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DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

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

Notice of Initiation of Disqualification Proceeding
And Opportunity to Explain

By Certified Mail – Return Receipt Requested
And By Federal Express

August 27, 2008

Charles E. Runels, Jr., M.D.
750 Downtowner Loop West
Mobile, Alabama 36609-5528

Dear Dr. Runels:

The Food and Drug Administration (FDA, or the Agency) has investigated allegations that you failed to fulfill the responsibilities of a clinical investigator for studies utilizing an unlicensed biological investigational new drug, a (b)(4) vaccine, in violation of FDA regulations governing investigational new drugs. FDA investigators from the New Orleans District Office met with you during two inspections and reviewed the records relating to your use of an investigational (b)(4) vaccine. The inspections were conducted from May 8 to 12, 2006, and September 18 to 21, 2006. FDA conducted these inspections under the Agency's Bioresearch Monitoring Program, which includes inspections designed to review the conduct of clinical research involving investigational products. Both of the inspections focused on the following two studies:

(b)(4)

(b)(4)

The investigators issued Form FDA 483, Inspectional Observations, to you at the end of each inspection and discussed their findings with you. You responded to FDA in a letter dated August 2, 2006, (hereafter referred to as "your letter") regarding the findings of the first inspection, but you did not write to the Agency regarding the second inspection.

Based on the results of the two inspections and other information available to the Agency, we believe that you repeatedly or deliberately violated regulations governing the proper conduct of clinical studies involving unlicensed biological investigational new drugs in violation of Title 21, Code of Federal Regulations (CFR), Parts 312 and 50. The regulations are available at http://www.gpoaccess.gov/cfr/index.html.

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 entitled to receive investigational new drugs, as set forth in 21 CFR § 312.70.

A listing of the violations follows, and the applicable provisions of the CFR are cited.

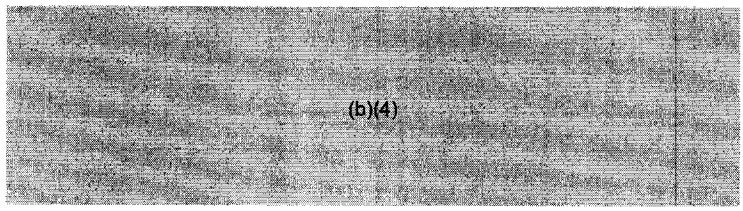
1. **You failed to protect the rights, safety, and welfare of the subjects under your care, and you failed to conduct the investigations according to the investigational plan, the signed investigator statement, and applicable regulations, including Part 50. [21 CFR § 312.60].**

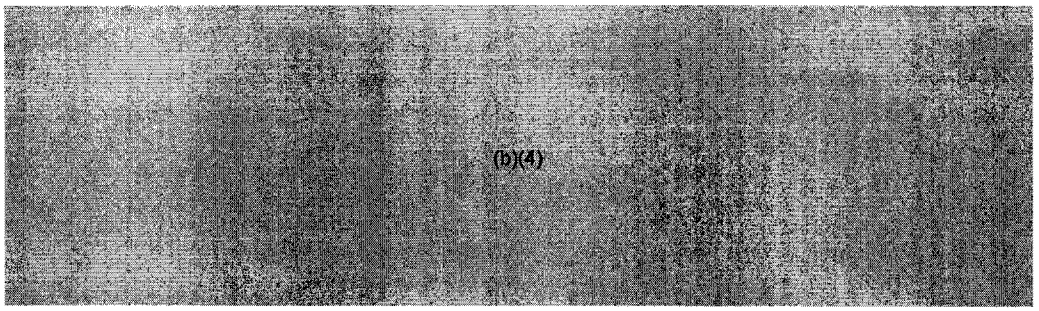
   A. You enrolled 21 indigent persons from a multi-service center for the homeless into either study (b)(4) or (b)(4) Only after enrolling eight of these subjects, you received approval from the Institutional Review Board (IRB) to enroll vulnerable subjects, as described below. Regardless of the IRB's decision to approve the enrollment of vulnerable populations, persons utilizing the multi-service center for the homeless were unsuitable for consideration for these studies for many reasons, including, but not limited to the following:

      i. These individuals were unsuitable because they were economically and/or educationally disadvantaged. Some subjects could not understand or follow the protocol requirements. For example, subjects (b)(6) and (b)(6) did not understand how to measure his/her temperature in order to complete his/her daily diary, as they reported body temperatures ranging from 84°F to 97°F.

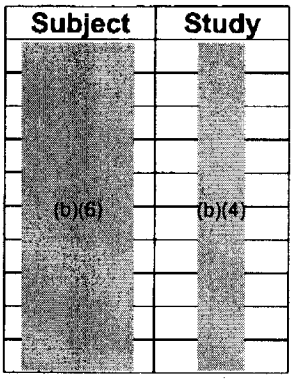
      ii. A multi-service center for the homeless lacks the appropriate environment for (b)(4) (b)(4) described in the "Instructions for the Subject for (b)(4) Although these instructions instructed subjects (b)(4) (b)(4)

      For example, the multi-service center (b)(4) (b)(4) The Instructions state:



iii. Section 4.1, Inclusion Criteria, in both protocols required that subjects must be available for participation during the entire study, and must agree to comply with all protocol requirements. The subjects recruited at the multi-service center for the homeless were placed at increased risk because you could not ensure that they were available for the required health status assessments after vaccination. Although your staff repeatedly attempted to contact these individuals, many subjects were not able to be contacted for required 3- and/or 6- month safety follow-up telephone interviews because they lacked a permanent address and/or phone number. Examples include the following:



iv. The 19 page informed consent document for these studies contains technical and complex medical terminology that an educationally disadvantaged subject would have difficulty in reading and fully comprehending.

B. The "(b)(4) Vaccine Risk Assessment Questionnaire" was to be completed at least six times during the study (during screening, prior to vaccination, and during all follow-up visits). This questionnaire asks about the health and medication use of the subjects' household contacts. Because "household contacts" include every user, staff member, or volunteer at the multi-service center, subjects from the Center could not be expected to provide reliable information about the health conditions and medications of all household contacts. You proposed, and the IRB approved, to have an impartial witness observe the informed consent discussion during recruitment of subjects from the multi-service center for the homeless. However, you did

not implement this protocol appropriately because, among other deficiencies, you did not establish criteria for who qualified as an impartial witness.

i. In addition, the use of an impartial witness to add extra protections for vulnerable subjects was compromised: (b)(6) signed as the "impartial witness" on the consent form for Subject (b)(6) when she was also a subject in the study (subject (b)(6)), and was, therefore, not "impartial."

ii. The dates on the informed consent form for Subject (b)(6) do not show that the subject's consent was witnessed and the informed consent discussion occurred at the same time. Subject (b)(6) signed the informed consent document on 2/18/04. The person conducting the informed consent discussion did not sign the form until 3/1/04, and the witness did not sign the form until 2/25/04. You signed the form as the clinical investigator on 2/27/04. A handwritten note on the form states "witnessed on 18 Feb 04. Inadvertently [sic] not signed until 25 Feb 04." The subject was vaccinated on 2/25/04.

C. You enrolled at least two relatives of one of the unblinded vaccinators who had full access to the randomization log. This practice raises concerns about the integrity of the randomization process at your site.

D. You performed screening procedures on several prospective subjects who did not meet the inclusion criteria, such as age and prior (b)(4) vaccination status. These prospective subjects underwent EKGs, and provided blood and urine samples even though they were obviously ineligible to participate in the studies.

E. You failed to promptly inform the IRB of all serious adverse events (SAEs) for the (b)(4) study. Section 5.6.2 of the protocol required each investigator to promptly report all serious and unexpected adverse events to their IRB, and to maintain copies of records that document that the IRB was properly notified. Examples of your failure to follow this requirement include:

i. Subject (b)(6) was referred to a cardiologist for follow-up of an abnormal EKG performed on 2/27/04, study day 10. The subject was later found to have acute myocarditis and was subsequently hospitalized for chest pain. You did not notify the IRB about this serious adverse event until 16 days later, in a letter dated 3/15/04.

ii. Subject (b)(6) was hospitalized for possible peripheral neuropathy, with an onset of 4/1/04, which was later diagnosed as somatic transformation. You did not notify the IRB of this SAE until two and a half months later in a letter dated 6/18/04.

In your letter you state that you had assigned the reporting of serious adverse events to one of your staff who failed to follow the procedures. While certain research functions may be delegated to staff members, as the clinical investigator, you remain ultimately responsible for all aspects of the clinical research. Due to the suspected risk of cardiac SAEs associated with the study vaccines, it was critical that the IRB be promptly informed of these SAEs.

F. You did not perform serum pregnancy tests on women of childbearing potential at all visits for which testing was required according to the protocol and informed consent.

Subject	Serum pregnancy test not done or results not received
(b)(6)	Day 21 2/19/04
	Day 21 2/20/04
	Day 0 2/20/04
	Day 21 3/15/04
	Day 0 2/27/04

G. Critical safety assessments at days 7, 10, 21, and 30 were not conducted by qualified health care professionals. The Site Personnel Log for each study documents that you delegated duties to study personnel who were not medically qualified to perform those tasks. For example, study coordinator (b)(6) who claimed to be a Certified Clinical Research Coordinator, conducted assessments of adverse experiences, and determined severity and relationship of the adverse events to the test articles. Under the protocol, these assessments should be performed by physicians, cardiologists and neurologists.

H. You did not review the results of screening laboratory tests for subject (b)(6) until after the subject was vaccinated. The results were reported on 2/28/04, the subject was vaccinated on 3/2/04, but you did not review the results until 3/5/04.

I. You did not perform the cardiac physical exam and test for CPMB or follow the required cardiac algorithm for subject (b)(6) who was found to have cardiac related abnormalities on day 10. You did not review the troponin lab result from day 10, which was March 12, 2004, until May 4, 2004, after the active phase of the study. Furthermore, you did not review the lab reports for day 21 as documented on the case report form.

J. You did not obtain vital signs for the following subjects as required by the protocols:

Subject	Days vital signs not measured
(b)(6)	Day 10
	days 7, 10, and 21
	Days 0, 7, 10, 21, 30
	Days 7 and 21
	Days 0, 7, 10, and 21
	Days 10 and 21
	Day 30
	Day 10
	Days 0, 7, 10, and 21
	Days 0, 7, 10, and 21

2. **You made changes in the research without IRB approval and failed to promptly report all changes in the studies. [21 CFR § 312.66].**

You began the practice of recruiting vulnerable subjects from the multi-service center for the homeless before you received IRB approval to do so. On 2/24/04 you requested approval to include economically or educationally disadvantaged people as a potential source for subject recruitment. You had already enrolled three vulnerable subjects by this date, and had screened others. The IRB approved your request on March 2, 2004, but your site did not receive the notification and the approved consent form revision until March 8, 2004, by which time you had enrolled at least eight subjects. In the application for IRB review, the IRB specifically asked if you intended to enroll individuals from a list of 20 vulnerable populations, which includes: homeless persons, unemployed or impoverished persons, ethnic minority groups, mentally ill, limited or non-readers, or others that may be vulnerable to coercion. You checked the box "No."

In your letter you state that once you realized that your study staff was recruiting and enrolling subjects from a multi-service center for the homeless, you requested that the IRB review and approve additional safeguards, consisting of a revised informed consent form that added a signature line for an impartial witness.

3. **You failed to maintain adequate and accurate case histories, including all observations and other data pertinent to the investigation. [21 CFR § 312.62(b)].**

A. You signed case report pages for subjects' visits days before the visits actually occurred. For example, subject (b)(6) was seen on 2/27/04 (Day 10). You signed forms for this visit in at least four places, in which you dated your signature as 2/18/04, 2/20/04, 2/25/04, or 2/26/04.

B. The entire case history for subject (b)(6), who experienced a serious adverse event of pericarditis, was missing for many months, and there is no documentation of a conversation or correspondence informing the monitor or sponsor of the missing file. The file was located two years after the study ended.

On the basis of the above listed violations, FDA asserts that you have repeatedly or deliberately failed to comply with the cited regulations. Accordingly, FDA proposes that you be disqualified as a clinical investigator. You may reply to the above stated issues, including any explanation of why you believe you should remain eligible to use investigational drugs and not be disqualified as a clinical investigator, in a written response or at an informal conference in my office. This procedure is provided for by regulation 21 CFR § 312.70(a).

Within fifteen (15) days of receipt of this letter, write to me to arrange a conference time or to indicate your intent to respond in writing. Your written response must be forwarded within thirty (30) days of receipt of this letter. Your reply should be sent to:

Mary A. Malarkey, Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Suite 200N
Rockville, MD 20852-1488

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 thirty (30) days of your request.

At any time during this administrative process, you may enter into a consent agreement with FDA regarding your future use of investigational products. Such an agreement would terminate this disqualification proceeding. Enclosed you will find a proposed agreement between you and the Center.

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 response to our allegations is unsatisfactory, or we cannot come to terms on a consent agreement, or you do not respond to this notice, you will be offered the opportunity to request a regulatory hearing before FDA, pursuant to 21 CFR Part 16 (available at the Internet address identified at the top of page 2 of this letter) and 21 CFR § 312.70. 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 receive investigational products. 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,

for

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

Enclosures: Proposed consent agreement