



DEPARTMENT OF HEALTH & HUMAN SERVICES

WARNING LETTER

Food and Drug Administration
Rockville MD 20857

CERTIFIED MAIL - RESTRICTED DELIVERY
RETURN RECEIPT REQUESTED

Ref: 00-HFD-45-0301

MAR 29 2000

Cal K. Cohn, M.D.
The Cohn Center for Psychiatry
7777 Southwest Freeway
Houston, Texas 77074

Dear Dr Cohn:

Between October 27 and November 18, 1999, Ms. Andrea A. Branche, representing the Food and Drug Administration (FDA), met with you to review your conduct of the following clinical studies performed for Janssen Research Foundation:

Protocol [] "Risperidone vs. Olanzapine in the Treatment of Schizophrenia," involving the investigational drugs Risperdal (risperidone) and Zyprexa (olanzapine)

Protocol [] "Risperidone vs. Olanzapine in the Treatment of Schizophrenia," (extension of protocol [] involving the investigational drugs Risperdal (risperidone) and Zyprexa (olanzapine)

Protocol [] "Comparison of Risperidone and Haloperidol for Prevention of Relapse in Subjects with Schizophrenia and Schizoaffective Disorders," involving the investigational drugs Risperdal (risperidone) and Haldol (haloperidol)

Protocol [] "A Randomized, Double Blind, Placebo Controlled Study of Risperidone for Treatment of Behavior Disturbances in Subjects with Dementia," involving the investigational drug Risperdal (risperidone)

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report, the documents submitted with that report, materials provided by the sponsor, and your written response dated December 10, 1999, we conclude that you did not adhere to all pertinent federal regulations and/or good clinical investigational practices. We note that at the conclusion of the inspection, Ms. Branche presented and discussed with you her findings, which were listed on Form FDA 483, Inspectional Observations.

Your verbal and written responses to item 4 on Form FDA 483 have been considered and are accepted. In addition, your written response regarding subject [] has been reviewed, and we

agree that there was no subject by these initials enrolled in protocol [] However, the Form FDA 483 entry regarding subject [] contains a typographical error; this finding actually pertains to subject [] who was enrolled in protocol []

Please note the following additional comments, which are being conveyed to you at this time.

SUMMARY OF VIOLATIONS RELATED TO YOUR FAILURE TO CONDUCT THE INVESTIGATION ACCORDING TO THE SIGNED INVESTIGATOR STATEMENT (21 CFR 312.60)

You failed to personally conduct or adequately supervise the investigation for three subjects [] enrolled in protocol [] by allowing a member of your staff, Ms. [] to perform assessments that she was not qualified to perform. For subjects [] and [] Ms. [] completed the Positive and Negative Syndrome Scale for Schizophrenia (PANSS), Extrapyramidal Symptom Rating Scale (ESRS) and Clinical Global Impression (CGI); and for subject [] the CGI assessment.

It is important to note that you were previously inspected in 1989, at which time violations were noted that also pertained to your permitting staff members to perform certain functions that they were not qualified to perform. Those findings were again brought to your attention in an April 4, 1990, letter that stemmed from the 1989 inspection.

SUMMARY OF VIOLATIONS RELATED TO RECORDKEEPING AND CASE HISTORIES [21 CFR 312.62(b)]

You failed to maintain adequate records for subject [] enrolled in protocol [] for subject [] enrolled in protocols [] and [] and for subject [] enrolled in protocol [] Specifically, no past medical records were obtained for subject [] past medical history was not documented for subject [] and no medical records were available for subject [] It is noted that you provided satisfactory verbal and written responses that explained why no medical records were obtained for subject [] However, the particular entry on the progress note that was provided to support your explanation at the inspection was not dated, as it should have been.

You failed to properly correct errors on source documents for subjects [] and [] enrolled in protocol [] It is noted that "white-out" was used to alter a Visit 5 progress note for subject [] and to alter a Visit 28 source document for subject []

In 1991, you signed a voluntary "Agreement with respect to Investigational Drugs." That Agreement contained, among other things, a statement by you that you had implemented standard operating procedures whereby you would procure pertinent medical records and information about medications prescribed outside the realm of clinical studies for research subjects enrolled by you in clinical studies. The 1991 Agreement also outlined the acceptable

methods for correction of errors in case report forms and source documents. Based on the findings noted in the foregoing two paragraphs, you have failed to abide by the terms of the 1991 Agreement.

SUMMARY OF VIOLATIONS RELATED TO REQUIREMENTS FOR INVESTIGATOR REPORTING TO IRB (21 CFR 312.66)

You failed to document hospitalizations in the adverse-event section of the case report forms (CRFs) for seven subjects [] enrolled in protocol [] In addition, you failed to promptly report these serious adverse events (SAEs), as well as the hospitalization of another subject [] to the IRB. Specifically, we note the following:

1. Subject [] was hospitalized from March 7 – 11, 1997, for exacerbation of psychosis (including increased auditory and visual hallucinations). This SAE was not reported to the IRB until June 1998.
2. Subject [] was hospitalized from August 4 – 11, 1997, for exacerbation of psychosis (including guarded behavior, auditory hallucinations, and flight of ideas). This SAE was not reported to the IRB until October 1998.
3. Subject [] was hospitalized from November 5 – 6, 1996, for increased agitation and aggressive behavior. Although the reason for this hospitalization was noted in the adverse-event section of this subject's CRF, the hospitalization was not documented anywhere in the subject's completed CRF that was submitted to the sponsor. In addition, this SAE was not reported to the IRB until March 1998.
4. Subject [] was hospitalized from September 19, 1997, through October 1, 1997, for hypoglycemia and syncope. This SAE was not reported to the IRB until March 1998.
5. Subject [] was hospitalized from August 18, 1996, through September 4, 1996, for exacerbation of psychosis (not otherwise specified). This SAE was not reported to the IRB until March 1998.
6. Subject [] (subject #30440, noted to have two different sets of initials used on study documents) was hospitalized from October 18 – 21, 1996, for exacerbation of psychosis (including increased paranoia and visual and auditory hallucinations). This SAE was not reported to the IRB until May 1998.
7. Subject [] was hospitalized from November 29, 1996 through December 2, 1996, for seizure and acute exacerbation of psychosis (not otherwise specified). This serious adverse event was not reported to the IRB until March 1998.
8. Subject [] was hospitalized from September 8 – 11, 1997, for exacerbation of psychosis (not otherwise specified). This SAE was not reported to the IRB until March 1998.

Because of the departures from FDA regulations discussed above, we request that you notify this office, in writing, within 15 working days of your receipt of this letter, of the actions you have taken or plan to take to prevent similar violations in the future. Failure to adequately and promptly correct these matters may result in further regulatory action, without further notice. If,

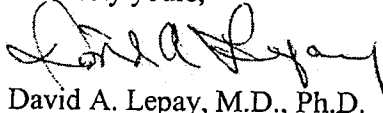
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in the future, you do not strictly abide by the 1991 Agreement signed by you, we may consider steps that will lead to your disqualification in accordance with 21 CFR 312.70.

If you have any questions, please contact Dr. Antoine El-Hage, at (301)594-1032, FAX (301)827-5290. Your written response and any pertinent documentation should be addressed to:

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

Sincerely yours,



David A. Lepay, M.D., Ph.D.

Director

Division of Scientific Investigations, HFD-45

Office of Medical Policy

Center for Drug Evaluation and Research

7520 Standish Place

Rockville, MD 20855