



JUL 10 2006

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

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CBER - 06 - 007

Warning Letter

Elizabeth L. Hohmann, M.D.
Massachusetts General Hospital
55 Fruit Street
Jackson 518
Boston, Massachusetts 02114

Dear Dr. Hohmann:

This letter describes the results of a Food and Drug Administration (FDA) inspection that was conducted from February 28, 2006 to March 10, 2006. FDA investigators Patricia Murphy and Karen McNabb-Noon met with you to review your conduct of the following clinical studies for which you are the sponsor and clinical investigator:

Study 1: Safety and Shedding of Attenuated *Listeria* Vaccine [REDACTED]

Study 2: Safety and Immunogenicity of Attenuated Salmonella Typhimurium [REDACTED]

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

The FDA investigators issued and discussed with you the Form FDA 483, Inspectional Observations, at the end of the inspection. You responded in a letter to FDA dated March 16, 2006. We reviewed the inspection report, the Form FDA 483, your response, and associated FDA records.

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), Parts 50 and 312 (available at <http://www.gpoaccess.gov/cfr/index.html>). The applicable provisions of the CFR are cited for each violation listed below. Some of the violations were not cited on the Form FDA 483, but were evident from the documents that the FDA investigators collected during the inspection.

1. **You failed to submit an Investigational New Drug Application to FDA for your clinical investigation. [21 CFR § 312.20(a)].**

In Study 1 you administered an unapproved attenuated strain of *Listeria* vaccine [REDACTED] to at least 20 subjects between October 14, 1999 and December 2001 and continued this study until August 2, 2004, without submitting an Investigational New Drug Application (IND) to the FDA.

During the inspection you explained that in 2001, after you had dosed the last subject with the Study 1 investigational vaccine, you sought FDA guidance for the need for an IND. An FDA representative told that you needed an IND to conduct the study. Nevertheless, you failed to submit an IND to FDA, and continued to follow the subjects from this study through August 2004 when you informed the IRB that the study was closed.

In your letter you acknowledge and accept responsibility for this violation.

2. **You failed to ensure that informed consent was obtained according to the provisions of 21 CFR Part 50. [21 CFR § 312.60].**
 - A. You obtained informed consent from some subjects using consent form versions for Study 1 that were not approved by the Institutional Review Board (IRB). Informed consent from the subject is not legally effective if the form that is signed has not been approved by the IRB or if the consent form describes the wrong procedures. The following table illustrates the deficiencies noted in the informed consent process for 8 of the 20 enrolled subjects.

Subjects	Signature date of informed consent (IC)	Informed consent deficiencies
[REDACTED]	3/27/00	Signed a revised informed consent form before it was approved by the IRB on 4/4/00.
[REDACTED]	5/22/00	Signed a revised informed consent form before it was approved by the IRB on 5/26/00.
[REDACTED]	5/30/00	Signed an obsolete 7/27/99 version of the informed consent form; subjects should have signed the 5/26/00 version.

In your letter you acknowledge and accept the responsibility for these violations of the informed consent process. You explain that the IRB did

not require any additional changes in the consent forms it subsequently approved. You had no way of anticipating whether the IRB would require additional changes after its review. 21 CFR Part 50.27 requires that you obtain and document the informed consent from subjects by the use of a consent form approved by the IRB.

3. You failed to maintain adequate and accurate case histories. [21 CFR § 312.62(b)].

The administration dates of the investigational vaccine are discrepant in subjects' case histories for subjects [REDACTED] and [REDACTED] enrolled in Study 1. The hospital discharge summaries indicate that the two subjects were administered the investigational vaccine on 3/28/00 but you reported to the IRB that the vaccine was administered to the two subjects on 4/1/00. Due to these discrepancies we cannot determine if these subjects were hospitalized for 14 days to monitor for safety as required by the protocol.

4. You failed to promptly report to the IRB all changes to the research activity and failed to promptly report all unanticipated problems involving risk to human subjects. [21 CFR § 312.66].

A. You failed to promptly notify the IRB that Study 2 was placed on clinical hold. In your absence, FDA notified subinvestigator [REDACTED] on 9/25/03 that the study was placed on clinical hold, and FDA sent you a letter dated 10/17/03 listing the clinical hold issues. You did not inform the IRB about the clinical hold until 1/2/04, when you submitted a protocol amendment and revised consent form.

B. You failed to promptly report the unexpected adverse events experienced by the study subjects to the IRB as shown in the following examples.

The IRB approval letter dated 9/1/99 for Study 1 required you to report any unexpected event experienced by the subjects within 24 hours followed by a written report within 10 working days of the event. You did not report the unexpected adverse event of increase in transaminases experienced by subject [REDACTED] on 4/4/00 until 5/19/00, nearly six weeks after the adverse event occurred. We note that you revised the consent form to include the additional risk of increased liver enzymes based on this adverse event.

Similar liver function tests were elevated in two subjects enrolled in Study 2. The IRB policy on adverse event reporting provided that mild or moderate, possibly related, and unexpected adverse events should be reported in writing to the IRB within 30 calendar days. You reported to the IRB on 9/27/04, the unexpected adverse events experienced by subjects

█ and █ on 6/11/04, and 8/13/04, respectively, more than 45 calendar days after you became aware of them.

In your letter you acknowledge these violations. You explained that the IRB received the Study 2 information through reports from the Data Safety Monitoring Board. In your letter you propose plans to track and report future adverse events promptly to the IRB.

Based on our review of Study 1, we request further explanations for the discrepancies between the amount of monetary compensation to subjects provided on the consent form approved by the IRB and the amount of monetary compensation calculated in the protocol. For example, the consent forms approved by the IRB on 10/19/99, and 5/16/00, advised that the subject would receive compensation of █ and █ respectively, whereas the corresponding compensation calculations in the protocol for the required hospital stay and outpatient study visits included amounts of █ and █ respectively.

This letter is not intended to contain an all-inclusive list of deficiencies in your clinical studies of investigational drugs. It is your responsibility 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 a clinical investigator ineligible to receive investigational new drugs.

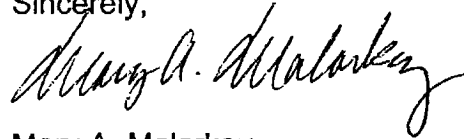
Please send your written response to:

Ms. Bhanu Kannan
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, Maryland, 20852-1448
Telephone: (301) 827-6221

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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:

Gail T. Costello, District Director
Food and Drug Administration
One Montvale Avenue, 4th Floor
Stoneham, Massachusetts 02180

