



**NOTICE OF INITIATION OF DISQUALIFICATION PROCEEDINGS AND
OPPORTUNITY TO EXPLAIN (NIDPOE)**

DEC 3 2003

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Maria Carmen Palazzo, M.D., Ph.D.
3450 Chestnut Street, 7th Floor
New Orleans, Louisiana 70115

Dear Dr. Palazzo:

Between July 23 and August 28, 2001, Ms. Barbara D. Wright and Ms. Dana M. Daigle, representing the Food and Drug Administration (FDA), conducted an investigation and met with you regarding allegations received by the Division of Scientific Investigations (DSI) that you violated federal regulations in the conduct of the following 3 clinical studies.

Protocol [] entitled "A Randomized, Multi-Center, 10-week, Double-Blind, Placebo-Controlled, Flexible-Dose Study to Evaluate the Efficacy and Safety of Paroxetine in Children and Adolescents with Obsessive-Compulsive Disorder (OCD)", and

Protocol [] entitled "A Multi-Center, Open-Label, Six-Month Extension Study to Assess the Long Term Safety of Paroxetine in Children and Adolescents with Major Depressive Disorder (MDD) or Obsessive Compulsive Disorder", performed for SmithKline Beecham.

The FDA inspection also included a brief review of your participation in another clinical study:

Protocol [] entitled "Cost-Effectiveness and Functional Outcomes of Olanzapine in the Treatment of Schizophrenia in Usual Clinical Practice: A Randomized Clinical Study", performed for Eli-Lilly and Company.

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

At the conclusion of the inspection, Ms. Wright and Ms. Daigle presented and discussed with you the items listed on the Form FDA 483, Inspectional Observations. We have reviewed your letter of October 12, 2001, sent in response to the inspectional observations and accepted some of your response. However, we do not find your explanation acceptable in addressing the remaining matters under complaint.

Based on our evaluation of the information obtained, the Center for Drug Evaluation and Research (Center) believes that you have repeatedly or deliberately violated regulations governing the proper conduct of clinical studies involving investigational products as published under Title 21, Code of Federal Regulations (CFR), Part 312 (copy enclosed) and that you submitted false information to the sponsor.

This letter provides you with written notice of the matters under complaint and initiates an administrative proceeding, described below, to determine whether you should be disqualified from receiving investigational products as set forth under 21 CFR 312.70.

A listing of the violations follows. The applicable provisions of the CFR are cited for each violation.

Protocol [] and []

1. You submitted false information to the sponsor or FDA [21 CFR 312.70(a)].

- a. You falsified diagnoses of OCD and completed medical records containing other false information. You submitted false information in the visit 1 screening form to the sponsor resulting in at least six ineligible subjects being enrolled in Protocol [] as detailed below.

- 1) Subject 28133 [] – screened and enrolled on 11-20-00

Subject [] was first seen by you on 10-23-00. At that time, social work referral and summaries of the subject's past medical history indicated that she had Major Depressive Disorder (MDD) with impulse control disorder. She was being treated with Paxil, Depakote, and Wellbutrin for these illnesses. Your own evaluation on 10-23-00 reported symptoms consistent with MDD, not OCD, and you concurred with the diagnosis of MDD with impulse control disorder. However, your records contained a second psychiatric evaluation, also dated 10-23-00 and signed by you, that was identical to the first except for the diagnosis, which was changed to OCD. When you performed the psychiatric screening evaluation prior to enrolling subject [] on 11-20-00, there was again no mention of OCD symptoms. However, you recorded your diagnosis as OCD with past history of MDD and impulse control disorder in order to enroll [] in the trial. In addition, you completed the visit 1 screening form, indicating age of onset of OCD at 11 years 1 month (duration of two years). Available records provide no support for this contention.

- 2) Subject 28135 [] – screened and enrolled on 11-24-00

The clinical assessment section of [] referral, dated 11-13-00, noted behavioral symptoms (e.g., disruptive, oppositional, poor impulse control), but no symptoms consistent with OCD. Subject [] was first seen by you on 11-21-00. Your

psychiatric evaluation did not mention any OCD symptoms, except for some compulsive hand movements observed during the mental status examination (MSE). Despite the absence of any other signs or symptoms of OCD, your psychiatric diagnosis on 11-21-00 was OCD; Depressive Disorder; not otherwise specified (NOS); and Oppositional Defiant Disorder. In addition, you completed the visit 1 screening form, indicating age of onset of OCD at 10 years (duration of five years). Available records provide no support for this contention.

- 3) Subject 28173[]- screened and enrolled on 12-21-00

A Family Social Assessment dated 12-13-00 from another source identified behavior problems (e.g., disruptive behavior), but no symptoms consistent with OCD. A 12-13-00 referral to you also identified behavioral symptoms, but not OCD symptoms, and indicated that [] urgently needed an appointment due to extreme stress and anger. You completed two psychiatric evaluations dated 12-18-00 that were identical except for the diagnosis. One of your evaluations did not give a diagnosis, but you recommended screening for OCD. The other contained diagnoses of OCD and “to rule out ADHD.” In addition, you completed the visit 1 screening form, indicating age of onset of OCD at 7 years 4 months (duration of five months). Available records provide no support for this contention.

- 4) Subject 28174[]- screened and enrolled on 01-02-01

A clinical referral for subject [] dated 10-20-00 indicated that [] had symptoms of ADD and Disruptive Behavior Disorder, NOS and a history of hyperactivity and behavioral problems. You saw this subject for the first time on 12-07-00. You completed three psychiatric evaluations dated 12-07-00. One had no diagnosis or recommendation and the other two contained a diagnosis of OCD without any mention of OCD symptoms. Subject [] was screened and enrolled on 1-02-01. You completed the visit 1 screening form, indicating age of onset of OCD at 9 years (duration of four years). In addition, your evaluation dated 2-16-01 was identical to the 12-07-00 evaluations for OCD, but included a plan to admit [] to a hospital because of stealing, fighting, oppositional and out of control behavior.

- 5) Subject 28171[] screened and enrolled on 12-19-00

Subject [] was seen by you on 9-27-00. On that date, you completed three psychiatric evaluations that were identical except for the list of diagnoses and the treatment plan. In particular, each evaluation had a different Axis I diagnosis. One had a diagnosis of ADIID. Another had a diagnosis “to rule out Schizophrenia and multiple personality disorder.” A third evaluation had a diagnosis of OCD. Your psychiatric evaluations did not document any symptoms of OCD. Subject [] was enrolled on 12-19-00 without a concurrent psychiatric evaluation. Instead, you used the 9-27-00 evaluation with the diagnosis of OCD as the screening evaluation, and

you signed and dated it 12-19-00. You completed the visit 1 screening form, indicating age of onset of OCD at 6 years 4 months (duration of three years). In addition, your 2-5-01 psychiatric evaluation stated that [] is acutely “psychotic,” “oppositional,” “agitated,” and “depressed” and did not identify any symptoms consistent with OCD, yet you again diagnosed OCD.

You stated in your response to Form FDA 483 that because of the varying degrees of diagnostic ability among your staff, you modified their diagnoses. However, subject case histories and staff affidavits indicated that your diagnostic changes were limited to changing other Axis I diagnosis (e.g., MDD, ADHD) to OCD diagnoses. In addition, in certain of these cases, you changed your own diagnosis, not that of your staff.

- b. You submitted false study records and psychiatric assessment scales to the sponsor claiming you saw the subjects on dates when in fact you were not at the clinic. Information shows you were absent from the clinic on May 23-24, 2001 to attend a meeting for investigators in Dallas, Texas. In addition, your calendar indicated “MCP-Key Biscayne” on those dates. However, you submitted false study records to the sponsor purporting to document that you examined subjects 28175 [] and 28191 [] on May 23, 2001 and subject 28190 [] on May 24, 2001.

In your response, you stated that you were in town on May 23-24, 2001. You provided your progress notes of patients (not study subjects) from another facility, the Touro Infirmary, dated May 23, 2001. However, you did not provide any evidence that you were in the clinic on those dates and saw the study subjects.

2. You failed to conduct the study in accordance with the protocol [21 CFR 312.60].

- a. The following subjects were enrolled despite meeting exclusion criteria:

- 1) The protocol excluded subjects if they had taken certain psychoactive drugs within specified time frames [e.g., fluoxetine(Prozac) at least 5 weeks prior to the screening visit; antidepressants other than MAOI or fluoxetine, lithium and oral antipsychotics at least 14 days prior to the study screening visit]. Four of the seventeen subjects received the following prohibited medications until their screening and/or randomization visits.

Subject 28133 [] Prozac

You responded that the subject’s psychiatric evaluation documented no medication since 10/1/00 and the treatment plan did not include any medications on 10/23/00. However, we note your psychiatric evaluation of this subject on 10/23/00 documented that the subject was started on Prozac 20 mg po qam. The subject was screened for entry in the study on 11/20/00. This violates the protocol because the subject was started on fluoxetine (Prozac) within 5 weeks prior to the screening visit.

Subject 28138 [] Wellbutrin

Although you responded that Wellbutrin was discontinued on 11/22/00, we have information that the subject was taking Wellbutrin past the date of screening visit on 12/8/00 and at least until the day the subject started taking the study drug on 12/15/00.

Subject 28172 [] Risperdal, Tenex and Adderall (amphetamine product)

Your psychiatric evaluation of [] for study dated 12/19/00 stated the subject is currently on Risperdal 5 mg po bid and Tenex 5 mg po bid. You acknowledged the subject had been taking Adderall and documented that it was discontinued on 12/11/00. However, the drug screen was positive for amphetamine on 12/19/00. This violates the protocol because the subject has been taking psychoactive drugs until the screening visit on 12/19/00. According to your communication with the study monitor regarding this positive drug screen for amphetamine, the study monitor stated that in order for the subject to remain in the study, a negative result on repeat urine drug screen was necessary prior to randomization. In your response to the Form FDA 483, you stated that the subject was not randomized until he was off the medication for two weeks. There was no documentation to demonstrate that you obtained a negative urine drug screen result on this subject prior to randomization on 12/29/00.

Subject 28173 [] Adderall, Paxil and Anafranil

You responded that the subject had been on Adderall prior to seeing you and had no history of treatment with Paxil or Anafranil. You acknowledged that urine drug screen was positive for amphetamine. Your psychiatric evaluation of this subject dated 12/18/00 for study documented the subject is currently on Adderall 10 mg qam and that you planned to treat the subject with Paxil 20 mg qam and Anafranil 25 mg po qpm. This violates the protocol because the evidence demonstrate subject has taken psychoactive drugs including antidepressants other than MAOI or fluoxetine until (at least) 3 days prior to the study screening visit on 12/21/00.

- 2) The protocol excluded subjects with a history of a psychotic episode. Four of the seventeen subjects were enrolled despite having a history of auditory and/or visual hallucinations [28133 [] 28134 [] 28171 [] 28172 []]
- b. You failed to perform various psychiatric assessment scales (K-SADS-PL, CY-BOCS) at different time points as required by the protocol.
 - 1) You failed to complete the OCD supplement sections of the K-SADS psychiatric assessment for 13 subjects [28134 [] 28136 [] 28137 [] 28140 [] 28171 [] 28172 [] 28173 [] 28174 [] 28175 [] 28175 [] 28189 [] 28190 [] and 28191 []]

2) You failed to complete CY-BOCS assessments for the following subject visits:
28133 [] Visit 2; 28172 [] Visit 2; 28176 [] Visit 2; 28189 [] Visit
8; 28190 [] Visit 2 and Visit 8; and 28191 [] Visits 2 and 7.

c. The protocol [] requires treatment phase visits at certain time frames including the early withdrawal visit. You failed to conduct follow up visits with subjects 28133 []
28171 [] 28175 [] and 28191 [] after terminating the open-label study.

d. The protocol [] requires a diagnosis of OCD in those subjects completing protocol []
You allowed 8 subjects into protocol [] despite the fact that OCD diagnosis was never confirmed by the required assessment, the OCD supplement sections of the K-SADS psychiatric assessment.

e. CY-BOCS assessments were completed in handwritings other than yours although you initialed the records for five subjects [28133 [] 28136 [] 28137 []
(28140); [] (28171)] at certain visits as if you had completed these records. We have information indicating that your staff completed CY-BOCS assessments for you. Documents were not available to indicate that they were qualified to complete the patient assessments.

3. You failed to notify the IRB of all changes in the research activity [21 CFR 312.66].

You failed to promptly notify the IRB that on July 11, 2001, the sponsor terminated your participation in paroxetine studies [] and [] for not following the investigational plan and for compromising subject safety. Although you stated in your response dated October 12, 2001, that the IRB was notified, you did not provide a copy of the notification.

4. You failed to follow the informed consent procedure [21 CFR 312.60 and 50.20].

We have information indicating that you failed to discontinue subjects [] and [] participation in protocol [] after their mother rescinded her consent for her children's participation in the study.

5. You failed to maintain adequate and accurate records [21 CFR 312.62(b)].

There were numerous discrepancies between source documents and what was recorded in case report forms (CRFs).

a. Your psychiatric evaluations noted in the source documents conflict with what was recorded in the K-SADS-PL evaluation.

1) Subject 28133 [] had a history of depressive disorder, past suicidal attempt and conduct behavioral problems such as lying, stealing and truancy that were not documented in the K-SADS evaluation.

- 2) During their respective psychiatric evaluations, subject 28171 [] stated seeing two men and subject 28172 [] admitted having hallucinations. However, the K-SADS section for hallucination assessment was checked as “not present.”
 - 3) Your psychiatric evaluations for subject 28136 [] indicated negative for hallucinations and delusions yet the K-SADS noted a history of sub-threshold hallucinations and delusions.
- b. Your psychiatric evaluations were not reported accurately in the CRFs for the following subjects:
- 1) Subject 28172 [] In the ADHD supplement of K-SADS, 15 of the 17 behaviors were marked as “threshold” and concluded as “predominantly hyperactive-impulsive type”. Neither the history of ADHD nor schizophrenia of childhood was recorded in the CRF.
 - 2) Subject 28138 [] had a psychiatric evaluation and diagnosis of impulse control disorder, which was not reported in the CRF.
 - 3) Subject 28139 [] had psychiatric diagnoses of generalized anxiety disorder, major depression and mixed personality disorder, none of which were reported in the CRF.

Protocol # []

You failed to follow the protocol (21 CFR 312.60) in that subject randomization slips numbered 2826, 2827, 2828, 2829, 2830 and 2831 were unblinded prior to screening. We have information indicating that you instructed your study coordinator to tear off the randomization slips prior to screening so that you could control drug treatment assignments. Certain patients from your clinic, already on treatment, were then contacted for enrollment in a pre-selected treatment arm.

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 regulations.

On the basis of the above listed violations, the Center asserts that you have repeatedly or deliberately failed to comply with the cited regulations and submitted false information to both the sponsor and the FDA. The Center proposes that you be disqualified as a clinical investigator. You may reply in writing or at an informal conference in my office to the above stated issues, including an explanation of why you should remain eligible to receive investigational products and not be disqualified as a clinical investigator. This procedure is provided for by regulation 21 CFR § 312.70.

Within fifteen (15) days of receipt of this letter, write or call me at (301) 594-0020 to arrange a conference time or to indicate your intent to respond in writing. Your written response must be forwarded within thirty (30) days of receipt of this letter. Your reply should be sent to:

Joanne L. Rhoads, M.D., MPH
Director
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room #103
Rockville, Maryland 20855

Should you request an informal conference, we ask that you provide us with a full and complete explanation of the above listed violations. You should bring all pertinent documents with you, and a representative of your choosing may accompany you. Although the conference is informal, a transcript of the conference will be prepared. If you choose to proceed in this manner, we plan to hold such a conference within 30 days of your request. At any time during this administrative process, you may enter into a consent agreement with the Center regarding your future use of investigational products. Such an agreement would terminate this disqualification proceeding. Enclosed you will find a proposed agreement between you and the Center.

The Center will carefully consider any oral or written response. If your explanation is accepted by the Center, the disqualification process will be terminated. If your written or oral responses to our allegations are unsatisfactory, or we cannot come to terms on a consent agreement, or you do not respond to this notice, you will be offered a regulatory hearing before FDA, pursuant to 21 CFR 16 (enclosed) and 21 CFR 312.70. Such a hearing will determine whether or not you will remain entitled to receive investigational products. You should be aware that neither entry into a consent agreement nor pursuit of a hearing precludes the possibility of a corollary judicial proceeding or administrative remedy concerning these violations.

Sincerely yours,



Joanne L. Rhoads, M.D., MPH
Director
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research