Johnson & Johnson Pharmaceutical Research & Development, LLC 8/10/09

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Rockville, MD 20857

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ref: 09-HFD-45-07-02

Karen Grosser, Ph.D, M.B.A.
Johnson & Johnson Pharmaceutical Research & Development, LLC
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Raritan, NJ 08869-0602

Dear Dr. Grosser:

This Warning Letter is to inform you of objectionable conditions found during the U.S. Food and Drug Administration's (FDA) investigation into Johnson & Johnson Pharmaceutical Research & Development's (hereafter referred to as J & J PRD) role as sponsor of Study **(b) (4)** entitled **(b) (4)** and Study **(b) (4)** entitled **(b) (4)** of the investigational drug, **(b) (4)**).

The first study, **(b) (4)** was initiated by the original holder of IND **(b) (4)** (hereafter referred to as **(b) (4)** On February 2, 2005 **(b) (4)** entered into a worldwide partnership with **(b) (4)**, a Johnson & Johnson 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 J & J PRD and all rights and responsibilities for **(b) (4)** clinical trials were transferred to you. The second study, **(b) (4)** was conducted in its entirety by you.

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.

From our review of the establishment inspection report and the documents submitted with that report, and your letter written in response to the Form FDA 483, dated June 24, 2008, and your 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 are aware that at the conclusion of the inspection, Ms. Wydner presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

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

FDA regulations require that sponsors ensure proper monitoring of clinical investigations. Our investigation found that J & J PRD failed to properly ensure monitoring of the studies referenced above. Although J & J PRD contracted with **(b) (4)** (hereafter referred to as **(b) (4)** to conduct monitoring visits for **(b) (4)** and **(b) (4)**, **(b) (4)** did not ensure that the clinical investigators were properly monitored to fully assess and ensure site compliance with Studies **(b) (4)** and **(b) (4)** Inadequate monitoring resulted in deficiencies in recordkeeping with respect to case histories and drug accountability by clinical investigators participating in the above-referenced studies. As sponsor of Studies **(b) (4)** and **(b) (4)** conducted under Investigational New Drug Application **(b) (4)** and submitted in NDA **(b) (4)**, you were responsible for ensuring that these studies were adequately monitored for compliance with regulatory requirements, thereby ensuring that the data supporting the NDA was of good quality, and that the rights, welfare, and safety of study subjects were adequately protected. 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, you allowed enrollment of subjects at Site #520 to resume, based upon your 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 only 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, study coordinators documented administration of study drug to two different subjects at the same time, and 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.

We find that the response you provided in your June 24, 2008 letter to these observations was inadequate. You stated that source documents did not indicate that infusions were given in subjects' homes, and that the study coordinator at the site told you that these infusions must have been given in the office.

Given the site outpatient treatment plan and the 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 should have investigated further the reason for this irregularity. Your June 24, 2008 letter provided no explanation for your failure to notice these discrepancies and to seek an explanation from site staff before FDA's investigation revealed the discrepancies.

Moreover, despite the study coordinator's statement that these infusions must have been given in the office, based on the FDA investigation conducted at the site, we have determined that subjects enrolled in the study continued to self-administer study medications at 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) (4)** is documented as having administered study drug to the following subjects at 08:00-10:00:

(a) Subject #140616 **(b) (4)**
(b) Subject #140132 **(b) (4)**
(c) Subject #140617 **(b) (4)**
(d) Subject #140118 **(b) (4)**

ii) On May 20, the study nurse is documented as having stated placebo infusions to the following subjects at 10:00-11:00:

(a) Subject #140616 **(b) (4)**

(b) Subject #140132 **(b) (4)**
(c) Subject #140617 **(b) (4)**
(d) Subject #140118 **(b) (4)**

Based on the copies of the "*Notas De Enfermeria*" that you provided for each of these subjects in your submission to the FDA dated September 2, 2008, we find that the initials included in the nursing note for each of the doses noted in the bullets i)(a)-(d) and ii)(a)-(d) above are consistent with those recorded on the "*Planilla de estabilidad*" for each subject, and with the initials **(b) (6)** for the study nurse recorded on the "Site Personnel Responsibility Log." The documents provided with your September 2, 2008 submission thus confirm the FDA's findings. Study monitors should have recognized that on multiple occasions, the same individual was documented as having administered study drug to different subjects at precisely the same time, and should have investigated further the reason for this irregularity.

ii. Source documentation verification was completed by study monitors for Subject #141050 enrolled in Study **(b) (4)** at Site #551, according to the table you provided that was labeled "Subjects 100% Source Document Verification"; however, study monitors failed to identify

that no physical examination, wound assessment, or overall clinical assessment was documented in study source documents or in the Case Report Form (CRF) for this subject's Day 8 visit, as required by the protocol. We note that you did not address this observation in your June 24, 2008 letter to the Agency.

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) (6)** worksheet, the times that reconstituted study drug was delivered to the nursing unit were "not recorded" on at least four occasions for Subject #1118. We note that you did not address this observation in your June 24, 2008 letter to the Agency.

b) At Site #508, according to the worksheet, the times that reconstituted study drug was delivered to the nursing unit were "not recorded" on at least seven occasions for Subject #140005. We note that in your June 24, 2008 letter to the Agency, you confirmed that delivery times were not documented and that study monitors failed to document these deviations.

iv. Protocol **(b) (6)** 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, in e-mail correspondence between Site #509 and the study monitor dated October 20, 2004, the study monitor sought assurance 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 asked, the site never addressed how they would document the temperature storage conditions of the product in subjects' homes; site personnel only addressed how subject body temperatures were to be recorded. Study monitors failed to recognize that the site's response was incomplete and 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 infusions that were stored in subjects' refrigerators. Therefore, storage temperatures for these infusions could not be confirmed to have complied 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 "25 May 2005," 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."

We note that in your June 24, 2008 letter to the Agency, while you contended that stability of

the drug product was likely maintained in subjects' homes, you also confirmed that there was no documentation of study drug storage conditions in subjects' homes.

v. 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 had a "bell" showing (potentially signifying shipment did not maintain appropriate conditions for some reason). 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 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 appropriate follow-up instructions to the site regarding usage of the kits in this shipment.

In your response letter dated June 24, 2008, you stated that an additional stability study, completed after the drugs from this kit were dispensed to study subjects and after the May 25, 2005 Unblinded Monitoring Visit Report, supported "temperature excursions up to maximum 25°C are allowed for up to maximum 2 days." However, FDA notes that this stability study was conducted subsequent to shipment of referenced Order #1000739; therefore, 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 **(b) (4)** were to occur every 10 weeks.

FDA notes that in your response dated June 24, 2008 you state that the issue was recorded in the unblinded monitoring visit reports dated 27 January 2006 and 25 September 2006, along with documentation that the monitor requested completion of these worksheets, and that the site generate a Memo to File thatdocumented 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, 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 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) For Subject #1187, source documents indicate:

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) For Subject #1195, source documents indicate:

i) on 4/14/05, study drug was delivered at 09:00; study drug administration is documented as 08:05-09:05

c) For Subject #2671, source documents indicate:

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

We note that in your June 24, 2008 letter to the Agency, you state that differences in times occurred due to the site recording anticipated times of administration rather than actual times of administration, and you acknowledge that study monitors failed to identify these discrepancies in source documents.

viii. For Study **(b) (4)** and **(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, which were not identified by the monitors. For example:

a) Subject #1010 was enrolled in the study with Wound #2 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 10mm x 4mm; also documented was 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 25mm x 30mm. 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, a date which is 18 days prior to the date that this source document records the visit to have occurred.

b) For Subject #1186, the sub-investigator's progress note for 3/7/05 stated that the wound dimensions were 21mm x 25mm. Study source document worksheets for the 3/7/05 visit originally documented wound dimensions of 17mm x 15mm, but on 4/18/05 dimensions were lined through and revised to 21mm x 25mm. As this source document also stated that "wound assessment done per MD + reported to CRC," it is unclear why originally recorded dimensions were inconsistent with those documented in the sub-investigator's progress note. Similarly: 1) the sub-investigator's progress note for 3/14/2005 stated the wound dimensions were 23mm x 29mm, but the source document for the same day originally documented wound dimensions of 15mm x 10mm; then on 4/18/05, dimensions recorded on the source document were lined through and revised to 23mm x 29mm; and 2) the sub-investigator's progress note for 3/21/2005 stated the wound dimensions were 14mm x 23mm, but page 2 of 4 of the source document for the same day originally documented wound dimensions of 8mm x 6mm. On 4/18/04, the dimensions appearing on the source document were lined through and revised to 14mm x 23mm. On the corresponding CRF page for the 4/18/05 visit, the wound dimensions, however, were still documented as 8mm x 6mm. In addition, the subinvestigator's progress note for the 3/14/07 documents "much less inflammation and little drainage," but the source document for this visit date documents 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 13mm x 20mm and a wound assessment of "absent-reddness [sic], pain, edema, heat, flutuance [sic], funct impair, drainage," but on another page of the same source document dimensions were listed as 1mm x 0mm, 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 80mm x 95mm.

We note that in your June 24, 2008 letter to the Agency, you acknowledge that study monitors failed to identify these discrepancies in source documents.

b. Deficiencies in drug accountability:

For Study **(b) (4)** at Site #551, 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 having been 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:

(b) (4) Worksheet **(Kit-Vial)** **(Date)** **(Subject#)**	**Drug Accountability Form Worksheet** **(Kit-Vial)** **(Date)** **(Subject#)**
21148-8 1-Aug-06 #141059	21148-8 30-Jul-06 #141052
21148-1 1-Aug-06 #141059	21148-1 02-Aug-06 #141052
22609-2 2-Aug-06 #141059	22609-2 27-Jul-06 #141052
10131-8 5-Aug-06 #141059	10131-8 03-Aug-06 #141059
60126-1 03-Aug-06 #141062	60126-1 02-Aug-06 #141059
60126-18 03-Aug-06	60126-18 08-Aug-06

#141062	#141062
60126-7 07-Aug-06 and 08-Aug-06 #141062	60126-7 04-Aug-06 #141062
23631-15 11-Aug-06 #141066	23631-15 08-Aug-06 #141066
23631-8 11-Aug-06 #141066	23631-8 08-Aug-06 #141066
23110-18 14-Aug-06 #141067	23110-18 No Record of Being Dispensed
23110-4 14-Aug-06 #141067	23110-4 No Record of Being Dispensed

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. We note that you did not specifically address these observations in your June 24, 2008 letter to the Agency, or in any of the subsequent submissions to the Agency.

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:

Study monitors failed to ensure that planned study blinding procedures were correctly followed for Study **(b) (4)** at Site #063. 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.”

i. 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.

We note that you did not address this observation in your June 24, 2008 letter to the Agency.

ii. 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), since 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 writing, in some cases the covered writing could still be read, according to the **(b) (4)** Unblinded Monitoring Visit Report, dated 11-12 May 2006. The **(b) (4)** Unblinded Monitoring Visit Report, dated 11-12 May 2006, in relation to this finding, states that "the infirmary 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 includes instructions to the site from **(b) (4)** Monitors that are clearly inconsistent with International Conference on Harmonization Good Clinical Practice (GCP) guidelines, in that it states, "[w]e 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 **(b) (4)** monitors assigned to this site failed to appropriately make corrections to source documents for at least 5 subjects enrolled at the site.

We note that in your June 24, 2008 letter to the Agency, you acknowledge that GCP guidelines were not followed, and that in the future site managers and study monitors will be reminded through use of specific training modules of the importance of appropriate completion of source documents.

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 **(b) (4)** at Site #551, the drug infusion order was reversed for infusions #4 and #5 daily. For example, for Subject #141051 in the **(b) (4)** arm, the protocol required that the 4th dose be placebo given over 60 minutes, and that the 5th dose be **(b) (4)** given over 120 minutes; however, the site administered **(b) (4)** over 120 minutes as the 4th dose and placebo over 60 minutes as the 5th dose.

The response that you provided in your June 24, 2008 letter states that the site acknowledges that the drug infusion order/infusion duration was reversed for daily infusions #4 and #5, and you also acknowledge that the study monitor did not identify this issue during site monitoring visits.

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 greater than 7 days prior to enrollment. A Data Correction Form (DCF) dated 27-May-2005 stated that the subject received antibiotic treatment with **(b) (4)** with end date of 21-FEB-2005, and a CI comment in source documents stated that the subject had received the **(b) (4)** for treatment of the left foot abscess. Therefore, the left foot abscess was present for more than 7 days prior to enrollment, and this subject should not have been enrolled.

We find that the response you provided in your June 24, 2008 letter to this observation was inadequate. You stated only that the subject met inclusion criteria, but you did not address the fact that the index infection had been present for more than 7 days, which would have precluded the subject from study enrollment.

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 tests results for these subjects prior to enrollment, as was required for females of childbearing potential by the protocol.

We note that in your June 24, 2006 letter to the Agency, you confirmed that pregnancy test results for these subjects were not documented, and that study monitors failed to identify this issue.

iii. For Study **(b) (4)** at Site #063, study monitors failed to identify that Subject #140107 was not eligible for the study. Protocol **(b) (4)** required that infection at a site of prior surgery/trauma occur within 30 days of the surgery/trauma. However, for Subject #140107, the prior surgery was documented as having taken place 20 months prior to the study screening visit.

Based on the source documents for Subject #140107, and translations of those documents that you provided in your submission to the Agency dated September 2, 2008, you stated that the source documents do not support that a specific traumatic event precipitated the infection; and that Dr. **(b) (6)** further told you that this subject's old surgical site was intermittently inflamed, and that when the subject was enrolled, the site of infection was draining pus and was inflamed and painful, and that the infection had begun 30 days prior

to enrollment. While you did not concede in your September 2, 2008 submission that this subject did not qualify for enrollment, the additional information included in your September 2, 2008 submission supports 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 a time frame adequate 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

In your June 24, 2008 submission to the Agency, a copy of a monitoring report dated 15 Aug 2006 that stated, "Pharmacist to provide copies of CrCl for all patients. Done" was provided. However, this response is inadequate, as this does not provide assurance that CrCl values were forwarded to the pharmacist in a time frame that would have allowed appropriate dosing adjustments, if warranted.

3. Failure to secure investigator compliance with the investigational plan and applicable FDA regulations [21 CFR 312.56(b)].

Under FDA regulations, a sponsor who discovers that an investigator is not complying with the signed investigator agreement [Form FDA 1572], the general investigational plan, or the requirements of applicable FDA regulations, shall promptly either secure compliance or discontinue shipment of the drug to the investigator and terminate the investigator's participation. If the investigator's participation is terminated, the sponsor shall notify FDA. Our investigation found that you failed to adequately implement corrective actions at Site #063, for Study **(b) (4)** For example:

According to footnote 1) of the Schedule of Assessments in Clinical Protocol **(b) (4)** "all screening/predose 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, nine subjects 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 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.

We find that the response that you provided in your June 24, 2008 letter to these observations was inadequate. You stated that the protocol did not specify the duration of the predose phase of the study, nor how soon after screening, treatment needed to be started, but you acknowledged that "the expectation for the study was that all study treatments were to begin within 1 calendar day of randomization." The delay in administration of appropriate **(b) (4)** therapy for these nine patients, if they in fact 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 repetitively delaying study drug dosing post subject randomization. In addition, you failed to implement appropriate corrective actions to prevent this issue from recurring at the site.

4. Failure to ensure that only investigators who were qualified by training and experience were selected as appropriate experts to investigate a drug [21 CFR 312.53(a)].

J&J PRD failed to select a qualified investigator to conduct the study at Site #551. Specifically, J&J PRD selected Dr. **(b) (6)**(Site #551), despite a pre-study monitoring visit that documented that the investigator "is not recommended" for lack of compliance in completing regulatory documents (including IRB approvals), lack of diligence in study start up procedures and inadequate patient population. This study monitor also recommended that this site not be used because the site declined use of Spanish Informed Consent Forms when demographics of the region indicated a large population with native and preferred language of Spanish. These problems should have alerted you to the fact that this investigator's experience may not have qualified her as an appropriate expert to conduct the study.

In your response to the Agency, dated June 24, 2008, you stated that when you questioned **(b) (4)** representatives regarding why this site was selected despite the study monitor recommendation to not use the site, **(b) (4)** provided a memo dated June 3, 2008 that stated the CRO supervisor overruled the study monitor recommendation. According to the **(b) (4)** Work Order, however, J &J PRD, not **(b) (4)** was responsible for final approval of sites for participation in the study. Furthermore, J&J PRD failed to make this inquiry until after the FDA inspection. Based on your response, it appears that you either failed to actively participate in selection of the site or failed to review and address the study monitoring report that recommended the site not be used.

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

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research

Food and Drug Administration
Bldg 51, Room 5358
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely yours,
{See appended electronic signature page}
Leslie K. Ball, M.D.
Director
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LESLIE K BALL
08/10/2009