication, and the date your site documented that you filled out the source record for Visit 2. From the source records it appears that the subject took the first dose of study drug prior to it being dispensed to them.

In review of your SOPs entitled "Standard Operating Procedure for Regulatory Files and Subject Records" and "Standard Operating Procedure for Data Management," we note that the responsibilities of (1) the collection of the clinical research data reside mainly with the research nurse/coordinator; (2) the transcription of the data to the CRFs is delegated to the research nurse/coordinator and/or support staff; and (3) the quality assurance to ensure adequate and accurate case histories of only the first sets of completed CRFs is delegated to either the research manager and/or the research nurse/coordinator. We note that these SOPs provide no requirement for the investigator to review the documents to ensure the accuracy and adequacy of the information in the source records. In addition, per the SOP, the only quality assurance performed at your site to ensure adequate and accurate case histories is limited to only the first sets of completed CRFs. We further note that given that the research nurse/coordinator is also delegated to collect the study data, this could lead to the situation whereby the individual who is collecting and recording the study data is also auditing their own source records. Your response does not adequately address these concerns.

**5. You failed to promptly report to the IRB all unanticipated problems**

**involving  
risk to human subjects or others [21 CFR 312.66].**

A. Source records indicate that Subject #015 was enrolled into the study on March 15, 2006, was randomized on March 24, 2006, and took the first dose of study medication on March 30, 2006. In a memo to file dated April 6, 2006, your subinvestigator, Dr. **(b)(6)**, noted that on April 2, 2006, the patient called your site and reported that he had experienced rectal bleeding for the past 2 days and when he came to the office the following day, your site identified that the subject's hemoglobin level was 7.8 g/dL and the hematocrit (HCT) level was 24.8. The patient was then referred to the primary care physician, treated with transfusions in an outpatient setting, and underwent a workup to rule out a GI bleed. In a follow up written memo that was also dated April 6, 2006, Dr. **(b)(6)** noted that the GI workup revealed that the subject had colon cancer.

FDA notes that as your site was aware of the gastrointestinal bleed prior to the subject being discontinued from the study (dates of discontinuation were discrepant between source records: March 31, 2006 on two different source documents, April 2, 2006 on another source, April 3, 2006 on another source), and promptly after your site became aware the subject had colon cancer, your site should have reported this unanticipated problem to the IRB. FDA's investigation was unable to find documentation that this event had been reported to the IRB.

B. Source records show that Subject #059 was enrolled into the study on August 10, 2006 and was randomized to **(b)(4)** on August 17, 2006. The laboratory report generated on September 6, 2006, which provided information related to the samples that were collected on September 5, 2006, showed that the subject had (1) abnormally high values for the **(b)(4)** and (2) abnormally low values for the red blood cell count, hemoglobin and hematocrit. Source records further indicated that the subject was hospitalized on **(b)(4)** with a diagnosis of **(b)(6)**. A Serious Adverse Event report concerning the hospitalization was prepared by your site and dated June 17, 2008. FDA's investigation was unable to find documentation that this adverse event was reported to the IRB.

Per your December 29, 2008 written response, you promised that serious and nonserious AEs will be reported and documented in the required timeframe to both the sponsor and the IRB, and that your site has created and trained all members of the research team on the SOP that discussed the SAE reporting guidelines and reporting structure requirements for future studies. Your letter further noted that the study subjects will be carefully followed by the investigator, and if the diagnosis of cancer is made during the study, all of the safety measures are to take place immediately, and the association to the investigational product will be determined and evaluated by the investigator. The decision for an early termination visit will be determined by all parties involved, and the subject's safety will always be the priority.

Your SOP entitled "Standard Operating Procedure for Interactions with the Institutional Review Board" states that all communications about AEs and SAEs that occur during the course of the study are to be communicated to the IRB by either the research nurse/coordinator and/or support staff. Based upon the review of your SOP, FDA is unsure whether the responsibilities delegated in this SOP are shared responsibilities between the research nurse/coordinator and/or support staff or whether each could individually take on the responsibility without oversight or knowledge by the other. Please clarify this in your response. FDA further notes that this SOP does not provide a role for the investigator to review the AEs and SAEs and/or verify that the reports submitted to the IRB have accurate and adequate information, which would include information about whether or not the event was associated with the use of the investigational drug.

In addition, in the SOP entitled "Standard Operating Procedure for Adverse Event Reporting," the responsibility for follow up when the research subject experiences any adverse change from baseline or pretreatment condition is delegated to the principal investigator, subinvestigator, and/or research nurse/coordinator. Follow up for ensuring that the IRB is notified of all serious or alarming events occurring at the site during the approval period for the ongoing study is delegated to the principal investigator, research nurse/coordinator, and/or support staff. From the SOP, however, it cannot be determined if these responsibilities are shared responsibilities or whether one individual can take on the responsibility without oversight or knowledge by the others. If it is the latter, then the investigator does not have adequate oversight over the responsibility for reporting to the IRB unanticipated problems. Please clarify this in your response.

**6. You failed to report promptly to the sponsor adverse effects that may reasonably be regarded as caused by, or probably caused by, the drug [21 CFR 312.64(b)].**

A. Source records indicate that in September 2006, your site was informed that Subject #033 had stopped taking study medication due to stomach discomfort, which included symptoms of stomach pain, bloating and diarrhea. Your site filled out a CRF that noted that these AEs were related to the use of the study drug. FDA investigator Barreto-Pettit was unable to find documentation that these AEs were reported to the sponsor.

B. Source records indicate that during Subject #024's enrollment in the study, the subject experienced abdominal pain on June 30, 2006 and nausea and vomiting on August 28, 2006. Your site did not fill out the Adverse Event CRF until December 12, 2007, which was a significant amount of time after the subject was terminated from the study (i.e. date of termination from the study was January 9, 2007). In addition, the FDA investigator was unable to find documentation that these adverse events were submitted to the sponsor.

Per your December 29, 2008 written response, you promised that all serious and

nonserious AEs that may be reasonably be regarded as caused by, or probably caused by, an investigational product will be reported and documented in the required timeframe to the sponsor. You further noted that all members of the research team had been trained and received education on the SOP created by your site, which discussed SAE reporting guidelines and reporting structure requirements.

In FDA's review of your SOPs, we note that per Section A entitled "Managing Adverse Events" in the SOP entitled "Standard Operating Procedure for Adverse Event Reporting," the responsibilities of informing the sponsor about serious and/or unexpected AEs, recording the details of AEs in the source documentation, and completion of the CRFs is given to the principal investigator and/or the research nurse/coordinator. FDA could not determine if these responsibilities are to be shared between the investigator and research nurse/coordinator or if one or the other could handle the responsibility without the other party. FDA notes that allowing the research nurse/coordinator to independently handle the SAE recording and reporting without oversight by the investigator is unacceptable. Please clarify this in your response.

In addition, FDA notes that in Section C, entitled "Communications while the study is ongoing," of the SOP entitled "Standard Operating Procedure for Site-Sponsor/CRO Communications," it appears that the research nurse/coordinator is responsible for informing the sponsor/CRO about SAE(s) immediately. We note, however, that in this section the investigator does not have responsibility for making any assessments as to the relationship of the investigational drug to the AE or SAE. In addition, there is no information related to the investigator's role in reviewing the SAE reports to ensure the accuracy of the information within that report. Your response is inadequate to address the principal investigator's oversight over adverse event recording, reporting, and adjudication of adverse events.

**7. You failed to promptly report to the IRB all changes in research activity [21 CFR 312.66].**

Source records indicate that your site began having subjects sign a memorandum of notification indicating that your site was no longer participating in the study and requesting that the subject choose the option of either continuing to participate in the study at another site or withdrawing their participation/consent from the study and completing a final exam. At the time that many of the subject's signed this form, you had not yet received IRB approval for this change in research activity.

Per your December 29, 2008 written response, you promised that you will obtain IRB approval prior to distributing and/or presenting anything to the study subjects.

In your site's SOP entitled "Standard Operating Procedure for Interactions with the

Institutional Review Board," all communication with the IRB while the study is ongoing is delegated to the research nurse/coordinator and/or support staff. There appears to be no information related to the involvement of the clinical investigator in any correspondence, or review of any correspondence, to or from the IRB while the study is ongoing. The clinical investigator should be involved in IRB correspondence, in order to ensure the accuracy of the information that is being provided to the IRB. In addition, FDA cannot determine how the clinical investigator will ensure that the study team is adequately following protocol amendments, as the SOP does not provide information as to how the investigator will maintain knowledge about new requirements noted in the protocol amendments that have been approved by the IRB. Your response is inadequate, as adequate oversight by the principal investigator over IRB communications is not clearly addressed.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You should address these deficiencies and establish procedures to ensure that any on-going or future studies will be in compliance with FDA regulations.

Within fifteen (15) working days of your receipt of this letter, you should notify this office in writing of the actions you have taken or will be taking 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 Tejashri Purohit-Sheth, M.D., at 301-796-3402; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Tejashri Purohit-Sheth, M.D.  
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Sincerely yours,  
{See appended electronic signature page}  
Leslie K. Ball, M.D.  
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Center for Drug Evaluation and Research

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/s/

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LESLIE K BALL  
06/12/2009