DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

FEB 18 1998

WARNING LETTER

Certified Mail
Return Receipt Requested

Abdollah Iravani, M.D.
Central Florida Medical Research Center
1720 South Orange Avenue, Suite 401
Orlando, Florida 32806

Dear Dr. Iravani:

Between 24 February and 4 April 1997, Ms. Brunilda Torres and Dr. Mathew T. Thomas, representing the Food and Drug Administration (FDA), conducted an inspection of your conduct, as the investigator of record, of the following clinical studies of investigational new drugs:

1. Protocol #

2. Protocol #

3. Protocol #

4. Protocol #

5. Protocol #

6. Protocol #

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 have been protected.

At the conclusion of the inspection Ms. Torres discussed the inspectional findings with you, and issued to you a Form FDA 483. The inspectional findings, the inspection report, and the documents collected during the inspection indicate that you have violated federal laws and regulations that apply to clinical new drug studies and you have submitted inaccurate information to sponsors in required reports for studies of investigational drugs.

In summary:

I. You failed to conduct clinical studies in accordance with the approved protocols [21 CFR 312.53(vi)(a), and 312.60].

1. For protocol #

i. For subjects #3188 and #3193, who were women of child bearing potential, you failed to obtain prestudy (negative) pregnancy tests or to document whether they were practicing effective methods of birth control.

ii. You failed to exclude subject #3184, who had a medication compliance of only 75% during the placebo run-in period, although 80% medication compliance was required by the protocol for inclusion in the study.

iii. Subject #3188 was taking (t½ = 12 hours) until the day prior to visit #2 on 11 January 1996, but you failed to exclude this subject from the study as required by the protocol. The protocol required exclusion of subjects taking medications for if those medications were not discontinued for a minimum of five half-lives prior to visit #2.

2. For protocol #

i. You did not discontinue subjects #7 and #38 from study treatment despite negative pretreatment laboratory culture reports for S. pyogenes.

ii. The study design required the investigator to remain unaware of the study medication administered to each subject; however, you frequently handed your study coordinators the non-blinded study drugs to reconstitute and dispense to the study subjects.

3. For protocol # you failed to collect endocervical specimens from subject F2768769 for Ureaplasma urealyticum and Mycoplasma hominis cultures, as required by the protocol on study visit #1.

II. You failed to prepare and maintain adequate and accurate records of all observations and other data pertinent to the investigation on each individual treated with the investigational drug or employed as a control in the investigation, as required under 21 CFR Part 312.62(b), in that:

1. For protocol #

i. For subject #3188, the clinic chart shows that (a psychotropic medication prohibited by the protocol) was being taken by this subject at the time of study visit #4. You failed to report this subject's use of on the Concomitant Medication page of the case report form (CRF).

ii. You reported inaccurate information on study related records. For example, during the inspection you provided to FDA personnel the information that study coordinator SG worked at your clinic between 13 February 1996 and 21 March 1996, and that study coordinator RZ started working at your clinic on 2 February 1996. This contradicts information on several study related source documents, viz., the study's drug dispensing logs for six subjects (#3182, #3186, #3187, #3188, #3189, and #3190) report that SG dispensed medications to these subjects between 4 December 1995 and 13 February 1996; the vital signs section of the clinic chart of subject #3189 indicate that SG completed the chart for visit #2c on 8 February 1996; the vital signs section of the clinic chart of subject #3181 indicates that RZ

completed the chart during the subject's visit #4 on 31 January 1996, and the vital signs section of the clinic chart of subject #3186 indicates that RZ completed the chart during the subject's visit #4 on 1 February 1996.

iii. The Compliance Assessment Form for visit 3 (on 17 January 1996) of subject #3184 shows a change in the reported number of doses taken by this subject. The reported doses were changed from 9 to 11 on 11 September 1996, which is about 8 months after visit 3. No source documents were available during the inspection to support this record change.

iv. The time on the EKG tracing for subject #3182 (visit date 27 February 1996) was obliterated, thereby making it impossible to determine if this assessment was performed within 24±2 hours of the previous day's dose of study medication, as required by the study protocol.

v. For subject #3184, the ECG and vital signs for visit 2a were dated 22 December 1995, while the laboratory report for the same visit showed the specimen was collected on 21 December 1995. The date on the progress notes was changed from 22 December 1995 to 21 December 1995 and then back to 22 December 1995. The date on the vital signs chart was changed from 21 December 1995 to 22 December 1995.

vi. For subject #3187, the time of the blood pressure assessment for visit 2b on 1 February 1996 is recorded in the CRF as 3:50 PM; and the vital signs chart reports this time as 2:35 PM. For the same subject, the time of the blood pressure assessment for visit 2c on 8 February 1996 is recorded in the CRF as 4:15 PM; the vital signs chart reported this time as 3:00 PM.

vii. On the Form FDA 1572, you failed to identify the study site at where at least three subjects were enrolled and participated in this study [21 CFR 312.53(c)(1)(iii) and (iv)]; you also failed to identify the institutional review board (IRB) that was responsible for the continuing review and approval of the study at this clinic [21 CFR 312.53(c)(1)(v)].

2. For Protocol #

   i. For subject #10, the medical chart reports treatment with (an antibiotic) between 18 and 21 March 1994. You failed to report on the CRF this subject's use of an antibiotic, which is prohibited by the protocol.

   ii. For subject #001, the CRF indicated that entries were made by study coordinator SB on 2 March 1994 (CRF Form 3 "Infection History"), on 7 March 1994 (CRF Form 11 "Telephone Contact"), and on 2 March 1994 (CRF Form 6 "Physical Examination"). These entries are not in agreement with the information you provided to FDA personnel during the inspection indicating that SB started to work in your office only on 15 March 1994. No other source documents were available during the inspection to support these entries on the CRF.

3. For protocol #

   i. For subject #70 the clinic chart reports you prescribed antibiotics on 7 December 1993 (for 7 days), on 28 December 1993 (for 10 days), and on 17 January 1994 (for 14 days). You enrolled subject #70 in this study on 27 January 1994, and inaccurately reported in the medical history section of this subject's worksheet, "Reccurrent UTI's. last episode in mid Dec 1993. She has been off antibiotic for over a month. Occational [sic] Hx/o URI." Form 1 of the CRF (Exclusion Criteria) also appears to inaccurately report that this subject was not on antibiotic treatment within 3 days prior to starting the study on 27 January 1994.

   ii. Three different screening logs for the study were available during the inspection. These logs failed to record all the subjects enrolled in the study.

   iii. For subject (subject #67), one screening log indicates that the subject was screened on 12 January 1994 and not enrolled in the study because "parents refused." Another screening log contradicts this information and reports that on 12 January 1994 this subject was screened and

enrolled as subject #67, and the consent form was signed by the subject's mother on 12 January 1994.

iv. The diaries, which were given to the study subjects in protocol # were prepared for another study (i.e. protocol #

v. There is a discrepancy between the Master Patient Log, which reports the last subject (#73) completed this study on 7 March 1994, and the 15 April 1994 letter to the IRB, which reports the Project Termination on 28 January 1994.

vi. Clinic charts were not available during the inspection for 55 of the 77 subjects enrolled in the study.

4. For subject #6 (in study #

you reported in the medical record and the CRF that this subject's x-ray on 11 September 1993 showed "RML, LLL Infiltrates," and you implied this subject had bacterial pneumonia confirmed by chest x-ray as required by protocol. This evaluation was not in agreement with the radiologist who reviewed the same chest X-ray of 11 September 1993 and reported that the subject had, "Cardiomegaly with congestive failure."

5. For subject #100 (in protocol #

you reported on the CRF negative urethral cultures on 8 April 1994 for Chlamydia trachomatous and Neisseria gonorrhea; in fact, the laboratory reports for both cultures were reported as positive.

III. For study #
you failed to obtain Institutional Review Board approval for enrolling subjects (three) at

As summarized above, the FDA inspection documented that you have violated federal laws and regulations governing the clinical study of investigational drugs. Within 15 calendar days of your receipt of this letter, (1) notify this office in writing of the corrective actions you have taken to prevent similar violations in your current and future clinical drug studies, and (2) provide this office in writing an explanation of the matters complained of above. Your failure to adequately and promptly correct and explain these matters may result in regulatory action without further notice.

Sincerely yours,

Stan W. Woollen /for

David Lepay, M.D., Ph.D.
Director
Division of Scientific
Investigations
Office of Compliance
Center for Drug Evaluation
and Research