

Inspections, Compliance, Enforcement, and Criminal Investigations

ICON Clinical Research, Inc.



Department of Health and Human Services

Public Health Service
Food and Drug
Administration
Silver Spring, MD 20993

WARNING LETTER

CERTIFIED MAIL

RETURN RECEIPT REQUESTED

Ref: #10-HFD-45-11-04

John W. Hubbard, Ph.D.
Global President, ICON Clinical Research
c/o ICON Clinical Research Limited
212 Church Road
North Wales, PA 19454

Dear Dr. Hubbard:

This Warning Letter is to inform you of regulatory violations found during the U.S. Food and Drug Administration's (FDA) investigation into ICON Clinical Research LTD's (hereafter referred to as ICON) role as the contract monitoring organization (CRO) contracted by **(b) (4)** (hereafter referred to as **(b) (4)**) to provide clinical study management services for Study **(b) (4)** entitled **(b) (4)**" and Study **(b) (4)** entitled **(b) (4)** of the investigational drug **(b) (4)**

This inspection is a part of the FDA's Bioresearch Monitoring Program, which is 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.

Another objective of the program is to ensure that data submitted in support of New Drug Applications are scientifically valid and accurate.

The first study, **(b) (4)** was initiated by the original holder of **(b) (4)** (hereafter referred to as **(b) (4)**) On February 2, 2005 **(b) (4)** entered into a worldwide partnership with **(b) (4)**, a **(b) (4)** company, to develop and market **(b) (4)** (referred to as **(b) (4)**) Under the terms of the agreement, **(b) (4)** was to be developed further by **(b) (4)** and all rights and responsibilities for **(b) (4)** clinical trials were transferred to **(b) (4)**. Of note, with the transfer of development to **(b) (4)**, all clinical trial monitoring agreements between **(b) (4)** and ICON Clinical Research LTD (ICON) remained in effect (including those in place for **(b) (4)**) The second study, **(b) (4)** was initiated by **(b) (4)** As was the case with **(b) (4)** contracted ICON to provide clinical research management for **(b) (4)**

On May 18, 2007, **(b) (4)** submitted the data from **(b) (4)** and **(b) (4)** to the FDA to support the approval of **(b) (4)** for the indication of treatment of **(b) (4)**. Subsequent data validation inspections of clinical investigators participating in these studies revealed significant violations of FDA regulations codified at 21 CFR 312.

Between May 26, 2008 and June 12, 2008 FDA inspected **(b) (4)**. According to contracts between **(b) (4)** and ICON, **(b) (4)** specifically transferred the following tasks associated with site monitoring to ICON:

- Develop and write monitoring plan specific to study;
- Schedule and conduct on-site monitoring visits according to monitoring-plan specifications;
- Schedule and conduct telephone follow-up visits according to protocol/monitoring-plan specifications;
- Write monitoring-visit reports, including follow-up letters, telephone contacts, etc.;
- Notify sponsor of any critical site issues (i.e., good clinical practice violations, noncompliance trends noticed at site) and for providing a proposed resolution plan;
- Conduct weekly teleconferences to review site-monitoring schedule, site status, communication plans, etc.; and
- Provide tracking of monitoring visits, telephone follow-up visits, monitoring-visit reports, and protocol violations.

ICON agreed to conduct site-initiation visits, interim blinded and unblinded monitoring visits, and closeout visits. At each interim monitoring visit, ICON personnel agreed to "review CRFs for completion, perform 100% source document verification (SDV) for all data, verify informed consent, ensure proper AE reporting, check record retention and adequacy of supplies and ensure proper drug storage and accountability." ICON also agreed to "ensure that the site is adhering

to the protocol and to applicable regulations and that the staff are motivated to conduct the study” and to “send a follow-up letter to the site that detailed any non-conformances [sic] and corrective actions to be taken.”

During FDA’s inspection of **(b) (4)** between May 26, 2008 and June 12, 2008, FDA obtained ICON monitoring records, which were provided to **(b) (4)** at the conclusion of ICON’s clinical study management services for these studies.

The regulations permit the transfer of obligations to a CRO by a sponsor [21 CFR 312.52(a)], and describe the responsibilities that the CRO incurs when obligations are transferred [21 CFR 312.52(b)]. Specifically, a CRO that assumes any obligation of a sponsor shall be subject to the same regulatory action as a sponsor for failure to comply with any obligation assumed under part 312. From our review of the **(b) (4)** establishment inspection report and the documents submitted with that report, **(b) (4)** written response to the Form FDA 483, dated June 24, 2008; and **(b) (4)** responses dated September 2, 2008, and September 4, 2008, in response to additional information requests from the FDA, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We wish to emphasize the following:

1. Failure to ensure proper monitoring of the clinical investigations [21 CFR 312.50 and 312.56(a)].

FDA regulations require that sponsors, or CROs to whom such responsibilities have been transferred, ensure proper monitoring of clinical investigations. Our investigation found that ICON failed to properly ensure monitoring of the studies referenced above. Inadequate monitoring resulted in deficiencies in recordkeeping with respect to case histories and drug accountability by clinical investigators participating in the above-referenced studies. Violations include, but were not limited to, the following:

a. Deficiencies in case histories:

i. Study monitors failed to identify that on multiple occasions, site personnel documented administration of study drug to different subjects at precisely the same time. For example:

a) For Study **(b) (4)** at Site #520, study monitors failed to identify that on multiple occasions, study coordinators documented administration of study drug to two different subjects at the same time. On April 27, 2005, enrollment of subjects at Site #520 was allowed to resume, based upon the Sponsor’s review of the site’s April 27, 2005, plan for “Outpatient Treatment Procedures.” Implementation of this plan was to begin on April 27, 2005. The Outpatient Treatment Procedures plan called for the first

dose of the study drug to be administered in the site's designated infusion center, and for the remaining doses to be administered by a study nurse or a home health nurse in the patient's home. In light of these procedures, study monitors should have identified that on multiple occasions, for subjects being treated as outpatients, study coordinators documented administration of study drug to two different subjects at the same time, and study monitors should have sought an explanation for these observations.

Specifically,

i) Study Coordinator **(b) (4)** was documented as having administered study drug to the following subjects at the same time on the same date:

(a) Subject #1266 at 09:00-10:00 and Subject #1267 at 09:00-10:00 on 7/2/05

(b) Subject #1266 at 09:00-10:15 and Subject #1267 at 09:00-10:15 on 7/3/05

(c) Subject #1266 at 21:00-22:00 and Subject #1267 at 21:00-22:00 on 7/5/05

(d) Subject #1266 at 21:00-22:00 and Subject #1267 at 21:00-22:00 on 7/6/05

(e) Subject #1266 at 09:00-10:00 and Subject #1267 at 09:00-10:15 on 7/7/05

ii) Study Coordinator **(b) (4)** was documented as having administered study drug to Subject #2273 at 10:00-11:00 and to Subject #2275 at 10:00-11:00 on 7/26/05.

Given the site outpatient treatment plan and study monitoring that was conducted for the identified subjects, study monitors should have noted that on multiple occasions, study site personnel documented administration of study drug to different subjects at precisely the same time, and further investigated the reason for this irregularity. Moreover, based on the FDA investigation conducted at the site, we have determined that subjects enrolled in the study continued to self-administer study medications in their homes beyond the time when the site's April 27, 2005, plan was to have been implemented. In addition, it would not be possible for the same study coordinator to begin study infusions on more than one subject at precisely the same time, even if the two subjects had been treated at the same location.

b) For Study **(b) (4)** at Site #063, study monitors failed to identify that on multiple occasions, the same study nurse, **(b) (4)** was documented in the "Planilla de estabilidad" as having administered study drug to different

subjects at precisely the same time, as follows:

i) On May 20, the study nurse **(b) (6)** is documented as having administered study drug to the following subjects at 08:00-10:00:

- (a) Subject #140616 **((b) (6))**
- (b) Subject #140132 **((b) (6))**
- (c) Subject #140617 **((b) (6))**
- (d) Subject #140118 **((b) (6))**

ii) On May 20, the study nurse **(b) (6)** is documented as starting placebo infusions to the following subjects at 10:00-11:00:

- (a) Subject #140616 **((b) (6))**
- (b) Subject #140132 **((b) (6))**
- (c) Subject #140617 **((b) (6))**
- (d) Subject #140118 **((b) (6))**

Study monitors should have recognized that on multiple occasions, the same individual was documented as administering study drug to different subjects at precisely the same time, and study monitors should have further investigated the reason for this irregularity.

ii. One hundred percent source documentation verification was completed by study monitors for Subject #141050, enrolled in Study **(b) (4)** at Site #551, according to ICON monitoring reports; however, study monitors failed to identify that no physical examination, wound assessment, or overall clinical assessment was documented in study source documents or on the Case Report Form (CRF) for this subject's Day-8 visit, as required by the protocol.

iii. Study monitors failed to identify that for both Study **(b) (4)** and Study **(b) (4)** the times that infusions were "delivered to Nursing Unit" were not recorded. For example:

a) At Site #502, according to the **(b) (4)** worksheet, the times that reconstituted study drug was delivered to the nursing unit were "not recorded" on at least four occasions for Subject #1118.

b) At Site #508 according to the "**(b) (4)** worksheet, the times that reconstituted study drug was delivered to the nursing unit were "not recorded" on at least seven occasions for Subject #140005.

iv. For Study **(b) (4)** at Site #509, study monitors failed to ensure that reconstituted study drug infusion solutions were stored appropriately. Protocol **(b) (4)** stated that reconstituted study drug infusion solutions

should "be stored at room temperature (25°C) and used within 6 hours, or stored for up to 16 hours under refrigeration (5°C) and used within 3 hours after removal from the refrigerator." Because the study protocol did not outline outpatient dosing conventions, the study monitor sought assurance, in e-mail correspondence between Site #509 and the study monitor dated October 20, 2004, that there was documentation to show that study medication was being maintained and stored under proper temperature conditions by patients who were to self-administer the study drug in their own homes. Although they were asked by ICON monitors, the personnel at the site never addressed how they would document the temperature storage conditions of the product in subjects' homes; site personnel only addressed how subjects' body temperatures were to be recorded. Study monitors failed to recognize that the site's response was incomplete; rather, they accepted this response as complete. Subject diaries were then created and used by the site that did not include a place to record storage temperatures of study medication that was stored in subjects' refrigerators. Therefore, storage temperatures for these medications could not be confirmed as complying with storage conditions specified by the protocol. The importance of maintaining proper temperature conditions in patients' homes is evidenced by page three of the "**(b) (4)** Outpatient Study Drug Procedure," dated "25May2005," which stated that the "receiving site storage conditions must be confirmed upon delivery of the study medication. Clinic, investigator office and/or patient refrigerator temperatures must be recorded and the plan must specify where and by whom."

v. For Study **(b) (4)** at Site #520, study monitors failed to document the out-of-range temperature readings noted at this site, and failed to provide appropriate follow-up instructions to the site regarding the usage of the kits in a particular shipment. Drug shipments from **(b) (4)** contained "Refrigerated Shipment Inspection Instructions" that included instructions to fill out readings from a temperature-recording device on the bottom of the Packing List, and to return this device to **(b) (4)** if the device screen displayed a "bell" symbol (potentially signifying that the shipment did not maintain appropriate conditions). If no bell was seen, the shipment maintained appropriate temperatures, and the contents could be used. An April 4, 2005, Packing List for Order #1000739, shipped to Site #520 for Study **(b) (4)** was identified for which temperatures were recorded as being out of range on the bottom of the sheet; however, no documentation was present for the return of the temperature-recording device or for follow-up to the site regarding the acceptability of the use of the kits contained in this shipment. Source documents demonstrated that drug from kits contained in this shipment were dispensed and administered to study subjects between April and June 2005. The Unblinded Monitoring Visit Report (dated May 25, 2005) encompassing monitoring of Site #520 for the time frame when this

shipment was received, failed to document the out-of-range temperature readings or the appropriate follow-up instructions to the site regarding the usage of the kits in this shipment.

Based on documentation available at the time, study monitors conducting the Unblinded Monitoring Visit should have recognized that drug kits from Order #1000739 should not have been administered to subjects.

vi. For Study **(b) (4)** at Site #146, "IV stability" worksheets were missing for all 39 subjects enrolled, and corrective actions by study monitors were inadequate to correct this deficiency throughout the study. According to the Work Order for this study, unblinded monitoring visits by ICON were to occur every 10 weeks. This issue was documented in the unblinded monitoring visit reports dated 27 January 2006 and 25 September 2006. In addition, the monitor requested that personnel at the site complete these worksheets, and that the site generate a Memo to File that documented the IV temperature stability conditions for previously enrolled subjects. However, the issue should have been addressed again prior to the 25 September 2006 unblinded monitoring visit. The Memo to File that was finally written on 16 November 2006, after completion of subject enrollment at the site, stated only that "i.v. stability has been maintained according to the IV label, which states start/finish time and the expiry time of the infusion, [sic] patient number." This statement does not provide sufficient detail to ensure that temperature stability conditions for the drug were maintained adequately.

vii. For Study **(b) (4)** at Site #520, study monitors failed to identify discrepancies in the time of delivery of study drug to the nursing unit, as recorded on **(b) (4)** worksheets; and the time of administration of the study drug, as recorded on "Administration of Study Medication" worksheets for multiple subjects. For example:

a) Subject #1187's source documents indicate that:

- i) on 3/1/05, study drug was delivered at 19:05; study drug administration time is documented as 18:00-19:00
- ii) on 3/2/05, study drug was delivered at 19:10; study drug administration time is documented as 18:00-19:00
- iii) on 3/11/05, study drug was delivered at 18:05; study drug administration time is documented as 18:00-19:00
- iv) on 3/12/05, study drug was delivered at 18:40; study drug administration time is documented as 18:00-19:00.

b) Subject #1195's source documents indicate that:

- i) on 4/14/05, study drug was delivered at 09:00; study drug

administration is documented as 08:05-09:05

c) Subject #2671's source documents indicate that:

- i) on 5/11/05, study drug was delivered at 10:00; study drug administration is documented as 09:30-10:30
- ii) on 5/12/05, study drug was delivered at 09:55; study drug administration is documented as 09:30-10:30
- iii) on 5/13/05, study drug was delivered at 09:50; study drug administration is documented as 09:30-10:30

viii. For Study **(b) (4)** study monitors failed to identify discrepancies in study records related to observations and data pertinent to the investigation. For example:

For Study **(b) (4)** at Site #520, source documents and study documents contain conflicting information related to wound dimensions, debridement of wounds, and signs and symptoms of infection for multiple subjects; however, this conflicting information was not identified by the monitors. For example:

a) For Subject #1010, Wound #2 was documented as the qualifying study wound for study enrollment, according to a source document for the baseline visit. In the sub-investigator's "Outpatient Wound Care Progress Note" for 3/22/05, the dimensions of the wound were documented as 10 mm x 4 mm; the progress note also stated that the wound was too sensitive for debridement. However, a wound-care source document dated 3/23/05, documented that the study wound had been debrided on 3/22/05, and that the wound dimensions were 25 mm x 30 mm. We also note that page 2 of 4 of the source document for the "Test of Cure, Clinical Assessment," dated 3/23/05, was initialed and dated "3/5/05" by the sub-investigator; however, this date is 18 days before this source document states that the visit occurred.

b) For Subject #1186, the sub-investigator's progress note for 3/7/05 stated that the wound dimensions were 21 mm x 25 mm. Study source document worksheets for the 3/7/05 visit originally documented wound dimensions of 17 mm x 15 mm, but on 4/18/05, those dimensions were lined through and revised to cite the wound dimensions as 21 mm x 25 mm. Because this source document also stated that "wound assessment done per MD + reported to CRC," it is unclear why the originally recorded dimensions were inconsistent with those documented in the sub-investigator's progress note. Similarly, the sub-investigator's progress note for 3/14/2005 stated that the wound dimensions were 23 mm x 29 mm, but the source document for the same day originally documented wound dimensions of 15 mm x 10 mm; then, on 4/18/05, the dimensions

originally recorded on the source document were lined through and revised to cite the wound dimensions as 23 mm x 29 mm. In addition, the sub-investigator's progress note for 3/21/2005 stated that the wound dimensions were 14 mm x 23 mm; however, page 2 of 4 of the source document for the same day originally documented wound dimensions of 8 mm x 6 mm. On 4/18/04, the dimensions originally appearing on the source document were lined through and revised to cite the wound dimensions as 14 mm x 23 mm. However, the corresponding CRF page for the 4/18/05 visit still documented the wound dimensions as 8 mm x 6 mm. In addition, the sub-investigator's progress note for 3/14/07 documented "much less inflammation and little drainage"; however, the source document for the date of this visit documented drainage or discharge as "absent" and erythema as "absent."

c) For Subject #2274, the source document for the End of Treatment visit, dated 7-26-05, documented wound dimensions of 13 mm x 20 mm and a wound assessment of "absent-reddness [sic], pain, edema, heat, flutuanace [sic], funct impair, drainage"; however, on another page of the same source document, wound dimensions were listed as "1 mm x 0 mm," drainage or discharge was checked as "improved," and pain or tenderness to palpation was checked as "unchanged." The corresponding CRF page for the End of Therapy visit documents wound dimensions as "80 mm x 95 mm."

b. Deficiencies in drug accountability:

For Study **(b)(4)** at Site #551, monitors failed to identify that study documents contained conflicting information regarding accountability of the drug. When "**(b)(4)**" and Drug Accountability Form source document worksheets were compared, it appears that on multiple occasions, the same kit vial was recorded as being given to more than one subject; and/or on more than one occasion, to the same subject; or the recorded kit-vial information was incomplete. Examples include, but are not limited to, the following:

**(b)(4) Worksheet
(Kit-Vial)
(Date)
(Subject#)**
21148-8
1-Aug-06
#141059

**Drug Accountability Form
Worksheet
(Kit-Vial)
(Date)
(Subject#)**
21148-8
30-Jul-06
#141052

21148-1	21148-1
1-Aug-06	02-Aug-06
#141059	#141052
22609-2	22609-2
2-Aug-06	27-Jul-06
#141059	#141052
10131-8	10131-8
5-Aug-06	03-Aug-06
#141059	#141059
60126-1	60126-1
03-Aug-06	02-Aug-06
#141062	#141059
60126-18	60126-18
03-Aug-06	08-Aug-06
#141062	#141062
60126-7	60126-7
07-Aug-06 and 08-Aug-06	04-Aug-06
#141062	#141062
23631-15	23631-15
11-Aug-06	08-Aug-06
#141066	#141066
23631-8	23631-8
11-Aug-06	08-Aug-06
#141066	#141066
23110-18	23110-18
14-Aug-06	No Record of Being Dispensed
#141067	
23110-4	23110-4
14-Aug-06	No Record of Being Dispensed
#141067	

The study monitors failed to notice these discrepancies, despite the fact that the contents of a single vial, which would constitute a single treatment course for one subject, were documented to have been used multiple times.

2. Failure to ensure that an investigation was conducted in accordance with the general investigational plan and protocols, as specified in the IND [21 CFR 312.50].

- a. Study monitors failed to ensure that the investigation was conducted in

accordance with the investigational plan for Study **(b) (4)** For example:

i. At Site #063, for Study **(b) (4)** study monitors failed to ensure that subjects received study medication as specified in the protocol. According to footnote 1) of the Schedule of Assessments in Clinical Protocol **(b) (4)** "All screening/pre-dose assessments will be considered as baseline and must be performed and reviewed before **randomization and dosing on Day 1** [emphasis added], with the exception of the PK sample collections". Based on this statement and on other training and materials made available to clinical investigators, all patients should have begun dosing on the same day as randomization. For Study **(b) (4)** at Site #063, however, nine subjects of forty-five did not receive study drug for more than 24 hours after randomization, ranging from approximately 48 hours to eleven days post randomization. For example, Subject #140117 was randomized on 05 May 2006 and received the first dose of medication on 16 May 2006. According to the Unblinded Monitoring Visit Report dated 06 Sep 2006, the delay was due to "personal problems of the patient." This was noted as a minor issue in the post-monitoring visit letter to unblinded site staff, and was not mentioned at all in the post-monitoring visit letter to the Clinical Investigator. In addition, no corrective action was documented in monitoring reports or follow-up letters to Site #063.

The delay in administration of appropriate antibacterial therapy for these nine patients, if in fact they had complicated skin and skin structure infections, would have placed them at increased risk for worsening of primary infection, dissemination of infection, sepsis, and death. We have determined that study monitors failed to fully recognize the significance of the clinical investigator's practice of repeatedly delaying study drug dosing after subject randomization and failed to implement appropriate corrective actions to prevent this issue from recurring at the site.

ii. At Site #063, for Study **(b) (4)** study monitors failed to ensure that planned study blinding procedures were correctly followed. This study was to be conducted in a double-blind fashion. According to the Protocol (Section 6.2 Blinding and Randomization), "The unblinded pharmacist will be responsible for preparing the study medication for each subject in such a way that investigators and staff remain blinded to the medication being administered."

a) At Site #063, study nurses, rather than the unblinded pharmacist, were responsible for completing drug dissolution and reconstitution, as well as administering study drug infusions and caring for the subjects. Therefore, nursing personnel caring for subjects (i.e. study staff) were not blinded to study treatment, as specified by the protocol.

b) At Site #063, for Study **(b) (4)** investigators may have been unblinded to the treatment group for five subjects (#140103, #140107, #140114, #140111, and #140112), because the nursing notes included the name of blinded medication infused. Nursing notes were viewed by clinical investigators at the site. Although it appears that the nurses used correction fluid to cover their handwriting, in some cases the covered handwriting could still be read, according to the ICON Unblinded Monitoring Visit Report, dated 11-12 May 2006. In relation to this finding, this report stated that "the infirmity notes are to be seen by the blinded staff, so we do not know for sure if these notes were seen by them." This report also included instructions that are clearly inconsistent with International Conference on Harmonization Good Clinical Practice (GCP) guidelines, to the site from ICON Monitors, in that it stated, "We called the Lead Study Monitor and she instructed to strike out these inclusions with black marker to prevent further potential of unblinding. This procedure was done by the Lead Study Nurse, who included her initials and date." GCP guidelines generally state that any change or correction to a document should be dated, initialed, and explained (if necessary), and should not obscure the original entry; therefore, both Site #063 personnel and the ICON monitors assigned to this site failed to make corrections to source documents appropriately for at least five subjects enrolled at the site.

b. Study monitors failed to identify that, for at least fourteen subjects (#141051, #140040, #140051, #141050, #141074, #141080, #141061, #141067, #141066, #141062, #141068, #141059, #141060, and #141079) enrolled in Study BAP00414 at Site #551, the drug-infusion order was reversed daily for infusions #4 and #5. For example, for Subject #141051 in the **(b) (4)** arm, the protocol required that the fourth dose be placebo, given over 60 minutes, and that the fifth dose be **(b) (4)** given over 120 minutes; however, the site personnel administered **(b) (4)** over 120 minutes as the fourth dose, and placebo was administered over 60 minutes as the fifth dose.

c. Study monitors failed to identify that for both Study **(b) (4)** and Study **(b) (4)** subjects who did not meet eligibility criteria were enrolled. For example:

i. For Study **(b) (4)** at Site #520, Subject #1011 was enrolled on March 3, 2005, for treatment of a left-foot abscess. This subject did not meet the inclusion criterion for enrollment of a subject with diagnosis of abscess, because the onset of the abscess was more than seven days before enrollment. A Data Correction Form (DCF) dated May 27, 2005, stated that the subject received antibiotic treatment with Bactrim DS, with the

end date "21-FEB-2005"; also, a CI comment in source documents stated that the subject had received the Bactrim for treatment of the left-foot abscess.

ii. For Study **(b) (4)** at Site #551, study monitors failed to identify that while Subjects #141061 and #141074 were documented to have had pregnancy tests done, the site did not have the test results and/or did not document the negative pregnancy test results for these subjects before their enrollment, as was required by the protocol for females of childbearing potential.

iii. For Study **(b) (4)** at Site #063, study monitors failed to identify that Subject #140107 was not eligible for the study. Protocol required that infection at a site of previous surgery/trauma occur within 30 days of the surgery/trauma. However, for Subject #140107, the previous surgery was documented as having taken place 20 months prior to the study screening visit. Furthermore, additional source documents obtained from the site demonstrated that this subject also did not qualify for enrollment based on criteria for any of the other types of complicated skin and skin structure infections described in the inclusion criteria.

d. For Study **(b) (4)** at Site #551, study monitors failed to identify that the unblinded site pharmacist did not receive baseline creatinine clearance (CrCl) results in time to ensure appropriate study drug dosing calculations, as required by the protocol. For example,

i. The following CrCls were not faxed to the study pharmacist until August 12, 2006, which was well after subjects' enrollment and start of dosing:

- a) Subject #141060, randomized August 1, 2006
- b) Subject #141061, randomized August 2, 2006
- c) Subject #141066, randomized August 7, 2006
- d) Subject #141067, randomized August 8, 2006
- e) Subject #141068, randomized August 9, 2006

ii. The following CrCls were not faxed to the study pharmacist until November 14, 2006, which was 2-3 months after their respective end of treatment visits:

- a) Subject #141062
- b) Subject #141069
- c) Subject #141079
- d) Subject #141080
- e) Subject #141050
- f) Subject #140040

- g) Subject #141069
- h) Subject #141074
- i) Subject #140051
- j) Subject #140076
- k) Subject #140063

While the monitoring report dated 15 Aug 2006 stated, "Pharmacist to provide copies of CrCl for all patients. Done," this documentation is inadequate, as it does not provide assurance that CrCl values were forwarded to the pharmacist in time to allow appropriate dosing adjustments, if warranted.

This letter is not intended to be an all-inclusive list of deficiencies with your monitoring of clinical studies 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 ongoing 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:

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Sincerely yours,
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Leslie K. Ball, M.D.
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11/27/2009