June 14, 2010

Ms. Emma R. Singleton
District Director, Florida District
United States Food & Drug Administration
HDR-SE200
555 Winderley Place, Suite 200
Maitland, FL 32751

Re: Department of Health and Human Services Food and Drug Administration Form FDA 483 Inspectional Observations -FEI # 3008127817
Issued to: Rajiv Chandra, M.D., Ph.D., Site Investigator (May 24, 2010)

Dear Ms. Singleton:

Please accept this letter (and accompanying supporting exhibits) in response to the above-referenced Investigational Observations issued May 24, 2010, following an FDA inspection of the (b) (4) Florida clinical site (Dr. Rajiv Chandra, Site Investigator) of the Trial to Assess (b) (4) The inspection was conducted by FDA Investigators Randall L. Morris (sole signee), Andrea H. Norwood, and Jose Santiago, on intermittent days, from April 12, 2010 through May 24, 2010. This letter is co-signed by Dr. Rajiv Chandra, the Site Principal Investigator, and (b) (6), the overall Study Chairman for (b) (4) and Sponsor for IND (b) (4). It should be noted that (b) (6)' involvement is limited to the (b) (4) study and does not also encompass the observations regarding the (b) (4) study.

PRELIMINARY STATEMENT AND STUDY OVERVIEW

Although disodium (b) (4) has been widely practiced in the medical community for many years, reliable data for its efficacy have been lacking. The (b) (4) study, a response to an NIH RFA, is a multicenter investigation designed to evaluate the effectiveness of (b) (4). There is a portion of the study that will evaluate effectiveness of (b) (4). The IND in this study, however, is approved only for the (b) (4)), and does not encompass the (b) (4) study vitamins under its regulatory scope. In other words, the (b) (4) study vitamins are not considered investigational under this IND; rather, the (b) (4) evaluated in (b) (4) is equivalent to over-the-counter dietary supplements, as defined in the Dietary Supplement Health and Education Act (DSHEA) of 1994.

The study is co-funded by the (b) (4), and (b) (4) and the (b) (4). The study (b) (4) is at (b) (4), and the (b) (4) is at the (b) (4) (b) (6) is the (b) (4) Principal Investigator at (b) (4) The (b) (4) has been responsible for monitoring of all study sites, including the (b) (4) which is the subject of this response.

The (b) (4) Study leadership and personnel at the (b) (4) clinical site are fully committed to the highest standards in human subjects' protection. To date, 32 independent institutional review boards (IRBs) have approved the (b) (4) study protocol, consent form and other materials. These IRBs include (b) (4) IRB and the IRBs of numerous hospitals and universities. Comprehensive training is required of all (b) (4) sites, investigators and coordinators. The required training includes:

(a) Office of Human Research Protections "Protecting Human Research Participants,"
(b) Clinical Trials Networks Best Practices "Clinical Research Introduction", and
(c) (b) (4) specific training (e.g., online or at an Investigators' meeting).

All (b) (4) data are subject to continuing systematic review of safety and related issues through an independently appointed Data and Safety Monitoring Board chosen by the National Institutes of Health. In addition, the FDA has been apprised at least once yearly on the status of the study.

Notwithstanding these facts, the (b) (4) Study leadership and personnel at the (b) (4) site continuously strive to maintain and improve the safety of the (b) (4) trial by vigorously responding to potential issues as soon as they are made known. Thus, we take seriously the observations issued by the Agency as a Form FDA 483, and view these observations as an opportunity to re-commit our full compliance with all policies and procedures and to implement specific remedial measures to ensure that all (b) (4) activities adhere to applicable regulations and the highest standards of patient safety.

As a preliminary step after consultation with (b) (4) leadership, (b) (4) and (b) (4) we have voluntarily decided to suspend study enrollment in the (b) (4) trial at the (b) (4) site pending substantial completion of the remedial steps outlined below (expected on or before August 31, 2010). All members of the (b) (4) (b) (4) Study Team have committed to attend comprehensive re-training on Good Clinical Practices offered by the Project Leader (b) (6), and the Lead CRA (b) (6), from the (b) (4) on June 30, 2010 (**Tab 1**). Upon completion of all steps in the corrective action plan outlined in this response, the efficacy of the re-training will be assessed by an independent monitor ((b) (6) - **Tab 2**). (b) (6) will perform a comprehensive follow-up and review of the implementation of the Corrective Action Plan as detailed in this letter and in **Tab 1,** based on Federal regulations and ICH Guidelines. Any deficiencies noted during that follow-up audit will be immediately addressed and resolved at the site, with a follow-up assessment if necessary.

Ms. Emma R. Singleton
District Director, FDA Florida District
June 14, 2010

RESPONSE TO SPECIFIC OBSERVATIONS

OBSERVATION 1

An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

1. *You did not adequately supervise the conduct of the (b) (4) study by ensuring that subject's informed consent was obtained by an authorized individual per the delegation of authority log. The informed consent, however, was obtained by (b) (6) with assigned duties of code #9, clerical coordination activities only. This individual obtained informed consent for all (b) (4) (b) (4) subjects in the (b) (4) study.*

Response and Corrective Action Plan

As Site Investigator, Dr. Chandra delegated to (b) (4) the study-related task of obtaining informed consent based on her education, training, and experience (*curriculum vitae* (CV) and training records attached, **Tab 3**). However, the (b) (4) Site Responsibility and Signature Log did not completely represent all authority delegated by the site investigator and did not specifically confer upon (b) (6) this specific task in this important study document.

Accordingly, we have revised the Delegation of Authority (DOA) Log to directly specify that informed consent may be obtained by (b) (6) and other individuals authorized by the Site Investigator (see Revised DOA Log, **Tab 4**).

In addition, the requirements for the appropriate review, updating, and utilization of the DOA Log have been included in the special training session to be provided to all members of the (b) (4) Study Team on June 30, 2010 (**Tab 1**).

2. *You did not ensure that all associates, colleagues and employees assisting in the investigation were informed about their obligations in following the investigational plan as evidenced by:*

   (a) The inclusion/exclusion criteria was assessed by (b) (6) for Subjects # (b) (6), (b) (6) (b) (6) and (b) (6) was not authorized to assess inclusion/exclusion criteria per the delegation of authority log.

   (b) The inclusion/exclusion criteria was assessed by (b) (6) for Subject (b) (6) However, (b) (6) was not authorized to assess inclusion/exclusion criteria per the delegation of authority log.

Response and Corrective Action Plan

As Site Investigator, Dr. Chandra had delegated to (b) (6) and (b) (6) the study related task of collecting inclusion/exclusion criteria on a study worksheet based on their education, training, and experience (CV and training records attached, **Tab 3**). The inclusion/exclusion criteria were collected by (b) (6) and (b) (6) on the worksheet and then subsequently reviewed, assessed and signed off by Dr. Rajiv Chandra, the Site Investigator, in the electronic data capture system (b) (4) ®) as evidenced by the audit trails included in **Tab 5**.

However, the (b) (4) DOA Log did not completely represent all authority delegated by the site investigator, was not properly monitored and did not specifically confer upon them this task in this study document.

Accordingly, we have corrected this error and revised the DOA Log to specify who is authorized to evaluate inclusion/exclusion criteria. [see Revised DOA Log, (**Tab 4**)] Please note that (b) (6). is no longer working on the (b) (4) study at our clinical site.

Please also see comments above regarding training provided to the Research (b) (4) Study Team on this issue (**Tab 1**). Further retraining will include instructions regarding cosigning the worksheets by the study member making any assessments based upon the information collected in the worksheets.

(c) Subjects (b) (6), # (b) (6), (b) (6), # (b) (6), and (b) (6) source documents reflect that (b) (6) assessed adverse events. However, (b) (6) is not authorized to assess adverse events per the delegation of authority log. This individual did not consistently assess if the patient denies congestive heart failure "CHF" symptoms and intermittent claudication since previous visit as noted on the CRF. The delegation of authority log does not specify what "other" clinical assessments (b) (6) is authorized to perform.

Response and Corrective Action Plan

Based on her qualifications (b) (6) was delegated the task of subject follow-up. This study task included querying subjects about their health status and recording their answers in the study worksheets and electronic records. There was no assessment of causality or severity performed by (b) (6) was simply completing the follow-up visit questions from a scripted patient dialogue. As described in the (b) (4) Study Manual, (**Tab 6,** Page 57) only the Site Investigator assigns causality of the serious adverse event to study infusion. (b) (6). was not assigning causality.

The (b) (4) DOA Log was not accurately completed and monitored to directly reflect the tasks that were delegated to appropriate study staff. In response to this observation, we have updated the DOA Log (**Tab 4**)

In reference to the portion of this observation suggesting that there was an inconsistent evaluation of symptoms of congestive heart failure and intermittent claudication, we have reviewed the study worksheet in question (**Tab 6,** Page 17, 19). This information was to be collected at each infusion visit, per (b) (4) protocol. The question to be checked on the Worksheet reads: "Patient denies CHF symptoms **and** intermittent claudication since previous visit." (emphasis added). While (b) (6) is no longer working at the site, and therefore, we are unable to confirm this, it is our view that not checking this box, meant that the subject did not deny both of these symptoms, and not necessarily that the question was not consistently asked. Moreover, the form itself does not permit the questioner to indicate that the questions were asked, and that they were responded to in the negative. Thus, this does not represent an inconsistent evaluation of symptoms, but rather an inadequate form. We thank the FDA Investigator for pointing this out, and have made the attached change in the follow-up form (**Tab 7**), which will be included in the electronic data entry system on or before August 31, 2010.

Nevertheless, all site staff authorized to collect this information will be re-trained on the importance of performing consistent evaluations at each patient encounter in the special training session to be provided to all members of the Research/(b) (4) Study Team on June 30, 2010 (**Tab 1**).

(d) Subjects (b) (6) and # (b) (6) source documentation reflected that sections of the CRF, for documenting assessments of Interval Cardiovascular events, were (b) (4) by (b) (6) prior to the subject arriving for their study related visit. (b) (6) is not authorized per the delegation of authority log to perform assessments of study subjects.

Response and Corrective Action Plan

Based on her qualifications (b) (6) was delegated the task of subject follow-up. This study task includes asking subjects about their health status and any cardiovascular events since their last visit. The (b) (4) DOA Log was not properly updated to directly reflect this delegation of authority. There was no assessment of causality or severity performed by (b) (6) As previously stated, (b) (4) was simply completing the follow-up visit questions from a script.

In response to this observation, we have updated the Site DOA Log (**Tab 4**) to specify that the identified study activities will be carried out only by qualified individuals. A copy of the curricula vitae of all individuals authorized under the updated DOA Log to perform these activities is attached (**Tab 3**).

We recognize that the practice of (b) (4) of Case Report Forms carries with it the risk that the final data recorded for a study encounter may be inaccurate. In conversations with (b) (6), some minor information was collected by phone the day prior to the scheduled visit to improve efficiency. We agree that this action goes against good clinical practices, and may lead to inaccuracy of data should there be a change in status between the telephone call and the visit.

Accordingly, in the comprehensive re-training to be provided to all (b) (4) Study staff members on June 30, 2010 (**Tab 1**), the practice of (b) (4) forms will be discussed and forbidden. In addition, this will be done in the context of explaining the need to ensure that all data recorded at each patient encounter are current and accurate, and that all worksheets are co-signed and dated by the study members using that collected information for an assessment.

(e) Subjects #(b) (6) (visit#40) and (b) (6) 5 (visits # 19, 27, and 31) source documentation reflected that (b) (6) signed the CRF-Infusion visit Worksheet in the spot designated for the study staff members that performed the physical assessments, assessed adverse events, and administered the investigational drug study. However, per the delegation of authority log (b) (6), is not authorized to perform these duties.

Response and Corrective Action Plan

We respectfully disagree with this observation. In review of the above-referenced infusion visit worksheet, we noted that it reads "signature of person completing the form" (**Tab 6**, Page 18); however, (b) (6) was merely acting as a scribe for the study personnel performing the physical assessments, assessing adverse events, and administering the investigational study drug, while the study personnel tended to the medical needs of the patient. That was the reason for (b) (6) signing in that spot – leading to the misunderstanding that signing the form indicated she herself had performed the above activities. Indeed, her signature indicated that the aforementioned activities had been performed, not that she herself had performed them.

In the comprehensive re-training to be provided to all (b) (4) Study staff members on June 30, 2010, emphasis will be placed on the importance of proper completion of source and regulatory documents (**Tab 1**). From this point forward, we will ensure that the designated staff member performing these tasks is also co-signing and dating the forms.

(f) (b) (6) made trial-related medical decisions for the adverse bleeding event reported 9/22/2009 for subject # (b) (6) in the (b) (4) study. (b) (6) classified the intensity of the event as mild, and not related to the study drug. (b) (6) is not authorized to make trial-related medical decisions per the delegation of authority log.

Response and Corrective Action Plan

On 9/22/09 Subject (b) (6) in the (b) (4) study called the office to complain that she had scratched her ear and that it was bleeding. Dr. Chandra was consulted and the subject was advised to clean the ear and leave it. A return call was made to the subject to determine if the bleeding was stopped. Upon confirmation from the subject that the bleeding had discontinued, an assessment was made by Dr. Chandra that this event was not a serious event. A note was scribed by (b) (6) in the subject's source documentation (**Tab 8**)

Site personnel was re-trained regarding more complete documentation requirements. Further retraining will include instructions regarding cosigning and dating the documents by the study member who made the assessment.

(g) You did not list all Sub-Investigators on the Form FDA 1572. (b) (6) is not listed on the Form FDA 1572, however his curriculum vitae and email correspondence reflects serving in this capacity since joining the site.

Response and Corrective Action Plan

We respectfully disagree with this observation. (b) (6) is not now nor ever has been a (b) (4) investigator. Therefore, he was not listed on the Form FDA 1572 for the (b) (4) Study. (b) (6) CV, however, did contain erroneous information about his participation in the (b) (4) study, which was corrected immediately upon notice as explained to the FDA Investigator during the inspection. An amended CV for (b) (6), accurately listing his active trials, is available for your review as needed.

Nonetheless, we are grateful for the FDA Investigator's observation, which has led us to update our current Form FDA 1572 (**Tab 9**) to include every study staff member that makes a direct and significant contribution to the clinical data, consistent with the current procedural guidance document regarding Form FDA 1572, released in May 2010. The proper completion and, importantly, regular updating of this form will also be covered in the scheduled re-training, which will take place on-site on June 30, 2010 (**Tab 1**).

3. *IRB correspondence, dated 11/5/09, to the site specifies that all current enrollees and all new enrollees should sign the revised informed consent (version date 8/26/09). However, documentation provided reflects that only three (3) subjects signed this consent as required by the IRB.*

Response and Corrective Action Plan

This observation is correct, and it stems from a miscommunication between the (b) (4) and the (b) (4) clinical sites, rather than to neglect or malfeasance at the (b) (4) site. The communication from the (b) (4) Clinical Coordinating Center to the sites dated 8/26/09 had different instructions than the (b) (4) IRB correspondence dated 11/5/09 (**Tab 10**). In response to this FDA observation, the (b) (4) Clinical Coordinating Center requested clarification from (b) (4) IRB on 6/1/10 about this issue, and the Board affirmed their determination that the revised consent document, (version date 8/26/09), should be signed by all current and new enrollees, requiring a corrective action plan to be placed into effect.

In response to this observation and (b) (4) IRB's clarification, all currently active study participants who have not been re-consented with the revised (b) (4) informed consent version dated 8/26/09 are being contacted by phone, and all will be asked to complete a new consent

following discussions with the Study Staff. We anticipate completion of this process by August 31, 2010.

Our principal responsibility is to always conduct the investigation in accordance with the signed statement of the investigator and the investigational plan. Every effort is being made to address the observations listed in this letter.

OBSERVATION 2

Failure to report promptly to the IRB all unanticipated problems involving risk to human subjects or others.

1. *You did not report the death of subject* (b) (6) *in accordance with the designated IRB requirements that specified all serious and unexpected adverse events that occur at your site must be reported within 10 business days of the Investigator's knowledge of the event and all fatal or life threatening events should be reported immediately. Subject #* (b)(6) *received an intravenous infusion of the investigational drug on 7/19/2006 and died on 7/21/2006. Documentation provided during inspection reflects you became aware of this death on or about 7/31/2006. However, no documentation was provided to show that this death had been reported to the IRB.*

Response and Corrective Action Plan

We seek to diligently follow proper reporting procedures at our site, but we have been unable to locate the documentation showing that this event was promptly reported to the IRB. The death was reported in the study electronic data capture system and reviewed by the medical monitor at the (b) (4), who evaluated this death as not study-related (**Tab 11**). We have submitted a late notification of this event to the IRB (**Tab 11**).

We take this observation very seriously and proper reporting of (b) (4) adverse events will be reviewed and emphasized with the study staff as a part of the re-training to be provided on June 30, 2010 (**Tab 1**).

2. *You did not report the deaths of subjects #*(b) (6) *and #*(b) (6) *in accordance with the designated IRB requirements, as evidenced by:*

   (a) *Subject #* (b) (6) *died on 11/1/2007. Documentation provided during inspection reflects you became aware of this death on or about 11/5/2007, however you reported the death of this subject to the IRB on 11/13/2007.*

   (b) *Subject #* (b)(6) *died 2/12/2006. Documentation provided during inspection reflects you became aware of this death on or about 2/24/2006, however you reported the death of this subjects to the IRB on 6/13/2006.*

(c) *Subject #(b) (6) died 4/5/2006. Documentation provided during the inspection reflects you became aware of this death on or about 4/7/2006. You reported the death of this subject to the IRB on 6/13/2006.*

(d) *Subject #(b) (6) died 7/2/2008. Documentation provided during the inspection reflects you became aware of this death on or about 7/10/2008. You reported the death of this subject to the IRB on 7/25/2008.*

Response and Corrective Action Plan

We respectfully clarify this observation. The deaths of the 4 subjects listed above (a-d) occurred more than 30 days following the cessation of active chelation infusions and thus are ***not*** defined in the (b) (4) protocol as serious adverse events related to the study treatment nor are they unanticipated due to the subject's underlying medical conditions (**Tab 12**, pages 52-53). Therefore, while it was not required by the IRB-approved (b) (4) Study Protocol to report these deaths as SAEs to the IRB, the site still reported them in abundance of precaution. Sites were required only to report these events in the (b) (4) electronic data capture system – (b) (4) for clinical endpoint data collection.

Nevertheless, proper reporting of (b) (4) adverse events, serious adverse events and endpoints will be reviewed with the study staff as a part of the re-training to be provided on June 30, 2010 (**Tab 1**).

3. *Subject #(b) (6) was hospitalized from 11/26-27/2004 for ventricular fibrillation (V-Fib). Subject last received intravenous study drug on 5/5/2005. An adverse event was entered into (b) (4) by (b) (6) for medical condition of (V-Fib) on 12/1/2004. Adverse event was noted to be serious on 3/8/2005. No serious adverse event was filed.*

Response and Corrective Action Plan

In regards to this observation, this serious adverse event for subject (b) (6) was entered in (b) (4) as SAE 1. Inexplicably, it has now vanished for the data capture system. The site coordinator kept a screen print of the missing SAE 1 and the event has been re-entered in the system (**Tab 13**), while we investigate this issue with the software manufacturer and the DCC.

4. *Subject #(b) (6) was hospitalized on 11/3/2005 with shortness of breath rule out myocardial infarction. Subject last received intravenous study drug on 10/20/2005. No adverse event was entered into (b) (4) for medical condition of shortness of breath.*

5. *Subject (b) (6) was hospitalized on 3/24/2006 with altered mental status rule out myocardial infarction. History of the present illness reflects that the family of subject reported subject had a change in mental status which started approximately 6 weeks before the 3/24/2006 hospital admission. No adverse event was entered into (b) (4) for medical condition of altered mental status.*

Response and Corrective Action Plan

We acknowledge these observations, and are mindful of the requirement that adverse events be promptly reported to the IND Sponsor and the IRB. (b) (4) Protocol instructions regarding the reporting of adverse events will be reviewed with study staff, and covered as a part of the re-training for study staff on June 30, 2010 (**Tab 1**). We have entered the missing events for the two (2) subjects listed in the above observations into (b) (4) as evidenced in **Tab 14**.

Please note that statements *2.3, 2.4 and 2.5* relate to data entry into (b) (4), and have no bearing upon prompt IRB reporting as mentioned in Observation 2. The (b) (4) site is an active site that has correctly reported and entered over 170 adverse events during a period of six years.

OBSERVATION 3

Failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation.

1. *Source records revealed inadequate documentation of who actually performed study related activities in accordance with delegation of authority log as evidenced by:*

   (a) *Subjects* (b) (6) *urinalysis results do not reflect the "clarity" of the specimen, did not identify who performed the test, does not identify all urinalysis test results by study subject number, nor are the out of reference range laboratory results deemed to be clinically significant or not clinically significant.*

Response and Corrective Action Plan

We recognize that source records did not consistently identify who performed the test, did not identify all urinalysis test results by study subject number, nor were all out of reference laboratory results deemed to be clinically significant or not clinically significant for the referenced study subjects. This should have been done in a consistent fashion and henceforth the study subject number and the name of the staff member that performs and reviews the tests will be included in all source documents. However, the (b) (4) protocol does ***not*** require sites to assess the "clarity" of urine. Instead, clinically significant study-related findings in the urine dipstick report are hematuria and/or proteinuria (**Tab 12,** Page 44).

All study personnel will be re-trained with regard to proper record keeping requirements to ensure that accurate identification is recorded in the source documents. Training will also be provided to all study staff concerning appropriate procedures to be followed when a test result is found to be outside of the reference range (**Tab 1**).

   (b) *Source documentation for Subjects* (b) (6) - (b) (6) *did not adequately identify the study staff members that completed in-clinic*

assessments, concomitant medication assessments, vitamin accountability, or weight assessments.

Response and Corrective Action Plan

Please see comments above regarding steps taken to ensure that source documents are fully and appropriately completed, including the name(s) of individuals performing in-clinic assessments, assessments of concomitant medications, weight assessments, and vitamin accountability checks. These topics are among those items to be covered in the re-training of all affected staff on June 30, 2010 (**Tab 1**).

(c) Subject #(b) (6) (b) (4) bleeding event source documents do not identify the staff member that recorded the positive fecal occult result during hospitalization.

Response and Corrective Action Plan

Subject #(b) (6) was hospitalized on 12/25/09 at a hospital under the care of physicians who are not a part of the study. During this hospitalization, the subject had stool examined for occult blood, which was reported as negative on 01/12/2010 (**Tab 15.**)

On Jan 16, 2010,(b) (6) ARNP, Sub-Investigator followed up with the patient after the hospitalization and after an intensive and thorough review of the hospital records found, documented and followed up on a lab test that was missed in the hospitalization physician's documents (**Tab 15**).
On Jan 22, 2010, (b) (6) ARNP, Sub-Investigator spoke with the subject regarding her status. A fecal occult test kit was sent to subject for follow-up, which is documented on **Tab 15.**

During the re-training further emphasis will be placed on documentation.

2. *Documentation was not made available at the site to show that the intravenous investigational study drug, with a volume of (b) (4) was infused at an administration rate of (b) (4) as specified in the Protocol and Study Manual. The site used a medical device, a Rate Flow Regulator IV Set, with incremental settings of ***(b) (4) (b) (4) ** for administration of the study drug and the dial on the device was set between (b) (4) and (b) (4).*

Response and Corrective Action Plan

We respectfully submit that there is a misunderstanding regarding the required flow rate for the infusion, the use of flowmeters, and the determination of flow rate according to protocol. The (b) (4) site did not violate (b) (4) protocol in calculating and delivering the study infusions of the test article. Neither flowmeters nor infusion pumps are required per protocol, and regulation of the IV by drip rate inspection is the study standard.

Indeed, the (b) (4) protocol and study manual call for the (b) (4) solution to be administered for "a (b) (4) at a rate of (b) (4) Additionally, both documents further state the infusion regimen will not exceed (b) (4) (**Tab 6**, pages 22, 140, and 177 & **Tab 12**, pages 24 and 28), since the safety concern related to edetate disodium, the test article, involves overly rapid infusions, rather that overly slow ones. Sites document in the electronic data capture system the start time and end time for each infusion in the appropriate worksheet, but, in the protocol approved by the IRBs and included in the IND, there are no requirements to include the exact hourly infusion rate in the source documents, nor any requirement regarding the use any type of infusion rate regulator.

Study-wide, any infusion given in less than 2 hours and 45 minutes (there is a 15 minute margin allowed) triggers an email alert to the site, sponsor and DCC to follow-up and determine cause and preventive strategies.

The Rate Flow Regulator noted by the FDA Investigator was used as an extra precaution at the (b) (4) site to prevent the infusion from completing in (b) (4), but it was not required by protocol. It is important to note that **2595** infusions were safely administered at this site, and only **1** occurred in less than the required (b) (4), because of premature discontinuation of the infusion (**Tab 16).**

3. *Source documentation of adverse events that were reported in the iCRF were not made available for review during the inspection.*

Response and Corrective Action Plan

The FDA investigator was provided with full access to all available (b) (4) study related records and source documentation of adverse events during the 6-week audit of the site.

We request clarification of this observation (3.3), as to which documents these are, so the study team can make them available as soon as possible. Any and all source documentation relating to this issue will be provided to the Agency for review within 15 business days after receipt of your request.

OBSERVATION 4

Investigational drug disposition records are not adequate with respect to dates, quantity, and use by subjects.

1. *Source documentation for Subjects (b) (6) - (b) (6) do not show the date and quantity of vitamins dispensed or returned by the subjects throughout the study. However, the (b) (4) Study Manual indicates that the*

number of study drug vitamins returned/or unaccounted for should be recorded on the visit record and in the iCRF on the vitamin accountability screen. Study drug accountability was only recorded in the iCRF vitamin accountability screen.

2. *Delivery Packing Slips for the receipt and packaging integrity of (b) (4) study drugs was not maintained in accordance with the Sponsors directions.*

Response and Corrective Action Plan

We respectfully note that the IND in this study is approved only for the (b) (4) (b) (4)), and does not encompass the (b) (4) study vitamins under its regulatory scope. In other words, the (b) (4) study vitamins are not considered investigational under this IND; rather, the (b) (4) evaluated in (b) (4) is equivalent to over-the-counter food supplements, and are not part of the IND. We are however, grateful for the observation made by the FDA Investigator, since (b) (4) procedures and Study Manual call for the recording of all relevant information concerning the administration and return of vitamins, both on the visit record and on the iCRF (**Tab 6,** pages 14 & 20), as well as the retention of records pertaining to the delivery of test article(s) to the site.

The requirements for appropriate recordkeeping with respect to the quantity of vitamins dispensed and returned, and the delivery and disposition of test drugs in compliance with (b) (4) Study requirements and FDA regulation 312.62(a) have been discussed with the study team and will be part of the re-training provided to all affected personnel on June 30, 2010 (**Tab 1**).

Please note that subject (b) (6) noted in observation 4.1 above, is not a (b) (4) study subject at this site.

OBSERVATION 5

Unused supplies of an investigational drug were not disposed of in accordance with sponsor instructions.

1. *Source documentation for Subjects (b) (6) (b) (6), #(b) (6), #(b) (6) (b) (6)-(b) (6), (b) (6) was inadequate and did not show the final disposition or disposal of study supplements. However, the (b) (4) Study Manual, May 2005, the Alpha-Medical/TruMed Ed Site Policy and Procedure for the Disposal of Unused, Expired or Returned Medications/Study Drugs, and Monitoring correspondence dated 2/5/2009 reflect that this should be recorded on the appropriate log – in this case the vitamin accountability log.*

Response and Corrective Action Plan

The (b) (4) Study Manual (**Tab 6,** Page 177) calls for the disposing of the used study drug and vitamin supplements, in accordance with each local site policies. Also the Monitor Communication- "Talk Talk" on February 2009 (**Tab 17**, Page 3) discusses these issues. There is

no specific requirement in the (b) (4) procedures to document the final disposition of the study drug or the vitamin supplements. (**Tab 6,** Page 177). The Alpha-Medical/TruMed Ed Site Policy and Procedure for the Disposal of Unused, Expired or Returned Medications/Study Drugs does state that medication returned, and/or unaccounted for should be recorded in the appropriate form **or** log (**Tab 17**) (emphasis added).

The requirements for appropriate recordkeeping with respect to test article(s) in compliance with the (b) (4) Study Manual and Good Clinical Practices have been discussed with the Study Team and will be also included in the specialized re-training to be provided to all affected personnel on June 30, 2010 (**Tab 1**).

As stated before, supplements are not part of the (b) (4) IND. and also patient (b) (6) noted in observation 5.1, is not a (b) (4) study subject at this site.

Ms. Emma R. Singleton
District Director, FDA Florida District
June 14, 2010

SUMMARY

As detailed above, we believe that we have responded fully and appropriately to the findings on the Inspectional Observations Form FDA 483. Each member of the study team has fully cooperated in all of these efforts. The (b) (4) study team further recognizes its responsibility to fully and comprehensively address these issues in an ongoing fashion so as to ensure that similar events may be avoided in the future and that all subjects involved in human subjects research are protected. We hope that the steps taken thus far and the additional efforts committed for the future are satisfactory. We look forward to the Agency's response.

Sincerely,

(b) (6)

Rajiv Chandra, MD, PhD
(b) (4) Site Investigator

(b) (6)
(b) (4) Study Chair

Enc.

Cc:
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