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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Christopher Chappel, M.D.
445 West Oak Street
Family Practice Associates
Kissimmee, FL 34741

Ref#: 09-HFD-45-01-02

Dear Dr. Chappel:

Between October 22, 2007 and November 21, 2007, Ms. Brunilda Torres, representing the U.S. Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of the following clinical investigations:

Protocol (b) (4) [(b) (4)] ("Protocol (b) (4)"), entitled "Double-blind, randomized, parallel-group, dose ranging, multi-center study to evaluate the efficacy and safety of (b) (4) [redacted], in patients with mild to moderate hypertension" of the investigational drug (b) (4) [redacted], performed for (b) (4) [redacted].

Protocol (b) (4) [redacted] ("Protocol (b) (4)"), entitled "A Phase 2 Study of the Combinatorial Effect of (b) (4) [redacted] and Atorvastatin in Subjects with Hypercholesterolemia" of the investigational drug (b) (4) [redacted], performed for (b) (4) [redacted].

Protocol (b) (4) ("Protocol (b) (4)"), entitled "A randomized, double-blind, double-dummy, placebo-controlled, (b) (4) [redacted] trial to evaluate (b) (4) [redacted] in combination with (b) (4) [redacted] after eight weeks of treatment in patients with Stage I or II hypertension, with an (b) (4) [redacted] sub-study" of the investigational drugs (b) (4) [redacted], performed for (b) (4) [redacted].

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.

We have reviewed the Form FDA 483, the establishment inspection report and the documents submitted with that report, and the two letters you wrote in response to the Form FDA 483 [the October 30, 2007 letter (October 30 Letter) and the undated letter to Florida District Director, Emma Singleton (Undated Letter)]. Upon review, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Ms. Torres presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

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

When you signed the investigator statements (Form FDA 1572) for the above-referenced clinical investigations, you agreed to take on the responsibilities of a clinical investigator at your site. Your general responsibilities 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 (21 CFR 312.60). 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 you permitted individuals to conduct study tasks which they had not been delegated the authority to execute, and that your supervision of personnel to whom you delegated study tasks was not adequate to ensure that the clinical trials were 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.

A. The following violations were noted for Protocol (b) (4) :

1. We note that per the "Delegation of Duties & Authorized Signatures Form," you and/or your sub-investigator were the only individuals at your site designated by you to make trial-related medical decisions and to perform critical trial-related procedures. You informed FDA Investigator Torres, however, that you gave to your study coordinator Ms (b) (6) the responsibility to determine subject eligibility into the study; the fact that she made such determinations is also evident in the medical and study records. Determination of subject eligibility is a trial-related medical decision, as well as a critical trial-related procedure. As such, this study task was not delegated to Ms. (b) . Permitting Ms. (b) to conduct study tasks for which she did not have authorization demonstrates your failure to conduct the study in accordance with the study plan and applicable regulations.
2. As discussed in more detail in Sections 3, 4, and 6 below, your failure to personally conduct certain aspects of the study and/or to supervise study personnel adequately resulted in serious problems with the study, including: the enrollment of ineligible subjects, the failure to follow numerous trial

protocols, the failure to maintain adequate case histories, and the failure to report to the Institutional Review Board (IRB) unanticipated problems involving risk to human subjects.

Moreover, you had notice that Ms. (b) was performing duties for which she did not have authorization, per the "Delegation of Duties & Authorized Signatures Form," and that she was not performing adequately duties which she did have authority to perform. Specifically, we note that monitors from (b) (4), the sponsor of this study, identified and documented such problems in correspondence to you:

- i. In letters of May 18 and October 13, 2006, and February 27, 2007, the monitor documented Ms. (b) improperly conducting a study eligibility assessment, failing to follow the protocol in evaluating exclusion criteria, and failing to ensure proper source documentation.
- ii. In a January 19, 2007 letter, the monitor documented similar findings, as well as your office's failure to notify the Institutional Review Board of certain events.

B. The following violations were noted for Protocol (b) (4) :

1. Similar to the events noted in Paragraph 1.A.2 above, the nature and severity of the problems relating to this study, as detailed in Sections 2, 3, 4, and 5 below, indicate that you failed to personally conduct and/or adequately supervise the clinical investigation.

We note again that you received notice from the study sponsor's monitors that there were significant problems at your site related to Ms. (b) (6) activities. For example, in a letter dated August 8, 2006, the monitor found that: (1) source worksheets and data for entire subject visits were missing from subjects' research charts; (2) several piles of study-related documents were scattered on the study coordinator's floor and/or desk intermixed with documents from other clinical trials; (3) source documentation for subject visits was minimal and mainly consisted of one sheet of check marks for items required at each visit; (4) medical histories, adverse events, and concomitant medications either were not assessed or were not documented appropriately; and (5) drug accountability logs were not completed, as the study coordinator was not aware of the log. We note that at the time of this monitoring visit, 21 subjects had been screened for this study. The letter summarized the monitor's assessment of your site: "Overall, this study has been neglected at this site. Subject safety has been in question since so many research charts were missing previous visit source documents that the Study Coordinator would need to reflect on for her current Subject visits, and ECG [electrocardiogram] and lab alerts were not assessed for clinical significance or followed up with the Subjects."

2. In a letter dated September 24, 2006, in follow-up to a monitoring visit that occurred between September 19 and 21, 2006, the monitors noted that,

overall, your site had shown much improvement. However, it was noted that your staff continued having difficulty going backwards with resolving the source verification problems in terms of scant medical history as all subjects had completed the study at that point. In our review of the FDA inspectional report and the documents submitted with that report, we note that there were still problems with source documentation with respect to records reviewed for this study and that late entries noted within the source documentation could not be verified as to where the information was derived.

We note that Ms. (b) (6) served as the primary study coordinator for both of the above-discussed studies and that Ms. (b) (6) employment was terminated from your site as of December 4, 2006. We wish to emphasize, however, that as the clinical investigator, it was your ultimate responsibility to ensure that the studies were conducted properly and in compliance with FDA regulations to protect the rights, safety, and welfare of study subjects. We note that the monitors from two different studies notified you on multiple occasions that Ms. (b) (6) was failing to follow the protocols and/or incorrectly completing certain study-related tasks. Among the tasks identified by the monitors were those for which she had not been delegated authority. The fact that you permitted her to continue as study coordinator despite these repeated notices indicates your failure to conduct the study in accordance with the investigational plans and the lack of adequate supervision on your part. These letters from the monitors, especially those sent in fall 2006 and early 2007, also call into question your assertion in your October 30 Letter that you “worked diligently to help Ms. (b) (6) correct the discrepancies.” We find that you failed to have adequate involvement and oversight over the studies to ensure that they were properly conducted in compliance with FDA regulations.

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.

- A. For Protocol (b) (4), we were unable to determine from your site records if subjects gave informed consent prior to participation in the study and/or if subjects were given sufficient opportunity to consider whether or not to

participate in the study. Specifically, we note that your site routinely used sign-in sheets to document the date and time of arrival of subjects.

Based on the times recorded for appointment time, sign-in, and the commencement of protocol procedures, it does not appear possible that you obtained legally effective informed consent from the subjects in the chart below, in compliance with 21 CFR 50.20 and 50.27. This is because either 1) study-related procedures are listed as having taken place prior to the scheduled appointment time and/or prior to the time the subject signed in, or 2) based on the study records, the time between the appointment time, the time the subject signed in and/or the commencement of the procedure(s) did not provide adequate opportunity for the subjects to read the informed consent document, and to consider whether or not to participate in the study, before signing the informed consent form. For example, Subject (b) (6) was enrolled into the study on March 25, 2006. The sign in sheet notes that Subject (b) (6) arrived at your site at 9:00 a.m. However, source documents showed that study related procedures were performed prior to the subject's arrival (i.e., a blood sample was drawn at 8:50 a.m. In addition, as detailed below:

Subject	Date Informed Consent Obtained	Sign-in Date	Sign-in Time	Appointment Time	Blood Pressure Measured	Blood Samples Taken	ECG Conducted
(b) (6)	Unclear from records	3/23/06	9:38 a.m.	9:30 a.m.	9:20 a.m.	9:40 a.m.	9:35 a.m.
(b) (6)	3/23/06	3/23/06	9:38 a.m.	9:30 a.m.	9:00 a.m.	9:20 a.m.	9:15 a.m.
(b) (6)	7/20/06	7/20/06	9:48 a.m.	10:00 a.m.	8:30 a.m.	9:30 a.m.	8:44 a.m.
(b) (6)	8/8/06	8/8/06	9:11 a.m.	9:30 a.m.	9:05 a.m.	9:45 a.m.	8:20 a.m.
(b) (6)	8/16/06	8/16/06	No time indicated; most likely between 9:00 a.m. and 9:30 a.m. based on other patients' recorded sign-in times that day	No time indicated	8:38 a.m.	8:53 a.m.	8:50 a.m.

B. The following violations were noted for Protocol (b) (4) :

1. Similar to Paragraph 2.A.1. above, it does not appear possible, based on the times recorded for appointment time, sign-in, informed consent, and the commencement of protocol procedures, that you obtained legally effective informed consent from the subjects listed below in compliance with 21 CFR 50.20 and 50.27. This is because 1) study-related procedures are listed as having taken place prior to the scheduled appointment time and/or prior to the time the subject signed in, or 2) because the time between the appointment time, the time the subject signed in, and/or the commencement of the procedure(s) did not provide adequate opportunity for the subjects to read the informed consent document, and to consider whether or not to participate in the study, before signing the informed consent form. As detailed below:

Subject	Consent Date	Consent Time	Visit 1 Date	Visit 1 Sign-In Time	Visit 1 Appointment Time	Patient Seated for Blood Pressure Measurement	ECG Conducted
(b) (6)	6/19/06	10:15 a.m.	6/19/06	10:30 a.m.	10:30 a.m.	10:25 a.m.	10:45 a.m.
(b) (6)	7/19/06	8:35 a.m.	7/19/06	8:50 a.m.	8:30 a.m.	8:37 a.m.	*
(b) (6)	8/3/06	8:25 a.m.	8/3/06	9:30 a.m.	9:00 a.m.	8:30 a.m.	8:50 a.m.
(b) (6)	10/31/06	9:25 a.m.	10/31/06	9:50 a.m.	9:00 a.m.	9:30 a.m.	9:50 a.m.
(b) (6)	11/1/06	9:15 a.m.	11/1/06	9:50 a.m.	10:00 a.m.	9:20 a.m.	9:40 a.m.

(* - Time ECG Conducted is not dispositive to finding of violation)

2. In addition, your site performed a study related procedure on Subject (b) (6) prior to obtaining the subject's informed consent. Specifically, the source records showed that the subject received the protocol specified blood pressure readings at 8:30 am, while informed consent was not documented until 8:45 am.

C. The following violation was noted for Protocol (b) (4) :

1. It does not appear that you obtained informed consent from Subject (b) (6) prior to conducting study-related procedures. The sign-in sheet for February 10, 2006 indicates that Subject (b) (6) signed in at 12:20 p.m., but that study-related procedures were conducted at 12:15 p.m.

With respect to the findings noted above for these three studies, in your Undated Letter, you noted that documentation of arrival time for each subject was not routinely recorded immediately upon arrival and/or before the subject was taken from the waiting room, which you stated resulted in the appearance of contradictory times between arrival, the informed consent process, and the beginning of study-related procedures, as well as the appearance of inadequate time intervals for the informed consent process itself. You stated, however, that all subjects had adequate time to read the informed consent form and that the informed consent process was always completed prior to the start of any other study-related procedures.

We cannot verify the accuracy of your assertion in light of the time discrepancies reflected in the records for these protocols, and as noted above. Therefore, as discussed above, we conclude, based on the records reviewed, that it was not possible for you to obtain legally effective informed consent as specified in 21 CFR 50.20 and 50.27.

We acknowledge that in your Undated Letter you describe the corrective actions you have taken to prevent the recurrence of this finding. 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 here, and which raises our concern for your approach to assuring appropriate human subject protection.

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

A. The following protocol violations were noted for Protocol (b) (4) :

1. The protocol inclusion criteria specified that at the first qualifying visit during the placebo lead-in phase (Visit P2), the subject was to have a mean of at least three readings for seated systolic blood pressure (SeSBP) of ≥ 140 mm Hg and < 180 mm Hg and for seated diastolic blood pressure (SeDBP) of ≥ 90 mm Hg and < 110 mm Hg. The protocol inclusion criteria further specified that at the second qualifying visit during the placebo lead-in phase (Visit P3), the subject was to have a mean of at least three readings for the SeSBP to be ≥ 140 mm Hg and < 180 mm Hg, and for SeDBP ≥ 90 mm Hg and < 110 mm Hg. If the subject did not meet the qualifying blood pressure criterion at Visit P3, the protocol specified that a third qualifying visit (Visit P4) was to be performed. If the patient did not meet the inclusion criteria at Visit P4, he or she would not be qualified for randomization.
 - i. Subject (b) (6) did not meet the inclusion criterion at either Visit P2, when the SeDBP was 85, or Visit P3, when the SeDBP was 87, but nevertheless was enrolled into the study.

We note further that there were two source documents signed and dated August 28, 2006, found for this subject for the P3 visit. As referenced above, according to one of these source documents, Subject (b) (6) had a non-qualifying mean SeDBP of 87. The case report forms (CRF) showed that the subject was initially randomized based on this non-qualifying BP (i.e., SeDBP of 87). The second source document listed a qualifying mean SeDBP of 90.

- ii. Subject (b) (6) did not meet the protocol-specified blood pressure inclusion criterion at either Visit P2 (SeSBP of 129, and SeDBP of 65), Visit P3 (SeDBP of 86 originally, then crossed out in 2007 to read 85), or Visit P4 (SeDBP of 85), but was randomized into the study. That the sponsor ultimately permitted this subject to remain in the trial does not mitigate this initial failure to follow the protocol.

2. The protocol specified that if the variability between the mean blood pressure measurements on two qualifying visits was more than 7 mm Hg for SeDBP, then the subject was to be excluded from the study.

At Visit P2 on December 27, 2006, Subject (b) (6) had a mean SeDBP of 93 and at Visit P3 on January 10, 2007, there were two separate source documents listing the mean SeDBP as either 105 or 106, respectively. We note that using either of the mean SeDBPs for Visit P3, the variability was greater than 7 mm Hg, and therefore the subject still met the exclusion criterion and should not have been enrolled into this study. Moreover, in a note to file dated February 7, 2007, you acknowledge that this subject was enrolled into the study despite having variability greater than 7 mm mean SeDBP over two visits.

3. The protocol specified that women of child bearing potential, defined as female patients who were not postmenopausal or surgically sterile, who had a positive serum pregnancy test or who did not agree to use an accepted method of contraception, were to be excluded from the study. The protocol further specified that pregnancy tests were to be taken at the Visits P1 and T1. Protocol-specified pregnancy tests were not performed for Subjects (b) (6) and (b) (6) on one and/or both of these visits.
4. The protocol specified that at Visit T1, the investigator should call the (b) (4) to receive the medication kit number that was to be allocated to the patient and then allocate that kit accordingly. As reflected on the relevant (b) (6) record, Subject (b) (6) should have been dispensed Kit #100210, but your site dispensed Kit #100201 instead.
5. The protocol specified that at each scheduled study visit, study personnel should measure the pre-dose (trough) blood pressure (BP) and heart rate (HR). The protocol further set forth that certain procedures should be used to measure the BP and HR, including but were not limited to: (1) the patient first should be required to be seated for a minimum of five minutes prior to BP and HR data collection; and (2) study personnel then should take one HR/BP measurement after three minutes in the standing position. We note that this did not occur for several subjects at several visits throughout the course of their participation in the study. Examples include but were not limited to the following:

Subject	Study Visit	Time Seated	Sitting BP/HR Taken	Time Stood	Standing BP/HR Taken
(b) (6)	P1	8:55 a.m.*	9:00 a.m.*	9:05 a.m.	9:10 a.m.
	V2	9:00 a.m.	9:00 a.m.	9:10 a.m.	9:15 a.m.

Subject	Study Visit	Time Seated	Sitting BP/HR Taken	Time Stood	Standing BP/HR Taken
	V3	9:05 a.m.*	9:10 a.m.*	9:19 a.m.	No time indicated
	V4	8:00 a.m.	8:00 a.m.	8:09 a.m.	No time indicated
(b) (6)	V6	9:10 a.m.*	9:18 a.m.*	9:23 a.m.	No time indicated
(b) (6)	P1	No time indicated	8:40 a.m.	No time indicated	8:49 a.m.
	V2	7:40 a.m.	7:44 a.m.	7:52 a.m.	No time indicated
	V3	7:33 a.m.	7:33 a.m.	7:40 a.m.	No time indicated
(b) (6)	T2 and T3 indicated on record	7:00 a.m.*	7:05 a.m.*	7:10 a.m.	7:15 a.m.
	T5, T7, and T9 indicated on record	7:30 a.m.	7:32 a.m.	No time indicated	7:38 a.m.
(b) (6)	T5, T7, and T9 indicated on record	6:55 a.m.	6:57 a.m.	No time indicated	7:02 a.m.

(* - Note: for completeness, these items are listed in the table; however, they specifically do not represent a violation)

- The protocol required study personnel to obtain additional checks for biochemistry from blood samples at Visit T3. Subjects # (b) (6) did not have the protocol-specified blood samples drawn at this visit.

B. The following protocol violations were noted for Protocol (b) (4) :

1. The protocol specified that study personnel should perform a complete medical history and physical examination at the baseline visit for each subject. We were unable to determine whether Subjects # (b) (6) had either a complete medical history or a physical examination performed at the baseline visit. The source documents for this visit were limited to checkmarks that provide little to no information concerning the subject's physical examination or past medical history rather than actual documentation of the medical history or physical examination that should have been performed.
2. The protocol specified that subjects who experienced a designated adverse event (DAE) #5 consisting of an elevation in their alanine aminotransferase (ALT) level > 1.5 but ≤ 3 Upper Limits of Normal (ULN) were to have repeat tests done weekly until the ALT dropped to $< 1.5 \times$ ULN or met another criterion [DAE# 2, 3, or 4]. We note that Subjects (b) (6) did not have the weekly protocol-specified ALT tests repeated despite elevated ALTs.
3. The protocol specified that subsequent to the collection of an ECG and initial interpretation by a qualified physician, the ECGs were to be sent for analysis to a centralized ECG vendor. Once this "overread" ECG (as described by the protocol) was returned from the centralized ECG vendor, the investigator or qualified designee was responsible for determining if any change to the medical management of the subject was needed, and for documenting his/her review by signing and dating the ECG, to ensure subject safety. You did not review and clinically evaluate the ECG Alerts for Subject (b) (6) dated January 27, 2006 until August 5, 2006, March 30, 2006 until April 12, 2006, and May 1, 2006 until August 9, 2006; and an ECG Alert for Subject (b) (6) dated April 17, 2006 until August 5, 2006. Because your review took place significantly after you received the "overread" ECG readings, you could not have made the necessary adjustments to subject medical management as required by the protocol over the course of the study.
4. The protocol specified that at Visit 1, subjects should be instructed on being on the NCEP TLC diet. Source documents did not verify that Subjects (b) (6), (b) (6) were instructed on the diet.

In your Undated Letter, you noted that the above findings were only found within the two studies conducted by Ms. (b) (6). You further stated that in the past, the procedures at your site were reliant on the study coordinator having 100% knowledge of the protocol inclusion/exclusion criteria. To correct these findings you indicated that while you still require study coordinators have such knowledge of the protocol, you now mandate that the Director of Clinical Operations draft an inclusion/exclusion checklist to be used at all appropriate visits leading up to and

including the randomization visit prior to beginning enrollment for a study. The only exception to use of this list is when the sponsor provides such a checklist itself.

This response is inadequate. First, as noted above, you did not delegate to Ms. (b) (6) the authority to conduct these procedures in Protocol (b) (4) . Second, while Ms. (b) (6) was the primary study coordinator for both protocols, it was your responsibility as the clinical investigator to ensure the studies were conducted according to the investigational plan. Further, we note that not all protocol violations delineated above resulted from Ms. (b) (6) conduct.

4. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual [21 CFR 312.62(b)].

A. The following violations were noted for Protocol (b) (4) :

1. We found two source documents signed and dated August 28, 2006, for Subject (b) (6) for Visit P3. One of the source documents listed a non-qualifying mean SeDBP of 87. The other source document listed a qualifying mean SeDBP of 90. The case report forms (CRFs) showed that the subject was initially randomized based on the non-qualifying SeDBP of 87.

In your Undated Letter you noted that the documentation issues arising from multiple worksheets for the same visit resulted from past processes in which you did not routinely discuss or stress documentation, that currently documentation is discussed routinely at staff meetings, and that specific guidelines have been developed and implemented in the arena of documentation. This response is inadequate. It does not explain why one source document shows the subject was ineligible for the study while the other shows the subject was eligible.

2. We cannot determine on what date Subject (b) (6) signed the informed consent form and was enrolled into the study. The subject and Ms. (b) (6) dated the informed consent document on March 22, 2006, and per the enrollment log the subject was enrolled into the study on this day. We note, however, that the March 22, 2006 sign-in sheet does not document that the subject was present at your site on this date. Rather, screening source documents and your site's sign-in sheet show that Subject (b) (6) arrived at your site on March 23, 2006 and was screened for enrollment into the study on this date.
3. Subject (b) (6) signed the informed consent document February 1, 2006. However, the February 1, 2006 sign-in sheet does not show that this subject was at your site on this date.
4. Ms. (b) (6) signed a November 21, 2006 record stating that Subject (b) (6) was "dosed from kit #203841 on 11/21/06 @ 0645" and that the next visit for this subject was going to be February 13, 2007 at 0600. However, the new study coordinator for this protocol recorded in a progress note dated December 7, 2006, that the subject had notified her that he/she was "withdrawing consent"

from participation in the study and already had returned the drug to Ms. (b) (6). The progress note further mentioned that your new study coordinator later had found the medication box unopened under the sink. Thus the subject was never dosed with the study medication on November 21, 2006 as indicated in the initial source record.

In your Undated Letter, you conceded that Ms. (b) (6) erroneously recorded that the medication had been administered to the subject when in fact she had dispensed an unopened container. You further stated that your current procedures require specific documentation of whether the drug is dispensed or administered, and that this issue is discussed in the new hire coordinator class that all newly-hired coordinators attend.

This response is inadequate. Specifically, we note that Ms. (b) (6) used the word "dosed" for all subjects to whom she purportedly administered investigational drug on days on which the subjects were seen at your site for study-related visits. If in fact as you noted in your letter the word "dosed" could imply the subject only was dispensed an unopened container, and you did not verify that the subjects actually took the study drug during the office study visits as specified in the protocol, we cannot be assured to any degree that subjects enrolled into the study received and/or took the investigational drug.

- B. The following violations were noted for Protocol (b) (4) :
1. There were entries made on subject source documents long after those documents were created that provided information concerning the results of adverse events, concomitant medication assessments, alcohol and smoking habits, and/or study drug dosing. However, there is no documentation concerning from where or when this information was obtained. For example:
 - i. An entry dated September 1, 2006 was written on the source documents for Subject (b) (6) noting no adverse events and no changes in concomitant medications for Visits V3 (2/13/06), V4 (3/6/06), V5 (3/13/06), and V6 (3/27/06). An entry dated July 31, 2006 was written on the source documents for this subject noting no adverse events and no changes in concomitant medications for Visits V8 (4/24/06) and V9 (5/9/06).
 - ii. Subject (b) (6) withdrew from the study on March 30, 2006. However, an entry dated August 12, 2006 was made on the source record for the January 17, 2006 visit indicating that the subject did not smoke and/or consume alcohol.
 - iii. Subject (b) (6) had his/her Visit V8 on May 25, 2006. An entry dated October 25, 2006 indicated that the subject's dosing for the May 25, 2006 visit occurred on October 23, 24, and 25, 2006.

2. Concomitant medication assessments were not documented in the source records at several visits for Subjects (b) (6) as required by the protocol.
5. **You failed to maintain investigational drug disposition records with respect to use by subjects [21 CFR 312.62(a)].**

In Protocol (b) (4), the drug accountability logs for Subjects (b) (6) could not be found.

We acknowledge that in your Undated Letter you stated that you maintained drug accountability logs in the past only if the sponsor had provided one. You stated further that to correct this problem you have developed and implemented a drug accountability log to track and document drug dispensing and accountability. In addition, there now is a master drug accountability log that you created that the coordinator responsible for a specific trial will update every time the investigational product is received and dispensed. You also indicated that current procedures require the coordinators to have the medication number and (b) assigned number cross checked by another coordinator prior to it being given to the subject. While these corrective actions appear appropriate, it was the absence of such measures that led to the violations listed here.

6. **You failed to promptly report to the IRB all unanticipated problems involving risk to human subjects or others [21 CFR 312.66].**

In Protocol (b) (4), your site was informed on December 12, 2006 that Subject (b) (6) had been admitted to the hospital for a bilateral pulmonary embolism on (b) (4), and had remained in the intensive care unit for one week. You failed to notify the IRB per IRB requirements within three business days of becoming aware of this serious adverse event, and you reported this event to the IRB on February 12, 2007 as a protocol deviation rather than an adverse event.

In your Undated Letter, you noted in response that Ms. (b) was the primary study coordinator for this protocol. This response is inadequate, because your site became aware of this event after Ms. (b) (6) employment termination from your site. In addition, "(b) (6)," rather than Ms. (b), made this notation after speaking to the subject on December 12, 2006.

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 must address these deficiencies and establish procedures to ensure that any on-going or future studies will be in compliance with FDA regulations.

For those responses noted above that were found inadequate you must notify this office in writing within fifteen (15) working days of your receipt of this letter and 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.

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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.
Branch Chief
Good Clinical Practice Branch II
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Sincerely yours,

{See appended electronic signature page}

Leslie K. Ball, M.D.
Director
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/s/

LESLIE K BALL
02/02/2009