DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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

JAN 19 2005

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Louis F. Fabre, M.D., Ph.D.
Fabre Research Clinics Inc.
5503 Crawford
Houston, TX 77004

Dear Dr. Fabre:

Between October 21 and 25, 2002, Ms. Andrea A. Branche and Sriram Subramaniam, Ph.D., representing the Food and Drug Administration (FDA), conducted an inspection and met with you to review your conduct of the following clinical study in which you participated as the clinical investigator:

Protocol #[ ]entitled: "A Multiple-Dose Steady State Study Assessing the Relative Bioequivalence of Clozapine[ ]and Clozaril® 100 mg (Novartis) Tablets."

This inspection was conducted as part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to assure that the rights, safety, and welfare of the human subjects of these studies have been protected.

We have evaluated the inspection report, the documents submitted with that report, and pertinent information obtained by the Agency, including your written response of November 7, 2002. FDA's Center for Drug Evaluation and Research (the Center) believes that you have repeatedly or deliberately violated regulations governing the proper conduct of clinical studies involving investigational new drugs as published under Title 21, Code of Federal Regulations (CFR), Part 312 (copy enclosed).

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 drugs as set forth under 21 CFR 312.70. An itemized listing of the violations follows. The applicable provisions of the CFR are cited for each violation.

1. **You failed to satisfy the criteria for an exemption from IND requirements and failed to conduct this clinical study under an IND [21 CFR 312.2 and 312.20].**

   To be exempt from the requirements of 21 CFR part 312 (the IND regulations), a bioequivalence study must satisfy the criteria for an exemption from part 312 in 21 CFR §

320.31(d). You failed to satisfy all of the criteria. Section 320.31(d)(2) states that, to be exempt from part 312, "[a]n in vivo bioavailability or bioequivalence study in humans shall be conducted in compliance with the requirements for institutional review set forth in part 56 of this chapter, and informed consent set forth in part 50 of this chapter." You failed to provide informed consent containing all of the basic elements of informed consent (21 CFR 50.25) (see item 5 below). Therefore, the bioequivalence study you conducted was not exempt from the requirements of 21 CFR part 312. In addition to failing to conduct the study under an IND, you also failed to fulfill many of your responsibilities as a clinical investigator under 21 CFR part 312, as outlined below.

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

A clinical investigator is responsible for protecting the rights, safety, and welfare of subjects under the investigator's care. Our investigation indicates that you had little personal involvement in the conduct of the study. Rarely were you present at the clinical trial site. When you were not present, you delegated conduct of the study, including the clinical assessment and treatment of subjects, to individuals who lacked necessary medical qualifications. You, and the individuals to whom you delegated responsibility, failed to recognize or evaluate adverse events in a timely manner and failed to take appropriate action to protect subjects who experienced adverse events. For example, subject[ ]died from cardiac arrest secondary to myocarditis (a known risk of Clozaril® therapy). At the time of his death, the subject had been in the study and under your care and supervision in an inpatient facility for 23 days and had received clozapine for 22 days (Clozaril® for 14 days, followed by generic clozapine for an additional 8 days.)

The approved labeling for Clozaril® warns of an association between clozapine and an increased risk of fatal myocarditis. This warning is prominently featured in a BOXED WARNING. The warning indicates that the risk appears to be greatest during the first month of therapy and, if myocarditis is suspected, "clozapine treatment should be promptly discontinued." The WARNINGS section of the labeling further advises that " the possibility of myocarditis should be considered in patients receiving Clozaril® (clozapine) who present with unexplained fatigue, dyspnea, tachypnea, fever, chest pain, palpitations, other signs or symptoms of heart failure, or electrocardiographic findings such as ST-T wave abnormalities or arrhythmias. . . . Tachycardia, which has been associated with Clozaril® (clozapine) treatment, has also been noted as a presenting sign in patients with myocarditis. Therefore, tachycardia during the first month of therapy warrants close monitoring for other signs of myocarditis."

Subject[ ]was noted to have episodic tachycardia on Day 1 (pulse at study screening was 60 bpm) and persistent tachycardia from Day 2 until his death on Day 23. The progress notes do not reflect concern for this clinical finding. Typically, the notes merely indicate that vital signs were done, and occasionally repeated, but without further evaluation or attention to other signs and symptoms suggestive of myocarditis or other drug-related illness. Over the course of the study, subject[ ]developed increasingly persistent and significant signs and symptoms that did not receive appropriate medical evaluation, including severe and persistent diarrhea, fever, persistent hypotension, severe electrolyte imbalance, acute renal

failure, and electrocardiographic documentation of myocardial injury. Despite multiple signs and symptoms consistent with myocardial injury and drug toxicity, you or persons to whom you delegated responsibility continued to dose the subject with study drug until the day before he died. The autopsy report identified myocarditis as the cause of death. The major pathological findings were hypertrophied left and right ventricles, dilated right ventricle, histological features of myocarditis, pulmonary edema, and hepatomegaly.

It is evident that there were multiple opportunities throughout the study for appropriate medical evaluation of the subject, and appropriate intervention, including:

- Day 2 until subject's death: The subject had a persistent, aberrant tachycardia that began shortly after initiation of clozapine. You should have suspected that this adverse event was most likely drug related (it is mentioned in the Clozaril® labeling as a presenting sign of myocarditis), discontinued the drug, evaluated the subject for cardiac abnormalities, provided appropriate medical care, and closely monitored the subject until his symptoms resolved.
- Days 10-14, and until subject's death: The subject developed diarrhea, which continued to worsen in response to conservative therapy with fluids and oral antidiarrheal agents. Your staff originally attributed the diarrhea to a viral illness, but the Day 14 WBC was abnormal and inconsistent with that diagnosis. As the subject's diarrhea worsened, further evaluation and more aggressive treatment were clearly indicated due to the risk of dehydration, renal insufficiency caused by prerenal azotemia, and resulting drug accumulation, all of which were later documented by clinical and laboratory findings.
- Days 15 until subject's death: The subject had persistent hypotension that was never explained, evaluated, or treated.
- Day 16 until the subject's death: The subject's Day 16 laboratory findings indicated a life threatening electrolyte imbalance and acute renal failure (with a greater than 50% decrease in his glomerular filtration rate) requiring immediate medical intervention. At a minimum, the subject should have received intravenous rehydration, continuous cardiac monitoring, and a comprehensive evaluation of his acute renal failure. You didn't review the Day 16 laboratory findings until four days after they were obtained. At that point, you characterized them as "NCS" (not clinically significant). The patient's severely compromised renal function should have prompted major concern since it was potentially life threatening and because clozapine is primarily excreted through the kidney. You should have realized that the subject's renal insufficiency placed him at significant risk for drug accumulation, and therefore at higher risk for drug toxicity.
- Day 22 until the subject's death: You obtained repeat serum chemistries and an ECG on Day 22. The laboratory findings were again abnormal, indicating severe electrolyte imbalance and renal failure. The ECG provided clear evidence of myocardial injury. The subject remained hypotensive and tachycardic. These findings were a clear indication that immediate intensive medical intervention was necessary.

Notwithstanding the volume of clinical evidence consistent with drug-induced myocardial injury and drug toxicity generally, including the patient's persistent tachycardia (the onset of which coincided with initiation of clozapine), persistent hypotension, progressive clinical deterioration, grossly abnormal laboratory and electrocardiographic findings, and specific warnings in the Clozaril® labeling concerning the risk of myocarditis, the progress note you

wrote shortly after the patient died stated: "This AM patient was awake and well at 7:30....We feel that this [referring to his death] is not related to medication." Your conclusion is contradicted by pharmacokinetic analysis of clozapine levels in the subject's plasma. Based on analysis of samples obtained during the clinical study and at autopsy, from Day 12 to 23 of the study, the subject had accumulated a steady state serum drug concentration two-three times greater than the mean for other study subjects, and a maximum drug concentration (Cmax) three-four times greater than the mean for other study subjects.

3. **You failed to adequately supervise the above-referenced clinical investigation [21 CFR 312.60].**

When you signed the Statement of Investigator, Form FDA 1572, you agreed to take responsibility for the conduct of the clinical investigation at your site. You specifically agreed to personally conduct the clinical investigation or to supervise those aspects of the clinical investigation that you did not personally conduct. While you may delegate certain study tasks to individuals qualified to perform them, as clinical investigator you may not delegate your general responsibilities. Our investigation indicates that your supervision of personnel to whom you delegated study tasks was not adequate to ensure that the clinical trial was conducted according to the signed investigator statement, the investigational plan, and applicable regulations, and in a manner that protects the rights, safety and welfare of human subjects.

a. You failed to adequately supervise individuals to whom you delegated study tasks.

The individuals to whom you delegated study tasks had little or no supervision in the conduct of these tasks. We understand that you often delegated independent medical authority to Ms.[ ]R.N., and Mr.[ ]without oversight. Although Mr.[ ]is reported to have had medical training in Mexico, he is neither licensed nor credentialed to practice medicine in the United States. Available documentation demonstrates that you did not adequately supervise individuals to whom you delegated tasks. There is no indication in the progress notes that you, or any physician, had any involvement in the evaluation, dosing, or treatment of subject[ ] except for a single reference to the principal investigator (PI) on Day 22 of the study and your note on Day 23, written after the patient was unable to be resuscitated. The one entry indicating your direct involvement is at 1515 in the Day 22 progress note, which states: "Pt. Was exam for complaints of diarrhea by[ ]PI ordered study meds to be discontinued (abnormal electrolyte results) diet clear fluids and lomotil as instructed by PI." All other progress notes are written and signed by nursing staff or Mr.[ ] without your co-signature and with no indication of supervision or consultation by you.

During the FDA investigation, you told our personnel that you maintained control of this study by evaluating adverse events, laboratory findings, and ECGs, and by being present on the first day of dosing. Your supervision of these matters was deficient as follows:

- In Section 7.7 (Adverse Events), the protocol states that the "question of the relationship of the adverse reaction to drug administration will be determined by the Investigator after thorough consideration of all the facts which are available.

The rationale for determining the relationship must be explained on the Adverse Event Report form." For adverse events that were reported, the Adverse Event Report forms did not explain the rationale for the relationship between the event and the study drug, as required by the protocol. In addition, not all adverse events were reported. For example, some of the serious adverse events experienced by Subject[ ]were not reported as required by the protocol and 21 CFR 312.64 (b) (see items 2 and 6).

- Subject[ ]s abnormal laboratory findings on Day 16, which required immediate medical intervention, were not reviewed by you until four days after they were obtained (the date you signed the laboratory report).
- The only ECG obtained for subject[ ]during the study (in addition to the screening ECG) was done on Day 22 by Mr.[ ]who noted in the progress note at 1740: "ECGs were done and over-read requested." The computer interpretation of the ECG indicated significant abnormalities ("sinus tachycardia with occasional ventricular premature complexes...left axis deviation...intraventricular conduction delay...abnormal rhythm ECG"). The cardiologist who reviewed the ECG to check the accuracy of the computer interpretation (i.e., did the "over-read") confirmed that interpretation. There is no indication in the progress notes that the significance of these abnormal findings were recognized by Mr.[ ]or the nursing staff or that you were made aware of this ECG at the time it was obtained.
- The progress notes and dosing record for subject[ ]do not indicate that a physician was present during the first four hours of dosing on Days 1 and 14, as required by the protocol (see item 7 below).

b. You delegated certain study tasks to individuals not qualified to perform such tasks.

Our investigation indicates that when you were not present at the clinical trial site, you delegated conduct of the trial, including the clinical assessment and treatment of subjects, to persons who were not qualified to perform these tasks. Specifically, Mr.[ ]was responsible for assessing symptoms and physical findings, evaluating laboratory results, ECGs, and adverse events, and determining whether a subject should continue receiving study medication. Mr.[ ]is not a licensed medical practitioner in the U.S. and lacked the necessary medical qualifications to perform these tasks.

Your lack of supervision and personal involvement and inappropriate delegation of study tasks resulted in your failure to protect the rights, safety, and welfare of study subjects under your care, as well as some, if not all, of the other violations listed in this letter.

4. You submitted false information to the sponsor in required reports [21 CFR 312.70(a)].

You submitted false information to[ ]in the Serious Adverse Event Report for subject[ ] dated May 3, 2002 and reflecting the events of day 22, May 2, 2002. The computer interpretation of the ECG for this subject obtained on day 22 of the study indicated serious abnormalities ("sinus tachycardia with occasional ventricular premature complexes...left axis deviation...intraventricular conduction delay...abnormal

rhythm ECG"). The ECG also contained the statement "computer interpretation confirmed" and bears the stamped signature of the cardiologist who confirmed the computer findings. However, in your report to the sponsor, you stated that "An ECG was done with cardiologist overread, no serious abnormalities were noted."

5. You failed to provide informed consent that contains all of the basic elements of informed consent [21 CFR 50.25].

a. You failed to provide a description of reasonably foreseeable risks to subjects [21 CFR 50.25(a) (2)].

1. You failed to describe the risk of fatal myocarditis.

Protocol[ ]began at your site in September, 2001. Subject[ ]signed the informed consent on April 8, 2002. On January 14, 2002, FDA recommended that a BOXED WARNING regarding an increased risk of fatal myocarditis, especially during the first month of therapy, be placed in the approved labeling of Clozaril® (the innovator study drug in this bioequivalence study), and that additional detail about this risk be placed in the WARNINGS section. In February 2002, Novartis (the manufacturer of Clozaril®), sent a letter to medical practitioners informing them about these changes in the labeling.

The BOXED WARNING states that:
"Analyses of post-marketing safety databases suggest that clozapine is associated with an increased risk of fatal myocarditis, especially during, but not limited to, the first month of therapy. In patients in whom myocarditis is suspected, clozapine treatment should be promptly discontinued."

The WARNINGS section was also revised to include, among other things, the following discussion of the signs and symptoms of myocarditis:

". . . the possibility of myocarditis should be considered in patients receiving CLOZARIL who present with unexplained fatigue, dypsnea, tachypnea, fever, chest pain, palpitations, other signs or symptoms of heart failure, or electrocardiographic findings such as ST-T wave abnormalities or arrhythmias . . . Tachycardia, which has been associated with CLOZARIL treatment, has also been noted as a presenting sign in patients with myocarditis. Therefore, tachycardia during the first month of therapy warrants close monitoring for other signs of myocarditis."

The WARNINGS section also indicates that, as of August 2001, there had been 30 reports of myocarditis in the United States and 17 fatalities.

You amended the informed consent for this study (comparing Clozaril® to[ ] generic clozapine) on March 18, 2002. However, in the amended informed consent you failed to include a description of the increased risk of fatal myocarditis associated with Clozaril® therapy or a discussion of the signs and symptoms of myocarditis about which subjects taking clozapine should be aware.

2. You failed to describe the risk of fatal agranulocytosis.
The labeling of Clozaril® that was in effect in 2002 contains the following information in a BOXED WARNING:

"Because of the significant risk of agranulocytosis, a potentially life-threatening adverse event, Clozaril® (clozapine) should be reserved for use in the treatment of severely ill schizophrenic patients who fail to show an acceptable response to adequate courses of standard antipsychotic drug treatment. . . .."

The WARNINGS section also contains the following information: "Before initiating treatment with Clozaril® (clozapine), it is strongly recommended that a patient be given at least two trials, each with a different antipsychotic drug product, at an adequate dose, and for an adequate duration . . . . Because of the substantial risk for developing agranulocytosis in association with Clozaril® (clozapine) use, which may persist over a prolonged period of time, patients must have a blood sample drawn for WBC count before initiation of treatment with Clozaril® (clozapine) and must have subsequent WBC counts done at least weekly for the first 6 months of continuous treatment."

The WARNINGS section also indicates that agranulocytosis associated with Clozaril use can "prove fatal if not detected early and therapy interrupted. Of the 149 cases of agranulocytosis reported worldwide in association with Clozaril® (clozapine) use as of December 31, 1989, 32% were fatal."

The informed consent mentioned only a potential "drop in the white blood cell count." It failed to disclose that there is a significant risk of agranulocytosis associated with Clozaril, and that this condition can be fatal.

b. You failed to disclose appropriate alternative courses of treatment that might have been advantageous to the subject [21 CFR 50.25 (a) (4)].

The INDICATIONS section of the Clozaril labeling states that:

"Clozaril is indicated for the management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia. Because of the significant risk of agranulocytosis and seizure associated with its use, Clozaril should be used only in patients who have failed to respond adequately to treatment with appropriate courses of standard drug treatments for schizophrenia, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from the drug."

The WARNINGS section further states that:
"Before initiating treatment with CLOZARIL, it is strongly recommended that a patient be given at least 2 trials, each with a different standard drug product for schizophrenia, at an adequate dose, and for an adequate duration."
The informed consent stated only that "[o]ther treatments and therapies for schizophrenia are available. Those might include other medications and psychotherapy." It failed to

point out that there are several drugs indicated for the treatment of schizophrenia for which the labeling does not recommend that use be restricted to patients who have failed other schizophrenia treatments and that might have been beneficial in treating the subjects condition. It also failed to point out that, because of the significant risk of agranulocytosis, the approved labeling for Clozaril® strongly recommended that this drug be used only in severely ill schizophrenic patients who failed to have an adequate response to at least two of these other therapies.

6. You failed to report adverse effects to the sponsor [21 CFR 312.64]

As clinical investigator of this study, you were required to promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect was alarming, you were required to report the adverse effect immediately. Prior to his death, subject[ ] experienced multiple, serious adverse effects that might reasonably be regarded as caused by the drug-- including prolonged symptomatic hypotension, renal failure, severe electrolyte imbalance, myocarditis, and myocardial ischemia—that you failed to report to the sponsor. It appears that you either did not recognize these serious adverse effects when they occurred, or, as detailed in item 4 above, falsely represented serious adverse effects as normal or not clinically significant.

7. You failed to conduct the study according to the approved protocol [21 CFR 312.60]

a. The protocol required that the sponsor "be notified within one (1) day by telephone or by fax of serious adverse events, which are defined as fatal, life threatening, requiring or prolonging inpatient hospitalization, or as having permanent residual effects." (Sec. 7.7) As noted in item 6, subject[ ]experienced multiple, serious adverse effects that were not reported to the sponsor.

b. Section 7.5 of the protocol required that 'the attending physician will be present prior to dosing and will observe all subjects for the first 4.0 hours following drug administration on Days 1, 14 and 24." Your letter dated November 7, 2002 states that pharmacokinetic sampling records document the presence of a physician on Days 14 and 24. However, the records you provided only document the presence of a physician for 4 of the 7 subject cohorts. Furthermore, while you claim that a physician was present on Day 1, there is no documentation to support your claim.

This letter is not intended to be an all-inclusive list of deficiencies with your bioequivalence study of clozapine. It is your responsibility to ensure adherence to each requirement of the law and relevant regulations.

On the basis of the above listed violations, FDA asserts that you failed to satisfy the criteria for an exemption from IND requirements and failed to conduct this study under an IND, and have repeatedly or deliberately failed to meet your responsibilities under Form FDA 1572 and 21 CFR part 312. Therefore, FDA proposes that you be disqualified as a clinical investigator. You may reply to the above stated issues, including an explanation of why you should remain eligible to conduct FDA-regulated clinical investigations and not be disqualified as a clinical investigator, in a written response or at an informal conference in my office.

Within fifteen (15) business 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) calendar days of receipt of this letter. Your reply should be sent to me at Division of Scientific Investigations, Center for Drug Evaluation and Research, Food and Drug Administration (HFD-45), 7520 Standish Place (Room 103), Rockville, MD 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 with you all pertinent documents, and you may be accompanied by a representative of your choosing. 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 calendar days of your request.
At any time during this administrative process, you may enter into a consent agreement with FDA regarding your future conduct of FDA-regulated clinical investigations. Such an agreement would terminate this disqualification proceeding. Enclosed you will find a proposed agreement between you and FDA.

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. Before such a hearing, FDA will provide you notice of the matters to be considered, including a comprehensive statement of the basis for the decision or action taken or proposed, and a general summary of the information that will be presented by FDA in support of the decision or action. A presiding officer free from bias or prejudice and who has not participated in this matter will conduct the hearing. Such a hearing will determine whether or not you will remain entitled to conduct FDA-regulated clinical investigations. 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,

Joanne L Rhoads M.D.

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Enclosures:
Form FDA 1572
Consent Agreement