



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

95339d

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

By Certified Mail – Return Receipt Requested
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CBER – 05--015

Warning Letter

MAY 16 2005

Daniel Cohen, M.D.
Associate Medical Director
Research and Evaluation Department
Fenway Community Health
7 Haviland Street
Boston, Massachusetts 02115-8602

Dear Dr. Cohen:

This letter describes the results of a Food and Drug Administration (FDA) inspection that was conducted from January 20 through January 28, 2005. FDA investigator Karen McNabb-Noon met with you to review your conduct of a clinical study entitled [REDACTED]

FDA conducted this inspection under the agency's Bioresearch Monitoring Program that includes inspections designed to review the conduct of research involving investigational devices.

At the end of the inspection, a Form FDA 483, Inspectional Observations, was issued and discussed with you. We reviewed your letter in response to the Form FDA 483 received on February 14, 2005, addressed to Janet White at the FDA Center for Biologics Evaluation and Research.

We have determined that you violated regulations governing the proper conduct of clinical studies involving investigational devices, as published in Title 21, Code of Federal Regulations (CFR), Parts 50 and 812 (available at <http://www.access.gpo.gov/nara/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 investigational plan, the signed agreement, and applicable FDA regulations, including Part 50. [21 CFR § 812.100].**

- A. Protocol sections 8.0 and 9.0 require you to enroll positive and high risk subjects, while excluding from the study subjects with life threatening illnesses [REDACTED], as well as those with suppressed immune systems. Review of records for 227 subjects showed that you failed to document that those subjects met these health status enrollment criteria. In addition, you enrolled subject [REDACTED] in the study although this subject was receiving chemotherapy (which may be immune-suppressive) for cancer (a potentially life-threatening illness). In your letter, you state that the inappropriate enrollment of subject [REDACTED] was due to your failure to review this subject's record in a timely fashion and the absence of an inclusion/exclusion criteria checklist. You attached a draft "Standard Operation Procedure for Confirmation of Study Eligibility". If you amend your policies and procedures to require such a checklist for all research studies, your proposed corrective action appears to be adequate.
- B. Protocol section 7.3.1 describes the pool of [REDACTED] subjects as being drawn from [REDACTED]. You enrolled 111 subjects as known [REDACTED] subjects, but 15 of those subjects had no medical records on site documenting medical history and [REDACTED]. It is unclear how you concluded they met this criterion. In your letter you agree you never obtained outside [REDACTED] for the 15 identified cases.
- C. You enrolled subject [REDACTED] even though, according to the subject's study record, this subject did not fit into either the high risk or positive groups for this study. This violation was not included on the Form FDA 483.
- D. Protocol section 10.0 and [REDACTED] Clinical Trial Participant Consent Form, approved 11/5/03, do not provide for the recall of subjects for additional testing. Instead, protocol section 10.0 provides that, at when samples are obtained for testing, you should review the tests results before the subject leaves, "With the participant still available, compare the capillary result to the whole blood result. If they are not the same, retest the whole blood in duplicate and obtain a second capillary result and test in duplicate." Subject [REDACTED] had discordant test results, but you did not collect a second finger stick sample for duplicate testing at the initial visit, as the protocol required. You asked the subject to return for a second visit and repeated both the finger stick and venipuncture without obtaining informed consent. Furthermore, when the subject was recalled, specimen [REDACTED] was not tested according to the protocol. The protocol would have required no further testing after obtaining the concordant reactive results. Instead, you performed duplicate testing on all four sample matrices. Neither of the samples, initial [REDACTED] or repeat [REDACTED] was tested according to protocol.

Subject	Date	FS	WB	P	S	Discordant	Comments
█ Initial: Repeat for discordance only:	1/13/04	R	NR NR/NR	NR NR/NR	NR NR/NR	YES	Second finger stick not done as per protocol
█ Initial: Repeat for discordance only:	1/20/04	R R/R	R R/R	R R/R	R R/R	NO	No duplicate testing as per protocol (not discordant)

In your letter, you explain the repeat testing was requested by the study sponsor because the discordant result was not discovered until after the participant had left. You also included the letter from █ the sponsor's monitor, addressed to you requesting the repeat testing of this participant. You explain in your letter the participant was not asked to sign a new informed consent form due to an oversight by study staff. You do not explain why the testing was not done according to the protocol.

- E. Protocol section 15.0 requires that controls be run daily at a minimum. Controls were not run on the following nine days for 33 subjects.

Date	Subject(s)	# of Subjects
12/17/03	█	6
12/18/03	█	4
12/19/03	█	5
12/22/03	█	3
2/9/04	█	3
2/20/04	█	3
3/1/04	█	4
3/8/04	█	3
3/23/04	█	2

The Form FDA 483 did not list all of the deficiencies noted in the table above. Your letter acknowledges "these omissions occurred on a small number of days and were simply oversights on the part of research staff." In future studies you state you will ensure the staff's completion and documentation of study-specific training with attention to protocol-mandated procedures such as quality assurance activities. If this training is properly implemented, your proposed corrective action appears to be adequate.

- F. You violated protocol section 10.0 which provides that "Samples will be shipped to the █." Review of the specimen shipping forms shows that you failed to ship at least 156 samples to the central laboratory on the day they were obtained. The delay in shipping ranged from one to seven days.

In your letter you agree that the examples noted on Form FDA 483 are correct. You state in future studies you will ensure the staff's completion and documentation of study-specific training to include regular review of daily study procedures. If this training is properly implemented, your proposed corrective action appears to be adequate.

- G. According to the investigational plan, "each tech reading [REDACTED] in the Clinical Trial must perform [Proficiency Panel Testing] independently" in order to establish proficiency with the device. Nevertheless, you and your staff failed to complete the "Proficiency Panel Testing" prior to initiation of subject study testing. You enrolled and tested subjects beginning December 10, 2003 and ending March 30, 2004, but five of six testing personnel did not perform the "Proficiency Panel Testing" until the period of January 6 through January 10, 2004, and one of the testing staff did not complete the training and the "Proficiency Panel Testing" until April 1, 2004, after all 233 subjects were enrolled and the study was completed.

In your letter you agree proficiency testing was not done prior to the study opening for enrollment. You also state "study specific training was completed for most of the study staff." You state for future studies you "will explicitly document study-specific training with signed and dated training logs". You must also ensure that all required training and proficiency testing for all personnel occur.

- H. According to the [REDACTED] package insert, storage requirements for the [REDACTED] tests are [REDACTED]. You failed to document temperatures showing proper storage of the investigational device as required by the protocol.

This violation was not included on the Form FDA 483.

2. You failed to maintain accurate and complete records of each subject's case history, including data on the condition of each subject upon entering, and during the course of, the investigation and you failed to maintain accurate, complete and current records relating to the receipt, use, and disposition of devices. [21 CFR §§ 812.140(a)(2) and (3)].

- A. As described in item 1.A above, you failed to document that each of the enrolled subjects met the health status enrollment criteria.
- B. According to the monitor's final audit report, signed by you on 10/26/04, you received 1500 devices (3 [REDACTED]), used 1,453 devices for testing, proficiency, training and controls, and returned 47 devices (lot [REDACTED]).

According to your records documenting subject test results, control test results, and proficiency panel results, the total number of devices used is 1,430. Although these records do account of your use of 1430 devices as shown in the table below, this leaves a discrepancy of 23 unaccounted devices. Please provide documentation and include the quantity of devices with dates received/returned for each of the three lot numbers.

Devices used for testing:	Lot	Lot	Lot	Lot # (Not Recorded)	Totals	Documentation
Subjects					1208	Results Forms
Controls	30	36	120		186	Controls Forms
Proficiency Panels				36	36	Proficiency Panel Results
Totals	258	224	912	36	1430	

This letter is not intended to contain an all-inclusive list of deficiencies in your clinical study of investigational devices. 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 (15) business days of receipt of this letter, of the steps you plan to implement to prevent the recurrence of similar violations in future studies. Your response should include any documentation necessary to show that correction has been achieved.

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 actions and/or the commission of further violations may result in the initiation of enforcement action(s) without further notice. These actions could include injunction and initiation of clinical investigator disqualification proceedings, which may render you ineligible to receive investigational devices.

Please send your written response to:

Janet K. White
 Division of Inspections and Surveillance (HFM-664)
 Office of Compliance and Biologics Quality
 Center for Biologics Evaluation and Research
 Food and Drug Administration
 1401 Rockville Pike, Suite 200N
 Rockville, Maryland, 20852-1448

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

Sincerely,

A handwritten signature in cursive script, appearing to read "Mary A. Malarkey".

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

cc: Gail T. Costello, Director
New England District Office
Food and Drug Administration
One Montvale Ave., 4th Floor
Stoneham, MA 02180

William Dellea, Chair
Fenway Community Health Center Institutional Review Board
Department of Research and Evaluation
7 Haviland Street
Boston, Massachusetts 02115