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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

NOV 0 9 2007

Notice of Initiation of Disqualification Proceeding
And Opportunity to Explain

By Certified Mail – Return Receipt Requested
And By Facsimile Transmission

David N. Lofgren, M.D.
1434 East 9400 South, Suite 100
Sandy, Utah 84093

Dear Dr. Lofgren:

Between June 16 and July 22, 2005, Food and Drug Administration (FDA) investigator Thaddeus Steinke met with you to inspect records relating to the use of an investigational vaccine. The inspection focused on the clinical study entitled [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 drugs.

At the end of the inspection Mr. Steinke presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. You responded to the Form FDA 483 in a letter transmitted to FDA on September 8, 2005. We reviewed the inspection report, the supporting documents submitted with that report, and your response and consider your response (hereafter referred to as "your letter") to be unacceptable in addressing the matters outlined below.

Based on the results of this inspection and on other information available to the Agency, we believe that you repeatedly or deliberately 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. These 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 disqualified from receiving investigational products as set forth under 21 CFR § 312.70.

The applicable regulation is cited for each violation listed below. Certain of these violations were not listed on the Form FDA 483, but were evident from related documents that Mr. Steinke collected during the inspection.

1. **You failed to fulfill the general responsibilities of investigators. [21 CFR § 312.60].**

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation. 21 CFR § 312.60. You signed a Form FDA 1572, Statement of Investigator, on December 21, 2001, and on six more occasions thereafter, in which you agreed to conduct the study in accordance with the study protocol and applicable FDA regulations.

Our investigation revealed that you did not fulfill your obligations as a clinical investigator and you failed to adequately protect the rights, safety, and welfare of subjects.

You delegated study tasks to individuals not permitted by the protocol to perform those tasks, and failed to personally supervise study personnel to whom you delegated critical tasks. When you signed the Form FDA 1572, you agreed to personally conduct the above-referenced clinical investigation or to supervise those aspects of the study that you did not personally conduct. As a clinical investigator, you may delegate authority to perform certain study procedures to individuals qualified to perform them. However, such delegation requires adequate supervision of those to whom you delegate authority. You are responsible for the oversight of study personnel and for reviewing the work of the subinvestigators to ensure that they follow the investigational plan and protocol.

A. You delegated certain tasks to individuals not qualified to perform such tasks. For example, study protocol section 5.4 required history-directed physical examinations and 30-minute post vaccination observation during visit 1/month 0. As described further in item 2.A. below, you permitted these examinations and observations to be performed by individuals who were not authorized to perform these protocol-required tasks.

B. You also failed to supervise the individuals to whom you delegated study tasks to assure that study procedures were properly performed. For example, protocol section 6.1.2 required administration of the study vaccine with concomitant vaccines supplied by the sponsor. You were notified multiple times by the sponsor that concomitant vaccines not supplied by the sponsor had been administered to multiple subjects by personnel under your supervision. You did not take adequate steps to

address this protocol deviation, and concomitant vaccines not supplied by the sponsor continued to be administered in violation of the protocol.

In your letter you explain and attribute many of the deviations described in FDA's inspectional observations to a former study coordinator, employed by Although you attribute many of the deviations to this individual, other deviations involve your actions as well. Taken as a whole, these deviations illustrate that you failed to effectively supervise the individuals under your direction and failed to fulfill your responsibilities as an investigator.

2. **You failed to ensure that the investigation was conducted according to the investigational plan. [21 CFR § 312.60].**

A. Protocol section 5.4 requires history-directed physical exams to be performed at visit 1/month 0. The relevant records for subjects do not document that these exams were performed by authorized study personnel.

In your letter you explain that the pediatricians evaluating the newborns at performed the examination after birth. However, the pediatricians and nurses evaluating the newborns enrolled in your study were not delegated the authority to perform study-related procedures and were not listed as trained subinvestigators on the Forms FDA 1572 that you signed. Additionally, the "Physical Exam Findings" section of the source document forms initially recorded that you had performed these examinations for subjects Months later, you amended the forms to state that you did not do the examinations, and that they had been performed by was the unblinded study coordinator, and was not permitted to perform this task.

B. Protocol section 6.1.2 required administration of the study vaccine with concomitant vaccines) supplied by the sponsor. Subjects # were administered concomitant vaccines other than the required by the protocol. Subject # was administered another manufacturer's vaccine, and subject was administered a vaccine.

In your letter, you acknowledge that concomitant vaccines were administered outside of the protocol provisions to study subjects and that the study monitor had repeatedly informed you of this deviation from the protocol. Regarding subject your letter also cites a provision in protocol section 6.1.2 that allowed for administration of and provided that the vaccination series should be initiated with if it was expected that the series could not be completed with

However, subject # was administered for all three study doses, and the doses were administered months before the protocol amendment you cited was actually implemented.

C. Protocol section 6.4 required the vaccine number to be entered in the case report forms (CRFs). Moreover, according to protocol appendix B, corrections to CRFs were required to be initialed and dated. You did not record lot numbers in the CRFs as required by the protocol.

Instead, the hospital's "Newborn Assessment/Progress Note" documents the administration of the study vaccine, including lot numbers, to the neonates after birth. For 16 subjects, the inspection revealed that another manufacturer's vaccine number was initially entered in the progress notes, subsequently crossed out, and the study vaccine number was then entered (subjects). It appears that initialed four of the progress notes where the lot numbers were changed (subjects , and only one of these changes was dated (subject .

In your letter, you explain that the policy of in 2002 to 2003 was to initially enter the commercial lot number of the vaccine onto the Newborn Assessment/Progress Note prior to the delivery of the baby, and then to cross out and enter the study vaccine lot number when the mother agreed to participate in the study. You explained that the delivery room nurses administering the vaccine did not initial and date the corrections.

As a result, since the lot numbers were not recorded in the CRFs, the only documentation of lot numbers for study vaccines administered to most subjects was corrected by staff of unknown identity at unknown times.

D. Protocol Appendix G required that all doses of study and study-related concomitant vaccines be accounted for on the forms provided by the sponsor. You failed to account for all the concomitant vaccines supplied by the sponsor. For example, the vaccine reconciliation form dated 2/26/04 documents that you could not account for 223 study-related concomitant vaccine vials supplied by the sponsor.

Your letter explains that a representative of the State of Utah Department of Health confiscated cartons of on July 25, 2004, and states that this accounts for 61 vials of each vaccine. This, however, does not account for the remaining 40 vials.

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

A. You signed case report forms and source documents without adequately reviewing the information they contained, which in many cases was incomplete and inaccurate. Specifically, you signed source documents indicating that you performed physical examinations for study subjects when you did not actually perform these examinations yourself. The "Physical Exam Findings" section of the source document forms initially recorded that you had performed these examinations for subjects shortly after their birth. Months later, you amended the forms to state that you did not do the examinations, and that they had been performed by

You offered two contradictory explanations. Your letter states that the data under "Physical Examination Findings" were transcribed from the hospital's Newborn Assessment/Progress Notes by However, the letter also states that conducted physical examinations; this is consistent with a memo to the file that you signed on August 13, 2003, identifying 19 physical examinations performed by

B. You did not maintain adequate documentation identifying who conducted the 30-minute post-first vaccination observations The source documents do not specify who conducted these observations, and during the inspection you told the FDA investigator that you did not observe any of the study subjects for 30 minutes post-vaccination after the first dose was administered to study subjects at the hospital. However, your letter states that you "conducted the 30 minute post-vaccination examinations and reported [your] findings to to record in the primary source document." The letter also states that a memo to the file documented that you "conducted all the blinded study assessments." This memo to the file, however, states that you conducted "some but not all of the responsibilities" identified in the memo, such as conducting 30-minute post vaccination examinations (emphasis added). Thus, your records remain unclear regarding who conducted these observations.

C. For subjects # the hospital Newborn Assessment/ Progress Notes indicated these subjects were born on Your study records indicated these subjects were born on More than eight months later you obtained the correct birthdates from the subjects' relatives, as recorded in documents dated 6/25/03 and 2/26/04 for subjects # and # respectively.

4. You failed to maintain adequate records of the disposition of the drug. [21 CFR § 312.62(a)].

As an investigator, you are required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. The "Investigational Product Dispensing Record" contains extensive cross-outs and obscured entries that prevent an accurate accounting of the disposition of the investigational product.

During the inspection you stated that this study was essentially your first "real study" and that you do not intend to conduct any more clinical studies. However, in your letter you state that you "had conducted previous studies" with a different site management organization. As part of your reply to this letter, please provide a complete list of all the FDA regulated studies you are conducting or have conducted.

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 (HFM-600)
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike
Rockville, Maryland 20852-1448

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. 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.

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 responses to our allegations are 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 on page 1 of this letter) and 21 CFR § 312.70. 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,

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

Enclosure: Proposed consent agreement

cc: