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DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

MAR 29 2007

Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

By Certified Mail – Return Receipt Requested
And By Facsimile Transmission

CBER – 07 – 008

Warning Letter

Edward Chambers, M.D.
1370 Rosecrans Street, Suite A
San Diego, California 92106

Dear Dr. Chambers:

This letter describes the results of a Food and Drug Administration (FDA) inspection that concluded on November 20, 2006. FDA Investigator Mary Wilkerson-Brinsko met with you to review your conduct of two clinical studies entitled:

[REDACTED]

[REDACTED]

FDA conducted this inspection under the Bioresearch Monitoring Program, which includes inspections designed to review the conduct of research involving investigational drugs.

The FDA investigator issued and discussed the Form FDA 483, Inspectional Observations, at the end of the inspection. We have reviewed the inspection report, the Form FDA 483, and your letter dated 12/19/06 in response to the Form FDA 483.

We have determined that you violated regulations governing the proper conduct of clinical studies involving investigational new drugs, as published in Title 21, Code of Federal Regulations (CFR), Part 312 (available at <http://www.gpoaccess.gov/cfr/index.html>). The applicable provisions of the CFR are cited for each violation listed below.

1. **You failed to protect the rights, safety, and welfare of the subjects under your care, and you failed to ensure that the investigation was conducted according to the signed investigator agreement, the investigational plan, and applicable regulations. [21 CFR § 312.60].**

- A. Section 4.2 of the protocols required exclusion of [REDACTED]
[REDACTED]
[REDACTED] The protocols also listed several specific examples of abnormalities that must result in the exclusion of prospective subjects. Nevertheless, you enrolled subjects [REDACTED] and [REDACTED] who had [REDACTED] during the screening visit. You documented in the case report that the [REDACTED] for subject [REDACTED] was "normal," then changed the entry to "abnormal" almost six months later. You also documented that the screening [REDACTED] for subject [REDACTED] was "Abnormal * (Clinically significant)."

In your letter you explain that you used your clinical judgment as to eligibility. During the first monitoring visit the monitors instructed you to submit abnormal results to the medical monitor for review.

- B. A previous [REDACTED] was documented for subject [REDACTED] during screening for study [REDACTED], but you enrolled the subject anyway. In your letter you state that you later determined that there was no previous [REDACTED] and that the baseline antibody titer was negative. Our concern, however, is that you made those conclusions months later, as documented in the case history, well after the subject had been enrolled. You should not have enrolled this subject based on the information that you had at screening visit, and should have waited to confirm that the [REDACTED] was not actually from a [REDACTED] either through the antibody titer results or otherwise, before enrolling this subject.
- C. Sections 5.6.2 of the protocols require that all serious adverse events occurring after [REDACTED] should be reported to the sponsor's monitor within 24 hours of the occurrence. Subject [REDACTED] experienced [REDACTED] in February 2004, but you did not report this event to the sponsor or IRB until 3/30/04. Protocol section 1.4.4 identified [REDACTED] as a serious adverse event.

In your letter you admit that you were not aware of the specific time requirement for reporting this event, but that you will clarify reporting requirements in the future.

- D. You failed to conduct test procedures as required by the protocols. Examples include the following, and this is not a complete list:

Subjects	Test Procedures Not Conducted
[REDACTED]	Risk assessment questionnaire not done Day 0
	Risk assessment questionnaire not done Day 10
	Risk assessment questionnaire Day 21
	Records show the screening pregnancy test result was reviewed 1 to 6 days after [REDACTED]
	No pregnancy tests performed Day 10 [REDACTED] /or Day 30 [REDACTED]
	[REDACTED] not done Day 10
	No lymph node assessment Day 0
	[REDACTED] day exclusion question about [REDACTED] or abnormal not completed

There are many other examples of required assessments not done for several subjects, including the following: tenderness scores, structured interviews, temperature measurements, etc.

You explain in your letter that your site was retrained after these violations were noted by the study monitors. Your letter did not describe any subsequent monitoring or other step that you took to ensure that the retraining was effectively and fully corrected the problem. You stated that the pre-[REDACTED] pregnancy test results were reviewed by a study coordinator before [REDACTED], but we found no notations of that review.

- E. Some 3- and 6- month phone contacts are incomplete.
- F. Serum samples were not held at [REDACTED] as required by the protocol. Records show that the freezer temperature ranged from -16 to -19 on at least 60 days during the study.
2. **You failed to maintain accurate and complete records of each subject's case history. [21 CFR § 312.62(b)].**
- A. Case histories and drug accountability records are conflicting regarding the initials and [REDACTED] status of subjects [REDACTED] and [REDACTED].
- B. The concomitant medications for subject [REDACTED] were not entered into the electronic case report form.

- C. Documents from other subjects were mistakenly filed in the case histories of subjects [REDACTED] and [REDACTED].

Your letter states that these have been moved to the correct files.

- D. Day 7 photographs do not adequately capture the identification labels of subjects [REDACTED], [REDACTED], and [REDACTED].

- E. Other record-keeping deficiencies include, but are not limited to, the following:

Subject	Record problem
[REDACTED]	Day 7 photos are misidentified
[REDACTED]	Source screening visit has wrong subject ID
[REDACTED]	Screening [REDACTED] misidentified as [REDACTED]
[REDACTED]	Medical history is missing from case history
[REDACTED]	Medical records and electronic case report forms are discrepant -- abnormal dermatological finding of cellulitis and [REDACTED] were not submitted in the electronic case report form
[REDACTED]	Records are discrepant about the lymph node tenderness found on Day 7
[REDACTED]	Medical records and electronic case report forms are discrepant about Day 10 [REDACTED]
[REDACTED]	Day 10 case report form documents discrepant regarding [REDACTED] adverse events that had occurred

Your letter explains that corrected information has been submitted to the sponsor, where appropriate, and that the site was retrained to prevent future occurrences. You do not describe any subsequent monitoring or other steps that you took to ensure that the retraining was effective and fully corrected the problem.

This letter is not intended to contain an all-inclusive list of deficiencies in your clinical study of investigational drugs. It is your responsibility as the clinical investigator to ensure adherence to each requirement of the law and applicable regulations, and to protect the rights, safety, and welfare of subjects under your care.

You should notify this office, in writing, within fifteen business days of receipt of this letter, of the steps you plan to implement to prevent the recurrence of similar violations in future studies. Please identify all studies that you are currently conducting. For those studies, please describe the steps that you have implemented to prevent similar violations, and please submit documentation of those steps.

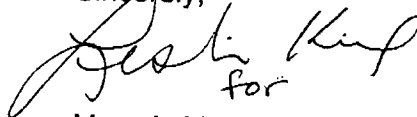
This Warning Letter is issued to you because of the serious nature of the observations noted at the time of the FDA inspection. Please be advised that failure to implement effective corrective and preventive actions and/or the commission of further violations may result in the initiation of enforcement action(s) without further notice. These actions could include clinical hold of ongoing studies, injunction, and initiation of clinical investigator disqualification proceedings, which may render a clinical investigator ineligible to receive investigational new drugs.

Please send your written response and any supporting documentation to:

Patricia Holobaugh
Division of Inspections and Surveillance (HFM-664)
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
1401 Rockville Pike, Suite 200N
Rockville, MD 20852-1448
Telephone: (301) 827-6348

We request that you send a copy of your response to the FDA District Office listed below.

Sincerely,



Mary A. Malarkey
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

Cc:

Alonza Cruse, Director
Los Angeles District Office
Food and Drug Administration HFR-PA200
19701 Fairchild, Suite 300
Irvine, California 92612-2506



IRB

