DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Saroj Brar, M.D.
2012 West 25th Street
Cleveland, Ohio 45237

Ref: 08-HFD-45-0301

Dear Dr. Brar:

Between April 24 and May 18, 2007, Ms. Karen Kondas, representing the Food and Drug Administration (FDA), conducted an investigation and met with you, to review your conduct of two clinical investigations:

- Protocol[ ]entitled "Phase 3: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Evaluating Paliperidone Palmitate in the Prevention of Recurrence in Subjects with Schizophrenia" [IND[ ], sponsored by Johnson & Johnson Pharmaceutical Research & Development LLC., and

- Protocol[ ] "A Phase 3, Randomized, Placebo-Controlled, Double-Blinded Trial Evaluating the Safety and Efficacy of[ ] in Subjects Continuing Lithium or Valproic Acid/Divalproex Sodium for the Treatment of an Acute Manic or Mixed Episode," sponsored by [ ]

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

From our review of the establishment inspection report and the documents submitted with that report, and of your June 6, 2006 [received by FDA on June 8, 2007] letter written in response to the Form FDA 483, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Investigator Kondas presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. **You failed to obtain informed consent of the subjects to whom the study drug was administered [21 CFR § 312.60; 21 CFR. § 50.20].**

   Section 4.2 of Protocol[ ]required that subjects sign the informed consent document (ICD) to indicate they understood the purpose of the study and procedures. The protocol also stated that subjects would be excluded if they could not provide their own consent. The investigation found that a guardian signed the ICD for Subject 607382 on February 20, 2006. The sponsor recommended this subject be immediately discontinued from the study for consenting reasons on April 18, 2006.

   Your response letter dated June 6, 2006 did not address the issue of consent related to Subject 607382. Your letter did address the issue of informed consent related to Subject 607086. This subject consented to the open-label phase of the study while hospitalized and suffering periods of delusion. You assert that this subject's consent was valid in part because the subject had been informed of the open-label phase of the trial at the time the subject first consented to trial participation. This assertion is improper. Knowledge of trial phases does not suffice to demonstrate informed consent to those phases. Moreover, a subject can withdraw consent at any time during a study, which underscores the fact that informed consent must be established independently at each trial phase required under the protocol [21 CFR § 50.25(a)(8)].

2. **You failed to protect the rights, safety, and welfare of subjects under your care [21 CFR § 312.60].**

   a. Section 6.1.3 of Protocol[ ]required that subjects be administered study medication every four weeks during the maintenance phase of the study, and that doses may be increased or decreased at Weeks 9, 13, 17 and 21 in response to subject clinical needs. The investigation found that Subject 607089 had his Period 6 Visit during the maintenance phase of the study, on December 27, 2005 and received study medication. Records document that Subject 607089 then presented for an unscheduled visit on January 4, 2006, eight days later, and was administered another dose of study medication.

      In your response letter dated June 6, 2006, you state that this mistake was recognized on the same day by the coordinator, that the sponsor was notified, and that an SOP was written. Records document that the sponsor advised you to contact the subject weekly for side effects. There is no documentation that you contacted this subject after January 4, 2006 to check for side effects.

   b. The investigation found that Subject 607384, who was enrolled into the study and administered study medication on February 28, 2006, began to decompensate and was admitted to the hospital on March 10, 2006. No record was found for the adverse event of exacerbation of symptoms of paranoid schizophrenia being reported to the IRB until May 24, 2006.

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

   a. Section 3.5.1 of Protocol [ ] allowed subjects to receive lorazepam during the screening phase at a maximum dose of 4 mg/day. Following baseline (Day 1) assessment, the protocol allowed a maximum of 2 mg/day during the first seven days of blinded therapy. Subjects were to be excluded from the study if unable to reduce their daily lorazepam intake. Subject 1006 was screened for the study on April 5, 2006 and began receiving blinded study medication on April 7, 2006. Records indicate that this subject was administered 4.5 mg lorazepam/four times a day on April 5, 2006; 3.0 mg lorazepam/three times a day on April 6, 2006; 5.0 mg lorazepam/four times a day on April 7, 2006; and 3.0 mg lorazepam/three times a day on April 8 and April 10, 2006. This was more than the doses allowed by the protocol during the screening phase and the first seven days of blinded therapy.

      In your response letter dated June 6, 2006, you state that Subject 1006 was not administered lorazepam during the screening phase and first seven days of the study. However, the Prior and Concomitant Medication Worksheet documents the aforementioned doses.

   b. Section 3.1.1 of Protocol [ ] states that subjects be treated continuously with lithium or valproic acid for at least two weeks immediately prior to screening. Furthermore, the protocol states that if the mood stabilizer trough serum concentration was not in the therapeutic range (0.6 – 1.2 mEq/L) at screening, the dose should be re-adjusted. If the mood stabilizer trough serum concentration at screening was sub-therapeutic, the mood stabilizer dose must be increased appropriately and the subject continued on this new dose for seven days prior to re-evaluation. The records indicate that Subject 1012 received lithium for only 12 days prior to screening rather than the required 14. The investigation also found that Subject 1011 was screened for the study on August 1, 2006. Records indicate that this subject's lithium level was in the sub-therapeutic range (0.5 mEq/L) at screening. The dose of lithium was adjusted upward to 1050 mg/day from 900 mg/day. This subject was randomized on August 4, 2006, four days later.

      Your response letter dated June 6, 2006 does not address the failure to ensure that Subject 1012 received lithium for the full two weeks prior to screening. Your letter agrees that Subject 1011 should have waited seven days after adjusting her lithium dose upwards and before being randomized.

   c. Section 3.1.2 of Protocol [ ] required that subjects receive a second dose of study medication one week after the baseline visit (on Study Days 1 and 8). The investigation found that Subject 607384 received an initial injection of study medication on February 28, 2006 and a second injection of study medication on March 10, 2006, or 10 days later.

4. **You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual [21**

CFR § 312.62(b)]. Specifically, the investigation found:

a. For Protocol[ ] the study medication worksheets document Subject 607084 received medication number 171466 on December 20, 2006, whereas the Visit Confirmation worksheet documents that this subject received medication from study kit 171398 on that date. Study medication records next indicate that Subject 607084 received study kit 171396 on January 4, 2007, whereas the Visit Confirmation worksheet shows study kits 171396, 171466, and 171467 were dispensed on that date. A later Subject Medication worksheet documents that Subject 607084[ ]received Oral Medication Number 171466 and 171467 on January 12, 2007, and received Injection Medication number 132306 on that date, but the Visit Confirmation worksheet shows only Injection Medication number 132306. In addition, the Subject Visit notes indicated that Subject 607084 received Injection Number 132306 at 14:55 on January 12, 2007.

   Your response letter dated June 6, 2006, states that medication kit 171466 was administered at 14:55, but does not provide a date, or explain the multiple discrepancies delineated above.

b. Section 3.7.3 of Protocol[ ]required that subjects completing the study on an outpatient basis be contacted at least once a week to check on their condition. The investigation found no documentation to verify that Subject 1007, who completed the 21-Day visit on May 1, 2006 and began treatment as an outpatient, was contacted to check on his/her condition, as required. Nor did the investigation find documentation to verify that Subject 1009, who was discharged on May 5, 2006 and completed the trial as an outpatient on July 18, 2006, or Subject 1012, who completed the trial as an outpatient on November 11, 2006, were contacted during the outpatient period.

   Your response letter dated June 6, 2006 states generally that you contacted subjects who completed the study "on a regular basis" as required, but that you did not document these contacts.

c. Section 4.6 of Protocol[ ]required that subjects who discontinued the study early, or completed the study, but did not enter the 40-week open-label extension trial, have a follow-up interview at days 7 and 30, to determine if adverse events had occurred. The investigation found that Subject 1011 discontinued the study on August 17, 2006, but there was no documentation to indicate that this subject was contacted on Days 7 or 30.

   Your response letter dated June 6, 2006 does not address this issue.

d. For Protocol[ ]source records document that Subject 1006 was seen for an unscheduled visit on May 11, 2006 due to exacerbation of their disease. This visit was not documented on a Case Report Form.

Your response letter dated June 6, 2006, states the sponsor was informed, and the study coordinator was told to collect any data on the following visit. You did not provide documentation that you contacted the sponsor or that you gathered any data at the following visit, however.

5. **You failed to maintain adequate drug disposition records [21 CFR § 312.62(a)].**

   a. Specifically, the investigation found that for Protocol [ ] the [ ] records document that Subject 607384 was randomized to study kit number 132154 on February 28, 2006. However, the study medication worksheet and the drug accountability records document that this subject received study kit 132165 on that date. Records indicate that study kit 132154 was returned to the sponsor with an explanation of "not used." This error was not documented in the study records until April 24, 2006.

   Your response letter dated June 6, 2006 states that the error was recognized and study kit 132165 was discarded. Your response does not adequately explain how study kit 132154 could have been returned to the sponsor as not used, and how study kit 132165 was discarded, as per your response.

   b. The investigation found that the concomitant medication worksheets and eCRFs concerning Lithium dosing for Subject 1011 in Protocol [ ] on August 1, 2006, and for Subject 1009 for April 19, 2006 and April 21, 2006, were inconsistent with hospital records.

   Your response letter dated June 6, 2006 states that the error was detected and that the sponsor was informed and the data were rectified. You did not provide any documentation that the records were rectified, however.

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

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 Joseph Salewski at (240) 276-3395; FAX (240) 276-8848. Your written response and any pertinent documentation should be addressed to:

Joseph Salewski
Branch Chief (Acting)
Good Clinical Practice Branch II,
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Office of Compliance
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
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Sincerely yours,

{See appended electronic signature page}

Leslie Ball, M.D., Director
Division of Scientific Investigations, HFD-45
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/

JOSEPH P SALEWSKI
03/20/2008